

Priyam Lizmary Cherian

Advocate, The High Court of Delhi
Patent Agent, Indian Patent Office

October 2, 2021

To,
The Controller of Patents
Patent Office,
Delhi

Re: Representation for Opposition to grant of patent under Section 25(1) to Patent Application No. 201817002543, titled “Antiviral Compound”, filed by Abbvie Inc.

Opponent: The Delhi Network of Positive People

In reference to the above-mentioned patent application number, we herein submit the following:

1. Notice of opposition on Form 7A as prescribed under Section 25(1) of the Patents Act and Rule 55 of the Patents Rules, 2003;
2. Exhibits: Exhibit A, Exhibit B, Exhibit C, Exhibit D, Exhibit E, Exhibit F, Exhibit G, Exhibit H, Exhibit I, Exhibit J, Exhibit K and Exhibit L;
3. Form 26.

You are kindly requested to take this opposition on record, and grant a hearing in due course.

Yours Sincerely,



Priyam Lizmary Cherian
IN/PA-2320
Counsel for the Opponent

**BEFORE THE CONTROLLER OF PATENTS,
THE PATENT OFFICE, DELHI**
IN THE MATTER OF A PRE- GRANT OPPOSITION UNDER SECTION 25(1)
AND RULE 55 OF THE PATENTS RULES, 2003

IN THE MATTER OF REPRESENTATION FOR OPPOSITION FILED BY
THE DELHI NETWORK OF POSITIVE PEOPLE, TO GRANT OF PATENT
TO APPLICATION NO. 201817002543OPPONENT

AND

IN THE MATTER OF PATENT APPLICATION NUMBER 201817002543
TITLED “SOLID PHARMACEUTICAL COMPOSITIONS FOR TREATING
HCV”, FILED BY **ABBVIE INC.**APPLICANT

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Dated this 2nd day of October, 2021



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TO

THE CONTROLLER OF PATENTS

PATENT OFFICE, DELHI

FORM 7A
THE PATENTS ACT, 1970
and
THE PATENT RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT

WE, Delhi Network of Positive People (DNP+) with our office at Flat No. A1-5, House No 141, Gali No 3, Near IGNOU, Neb Sarai, New Delhi 110068, hereby give representation by way of opposition to the grant of patent in respect of Indian Patent Application No. 201817002543 titled **SOLID PHARMACEUTICAL COMPOSITIONS FOR TREATING HCV** filed by **Abbvie Inc.**, on 22.01.2018 in India and published on 27.04.2018.

The patent application is opposed on the following grounds:

1. Section 25(1)(e)-That the invention claimed is obvious and does not involve any inventive step;
2. Section 25(1)(f)-That the subject of the claims of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act ;
3. Section 25(1)(g)- That the complete specification does not clearly and sufficiently describe the method by which the invention is to be performed.
4. Section 25(1)(h)- That the Applicant has failed to provide information as required under Section 8 of the Patents Act.

Our address for service in India is:

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Dated this the 2nd day of October 2021

For the Opponent

To

The Controller,

The Patent Office, DELHI

**BEFORE THE CONTROLLER OF PATENTS,
THE PATENT OFFICE, DELHI
THE PATENTS ACT, 1970 AND THE PATENTS RULES, 2003**

IN THE MATTER OF A PRE-
GRANT OPPOSITION UNDER
SECTION 25 (1) AND RULE 55 OF
THE PATENTS ACT, 1970

And

IN THE MATTER OF PATENT
APPLICATION NO. 201817002543,
TITLED 'SOLID
PHARMACEUTICAL
COMPOSITIONS FOR TREATING
HCV' IN THE NAME OF ABBVIE
INC. ...APPLICANT

And

IN THE MATTER OF
REPRESENTATION BY WAY OF
OPPOSITION FILED BY THE
DELHI NETWORK OF POSITIVE
PEOPLE (DNP+)
...OPPONENT

REPRESENTATION BY WAY OF OPPOSITION U/S 25(1)

1. A pre-grant opposition under Section 25(1), Patents Act, 1970 is hereby being filed by the Delhi Network of Positive People (DNP+) (hereinafter, "the Opponent") in the patent application no. **201817002543** (hereinafter, the "Present Application") titled 'Solid Pharmaceutical Compositions For

Treating HCV’ filed by Abbvie Inc. (hereinafter, “the Applicant”), filed before the Indian Patent Office on 22.01.2018.

OPPONENT’S BACKGROUND & *LOCUS STANDI*

2. The Opponent- Delhi Network of Positive People (DNP+) is registered trust and a network of PLHIV (People Living with HIV), working extensively in the area of access to medicines. The Opponent’s work includes but is not limited to service delivery, treatment literacy and community empowerment. The Opponent has over the years worked with HIV, Hepatitis and Tuberculosis communities to support diagnosis and treatment. The Opponent advocates for access to medicines as they believe that every individual should get treatment and no one should suffer and die due to lack of medicines. Thus, based on Opponent’s work and as per S.25(1), the Opponent has sufficient *locus standi* to file the present pre-grant representation.
3. Section 25(1) of the Patents Act states that a representation by way of notice of opposition can be instituted by “any person” as long as an application has been published but not granted. The Present Application was published on 27.04.2018 and is currently pending. Hence, the present representation can be entertained by the Hon’ble Controller of Patents, and is not time barred.

BACKGROUND

4. The Present Application by way of complete specification claims compounds that are used in the treatment of Hepatitis. Hepatitis C is a blood borne virus. The infection spreads from exposure to infected blood from unsafe injection practice, injecting drug use, transfusion of unscreened and unsafe blood products. India has an estimated 10 to 15 million chronic carriers of Hepatitis C Virus (Bhattacharya PK, Roy A (2015) Management of Hepatitis C in the Indian Context: An Update. J Liver 4:187 doi:10.4172/2167-0889.1000187). Estimates suggest that India has more than 37 million hepatitis C virus (HBV) carriers and between 6 and 12 million people are living with the hepatitis C virus (HCV).

5. According to WHO Global Hepatitis Report, 2017 an estimated 325 million people worldwide are living with chronic Hepatitis B or C virus infection. It is estimated that 71 million people to be living with chronic Hepatitis C infection. The majority of these people have limited access to life saving Hepatitis C Virus testing and treatment. Increasing mortality rates due to Hepatitis C infection when compared with HIV and Tuberculosis deaths is a cause of concern. In 2015, viral hepatitis caused 1.34 million deaths.
6. Access to Hepatitis C treatment and medicines continues to be abysmally low for people with active hepatitis C infection. Of the different barriers in access to Hepatitis C medicines, high prices due to patent monopoly on drugs for Hepatitis C drugs is one of major concerns.

ACCESS TO MEDICINES AND STRICT INTERPRETATION OF INDIAN PATENTABILITY STANDARDS

7. As indicated, patent monopoly is one of the factors contributing to high prices of Hepatitis C medicines. It is therefore important to ensure that patents on life-saving drugs are not granted erroneously, and issued only after examination of the strict application as per the patentability standards laid down in the Patents Act, 1970.
8. A 2018 study found that in a cohort of 2,293 pharmaceutical patents granted between 2009 and 2016, about 72 per cent patents were secondary patents, granted for marginal improvements over previously known drugs for which primary patents exist. That is, the strict standards of patentability laid down in Section 3 of the Patents Act, were not followed appropriately. (See Dr. Feroz Ali *et al*, *Pharmaceutical Patents Granted in India: How our safeguards against ever-greening have failed, and why the system must be Reformed*, Accessibsa, 2018).
9. The Opponent believes that proper application of the patentability standards set out in Section 3 of the Patents Act, as well as those laid down in Section 2(1)(j) and Section 2(1)(j)(a) of the Patents Act, will result in the rejection of the present application in its entirety.

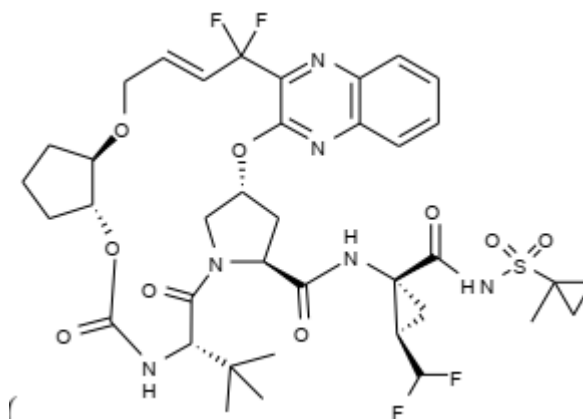
PRESENT APPLICATION

10. The Present Application was filed in India with 14 claims on 22.02.2018. The Present Application is a national phase application of the PCT Application no. PCT/US2016/039266. The Present Application claims priority from four US patent applications, viz. application no. 62/185145 dated 26.06.2015, application no. 62/186154 dated 29.06.2015, application no. 62/193639 dated 17.07.2015 and application no. 62/295309 dated 15.02.2016.
11. The Present Application was published on 27.04.2018. A First Examination Report (FER) was issued in the Present Application on 24.02.2020. The Applicant filed a response to the FER on 23.11.2020. With the response to the FER, the Applicant also amended the claims. The total number of claims after the amendment is 27.

CLAIMS

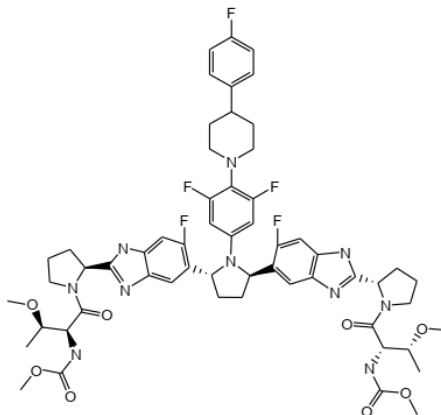
12. The Present Application was filed with 14 claims. To overcome the objections raised in the FER, the Applicant amended the claims, raising the total number of claims to 27. The 27 claims are described as below:

Claim 1: This is an independent claims covering a solid oral pharmaceutical composition comprising 50-80% of one or more pharmaceutically acceptable polymers, and 100 mg of compound 1



Wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the first composition,

and a second composition comprising 50-80% by weight of one or more pharmaceutically acceptable polymers, and 40mg of compound 2



Wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the second composition;
Wherein the formulation is a tablet comprising a first layer and a second layer, the first layer comprising the first composition and the second layer comprising the second composition; and
Wherein administration of three of the tablets to a population of healthy, non-fasted adult humans results in a mean C_{\max} value between 333 ng/mL and about 1113 ng/mL for Compound 1.

Claim 2: This claims a formulation of claim 1 where the first composition comprises a amorphous solid dispersion comprising compound 1.

Claim 3: claims a formulation of claim 1 wherein the second composition comprises a second amorphous solid dispersion comprising compound 2.

Claim 4: claims a formulation of claim 2, wherein the first amorphous solid dispersion comprises the one or more pharmaceutically acceptable polymers.

Claim 5: claims a formulation of claim 2, wherein the first amorphous solid dispersion comprises one or more pharmaceutically acceptable surfactants.

Claim 6: claims a formulation of claim 4, wherein the first amorphous solid dispersion further comprises one or more pharmaceutically acceptable surfactants.

Claim 7: claims the formulation of claim 3, wherein the second amorphous solid dispersion comprises the one or more pharmaceutically acceptable polymers.

Claim 8: claims formulation of claim 3, wherein the second amorphous solid dispersion comprises one or more pharmaceutically acceptable surfactants.

Claim 9: claims formulation of claim 7, wherein the second amorphous solid dispersion comprises one or more pharmaceutically acceptable surfactants.

Claim 10: claims formulation of claim 6, wherein one or more pharmaceutically acceptable polymers comprise copovidone, and the one or more pharmaceutically acceptable surfactants comprises Vitamin E TPGS.

Claim 11: claims the formulation of claim 9, wherein the one or more pharmaceutically acceptable polymers comprise copovidone, and the one or more pharmaceutically acceptable surfactants comprises Vitamin E TPGS.

Claim 12: claims a formulation of claim 11, wherein the one or more pharmaceutically acceptable surfactants comprise propylene glycol monocaprylate.

Claim 13: claims the formulation of claim 1, wherein the first composition comprises a first amorphous solid dispersion comprising Compound 1, one or more pharmaceutically acceptable polymers and one or more pharmaceutically acceptable surfactants; and

The second composition comprises a second amorphous solid dispersion comprising Compound 2, one or more pharmaceutically acceptable polymers and one or more pharmaceutically acceptable surfactants.

Claim 14: claims the formulation of claim 13 wherein wherein one or more pharmaceutically acceptable polymers comprise copovidone, and the one or more pharmaceutically acceptable surfactants comprise Vitamin E TPGS.

Claim 15: claims the formulation of claim 3, wherein the first amorphous solid dispersion comprises Compound 1, one or more pharmaceutically acceptable polymers comprising copovidone, and one or more pharmaceutically acceptable surfactants comprises Vitamin E TPGS; and the second amorphous solid dispersion comprises Compound 2, one or more

pharmaceutically acceptable polymers comprising copovidone, and one or more pharmaceutically acceptable surfactants comprising Vitamin E TPGS and Propylene glycol monocaprylate.

Claim 16: claims formulation of claim 1, wherein the first amorphous solid dispersion comprises 10% to 40% by weight of Compound 1, and the second amorphous solid dispersion comprises 5% to 20% by weight of Compound 2.

Claim 17: claims formulation of claim 1, wherein the first amorphous solid dispersion comprises 15% to 30% by weight of Compound 1, and the second amorphous solid dispersion comprises 5% to 15% by weight of Compound 2.

Claim 18: claims formulation of claim 13, wherein the first amorphous solid dispersion comprises 15% to 30% by weight of Compound 1, and the second amorphous solid dispersion comprises 5% to 15% by weight of Compound 2.

Claim 19: claims the formulation of claim 15 wherein the first amorphous solid dispersion comprises 15% to 30% by weight of Compound 1, and the second amorphous solid dispersion comprises 5% to 15% by weight of Compound 2.

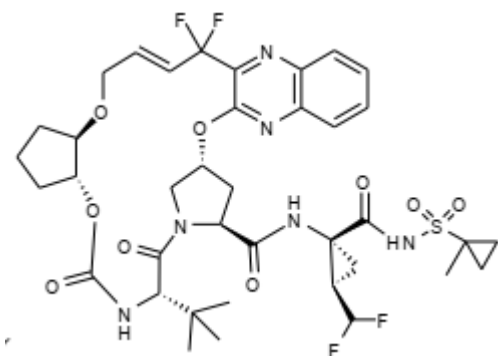
Claim 20: claims the formulation of claim 1, wherein the first layer further comprises a disintegrant.

Claim 21: claims the formulation of claim 20, wherein the disintegrant comprises Croscarmellose sodium.

Claim 22: claims the formulation of claim 1 wherein the first layer and the second layer further comprise a lubricant.

Claim 23: claims the formulation of claim 22, wherein the lubricant comprises sodium stearyl fumarate.

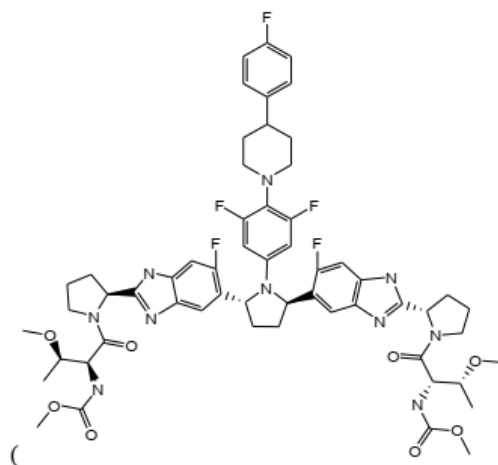
Claim 24: claims a solid oral pharmaceutical dosage formulation comprising a first composition comprising: 50% to 80% by weight of one or more pharmaceutically acceptable polymers, and 100 mg Compound 1



wherein the weight percentage of the one or more pharmaceutically acceptable

polymers is relative to the total weight of the first composition; and a second composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and 40 mg Compound 2



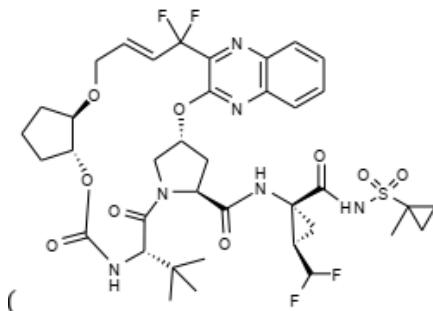
wherein the weight percentage of the one or more pharmaceutically acceptable

polymers is relative to the total weight of the second composition;

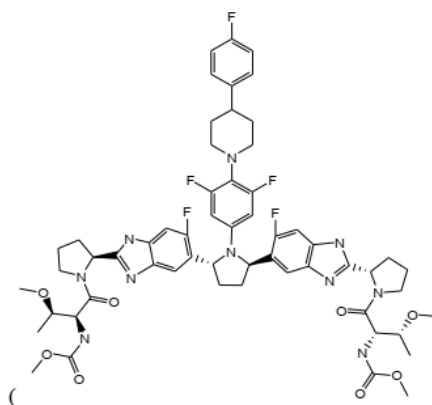
wherein the formulation is a tablet comprising a first layer and a second layer, the first layer comprising the first composition and the second layer comprising the second composition; and

wherein administration of three of the tablets to a population of healthy, non-fasted adult humans results in a mean AUC value between about 1099 ng·h/mL and about 3680 ng/mL for Compound 1.

Claim 25: claims a solid oral pharmaceutical dosage formulation comprising a first composition comprising: 50% to 80% by weight of one or more pharmaceutically acceptable polymers, and 100 mg Compound 1



wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the first composition; and a second composition comprising: 50% to 80% by weight of one or more pharmaceutically acceptable polymers, and 40 mg Compound 2



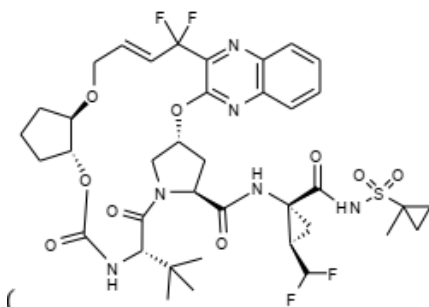
wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the second composition; wherein the formulation is a tablet comprising a first layer and a second layer, the first layer comprising the first composition and the second layer comprising the second composition; and wherein administration of three of

the tablets to a population of healthy, fasted adult humans results in a mean C_{max} value between about 85 ng/mL and about 684 ng/mL for Compound 1.

Claim 26: claims a solid oral pharmaceutical dosage formulation comprising:
a first composition comprising:

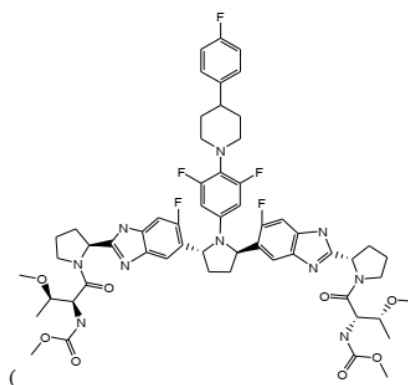
50% to 80% by weight of one or more pharmaceutically acceptable polymers,
and

100 mg Compound 1



wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the first composition;
and a second composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and 40 mg Compound 2



wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the second composition;

wherein the formulation is a tablet comprising a first layer and a second layer,

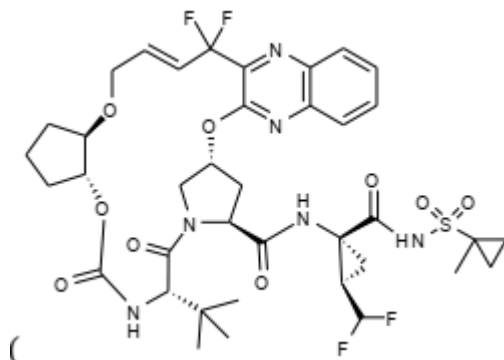
the first layer comprising the first composition and the second layer comprising the second composition; and

wherein administration of three of the tablets to a population of healthy, fasted adult humans results in a mean AUC value between about 429 ng·h/mL and about 2431 ng/mL for Compound 1.

Claim 27: claims a solid oral pharmaceutical dosage formulation that is bioequivalent to a solid oral tablet pharmaceutical dosage formulation comprising

- a. solid oral pharmaceutical dosage formulation that is bioequivalent to a solid oral tablet pharmaceutical dosage formulation comprising

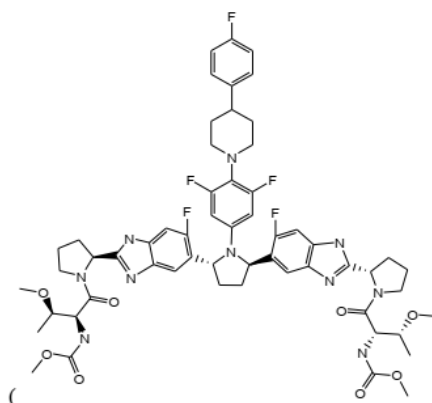
- i. 20% (100 mg) Compound 1



- ii. 69% copovidone,
- iii. 10% vitamin E TPGS, and
- iv. 1% colloidal silicon dioxide;

- b. 400 mg of Compound 2 10% extrusion granulation, comprising

- i. 10% (40 mg) Compound 2



- ii. 79% copovidone,
- iii. 8% vitamin E TPGS,

- iv. 2% propylene glycol monocaprylate, and
- v. 1% colloidal silicone dioxide;
- c. 26.3 mg croscarmellose sodium;
- d. 4.7 mg colloidal silicon dioxide;
- e. 4.7 mg sodium stearyl fumarate; and
- f. 28.1 mg HPMC coating.

SUMMARY OF GROUNDS FOR OPPOSITION

13. The Opponent brings this representation by way of opposition to grant of patent to the Present Application on the following grounds, each of which is without prejudice to the other:
 - a. **Section 25(1)(e)**: That claims 1-27 of the Present Application, lack inventive step, and do not meet the criteria laid down in Section 2(1)(j) and Section 2(1)(ja) of the Patents Act.
 - b. **Section 25(1)(f)**: That claims 1-27 of the Present Application does not cover an invention within the meaning of the Patents Act.
 - c. **Section 25(1)(g)**: That the complete specification does not clearly and sufficiently describe the method by which the invention is to be performed.
 - d. **Section 25(1)(h)**: That the applicant has failed to disclose the information required by section 8 or has furnished the information which in any material particular was false to his knowledge.

DETAILED GROUNDS

a. CLAIMS 1-27 OF THE PRESENT APPLICATION LACK INVENTIVE STEP AND MUST BE REJECTED UNDER S.25(1)(E) OF THE PATENTS ACT

14. The Opponent submits that claims 1-27 of the Present Application lack an inventive step and must be rejected.
15. The Patents Act, 1970 provides the definition of inventive step under Section 2(1)(ja) as '*a feature of an invention that involves technical step as compared to existing knowledge ...*' (emphasis supplied).

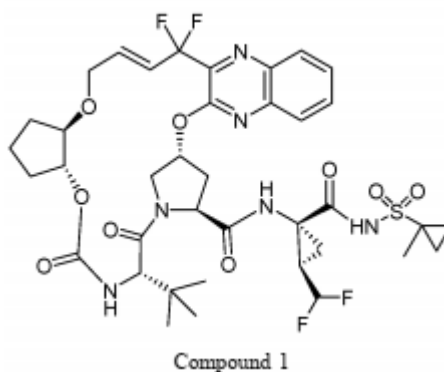
16. It is pertinent to note that the Applicant has in the complete specification of the Present Application admitted the following:
- a. That compound 1 known to be an HCV protease inhibitor was disclosed in US Patent Application Publication no. 2012/0070416 (see para 0005 of the complete specification);
 - b. Compound 2 known to be a potent NS5A inhibitor has been disclosed in US Patent Application No. 2012/0220562 (see para 0005 of the complete specification).

WO2014152514 (Published 25.09.2014)

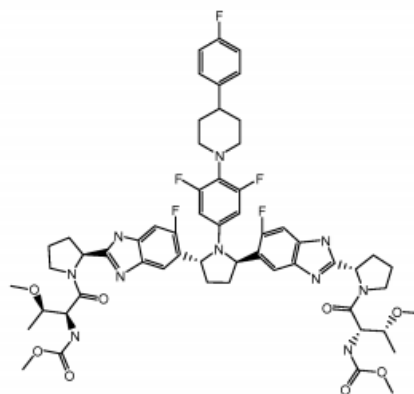
17. The Opponent relies on PCT publication no. WO 2014/152514 A1 (hereinafter “WO’514” and annexed herewith as **Exhibit-A**), published on 25.09.2014 titled, “Combination of Two Antivirals for Treating Hepatitis C”, filed by Abbvie Inc. who is also the Applicant in the Present Application. Given that WO’514 was published before the priority date of the Present Application, it can be relied on as a prior art document.
18. The Opponent submits that WO’514 discloses the combination of same compound 1 and compound 2 as claimed in the Present Application. Attention is drawn to the disclosure in WO’514 stating:
- ‘One aspect of the present invention features methods for treating HCV infection... The methods comprise administering at least two direct acting antiviral agents (DAAs) to the subject for a duration of no more than 12 weeks, or for another duration as set forth herein. The at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof).’* (see WO’514 at para [0005])
19. WO’514 further discloses that :
- “Preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 100 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 50 to 500 mg once daily. More preferably, Compound 1 (or a pharmaceutically*

acceptable salt thereof) is administered from 200 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. Highly preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 400 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. For instance, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered 120 mg once daily. For another instance, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) can be administered 240 mg once daily.” (see WO’514 at para [0010])

20. Compound 1 identified in the above reproduced paragraph is (see WO’514, para[0022]):



21. Compound 2 mentioned in the paragraph reproduced above is (see WO’514, para[0022]):



Compound 2

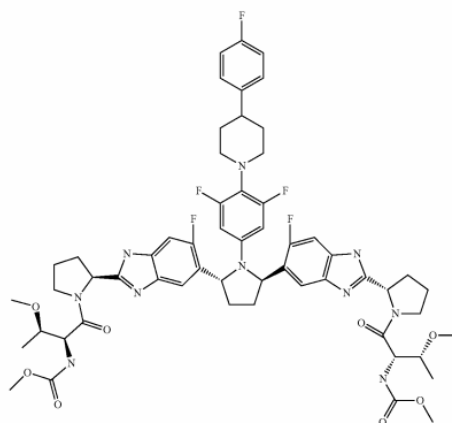
22. The compound 1 and compound 2 disclosed in WO'514 are the same as those identified and claimed in the Present Application.
23. In fact, WO'514 goes on to disclose a solid dosage form comprising both these compounds stating:

“Preferably, Compound 1 and Compound 2 are formulated in a single solid dosage form in which at least one of the DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. The other DAAs can also be in an amorphous form or molecularly dispersed in the matrix, or formulated in different form(s) (e.g., in a crystalline form). More preferably, each of the two DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant.” (see WO'514 at para [0062])
24. Therefore, before the priority date of the Present Application, the following was disclosed in WO'514:
 - Compound 1 and compound 2 could be administered together
 - Compound 1 and compound 2 could be administered together in a specified dose range

- The administration of these two compounds could be in a solid dosage form where they are in an amorphous dispersion matrix comprising a water soluble polymer and a surfactant.

US20140080868 A1 (Published: 20.03.2014)

25. The Opponent relies on US Patent Application Publication No. US20140080868 A1 (hereinafter referred to as “US’868” and annexed as **Exhibit-B**). US ’868 was published before the priority date of the Present Application and therefore can be relied on as a prior art document.
26. US’868 discloses a compound of formula (see US’868 at internal page 3):



27. It may be noted that this compound is the same as compound 2 identified in the Present Application. Compound 2 is also known as Pibrentasvir. US’868 discloses that Pibrentasvir along with combination with other drugs can be used. It states:

“... Compound 1 or the salt thereof is combined or co-administered with another anti-HCV agent. Non-limiting examples of said another anti-HCV agent include ... HCV protease inhibitors ...” (see US’868 at para [0007])

28. US’868 also discloses a solid dispersion comprising the compound disclosed with other components. US’868 states, “*Any method described herein can employ a solid composition which comprises (1) Compound 1 (or a pharmaceutically acceptable salt thereof) in amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a*

pharmaceutically acceptable surfactant. Compound 1 (or the salt thereof) and the polymer preferably are formulated in a solid dispersion. The surfactant may also be formulated in the same solid dispersion; or the surfactant can be separately combined or mixed with the solid dispersion. “ (see US’868 at para [0033])

29. US’868 further describes different embodiments of the composition including one where,

“In one embodiment, a solid composition employed in the invention comprises an amorphous solid dispersion or solid solution which includes Compound 1 (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable hydrophilic polymer. The solid composition also includes a pharmaceutically acceptable surfactant which preferably is formulated in the amorphous solid dispersion or solid solution. ... Preferably, the hydrophilic polymer is selected from ... copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40)... ... the surfactant is ... D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, or sorbitan monolaurate. More preferably, the surfactant is selected from sorbitan monolaurate or D-alpha-tocopheryl polyethylene glycol 1000 succinate. ...” (see US’868 at para [0041])

30. US’868 adds that, *“Various additives can also be included in the melt, for example, flow regulators (e.g., colloidal silica), binders, lubricants, fillers, disintegrants, plasticizers, colorants, or stabilizers (e.g., antioxidants, light stabilizers, radical scavengers, and stabilizers against microbial attack). ...” (see US’868 at para [0045]).* It also adds that, *“The solid dispersion produced by melt-extrusion, spray-drying or other techniques can be prepared into any suitable solid oral dosage forms. In one embodiment, the solid dispersion prepared by melt-extrusion, spray-drying or other techniques can be compressed into tablets. ... When a solid composition of the present invention comprises Compound 1 and another anti- HCV agent, it is possible to separately prepare solid dispersions of each individual*

active ingredient and then blend the optionally milled or ground solid dispersions before compacting.” (see US’868 at para [0054]).

31. Hence, on reading US’868, a person skilled in the art would be taught that Pibrentasvir can be in combination with other HCV protease inhibitor, and the same can be developed as solid dispersions along with surfactants, flow regulators (e.g., colloidal silica), binders, lubricants, fillers, disintegrants, plasticizers, colorants, or stabilizers etc.
32. Therefore, a person skilled in the art (POSITA) on reading US’868 would be taught that the disclosed compound-Pibrentasvir could be used with an HCV protease inhibitor. Therefore, the POSITA would be search for a HCV protease inhibitor, and on reading WO’514, would be motivated to combine the compounds disclosed in WO’514 with Pibrentasvir disclosed in US’868. In fact, there is sufficient teaching on combined reading of these prior art documents that a solid dispersion of compound 1 disclosed in WO’514 with Pibrentasvir disclosed in US’868 with other components would show some anti-HCV activity.
33. On reading WO’514 with US’868, a POSITA would be taught that:
 - Pibrentasvir can be combined with another HCV protease inhibitor ;
 - in a solid dosage form;
 - an amorphous dispersion matrix;
 - an amorphous dispersion matrix comprising water soluble polymer (copovidone being specifically mentioned) and
 - above amorphous dispersion matrix with a surfactant (vitamin E TPGS and other surfactants also specifically mentioned)
 - amorphous dispersion matrix above mention with other additives.

Chih Wei Lin *et al* (Poster presented in Journal in April 2015)

34. The Opponent relies on a poster titled “*Steady-state pharmacokinetics and safety of coadministration of pan-genotypic, direct acting protease inhibitor, abt-493 with pan-genotypic ns5a inhibitor, ABT-530, in healthy adult subjects*”, authored by Chih-Wei Lin *et al* (hereinafter referred to as “Chih-

Wei Lin *et al*” and annexed as **Exhibit-C**). This a poster that was presented at the 50th Annual Meeting of the European Association for the Study of the Liver, Vienna, Austria during April 22-26, 2015. This poster was also published in the Journal of Hepatology 2015 Vol. 62, S592. Chih-Wei Lin *et al* was published before the priority date of the Present Application and therefore can be relied on as a prior art document.

35. Chih-Wei Lin *et al* presented the paper on behalf of Abbvie Inc. which is also the Applicant of the Present Application. The poster discusses next generation direct acting antiviral combination of ABT-493 (generally known as Glecaprevir) and ABT-530 (generally known as Pibrentasvir). The poster discloses the administration of these two compounds at different doses. The different ranges of dose of each of these compounds used in the study is reproduced below:

ABT-530 dose	ABT-493 dose	Results
40 mg	100 mg	ABT-530 had minimal impact on ABT-493 ABT-493 increased ABT-530 to 1.5×
40 mg	400 mg	ABT-530 had minimal impact on ABT-493 ABT-493 increased ABT-530 to 6×
120 mg	400 mg	ABT-530 slightly increased ABT-493 exposures ABT-493 increased ABT-530 to 3–4×
160 mg	700 mg	ABT-530 slightly increased ABT-493 exposures ABT-493 increased ABT-530 to 5–7×
200 mg	1200 mg	Arm was prematurely discontinued, no steady state data were available

36. Hence, a POSITA on reading WO’514 with US’868 with Chih-Wei Lin *et al* would be taught a solid dispersion comprising Glecaprevir and Pibrentasvir formulated as amorphous dispersions in a hydrophilic polymer along with a surfactant with specific doses. It would be routine experimentation for a POSITA to examine the effect of different dosages of Pibrentasvir and Glecaprevir.

T. Wang *et al* (Poster published in Journal in April 2015)

37. The Opponent relies on a poster titled “*Pharmacokinetics of ABT-493 and ABT-530 is Similar in Healthy Caucasian, Han Chinese, and Japanese Adult Subjects*”, authored by T. Wang *et al* (hereinafter referred to as “T. Wang *et al*” and annexed as **Exhibit-D**). This a poster that was presented at the 50th Annual Meeting of the European Association for the Study of the Liver, Vienna, Austria during April 22-26, 2015. This poster was also published in the Journal of Hepatology 2015 Vol. 62, S660. T. Wang *et al* was published before the priority date of the Present Application and therefore can be relied on as a prior art document.
38. T.Wang *et al* studied pharmacokinetics of oral dose of ABT-493 and ABT-530 administered alone in combination in healthy Han Chinese, Japanese and Caucasian subjects. The poster states that there were no serious adverse effects, premature discontinuations and described laboratory abnormalities normalized/improved following completion of dosing.
39. Hence, a POSITA on reading WO’514 with US’868 with Chih-Wei Lin *et al* and T.Wang *et al* would be taught a solid dispersion comprising Glecaprevir and Pibrentasvir formulated as amorphous dispersions in a hydrophilic polymer along with a surfactant with specific doses. It would be routine experimentation for a POSITA to examine the effect of different dosages of Pibrentasvir and Glecaprevir.

Abbvie’s earlier layered formulations that are solid dispersion(s) of drug(s) in polymer

40. It is submitted that the Applicant of the Present Application has in the past developed solid dispersions comprising two drugs, including HCV drugs. The Opponent submits that solid dispersions of drugs with different doses are well known in the art, and have been used by the Applicant itself on several occasions. The Opponent submits below several patent applications filed by

the Applicant of the Present Application that disclose solid compositions containing several layers of compounds that show anti-viral activity.

WO 2005/039551 (published 06.05.2005)

41. The Opponent relies on international application published under the Patent Cooperation Treaty, namely WO 2005/039551 (hereinafter referred to as “WO’551” and annexed as **Exhibit-E**). WO’551 was published on 06.05.2005, much before the priority date of the Present Application and therefore can be relied on as a prior art document.
42. WO’551 is an application filed by the Applicant of the Present Application and discloses a tablet dosage form which included a solid dispersion comprising 2 HIV drugs (ritonavir and lopinavir) in a water-soluble polymer (Copovidone). The publication categorically states that (see WO’551 internal page 12, line 19-30):

“Dosage forms according to the invention may be provided as dosage forms consisting of several layers, for example laminated or multilayer tablets. ... Multilayer forms have the advantage that two active ingredients which are incompatible with one another can be processed, or that the release characteristics of the active ingredient(s) can be controlled. ... Multilayer tablets types may be produced by compressing two or more layers of granules. Alternatively, multilayer dosage forms may be produced by a process known as “coextrusion”. In essence, the process comprises preparation of at least two different melt compositions as explained above, and passing these molten compositions into a joint coextrusion die.”

WO2014130553 (published: 28.08.2014)

43. The Opponent relies on international application published under the Patent Cooperation Treaty, namely WO2014130553 (hereinafter referred to as “WO’553” and annexed as **Exhibit-F**). WO’553 was published on 28.08.2014, much before the priority date of the Present Application and therefore can be relied on as a prior art document.

44. WO'553 discloses discrete layered compositions wherein:-

“Each of the tablets comprises a lopinavir/ ritonavir layer and a lamivudine layer The lopinavir/ ritonavir layer comprises 200 mg lopinavir and 50 mg ritonavir which are dispersed in amorphous solid dispersion composed of copovidone and sorbitan monolaurate.” (see WO'553, internal page 7, para [0038])

45. Further, WO'553 discloses, *“...coated bilayer tablets with the same composition ..., except that the mean particle size of the lopinavir/ ritonavir solid dispersion was no more than 180 μm .”* (see WO'553, internal page 7, para [0040])

WO2011112558 (published: 15.09.2011)

46. The Opponent relies on international application published under the Patent Cooperation Treaty, namely WO2011112558 (hereinafter referred to as “WO'558” and annexed as **Exhibit-G**). WO'558 was published on 15.09.2011, much before the priority date of the Present Application and therefore can be relied on as a prior art document.
47. WO'558 discloses a solid dispersion composition of comprising anti-HCV compounds and methods of using the same to treat HCV infection (see WO'558, internal page 1, para [0003]). WO'558 further discloses: *“... a solid composition of the invention comprises an amorphous solid dispersion or a solid solution which comprises compound I (or a pharmaceutically acceptable salt thereof), copovidone, and a surfactant selected from polysorbate (preferably polysorbate 80), vitamin E TPGS or a combination of vitamin E TPGS and propylene glycol laurate (e.g., lauroglycol FCC).* A solid composition of the present invention may further include ritonavir, preferably a solid dispersion of ritonavir. Ritonavir and Compound I (or a pharmaceutically acceptable salt thereof) may be formulated in the same solid dispersion or solid solution; they may be also formulated in different

solid dispersions or solid solutions.” (see WO’558, internal page 4, paras [0014-0015])

WO’558 further discloses a solid composition which may further comprise another anti-HCV agent which may also be a HCV protease inhibitor. (see WO’558, internal page 4, para [0019])

48. WO’558 also discloses solid compositions containing several layers, for example laminated or multilayer tablets. (see WO’558, internal page 20, para [0074])
49. In fact, WO’558 also discloses the preferred weight of the anti-viral compound, copovidone and polysorbate 80 in the solid dispersion powder (see WO’558, internal page 20, para [0087]). In yet another embodiment, percentage of weight of the active ingredient, polymer and surfactant including the polymer copovidone and Vitamin E TPGS formulated in amorphous solid dispersion has been disclosed (see WO’558, internal page 20, para [0089]).

WO2011156578 (published: 15.12.2011)

50. The Opponent relies on international application published under the Patent Cooperation Treaty, namely WO2011156578 (hereinafter referred to as “WO’578” and annexed as **Exhibit-H**). WO’558 was published on 15.12.2011, much before the priority date of the Present Application and therefore can be relied on as a prior art document.
51. WO’578, discloses a formulation of an HCV drug with another protease inhibitor. It discloses
“... a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a compound [], (2) copovidone, and (3) a pharmaceutically acceptable surfactant (e.g., vitamin E TPGS, sorbitan monolaurate, or a combination of vitamin E TPGS and lauroglycol FCC). The amorphous solid dispersion or solid solution may also include another pharmaceutically acceptable surfactant.” (see WO’578, internal page 15, lines 3-9)

Another embodiment that WO'578 discloses is, "...a solid composition ...comprises an amorphous solid dispersion or solid solution which includes (1) 10%> by weight Compound [] (2) 82% by weight copovidone, and (3) 7% by weight propylene glycol monocaprylate (Capryol 90). The solid composition can also include 1% by weight colloidal silica." (see WO'578, internal page 15, lines 11-19)

One of the embodiments discloses also includes a solid composition including one or more other anti-HCV agents including HCV protease inhibitors, with several layers for example laminated or multilayer tablets. (see WO'578, internal page 16, line 1 and internal page 23, lines 28-30).

WO2013101550 (published: 04.07.2013)

52. The Opponent relies on international application published under the Patent Cooperation Treaty, namely WO2013101550 (hereinafter referred to as "WO'550" and annexed as **Exhibit-I**). WO'550 was published on 04.07.2013, much before the priority date of the Present Application and therefore can be relied on as a prior art document.
53. WO' 550 also discloses [0012] *an amorphous solid dispersion comprising selected HCV inhibitor, copovidone, and a surfactant selected from vitamin E TPGS, Span 20, or a combination thereof.* (see WO'578, internal page 4, para [0012]). It further clarifies that the composition may comprise another anti-HCV agent, for example HCV protease inhibitors, with the solid composition contain several layers, for example laminated or multilayer tablets. (see WO'578, internal page 4, para [0018], internal page 33, para [0095]).
54. Hence, on reading WO'551, WO'553, WO'558, WO'578, WO'550, it is clear that solid dispersions of anti-HCV drugs with polymer, surfactant(s), copovidone, in the form of a layered tablet has been state of the art, and has been in use including by the Applicant itself.
55. Therefore, a POSITA on reading WO'514 with US'868 with Chih-Wei Lin *et al* and T.Wang *et al* with WO'551, WO'553, WO'558, WO'578, WO'550

would be taught a solid dispersion comprising Glecaprevir and Pibrentasvir formulated as amorphous dispersions in a hydrophilic polymer along with a surfactant with specific doses. Combining the teachings of the above-discussed prior art documents, it would be obvious for a POSITA to arrive at the formulation claimed in claim 1, claims 24-27 of the Present Application.

56. Therefore, claim 1 of the Present Application lacks an inventive step, and cannot be granted a patent. Given that claims 2-23 of the Present Application are dependent on claim 1, the subject matter therein is also rendered as that lacking an inventive step. Claims 1-27 of the Present Application must therefore be not allowed, and must be rejected.

THE AMENDMENT OF CLAIMS IN THE PRESENT APPLICATION VIOLATES SECTION 59(1) OF THE PATENTS ACT

57. Without prejudice to other grounds raised herein, the Opponent submits that the claims of the Present Application falls foul of Section 59(1) of the Patents Act.

58. S. 59(1) provides that:

‘(1) No amendment of an application for a patent or a complete specification or any document relating thereto shall be made except by way of disclaimer, correction or explanation, and no amendment thereof shall be allowed, except for the purpose of incorporation of actual fact, and no amendment of a complete specification shall be allowed, the effect of which would be that the specification as amended would claim or describe matter not in substance disclosed or shown in the specification before the amendment, or that any claim of the specification as amended would not fall wholly within the scope of a claim of the specification before the amendment.’

59. It is submitted that on amendment of the claims, the Applicant introduced C_{max} values for compound 1 in claim 1. It may be noted that the complete specification does not even mention C_{max} value, let alone the reason for preference of compound 1 with this value.

60. Since this component was never present in PCT and the complete specification or the original claims, the amendment does not fall within the scope of the complete specification or the original claims.
61. Therefore, the amended claims 1-27 cannot be allowed in their current form.
62. The claims in patent application no. 1554/CHENP/2013 were refused on the ground that , “...*the applicant reworded the claims, where the entire scope of the invention has been changed when compared with the claims filed in international phase or while entering the national phase...In the present case, neither in the international phase, nor at national phase entry the application had a claim for A method of making a genetically modified mouse. So from the above discussion, it is amply clear that the claim which is not claimed at the time of filing is disclaimed and such amendments of claims are not allowable under section 59(1) of the Act...*” (see internal page 15 of the order dated 16.12.2020 in patent application no. 1554/CHENP/2013, herein annexed as **Exhibit-J**)

b. THAT CLAIMS OF THE PRESENT APPLICATION ARE NOT AN INVENTION WITHIN THE MEANING OF THE PATENTS ACT UNDER SECTION 3(D)

63. Without prejudice to other grounds raised herein, the Opponent raises objection under Section 25(1)(f) that the claims of the Present Application fail under Section 3(d).
64. Section 3(d) of the Patents Act lays out subject matter that is not considered as an invention under the Act. Section 3(d) disallows patents on modification of known substances. It is trite that S. 3(d) has to be satisfied independently of the tests of novelty and inventive step [see *Novartis AG versus Union of India and Others (2013) 6 SCC 1*]. The burden of showing enhanced (therapeutic) efficacy of modified known substance, under S. 3(d) is on the Applicant (see *Novartis AG versus Union of India and Others 2007 4 MLJ 1153*). Further, such data has to be provided by the Applicant in the complete specification (Hon’ble IPAB, *Novartis AG versus Union of India*, MIPR 2009 (2) 0345, para 9(xvii)).

65. It is submitted that the 27 claims of the Present Application, claim a formulation comprising of two known compounds- compound 1 and compound 2 (i.e. Glecaprevir and Pibrentasvir).
66. It is further submitted that the Applicant has submitted no data on the efficacy of the claimed bi-layered tablet over the known tablet forms of Glecaprevir and/or Pibrentasvir, or compositions comprising both of these drugs as discussed in **WO2014152514** (Exhibit-A).
67. A fixed dose combination prepared by combining known drugs and known pharmaceutical excipients with no clinical data on enhanced therapeutic efficacy fails to satisfy the requirements under Section 3(d), hence claims 1-27 are deemed not patentable.
68. The Hon'ble Deputy Controller of Patents and Designs rejecting a patent application titled, "Bilayer Tablet" had noted, *"In the instant case, the claimed bilayer tablet shows drug stability and increased dissolution in lesser time. Therefore, it is observed that the physical efficacy of the claimed bilayer tablet is enhanced in comparison to other forms. However, as no data or evidence had been offered to indicate that the claimed bilayer tablet will produce an enhanced or superior therapeutic efficacy than what could be achieved with the other comparable forms. Therefore it is opined that the claimed bilayer tablet does not qualify the test of Section 3(d)."* (see order dated 23.09.2016 in **2978/DELNP/2007** at page 12, annexed as **Exhibit-K**)

THAT CLAIMS OF THE PRESENT APPLICATION ARE NOT AN INVENTION WITHIN THE MEANING OF THE PATENTS ACT UNDER SECTION 3(E)

69. Without prejudice to other grounds raised herein, the Opponent raises objection under Section 25(1)(f), that the claims of the Present Application fail under Section 3(e).
70. It is submitted that claims 1-27 of the Present Application are to be rejected for failing to meet the requirements under Section 3(e). This provision requires that a combination of compounds must show the enhanced additive effect or synergism in the complete specification.

71. The Applicant in the Present Application discloses clinical trial related data, it does not correspond to the weight ration of the formulation claimed. In absence of specific data relating to the claimed weight ratios of each of the components of the formulation, the Applicant fails the test of Section 3(e).
72. The burden to show synergistic effect is not discharged by merely providing the composition of each of the ingredients in terms of weight. The Asst. Controller of Patents & Designs, while rejecting application no. 3725/CHENP/2006, on grounds of Section 3(e) noted, “*Applicant doesn’t provide any supportive experimental data or comparative examples highlighting the surprising and or synergistic effect of the claimed formulation over the prior art compositions. Instead examples 1, 2 and 3 provide only the amount of individual components in grams.*” (See the order of the Controller in 3725/CHENP/2006, hereto annexed as **Exhibit-L** at internal page 4. Para 8)
73. It is submitted that Claims 1-27 of the Present Application do not show a synergistic effect over the known effect of each of the components. Thus, the claimed invention does not overcome the test of S.3(e). Therefore, claims 1-27 of the Present Application are not an invention per Section 3(e) and must be rejected.
- c. **THAT CLAIMS 1-27 OF THE PRESENT APPLICATION ARE NOT COMPLETELY AND SUFFICIENTLY DESCRIBED IN THE COMPLETE SPECIFICATION**
74. Without prejudice to the grounds raised in this representation, the Opponent invokes Section 25(1) (g). It is submitted that the Present Application does not sufficiently and clearly describe the invention claimed or the manner in which the alleged invention is to be performed.
75. The Opponent would like to draw attention to the Applicant’s response to the FER, wherein it is submitted that the composition of claim 1 is that of a bilayer tablet.

76. The Opponent submits that there is no limitation that explicitly provides that the composition of claims 1-27 are bilayer tablets as suggested by the Applicant in response to the FER.
77. It is further submitted that claims 1-13 are vague and broad given that the claims use broad terms such as pharmaceutically acceptable polymers, pharmaceutically acceptable surfactants without specifically identifying which polymer or surfactant would be used.
78. Similarly claim 20 of the Present Application is broad for vaguely claiming that the pharmaceutical dosage formulation comprising a disintegrant without identifying which disintegrant is to be used.
79. Further, claim 22 of the Present Application is broad for vaguely claiming that the pharmaceutical dosage formulation with first and second layer comprising a lubricant without identifying which lubricant is to be used.
80. Hence, the alleged invention in claims of the Present Application have not been disclosed completely and have not been sufficiently described.
81. Further, the complete specification does not provide sufficient information to enable a POSITA to perform the invention over the full width of these claims without undue burden or the need for further invention.
82. Claims 1-27 of the Present Application therefore must be rejected.

d. THAT THE APPLICANT HAS FAILED TO DISCLOSE THE INFORMATION REQUIRED UNDER SECTION 8

83. Without prejudice to the grounds raised above, the Opponent raises an objection under Section 25(1)(h) on the ground that the Applicant has failed to provide information as required under Section 8 of the Patents Act.
84. It is submitted that the Applicant has not complied with the mandatory requirements of Section 8 of the Patents Act. It may be noted that when considering the issue of omission on behalf of the Applicant in submitting the information under Section 8, the Hon'ble High Court of Delhi in *Sukesh Behl vs. Koninklijke Phillips Electronics* [MANU/DE/2785/2014] has noted: "...the power to revoke a patent under Section 64(1) is discretionary and

consequently it is necessary for the Court to consider the question as to whether the omission on the part of the plaintiff was intentional or whether it was a mere clerical and bona fide error.” (emphasis supplied)

85. It is submitted that the FER directed the Applicant to submit statement and undertaking regarding the patent application filed outside India for same or substantially same invention, including details regarding search and/or examination report including claims of application allowed.
86. The Applicant did submit Form- 3 on 24.08.2020 in response to the directions in the FER. However, a perusal of the information reveals that information (particularly those relating to refusals from multiple patent offices) have not been disclosed.
87. An analysis of the filings made by the Applicant for same or substantially similar subject matter revealed the following:

US Document no.	Published	Status	Comment
62/185145		Provisional Application Expired	None of these details have been filed with the IPO. Importantly, the 2 abandonments that are post final rejections from US Patent Office have not been disclosed to the Indian Patent Office.
15/192211 filed on 24 June 2016	US20160375087	Abandoned -- Failure to Pay Issue Fee	
15/212,997 filed on 18 July 2016	US20160375017	Abandoned -- Failure to Pay Issue Fee	
15/227,994 filed on 20 Dec 2018	US20190216882	Abandoned -- Failure to Respond to an Office Action	

16/654,433 filed on 16 Oct 2019	US20200282004	Abandoned -- Failure to Respond to an Office Action	
16/654,442 filed on 16 Oct 2019	US20200253968	Docketed New Case - Ready for Examination	
17/239,816 filed on 26 April 2021	Not published as of 07 September 2021		

88. A search for status of corresponding patent applications in other countries gives the following information:

Publication	Description	Comment
AU2016283018	<p>Examination report 1 issued in May 2021 had an inventive step objection.</p> <p>Thereafter 27 claims were filed.</p> <p>Examination report 2 issued in June 2021 which objected to all 27 claims on the ground that Specification does not provide sufficient information to enable the skilled addressee to perform the invention over the full width of these claims without undue</p>	The IPO has not been informed of these 2 examination reports.

	burden or the need for further invention.	
JP2017567109	Refusal Notice for 14 claims (02 June 2020) Refusal Notice for 26 claims (25 May 2021) New claims have been refused on multiple grounds including addition of new matter, lacking an inventive step	Both these refusal notices have NOT been submitted to the Indian Patent Office.
JP2018501944	Refusal Notice for 26 claims (30 March 2021) Refusal Notice for 14 claims (02 June 2020)	Both these refusal notices have NOT been submitted to the Indian Patent Office.

89. It is submitted that the Applicant has failed to provide complete information relating to the corresponding applications in other jurisdictions. The omission has been made despite clear directions to submit such information. It is therefore submitted that the claims of the Present Application be rejected.

PRAYERS

In view of the above said references Opponent prays as follows:

- a) To be granted a hearing and be allowed to lead evidence (documentary and oral) before any order is passed;
- b) To reject the claims 1-27 of Application No. 201817002543 *in toto*;

- c) To allow the Opponent to file further submissions / documents as evidence, if necessary, to support the averments;
- d) To allow the Opponent to make further submissions in case the Applicant amends the claims;
- e) To be provided with a copy of any and all further submissions/ claim amendments /response by the Applicant;
- f) To allow amendment of the opposition as and when the need may arise;
- g) For costs in this matter;
- h) For any further and other relief in the facts and circumstances that may be granted in favour of the Opponent in the interest of justice.

Dated this 2nd day of October 2021.



[For the Opponent]

Settled by: Anand Grover, Senior Advocate

To
The Controller,
The Patent Office Branch
NEW DELHI

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Wei; 323 Aspen Pointe Road, Vernon Hills, Illinois 60061 (US). **WANG, Tianli**; 29537 N. Waukegan Road, Apt. 302, Lake Bluff, Illinois 60044 (US). **AWNI, Walid M.**; 14105 Edgewater Court, Green Oaks, Illinois 60048 (US).

(74) Agents: **ZHANG, Xu** et al; AbbVie Inc. 1 North Waukegan Road, AP34-2/V377, North Chicago, Illinois 60064 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

[Continued on nextpage]

(54) Title: COMBINATION OF TWO ANTIVIRALS FOR TREATING HEPATITIS C

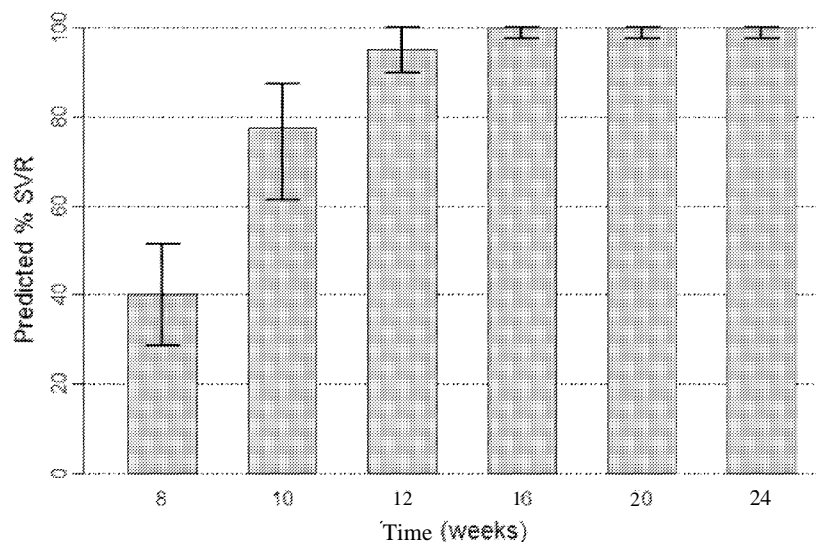


Figure 1

(57) Abstract: The present invention features interferon- and ribavirin-free therapies for the treatment of HCV. Preferably, the treatment is over a shorter duration of treatment, such as no more than 12 weeks. In one aspect, the treatment comprises administering at least two direct acting antiviral agents without interferon and ribavirin to a subject with HCV infection, wherein the treatment lasts for 12 weeks, and said at least two direct acting antiviral agents comprise (a) Compound 1 or a pharmaceutically acceptable salt thereof and (b) Compound 2 or a pharmaceutically acceptable salt thereof.

WO 2014/152514 A1

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
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— *with international search report (Art. 21(3))*

COMBINATION OF TWO ANTIVIRALS FOR TREATING HEPATITIS C

[0001] This application claims the benefit of U.S. Provisional Application No. 61/783,376, filed March 14, 2013, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to interferon-free and ribavirin-free treatment for hepatitis C virus (HCV).

BACKGROUND OF THE INVENTION

[0003] The HCV is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

[0004] Chronic HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often incomplete. Therefore, there is a need for new therapies to treat HCV infection.

BRIEF SUMMARY OF THE INVENTION

[0005] One aspect of the present invention features methods for treating HCV infection in a subject in need of such treatment. The methods comprise administering at least two direct acting antiviral agents (DAAs) to the subject for a duration of no more than 12 weeks, or for another duration as set forth herein. The at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). Preferably, the duration of the treatment is 12 weeks. The duration of the treatment can also be, for example, no more than 8 weeks. Preferably, the two or more DAAs are administered in amounts effective to provide a sustained virological response (SVR) or achieve another desired measure of effectiveness in the subject. The subject is not administered ribavirin during the treatment regimen. The subject is also not administered interferon during the treatment regimen. Put another way, the methods exclude the administration of interferon or ribavirin to the subject, thereby avoiding the side effects associated with interferon and ribavirin.

[0006] Another aspect of the present invention features methods for treating a population of subjects having HCV infection. The methods comprise administering at least two DAAs to the subjects for a duration of no more than 12 weeks. The at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). Preferably, the at least two DAAs are administered to the subjects in amounts effective to result in SVR or another measure of effectiveness in at least about 70% of the population, preferably at least about 80% of the population, or more preferably at least about 90% of the population.

[0007] In any method described herein, the at least two DAAs comprise (a) Compound 1 or a pharmaceutically acceptable salt thereof, and (b) Compound 2 or a pharmaceutically acceptable salt thereof. The at least two DAAs can also optionally comprise another anti-HCV agent. The other optional anti-HCV agent can be selected from protease inhibitors, nucleoside or nucleotide polymerase inhibitors, non-nucleoside polymerase inhibitors, NS3B inhibitors, NS4A inhibitors, NS5A inhibitors, NS5B inhibitors, cyclophilin inhibitors, or combinations thereof. For example, in some embodiments, the DAAs used in a method of the present invention comprise or consist of (a) Compound 1 or a pharmaceutically acceptable salt thereof, and (b) Compound 2 or a pharmaceutically acceptable salt thereof. For another example, the DAAs used in a method of the present invention comprise or consist of (a) Compound 1 or a pharmaceutically acceptable salt thereof, (b) Compound 2 or a pharmaceutically acceptable salt thereof, and (c) a HCV polymerase inhibitor, wherein said HCV polymerase inhibitor can be a nucleotide or nucleoside polymerase inhibitor or a non-nucleoside or non-nucleotide polymerase inhibitor.

[0008] Non-limiting examples of the other optional anti-HCV agent include PSI-7977 (sofosbuvir), PSI-938, BMS-790052 (daclatasvir), BMS-650032 (asunaprevir), BMS-791325, GS-5885 (ledipasvir), GS-9451 (tegobuvir), GS-9190, GS-9256, BI-201335, BI-27127, telaprevir, VX-222, TMC-435 (simeprevir), MK-5172, MK-7009 (vaniprevir), danoprevir, R7128 (mericitabine), and any combination thereof.

[0009] In any method described herein, the DAAs can be administered in any effective dosing schemes and/or frequencies; for example, they can each be administered daily. Each DAA can be administered either separately or in combination, and each DAA can be administered once a day, twice a day, or three times a day. Preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof) are administered once daily.

[0010] Preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 100 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 50 to 500 mg once daily. More preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 200 mg to 600 mg once daily, and Compound 2 (or a

pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. Highly preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 400 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. For instance, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered 120 mg once daily. For another instance, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) can be administered 240 mg once daily.

[0011] In yet another aspect, the present invention features a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof) for use to treat **HCV** infection. The treatment comprises administering the DAAs to a subject infected with **HCV**. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering interferon or ribavirin. Compound 1 (or the salt thereof) and Compound 2 (or the salt thereof) can be administered concurrently or sequentially. Preferably, Compound 1 (or the salt thereof) and Compound 2 (or the salt thereof) can be administered once daily. As a non-limiting example, the patient being treated is infected with **HCV** genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient is infected with **HCV** genotype 2. As another non-limiting example, the patient is infected with **HCV** genotype 3. As another non-limiting example, the patient is infected with **HCV** genotype 4. As another non-limiting example, the patient is infected with **HCV** genotype 5. As another non-limiting example, the patient is infected with **HCV** genotype 6. As yet another non-limiting example, the patient is a **HCV** -treatment naive patient, a **HCV** -treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. As used in this application, the interferon non-responder patients include partial interferon responders and interferon rebound patients. *See* **GUIDANCE FOR INDUSTRY - CHRONIC HEPATITIS C VIRUS INFECTION: DEVELOPING DIRECT-ACTING ANTIVIRAL AGENTS FOR TREATMENT** (FDA, September 2010, draft guidance) for the definitions of naive, partial responder, responder relapser (i.e., rebound), and null responder patients. The interferon non-responder patients also include null responder patients. In one example of this aspect of the invention, the treatment lasts for 12 weeks, and the subject being treated is a naive patient infected with **HCV** genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naive patient infected with **HCV** genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naive patient infected with **HCV** genotype

1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 3. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 3.

[0012] A treatment regimen of the present invention generally constitutes a complete treatment regimen, i.e., no subsequent interferon-containing regimen is intended. Thus, a treatment or use described herein generally does not include any subsequent interferon-containing treatment. Preferably, a treatment or use described herein does not include any subsequent ribavirin-containing treatment.

[0013] Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The drawings are provided for illustration, not limitation.

[0015] Figure 1 shows the predicted median SVR percentages and 90% SVR confidence intervals for interferon/ribavirin-free, 2-DAA regimens comprising the use of Compound 1 (400 mg once daily) and Compound 2 (120 mg once daily) to treat genotype 1 naïve subjects.

[0016] Figure 2 illustrates the predicted median SVR percentages and 90% SVR confidence intervals for interferon/ribavirin-free, 2-DAA regimens comprising the use of Compound 1 (400 mg once daily) and Compound 2 (60 mg once daily) to treat genotype 1 naïve subjects.

[0017] Figure 3 depicts the predicted median SVR percentages and 90% SVR confidence intervals for interferon/ribavirin-free, 2-DAA regimens comprising the use of Compound 1 (600 mg once daily) and Compound 2 (480 mg once daily) to treat genotype 1 naïve subjects.

[0018] Figure 4 shows the predicted median SVR percentages and 90% SVR confidence intervals for interferon/ribavirin-free, 2-DAA regimens comprising the use of Compound 1 (400 mg once daily) and Compound 2 (120 mg once daily) to treat genotype 3 naïve subjects.

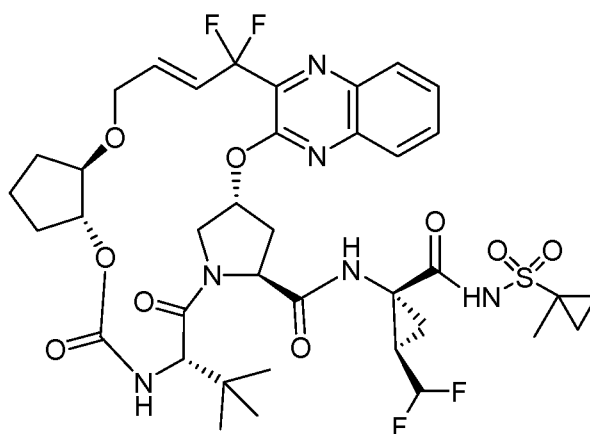
[0019] Figure 5 illustrates the predicted median SVR percentages and 90% SVR confidence intervals for interferon/ribavirin-free, 2-DAA regimens comprising the use of Compound 1 (400 mg once daily) and Compound 2 (60 mg once daily) to treat genotype 3 naïve subjects.

[0020] Figure 6 shows the predicted median SVR percentages and 90% SVR confidence intervals for interferon/ribavirin-free, 2-DAA regimens comprising the use of Compound 1 (600 mg once daily) and Compound 2 (480 mg once daily) to treat genotype 3 naïve subjects.

[0021] Figure 7 depict the synergistic effect of the combination of Compound 1 and Compound 2 on HCV inhibition *in vitro*.

DETAILED DESCRIPTION OF THE INVENTION

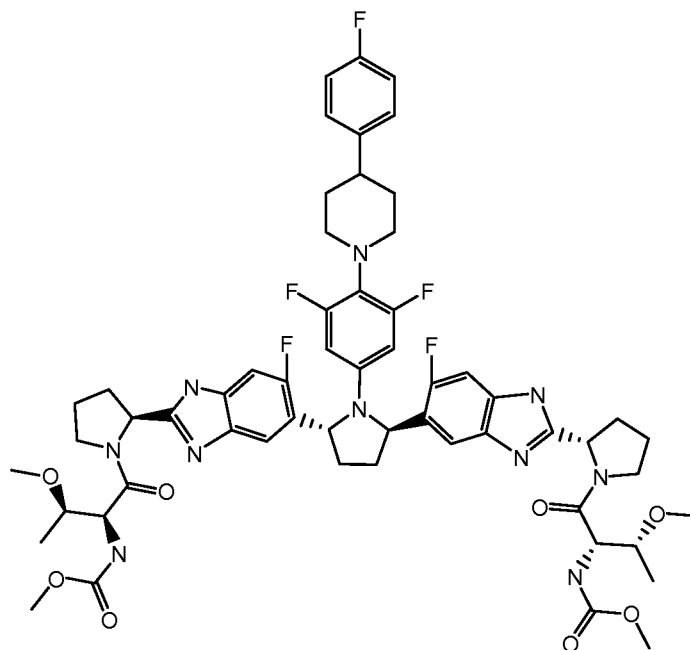
[0022] The methods of the present invention include administering Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof) to a subject in need thereof. Compound 1 has the following structure:



Compound 1

Compound 1 is a potent HCV protease inhibitor and is described in U.S. Patent Application Publication No. 2012/0070416.

[0023] Compound 2 has the following structure:



Compound 2

Compound 2 is a potent NS5A inhibitor and is described in U.S. Patent Application Publication No. 2012/0220562.

[0024] The current standard of care (SOC) for the treatment of HCV includes a course of treatment of interferon, e.g. pegylated interferon (e.g., pegylated interferon-alpha-2a or pegylated interferon-alpha-2b, such as PEGASYS by Roche, or PEG-INTRON by Schering-Plough) and the antiviral drug ribavirin (e.g.,

COPEGUS by Roche, REBETOL by Schering-Plough, or RIBASPHERE by Three Rivers Pharmaceuticals). The treatment often lasts for 24-48 weeks, depending on hepatitis C virus genotype. Other interferons include, but are not limited to, interferon-alpha-2a (e.g., Roferon-A by Roche), interferon-alpha-2b (e.g., Intron-A by Schering-Plough), and interferon alfacon-1 (consensus interferon) (e.g., Infergen by Valeant).

[0025] The interferon/ribavirin-based treatment may be physically demanding, and can lead to temporary disability in some cases. A substantial proportion of patients will experience a panoply of side effects ranging from a "flu-like" syndrome (the most common, experienced for a few days after the weekly injection of interferon) to severe adverse events including anemia, cardiovascular events and psychiatric problems such as suicide or suicidal ideation. The latter are exacerbated by the general physiological stress experienced by the patients. Ribavirin also has a number of side effects, including, anemia, high pill burden (e.g. 5-6 pills a day split BID) and teratogenicity restricting use in women of childbearing age.

[0026] The methods of the present invention provide effective treatment of HCV infection without the use of interferon or ribavirin and for a shorter period of time, for example and without limitation, a treatment duration of no more than twelve weeks, alternatively no more than eleven weeks, alternatively no more than ten weeks, alternatively no more than nine weeks, alternatively no more than eight weeks, alternatively no more than seven weeks, alternatively no more than six weeks, alternatively no more than five weeks, alternatively no more than four weeks, or alternatively, no more than three weeks.

[0027] In one aspect, the present invention features methods for treating HCV infection in a subject comprising administering at least two DAAs, in the absence of interferon and ribavirin, to the subject for a duration of no more than twelve weeks, alternatively no more than eight weeks. Put another way, the methods exclude interferon and ribavirin. The at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof), which can be co-administered, or administered separately or independently, with the same or different dosing frequencies. Preferably, the at least two DAAs are administered once a day. They can also be administered, for example, twice a day or three times a day.

[0028] Various measures may be used to express the effectiveness of a method of the present invention. One such measure is SVR, which, as used herein, means that the virus is undetectable at the end of therapy and for at least 8 weeks after the end of therapy (SVR8); preferably, the virus is undetectable at the end of therapy and for at least 12 weeks after the end of therapy (SVR12); more preferably, the virus is undetectable at the end of therapy and for at least 16 weeks after the end of therapy (SVR16); and highly preferably, the virus is undetectable at the end of therapy and for at least 24 weeks after the end of therapy (SVR24). SVR24 is often considered as a functional definition of cure; and a

high rate of SVR at less than 24 week post-treatment (e.g., SVR8 or SVR12) can be predictive of a high rate of SVR24.

[0029] In some embodiments, a treatment regimen of the invention comprises treating a population of subjects having HCV infection (e.g. treatment naïve subjects), and the regimen comprises administering at least two DAAs to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein the at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof), and are administered to the subjects in amounts effective to provide an SVR (e.g., SVR12 or SVR24) in at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, alternatively about 100% of the population. In some embodiments, a treatment regimen of the invention comprises treating a population of IFN experienced subjects (e.g., interferon non-responders) having HCV infection, and the method comprises administering at least two DAAs to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein the at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof), and are administered to the subjects in amounts effective to provide an SVR (e.g., SVR12 or SVR24) in at least about 50% of the population, alternatively at least about 55% of the population, alternatively at least about 60% of the population, alternatively at least about 65% of the population, alternatively at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, or alternatively about 100% of the population.

[0030] It was unexpected that an interferon-free and ribavirin-free treatment using a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof), and for a duration of no more than 12 weeks, can achieve significant SVR.

[0031] Accordingly, in one aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 8 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be

infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0032] In another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 7 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0033] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 6 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be

infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0034] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 5 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0035] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 4 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be

infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0036] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 3 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0037] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 24 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be

infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0038] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 13 to 23 weeks (e.g., the duration of the treatment is selected from 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 weeks) and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0039] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 12 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an

interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir. As used in this application, a HCV polymerase inhibitor can be a nucleoside polymerase inhibitor, a nucleotide polymerase inhibitor, a non-nucleoside polymerase inhibitor, or a non-nucleotide polymerase inhibitor.

[0040] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 11 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0041] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 10 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the

same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0042] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (or a pharmaceutically acceptable salt thereof). The treatment lasts 9 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naive patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof), said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0043] In each aspect, embodiment, example or method described herein, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered, for example and without limitation, from 100 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) can be administered, for example and without limitation, from 50 to 500 mg once daily. More preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 200 mg to 600 mg once

daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. Highly preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 400 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. Preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered 120 mg once daily. Also preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) can be administered 240 mg once daily.

[0044] A method of the present invention can be used to treat a naive patient or a treatment experienced patient. Treatment experienced patients include interferon non-responders (e.g., null responders), partial responders, and relapsers. A method of the present invention can also be used to treat patients who are not candidates for interferon treatment. Patients who are not candidates for interferon treatment include, but are not limited to, one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon.

[0045] In any method described herein, one or more additional DAAs can be optionally used in the treatment regimen in addition to Compound 1 (or a salt thereof) and Compound 2 (or a salt thereof). These additional DAAs can be HCV protease inhibitors, HCV nucleoside or nucleotide polymerase inhibitors, HCV non-nucleoside polymerase inhibitors, HCV NS3B inhibitors, HCV NS4A inhibitors, HCV NS5A inhibitors, HCV NS5B inhibitors, HCV entry inhibitors, cyclophilin inhibitors, or combinations thereof.

[0046] Preferred HCV protease inhibitors for this purpose include, but are not limited to, telaprevir (Vertex), boceprevir (Merck), BI-201335 (Boehringer Ingelheim), GS-9451 (Gilead), and BMS-650032 (BMS). Other suitable protease inhibitors include, but are not limited to, ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BMS-650032 (BMS), danoprevir (RG7227/ITMN- 191, Roche), GS-9132 (Gilead), GS-9256 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir (Schering-Plough Corp), PHX-1766 (Phenomix), TMC-435 (Tibotec), vaniprevir (MK-7009, Merck), VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof.

[0047] Preferred non-nucleoside HCV polymerase inhibitors for use in the present invention include, but are not limited to, GS-9190 (Gilead), BI-207127 (Boehringer Ingelheim), and VX-222 (VCH-222) (Vertex & ViraChem). Preferred nucleotide HCV polymerase inhibitors include, but are not limited to, PSI-7977 (Gilead), and PSI-938 (Gilead). Other suitable and non-limiting examples of suitable HCV

polymerase inhibitors include ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), ALS-2200 (Alicis BioPharma/Vertex), ALS-2158 (Alicis BioPharma/Vertex), or a combination thereof. A polymerase inhibitor may be a nucleoside or nucleotide polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Gilead), PSI-938 (Gilead), RG7128 (Roche), TMC64912 (Medivir), ALS-2200 (Alicis BioPharma/Vertex), ALS-2158 (Alicis BioPharma/Vertex), or a combination thereof. A polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as PF-00868554 (Pfizer), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir (Gilead), TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof.

[0048] Preferred NS5A inhibitors include, but are not limited to, BMS-790052 (BMS) and GS-5885 (Gilead). Non-limiting examples of suitable NS5A inhibitors include GSK62336805 (GlaxoSmithKline), ACH-2928 (Achillion), AZD2836 (Astra-Zeneca), AZD7295 (Astra-Zeneca), BMS-790052 (BMS), BMS-824393 (BMS), GS-5885 (Gilead), PPI-1301 (Presidio), PPI-461 (Presidio), A-831 (Arrow Therapeutics), A-689 (Arrow Therapeutics) or a combination thereof.

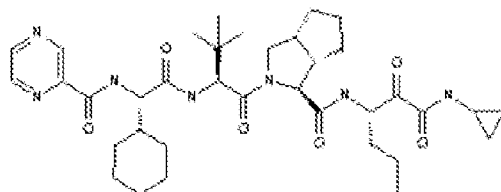
[0049] Non-limiting examples of suitable cyclophilin inhibitors include alisporovir (Novartis & Debiopharm), NM-811 (Novartis), SCY-635 (Scynexis), or a combination thereof.

[0050] Non-limiting examples of suitable HCV entry inhibitors include ITX-4520 (iTherx), ITX-5061 (iTherx), or a combination thereof.

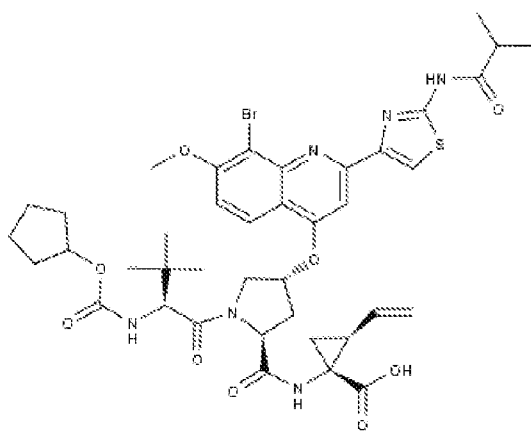
[0051] Specific examples of other DAA agents that are suitable for inclusion in a method of the present invention include, but are not limited to, AP-H005, A-831 (Arrow Therapeutics) (NS5A inhibitor), A-689 (Arrow Therapeutics) (NS5A inhibitor), INX08189 (Inhibitex) (polymerase inhibitor), ITMN-191 (Intermune/Roche) (NS3/4A Protease inhibitor), VBY-376 (Protease Inhibitor) (Virobay), ACH-1625 (Achillion, Protease inhibitor), IDX136 (Idenix, Protease Inhibitor), IDX316 (Idenix, Protease inhibitor), VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191 (Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), R7128 (Roche), PF-868554 (Pfizer) (non-nucleoside polymerase inhibitor), PF-4878691 (Pfizer), IDX-184 (Idenix), IDX-375 (Idenix, NS5B polymerase inhibitor), PPI-461 (Presidio), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), CTS-1027

(Conatus), GS-9620 (Gilead), PF-4878691 (Pfizer), RO5303253 (Roche), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), GSK62336805 (GlaxoSmithKline), or any combinations thereof.

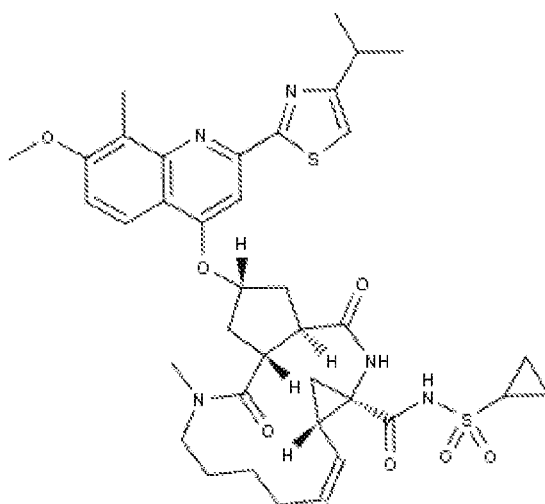
[0052] The chemical structures of some of these optional HCV inhibitors are provided below:



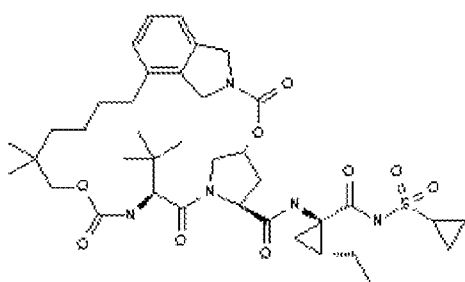
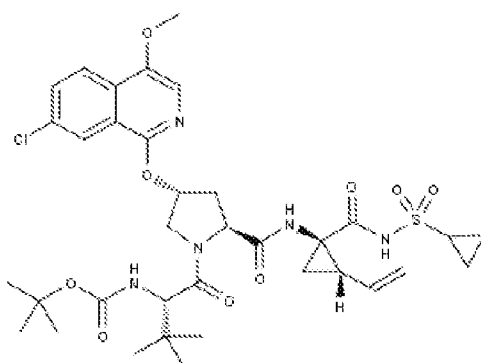
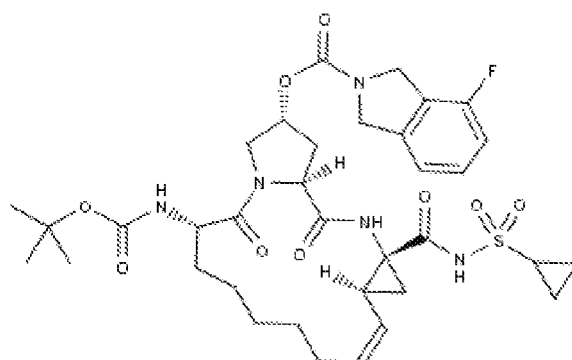
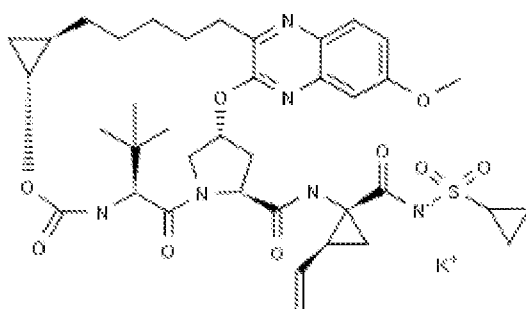
Telaprevir



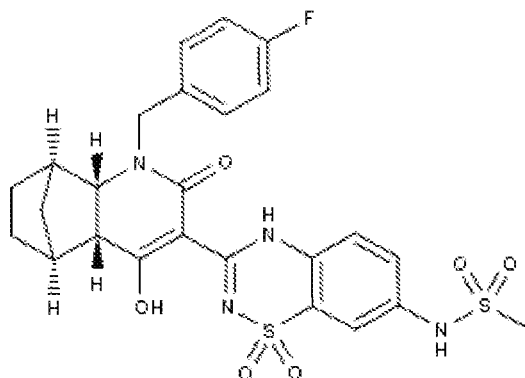
BI-201335



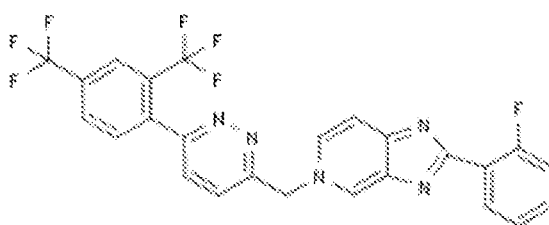
TMC-435 (TMC-435350)

**Vaniprevir, MK-7009****BMS-650032 (Asunaprevir)****danoprevir**

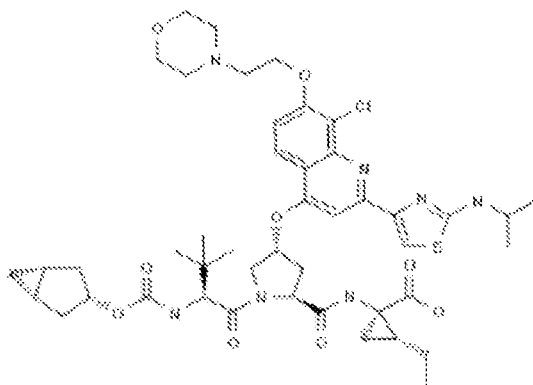
MK-5172



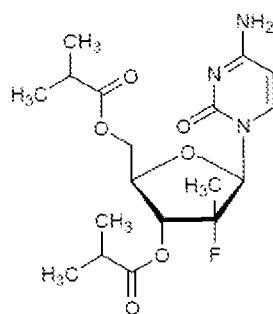
ANA-598 (Setrobuvir)

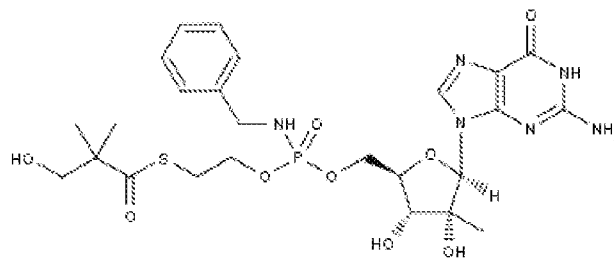
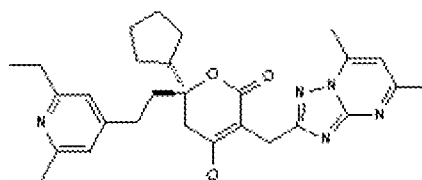
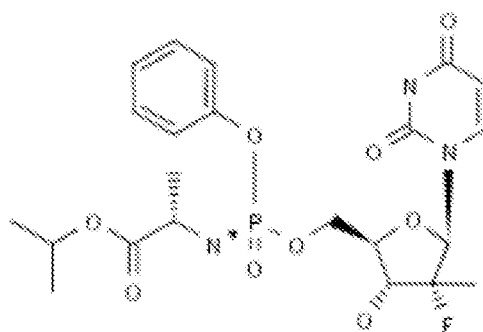
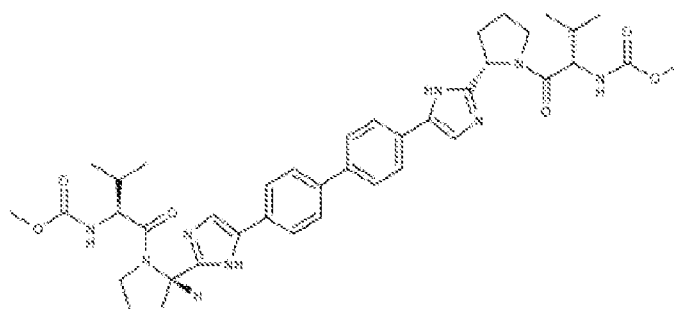


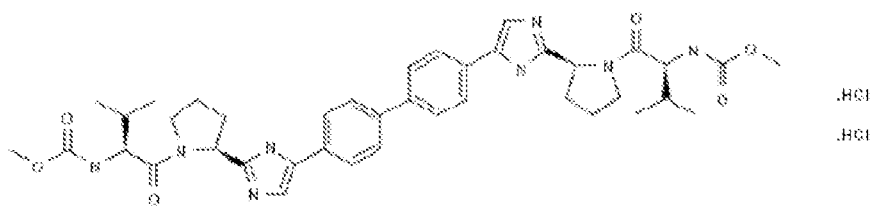
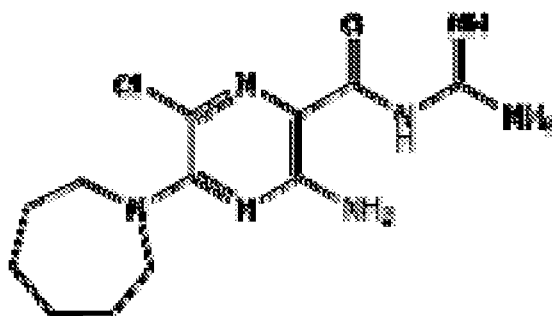
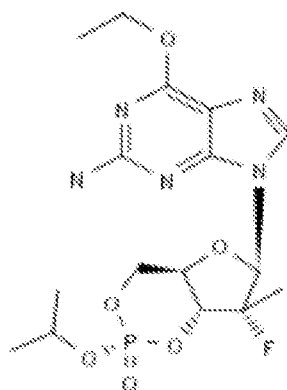
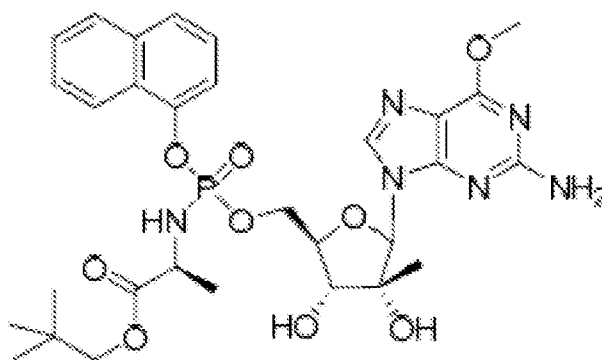
GS-333126 (GS-9190 or tegobuvir)

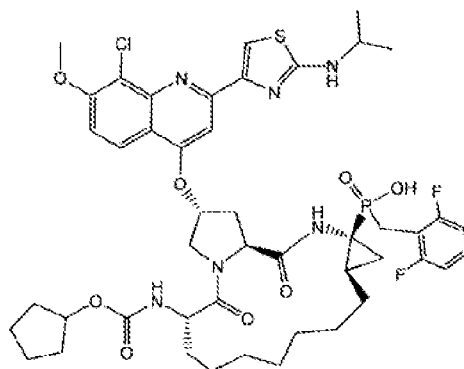
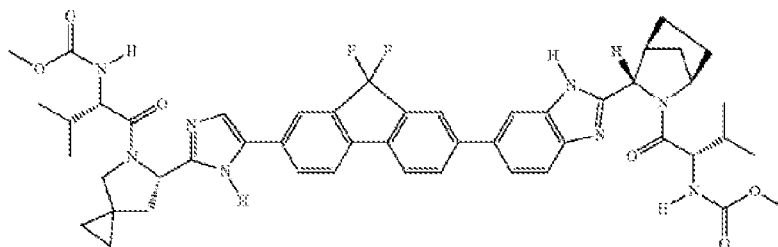


GS-9451



Mericitabine (R-4048 or RG7128)**IDX-184****filibuvir (PF-00868554)****PSI-7977****BMS-790052 (daclatasvir)**

**Daclatasvir dihydrochloride****BIT-225****PSI-352938****INX-189**

**GS-9256****GS-5885**

[0053] Any HCV inhibitor or DAA described herein encompasses its suitable salt forms when it is used in therapeutic treatments or pharmaceutical formulations.

[0054] In some embodiments, the present invention features methods for treating patients infected with HCV genotype 1, such as 1a or 1b. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0055] In some embodiments, the present invention features methods for treating patients with HCV genotype 2 or 3 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naive patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0056] In some embodiments, the present invention features methods for treating patients with HCV genotype 2 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naive patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0057] In some embodiments, the present invention features methods for treating patients with HCV genotype 3 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the

completion of the treatment. The patients may be treatment naive patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0058] In some embodiments, the present invention features methods for treating patients with HCV genotype 4 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naive patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0059] In some embodiments, the present invention features methods for treating patients with HCV genotype 5 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naive patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0060] In some embodiments, the present invention features methods for treating patients with HCV genotype 6 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g.,

the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof). Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0061] It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the disease undergoing therapy.

[0062] In any method described herein, Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) may be co-formulated in a single dosage form. Non-limiting examples of suitable dosage forms include liquid or solid dosage forms. Preferably, Compound 1 and Compound 2 are formulated in a single solid dosage form in which at least one of the DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. The other DAAs can also be in an amorphous form or molecularly dispersed in the matrix, or formulated in different form(s) (e.g., in a crystalline form). More preferably, each of the two DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant.

[0063] In any method described herein, the patient being treated can be a treatment-naïve patient.

[0064] In any method described herein, the patient being treated can be an interferon non-responder.

[0065] In any method described herein, the patient being treated can be an interferon null-responder.

[0066] In any method described herein, the patient being treated can be without cirrhosis.

[0067] In any method described herein, the patient being treated can be a cirrhotic patient.

[0068] In any method described herein, the patient being treated can be a patient with compensated cirrhosis.

[0069] It should be understood that the above-described embodiments and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

Example 1. Clinical Modeling for Interferon-free DAA Combination Therapies

[0070] Treatment regimens comprising administration of Compound 1 and Compound 2 were evaluated using clinical models described in U.S. Patent Application Publication No. 2013/0102526, filed October 19, 2012 and entitled "Methods for Treating HCV", which is incorporated herein by reference in its entirety. These treatment regimens comprised administration of Compound 1 and Compound 2, but did not include administration of either interferon or ribavirin.

[0071] Figure 1 shows the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimens consisting of the use of Compound 1 (400 mg once daily) and Compound 2 (120 mg once daily) to treat genotype 1 naïve subjects. Different treatment durations were assessed. The predicted SVR rate for a 12-week treatment was about 95%. As used in all of the figures of the present application, the vertical bar at the top of each SVR percentage column represents the 90% SVR confidence interval, and the x-axis ("Time (weeks)") indicates the duration of each treatment regimen.

[0072] Figure 2 illustrates the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimens consisting of the use of Compound 1 (400 mg once daily) and Compound 2 (60 mg once daily) to treat genotype 1 naïve subjects. Different treatment durations were assessed. The predicted SVR rate for a 12-week treatment was about 85-90%.

[0073] Figure 3 shows the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimens consisting of the use of Compound 1 (600 mg once daily) and Compound 2 (480 mg once daily) to treat genotype 1 naïve subjects. Different treatment durations were assessed. The predicted SVR rate for a 12-week treatment was about 100%.

[0074] Figure 4 depicts the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimen consisting of the use of Compound 1 (400 mg once daily) and Compound 2 (120 mg once daily) to treat genotype 3 naïve subjects. Different treatment durations were assessed. The predicted SVR rate for a 12-week treatment was about 95%.

[0075] Figure 5 illustrates the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimen consisting of the use of Compound 1 (400 mg once daily) and Compound 2 (60 mg once daily) to treat genotype 3 naïve subjects. Different treatment durations were assessed. The predicted SVR rate of a 12-week treatment was about 85-90%.

[0076] Figure 6 shows the predicted median SVR percentages and 90% SVR confidence intervals for 2-DAA regimens consisting of the use of Compound 1 (600 mg once daily) and Compound 2 (480 mg once daily) to treat genotype 3 naïve subjects. Different treatment durations were assessed. The predicted SVR rate of a 12-week treatment was about 100%.

Example 2. Combination of Compound 1 and Compound 2 *In Vitro*

[0077] Figure 7 shows that the combination of Compound 1 and Compound 2 exhibits significant synergistic effect on HCV inhibition as tested in HCV GT 1b Con-1 replication cells. The result was generated using Prichard and Shipman model (Prichard *et al.* ANTIVIRAL RESEARCH 14:181-205 (1990)).

[0078] Compound 1 inhibited replication of HCV stable subgenomic replicons containing NS3 genes from GT 1a, 1b, 2a, 3a, 4a, or 6a with EC₅₀ values ranging from 0.85 to 2.8 nM. Of note, Compound 1 was potent against replicon containing GT3a protease, with an EC₅₀ value of 1.6 nM. Compound 1 retained its activity against common GT1a and 1b variants at NS3 amino acid positions 155 and 168 that conferred resistance to other HCV protease inhibitors (Pis). Resistant colony selection studies in GT1a and 1b subgenomic replicon cells identified A156T in GT1a and A156V in GT1b as the most frequent variants, which conferred 1400- and 1800-fold reduced susceptibility to Compound 1, respectively. However, these variants had *in vitro* replication capacities of only 1.5% and 9.2% that of their corresponding wild-type replicons. In a replicon containing GT3a NS3 protease, Compound 1 selected very few colonies at concentrations \geq 100-fold over its EC₅₀ value. The colonies that survived the selection contained either A156G alone, or Q168R co-selected with Y56H, which conferred 1500- or 1100-fold loss in susceptibility to Compound 1, respectively.

Table 2. Antiviral Activity of Compound 1 in the HCV Subgenomic Stable Replicon Cell Culture Assay

HCV Replicon Subtype	N ^b	0% Human Plasma ^a
		Mean EC ₅₀ , nM, \pm Std. Dev.
Genotype 1a	9	0.85 \pm 0.15
Genotype 1b	8	0.94 \pm 0.35
Genotype 2a	2	2.7 \pm 1.1
Genotype 3a	2	1.6 \pm 0.49
Genotype 4a	4	2.8 \pm 0.41
Genotype 6a	4	0.86 \pm 0.11

a. The 0% human plasma assay contains 5% fetal bovine serum

b. Number of independent replicates

Table 3. Antiviral Activity of Compound 1 in the HCV Subgenomic Stable Replicon Cell Culture Assay

HCV Replicon Subtype	N ^b	40% Human Plasma ^a
		Mean EC ₅₀ , nM, \pm Std. Dev.
Genotype 1a	10	5.3 \pm 1.0
Genotype 1b	8	10 \pm 5.0

a. The 0% human plasma assay contains 5% fetal bovine serum

b. Number of independent replicates

[0079] When tested against common HCV genotype 1 NS3 resistance-associated variants, such as V36M, R155K, D168A and D168V in GT 1a (H77), or T54A, R155K, D168V and V170A in GT 1b (Con-1), Compound 1 showed inhibitory activity nearly equivalent to that against wild-type HCV replicon. Compound 1 was also shown to have potent activity against many NS5A inhibitor and NS5B inhibitor resistance-associated variants *in vitro* (e.g., M28T, M28V, Q30D, Q30R, Y93C, Y93H, Y93N, L31V+Y93H, C316Y, M414T, Y448C, Y448H, S556G and S559G in GT 1a, and L28T, Y93H, S282T, C316Y, Y448H and S556G in GT 1b).

[0080] The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method for treatment for HCV, comprising administering at least two direct acting antiviral agents (DAAs) to an HCV patient, wherein neither interferon nor ribavirin are administered to said patient during said treatment, and said treatment lasts for 8, 9, 10, 11 or 12 weeks, and wherein said at least two DAAs comprise:

Compound 1 or a pharmaceutically acceptable salt thereof, and
Compound 2 or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein said treatment lasts for 12 weeks.
3. The method of claim 1, wherein said patient is infected with HCV genotype 1.
4. The method of claim 1, wherein said patient is infected with HCV genotype 1a.
5. The method of claim 1, wherein said patient is infected with HCV genotype 2.
6. The method of claim 1, wherein said patient is infected with HCV genotype 3.
7. The method of claim 1, wherein said patient is infected with HCV genotype 4.
8. The method of claim 1, wherein said patient is infected with HCV genotype 5.
9. The method of claim 1, wherein said patient is infected with HCV genotype 6.
10. The method of claim 2, wherein said patient is infected with HCV genotype 1.
11. The method of claim 2, wherein said patient is infected with HCV genotype 1a.
12. The method of claim 2, wherein said patient is infected with HCV genotype 2.
13. The method of claim 2, wherein said patient is infected with HCV genotype 3.
14. The method of claim 2, wherein said patient is infected with HCV genotype 4.

15. The method of claim 2, wherein said patient is infected with HCV genotype 5.
16. The method of claim 2, wherein said patient is infected with HCV genotype 6.
17. The method of claim 1, wherein said patient is without cirrhosis.
18. The method of claim 1, wherein said patient is with compensated cirrhosis.
19. The method of claim 2, wherein said patient is without cirrhosis.
20. The method of claim 2, wherein said patient is with compensated cirrhosis.
21. The method of claim 1, wherein said patient is a treatment-naïve patient.
22. The method of claim 1, wherein said patient is an interferon non-responder.
23. The method of claim 2, wherein said patient is a treatment-naïve patient.
24. The method of claim 2, wherein said patient is an interferon non-responder.

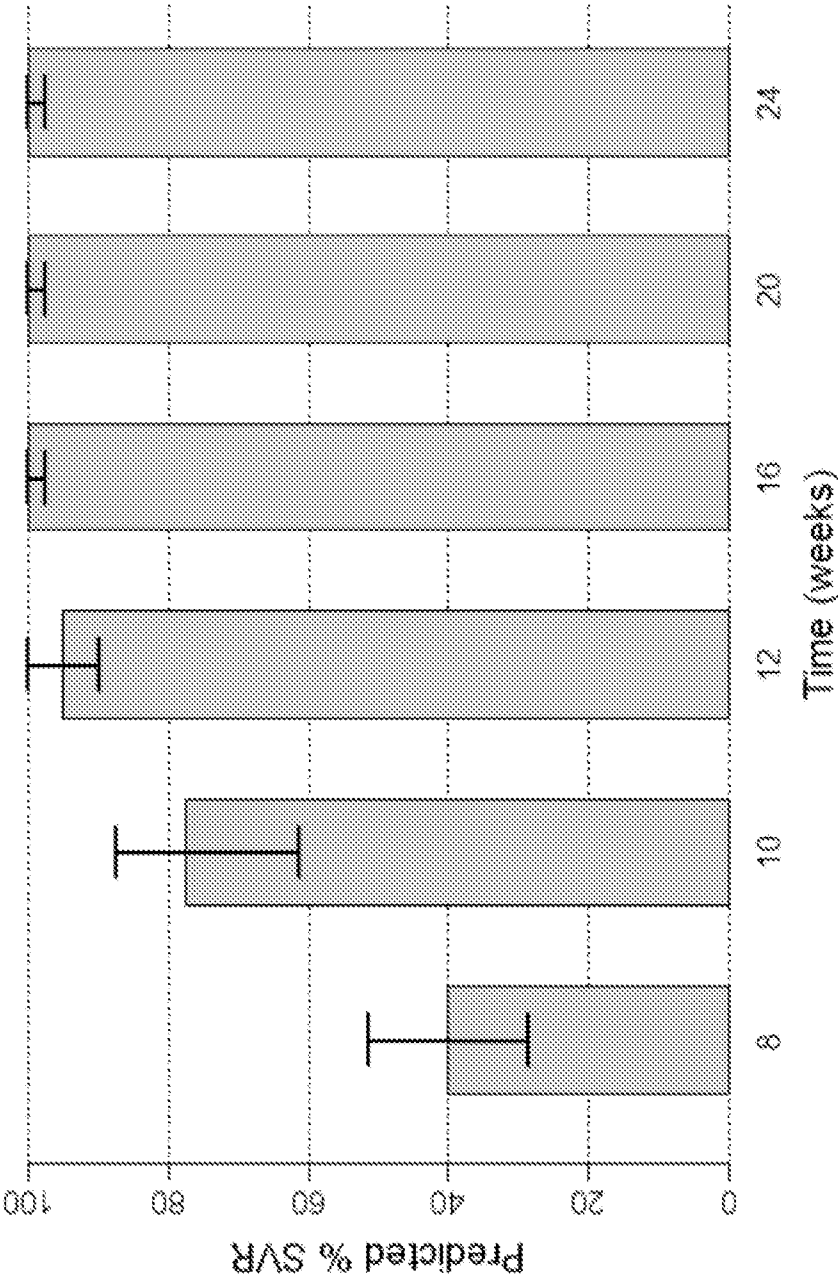


Figure 1

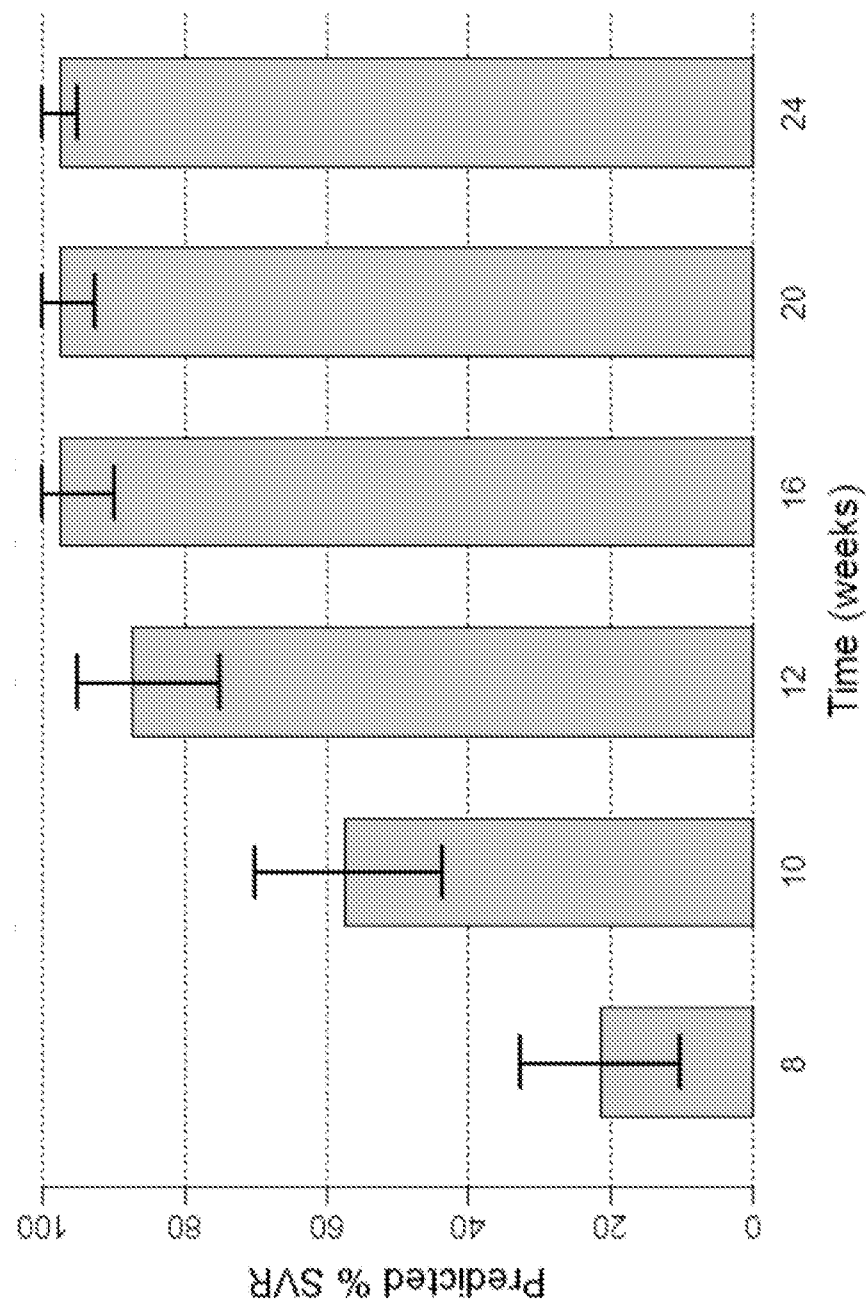


Figure 2

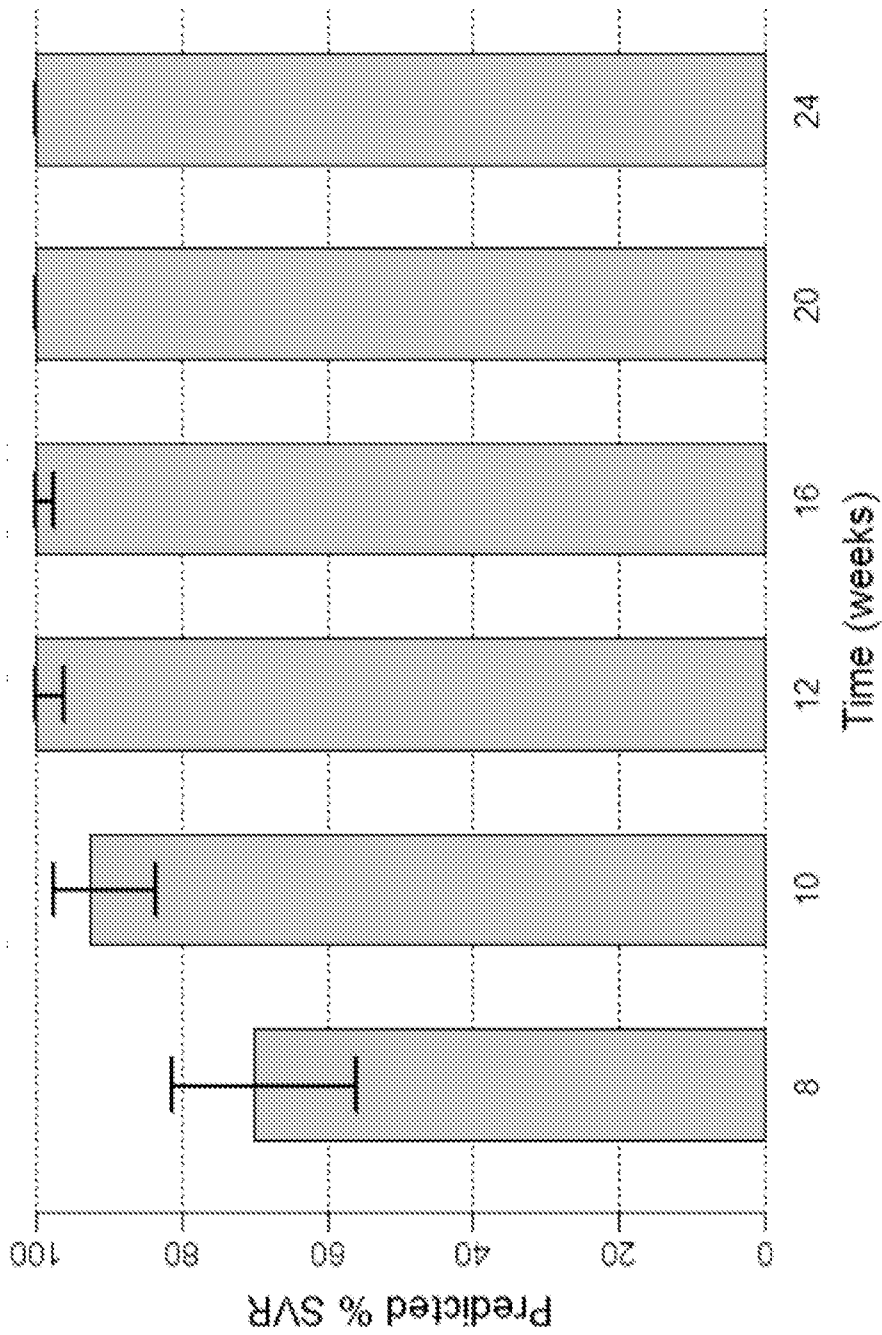


Figure 3

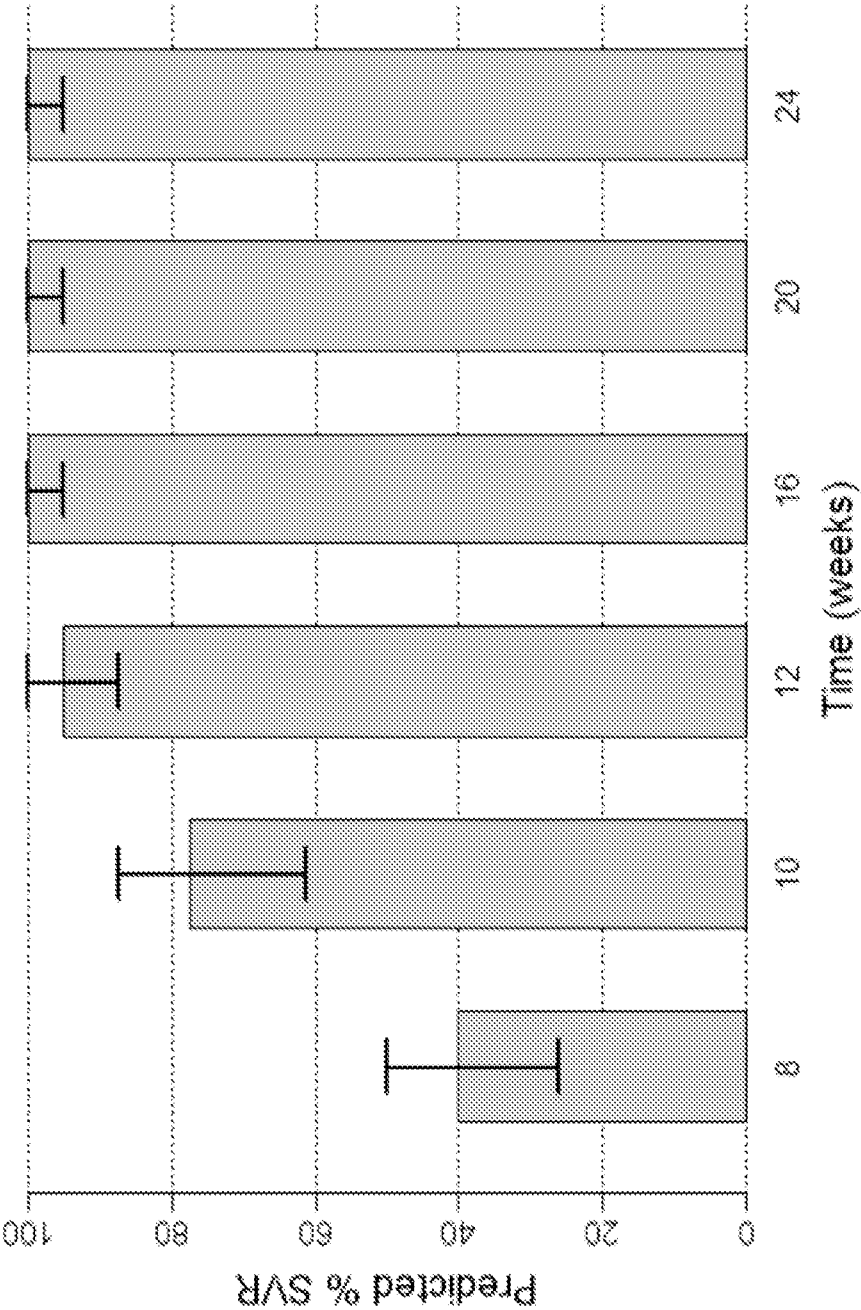


Figure 4

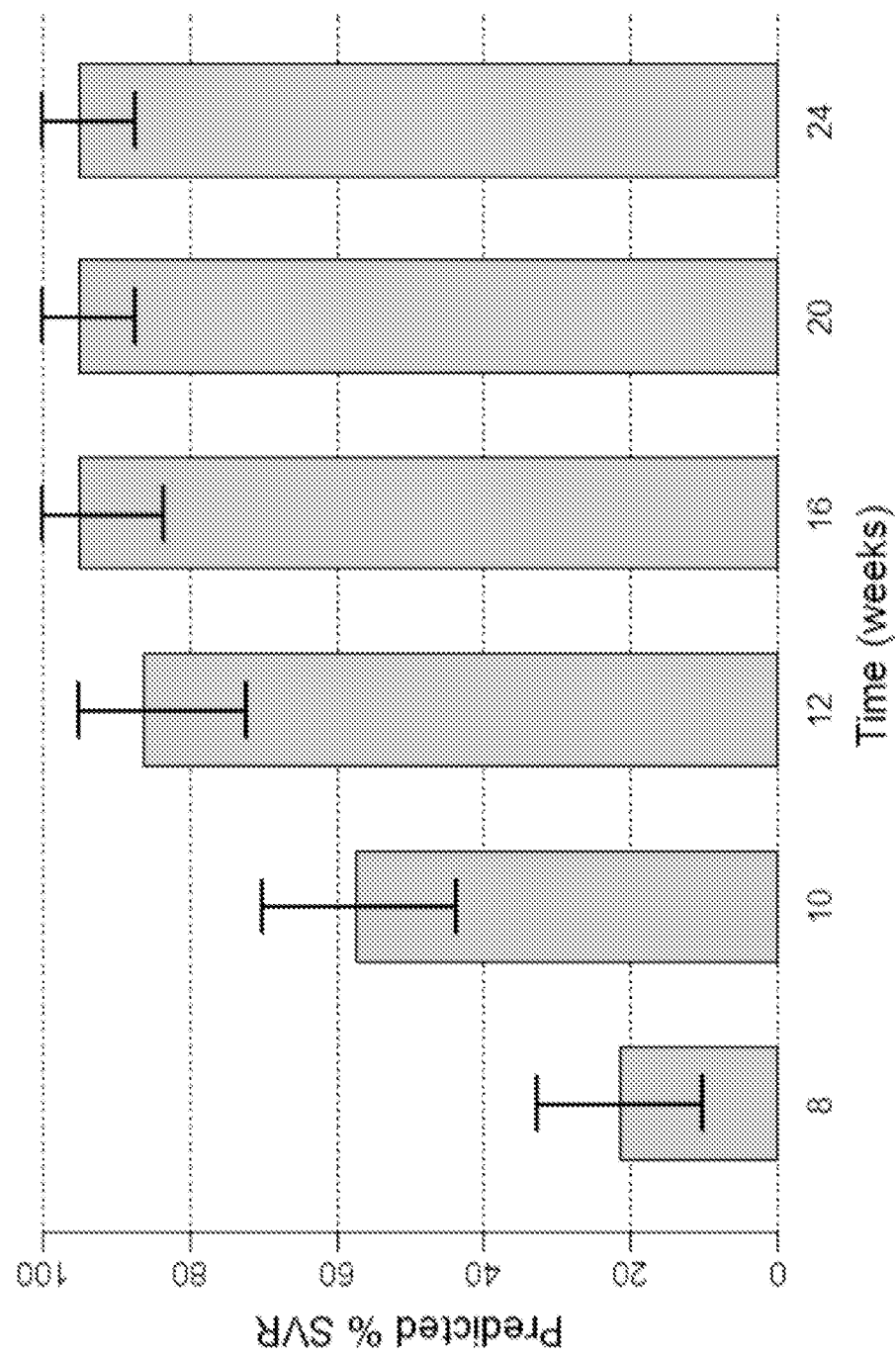


Figure 5

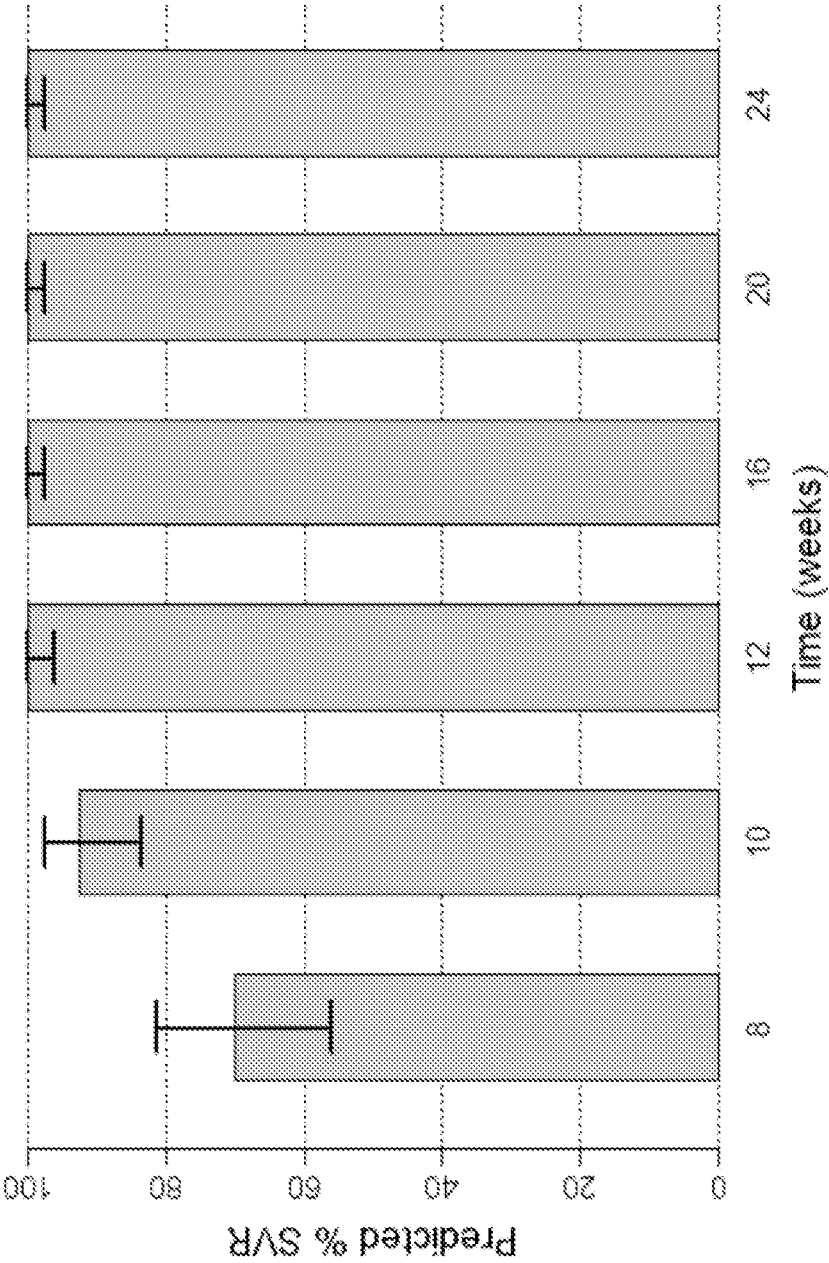


Figure 6

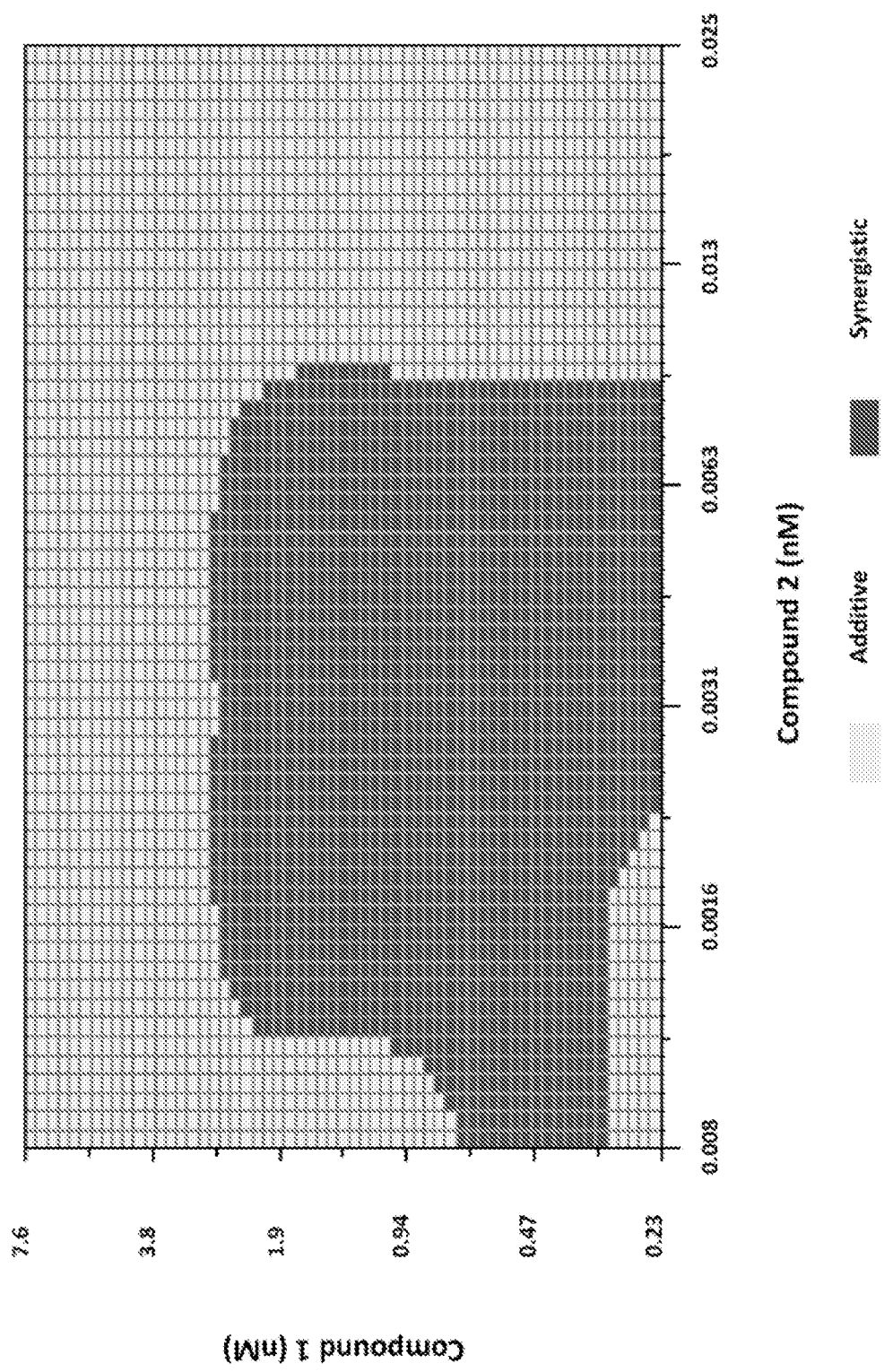


Figure 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/027423

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/454 A61K31/498 A61P31/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal , WPI Data, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/070416 AI (OR YAT SUN [US] ET AL) 22 March 2012 (2012-03-22) cited in the application page 47; example 268 page 84; example 268 page 52, paragraph 244 -----	1-24
A	US 2012/004196 AI (DEGOEY DAVID A [US] ET AL) 5 January 2012 (2012-01-05) claims 1,5, 18 -----	1-24
T	Wo 2014/047039 AI (ABBVI E INC [US]) 27 March 2014 (2014-03-27) page 15, paragraph 58 - paragraph 59; claims 1-12 -----	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

27 May 2014

Date of mailing of the international search report

04/06/2014

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Bonzano, Camilla

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/027423

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			WO 2014047039 AI 27-03-2014
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US 20140080868A1

Exhibit-B

(19) **United States**(12) **Patent Application Publication**
NG et al.(10) **Pub. No.: US 2014/0080868 A1**(43) **Pub. Date: Mar. 20, 2014**(54) **METHODS FOR TREATING HCV**(22) Filed: **Sep. 17, 2013**(71) Applicant: **AbbVie Inc.**, North Chicago, IL (US)**Related U.S. Application Data**(72) Inventors: **Theresa (Iok-Chan) NG**, Arlington Heights, IL (US); **Tami J. PILOT-MATIAS**, Green Oaks, IL (US); **Warren M. KATI**, Gurnee, IL (US); **Preeti KRISHNAN**, Gurnee, IL (US); **Clarence J. MARING**, Palatine, IL (US); **Neeta C. MISTRY**, Mundelein, IL (US); **Thomas J. REISCH**, Kenosha, WI (US); **Rolf WAGNER**, Antioch, IL (US); **Dachun LIU**, Vernon Hills, IL (US); **John K. PRATT**, Kenosha, WI (US); **Mark A. MATULENKO**, Libertyville, IL (US); **Ryan G. KEDDY**, Sebeka, MN (US)

(60) Provisional application No. 61/702,564, filed on Sep. 18, 2012.

Publication Classification(51) **Int. Cl.**
A61K 31/454 (2006.01)
A61K 45/06 (2006.01)
(52) **U.S. Cl.**
CPC **A61K 31/454** (2013.01); **A61K 45/06** (2013.01)
USPC **514/322**(73) Assignee: **ABBVIE INC.**, North Chicago, IL (US)(21) Appl. No.: **14/029,302**(57) **ABSTRACT**

Pan-genotypic HCV inhibitors are described. This invention also relates to methods of using these inhibitors to treat HCV infection.

METHODS FOR TREATING HCV

[0001] The application claims the benefit from and incorporates by reference the entire content of U.S. Provisional Patent Application No. 61/702,564, filed Sep. 18, 2012.

FIELD

[0002] The present invention relates to pan-genotypic HCV inhibitors and methods of using the same to treat HCV infection.

BACKGROUND

[0003] Hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

[0004] HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often inadequate. Therefore, there is a need for new drugs to treat HCV infection.

SUMMARY

[0005] It was surprisingly discovered that methyl {(2S, 3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate (hereinafter "Compound I") and its pharmaceutically acceptable salts are pan-genotypic HCV inhibitors. These compounds are effective in inhibiting a wide array of HCV genotypes and variants, such as HCV genotype 1, 2, 3, 4, 5, and 6.

[0006] Accordingly, a first aspect of the invention features methods for treating HCV. The methods comprise administering an effective amount of Compound 1 or a pharmaceutically acceptable salt thereof to an HCV patient, regardless of the specific HCV genotype(s) that the patient has. Therefore, the patient preferably is not genotyped before the treatment, and the treatment can be initiated without pre-screening the patient for specific HCV genotypes.

[0007] In one embodiment of this aspect of the invention, the patient is infected with genotype 2, such as genotype 2a or 2b. In another embodiment of this aspect of the invention, the patient is infected with genotype 3, such as genotype 3a. In another embodiment of this aspect of the invention, the patient is infected with genotype 4, such as genotype 4a. In yet another embodiment of this aspect of the invention, the patient is infected with genotype 5, such as genotype 5a. In still yet another embodiment of this aspect of the invention, the patient is infected with genotype 6, such as genotype 6a.

[0008] In another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with another anti-HCV agent. Non-limiting examples of said another anti-HCV agent include HCV polymerase inhibitors, HCV protease inhibitors, other HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0009] In yet another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor or an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0010] In another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0011] In another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0012] In another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor and an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0013] In this aspect of the invention, as well as each and every embodiment and example described hereunder, the treatment preferably lasts for less than 24 weeks and does not include administration of interferon to said patient. Such a treatment can, for example, comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor or an HCV polymerase inhibitor or a combination of an HCV protease inhibitor

tor and an HCV polymerase inhibitor, to said patient. For example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor, to said patient. For another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV polymerase inhibitor, to said patient. For yet another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient.

[0014] In this aspect of the invention, as well as each and every embodiment and example described hereunder, the treatment preferably lasts for no more than 12 weeks (e.g., the treatment lasts for 8, 9, 10, 11, or 12 weeks; preferably, the treatment lasts for 12 weeks), and does not include administration of interferon to said patient. Such a treatment can, for example, comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor or an HCV polymerase inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient. For example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor, to said patient. For another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV polymerase inhibitor, to said patient. For yet another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient.

[0015] In this aspect of the invention, as well as each and every embodiment and example described hereunder, the treatment may or may not include administration of ribavirin to said patient; for example, the treatment can include administration of ribavirin to said patient.

[0016] In a second aspect, the present invention features methods of treating HCV. The methods comprising administering an effective amount of Compound 1 or a pharmaceutically acceptable salt thereof to an HCV patient, wherein said patient is infected with HCV genotype 2, 3, 4, 5, or 6.

[0017] In one embodiment of this aspect of the invention, the patient is infected with genotype 2, such as genotype 2a or 2b. In another embodiment of this aspect of the invention, the patient is infected with genotype 3, such as genotype 3a. In another embodiment of this aspect of the invention, the patient is infected with genotype 4, such as genotype 4a. In yet another embodiment of this aspect of the invention, the patient is infected with genotype 5, such as genotype 5a. In still yet another embodiment of this aspect of the invention, the patient is infected with genotype 6, such as genotype 6a.

[0018] In another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with another anti-HCV agent. Non-limiting examples of said another anti-HCV agent include HCV polymerase inhibitors, HCV protease inhibitors, other HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5,

such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0019] In yet another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor or an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0020] In another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0021] In another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0022] In another embodiment of this aspect of the invention, Compound 1 or the salt thereof is combined or co-administered with an HCV protease inhibitor and an HCV polymerase inhibitor. In one example, the patient is infected with genotype 2, such as genotype 2a or 2b. In another example, the patient is infected with genotype 3, such as genotype 3a. In another example, the patient is infected with genotype 4, such as genotype 4a. In yet another example, the patient is infected with genotype 5, such as genotype 5a. In still yet another example, the patient is infected with genotype 6, such as genotype 6a.

[0023] In this aspect of the invention, as well as each and every embodiment and example described hereunder, the treatment preferably lasts for less than 24 weeks and does not include administration of interferon to said patient. Such a treatment can, for example, comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor or an HCV polymerase inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient. For example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor, to said patient. For another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV polymerase inhibitor, to said patient. For yet another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient.

[0024] In this aspect of the invention, as well as each and every embodiment and example described hereunder, the treatment preferably lasts for no more than 12 weeks (e.g., the treatment lasts for 8, 9, 10, 11, or 12 weeks; preferably, the treatment lasts for 12 weeks), and does not include administration of interferon to said patient. Such a the treatment can, for example, comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor or an HCV polymerase inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient. For example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV protease inhibitor, to said patient. For another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with an HCV polymerase inhibitor, to said patient. For yet another example, the treatment can comprise administering Compound 1 or a pharmaceutically acceptable salt thereof, together with a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, to said patient.

[0025] In this aspect of the invention, as well as each and every embodiment and example described hereunder, the treatment may or may not include administration of ribavirin to said patient; for example, the treatment includes administration of ribavirin to said patient.

[0026] The present invention also features Compound 1 or a pharmaceutically acceptable salt thereof for use to treat an HCV patient regardless of the specific HCV genotype(s) that

the patient has. Such uses are illustrated in the first aspect of the invention described above, including each and every embodiment and example described thereunder.

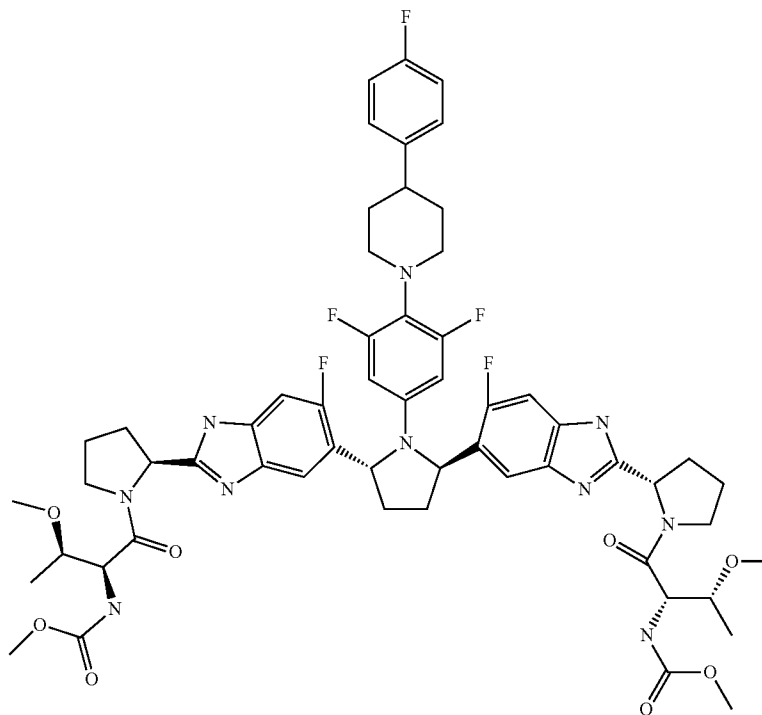
[0027] The present invention further features Compound 1 or a pharmaceutically acceptable salt thereof for use to treat an HCV patient infected with HCV genotype 2, 3, 4, 5, or 6. Such uses are illustrated in the second aspect of the invention described above, including each and every embodiment and example described thereunder.

[0028] Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description.

DETAILED DESCRIPTION

[0029] Compound 1, also known as methyl {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl]-1H-benzimidazol-5-yl]pyrrolidin-2-yl]-6-fluoro-1H-benzimidazol-2-yl]pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate, is described in U.S. Patent Application Publication No. 2012/0004196, the entire content of which is incorporated herein by reference.

Compound 1



[0030] Compound 1 was found to have EC_{50} values of less than 10 μ M against stable subgenomic replicons with NS5A from a broad range of clinically relevant HCV genotypes, such as HCV genotype 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a. In transient subgenomic replicon assays, Compound 1 was found to have EC_{50} values of less than 5 μ M against many HCV variants that are resistant to other NS5A inhibitors, such as genotype 2a T24A variant, genotype 2b L28F and L31V variants, genotype 3a M28T and Y93H variants, genotype 4a L28V and L30H variants, genotype 5a L28I, L31F and L31V variants, and genotype 6a L31V, T58N and T58A variants. The EC_{50} values were determined in the presence of 5% fetal bovine serum but in the absence of human plasma according to the procedures described below.

[0031] The present invention features the use of Compound 1 or a pharmaceutically acceptable salt thereof to treat HCV as described hereinabove. In any method or use described herein, Compound 1 or a pharmaceutically acceptable salt thereof can be formulated in a suitable liquid or solid dosage form. Preferably, Compound 1 or the salt thereof is formulated in a solid composition comprising Compound 1 (or a pharmaceutically acceptable salt thereof) in amorphous form, a pharmaceutically acceptable hydrophilic polymer, and optionally a pharmaceutically acceptable surfactant.

[0032] A non-limiting way to form an amorphous form of Compound 1 (or a pharmaceutically acceptable salt thereof) is through the formation of solid dispersions with a polymeric carrier. As used herein, the term "solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed throughout the other component or components. For example, an active ingredient or a combination of active ingredients can be dispersed in a matrix comprised of a pharmaceutically acceptable hydrophilic polymer(s) and a pharmaceutically acceptable surfactant(s). The term "solid dispersion" encompasses systems having small particles of one phase dispersed in another phase. These particles are often of less than 400 μ m in size, such as less than 100, 10, or 1 μ m in size. When a solid dispersion of the components is such that the system is chemically and physically uniform or homogeneous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion is called a "solid solution." A glassy solution is a solid solution in which a solute is dissolved in a glassy solvent.

[0033] Any method described herein can employ a solid composition which comprises (1) Compound 1 (or a pharmaceutically acceptable salt thereof) in amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant. Compound 1 (or the salt thereof) and the polymer preferably are formulated in a solid dispersion. The surfactant may also be formulated in the same solid dispersion; or the surfactant can be separately combined or mixed with the solid dispersion.

[0034] The hydrophilic polymer can, for example and without limitation, have a T_g of at least 50° C., more preferably at least 60° C., and highly preferably at least 80° C. including, but not limited to from, 80° C. to 180° C., or from 100° C. to 150° C. Preferably, the hydrophilic polymer is water-soluble. Non-limiting examples of suitable hydrophilic polymers include, but are not limited to, homopolymers or copolymers of N-vinyl lactams, such as homopolymers or copolymers of N-vinyl pyrrolidone (e.g., polyvinylpyrrolidone (PVP), or copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate); cellulose esters or cellulose ethers, such as alkyl-

celluloses (e.g., methylcellulose or ethylcellulose), hydroxyalkylcelluloses (e.g., hydroxypropylcellulose), hydroxyalkylalkylcelluloses (e.g., hydroxypropylmethylcellulose), and cellulose phthalates or succinates (e.g., cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, or hydroxypropylmethylcellulose acetate succinate); high molecular polyalkylene oxides, such as polyethylene oxide, polypropylene oxide, and copolymers of ethylene oxide and propylene oxide; polyacrylates or polymethacrylates, such as methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), and poly(hydroxyalkyl methacrylates); polyacrylamides; vinyl acetate polymers, such as copolymers of vinyl acetate and crotonic acid, and partially hydrolyzed polyvinyl acetate (also referred to as partially saponified "polyvinyl alcohol"); polyvinyl alcohol; oligo- or polysaccharides, such as carrageenans, galactomannans, and xanthan gum; polyhydroxyalkylacrylates; polyhydroxyalkyl-methacrylates; copolymers of methyl methacrylate and acrylic acid; polyethylene glycols (PEGs); or any mixture thereof.

[0035] Non-limiting examples of preferred hydrophilic polymers include polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) L100-55, Eudragit L100, Eudragit 5100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.

[0036] Of these, homopolymers or copolymers of N-vinyl pyrrolidone, such as copolymers of N-vinyl pyrrolidone and vinyl acetate, are preferred. A non-limiting example of a preferred polymer is a copolymer of 60% by weight of N-vinyl pyrrolidone and 40% by weight of vinyl acetate. Other preferred polymers include, without limitation, hydroxypropyl methylcellulose (HPMC, also known as hypromellose in USP), such as hydroxypropyl methylcellulose grade E5 (HPMC-E5); and hydroxypropyl methylcellulose acetate succinate (HPMC-AS).

[0037] The pharmaceutically acceptable surfactant employed can be a non-ionic surfactant. Preferably, the surfactant has an HLB value of from 2-20. A solid composition employed in the invention can also include a mixture of pharmaceutically acceptable surfactants, with at least one surfactant having an HLB value of at least 10 and at least another surfactant having an HLB value of below 10.

[0038] Non-limiting examples of suitable pharmaceutically acceptable surfactants include polyoxyethylene castor oil derivatives, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethyleneglycol 40 hydrogenated castor oil (Cremophor® RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate) or polyethyleneglycol 60 hydrogenated castor oil (Cremophor® RH 60); or a mono fatty acid

ester of polyoxyethylene sorbitan, such as a mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), or polyoxyethylene (20) sorbitan monolaurate (Tween® 20). Other non-limiting examples of suitable surfactants include polyoxyethylene alkyl ethers, e.g. polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether; polyoxyethylene alkylaryl ethers, e.g. polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether; polyethylene glycol fatty acid esters, e.g. PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate; alkylene glycol fatty acid mono esters, e.g. propylene glycol monolaurate (Lauroglycol®); sucrose fatty acid esters, e.g. sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate; sorbitan fatty acid mono esters such as sorbitan mono laurate (Span® 20), sorbitan monooleate, sorbitan monopalmitate (Span® 40), or sorbitan stearate. Other suitable surfactants include, but are not limited to, block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene polypropyleneglycol, such as Poloxamer® 124, Poloxamer® 188, Poloxamer® 237, Poloxamer® 388, or Poloxamer® 407 (BASF Wyandotte Corp.). As described above, a mixture of surfactants can be used in a solid composition employed in the invention.

[0039] Non-limiting examples of preferred surfactants include polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40, Cremophor EL, Gelucire 44/14, Gelucire 50/13, D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, and sorbitan monolaurate.

[0040] The solid dispersion employed in this invention preferably is a solid solution, and more preferably a glassy solution.

[0041] In one embodiment, a solid composition employed in the invention comprises an amorphous solid dispersion or solid solution which includes Compound 1 (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable hydrophilic polymer. The solid composition also includes a pharmaceutically acceptable surfactant which preferably is formulated in the amorphous solid dispersion or solid solution. The hydrophilic polymer can be selected, for example, from the group consisting of homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide, and polysaccharide. As a non-limiting example, the hydrophilic polymer is selected from the group consisting of homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene

oxide and propylene oxide, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan, and xanthan gum. Preferably, the hydrophilic polymer is selected from polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) L100-55, Eudragit L100, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, or poloxamer 407. More preferably, the hydrophilic polymer is selected from homopolymers of vinylpyrrolidone (e.g., PVP with Fikentscher K values of from 12 to 100, or PVP with Fikentscher K values of from 17 to 30), or copolymers of 30 to 70% by weight of N-vinylpyrrolidone (VP) and 70 to 30% by weight of vinyl acetate (VA) (e.g., a copolymer of 60% by weight VP and 40% by weight VA). The surfactant can be selected, for example, from the group consisting of polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate, mono fatty acid ester of polyoxyethylene sorbitan, polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester, and sorbitan fatty acid mono ester. As a non-limited example, the surfactant is selected from the group consisting of polyethyleneglycol 40 hydrogenated castor oil (Cremophor® RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate), polyethyleneglycol 60 hydrogenated castor oil (Cremophor® RH 60), a mono fatty acid ester of polyoxyethylene (20) sorbitan (e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), or polyoxyethylene (20) sorbitan monolaurate (Tween® 20)), polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, and sorbitan stearate. Preferably, the surfactant is selected from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40, Cremophor EL, Gelucire 44/14, Gelucire 50/13, D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, or sorbitan monolaurate. More preferably, the surfactant is selected from sorbitan monolaurate or D-alpha-tocopheryl polyethylene glycol 1000 succinate.

[0042] A solid dispersion employed in the invention preferably comprises or consists of a single-phase (defined in thermodynamics) in which Compound 1, or a combination of Compound 1 and another anti-HCV agent, is molecularly dispersed in a matrix containing the pharmaceutically acceptable hydrophilic polymer(s). In such cases, thermal analysis of the solid dispersion using differential scanning calorimetry (DSC) typically shows only one single T_g , and the solid dispersion does not contain any detectable crystalline Compound 1 as measured by X-ray powder diffraction spectroscopy.

[0043] A solid composition employed in the invention can be prepared by a variety of techniques such as, without limitation, melt-extrusion, spray-drying, co-precipitation, freeze drying, or other solvent evaporation techniques, with melt-extrusion and spray-drying being preferred. The melt-extrusion process typically comprises the steps of preparing a melt which includes the active ingredient(s), the hydrophilic polymer(s) and preferably the surfactant(s), and then cooling the melt until it solidifies. "Melting" means a transition into a liquid or rubbery state in which it is possible for one component to get embedded, preferably homogeneously embedded, in the other component or components. In many cases, the polymer component(s) will melt and the other components including the active ingredient(s) and surfactant(s) will dissolve in the melt thereby forming a solution. Melting usually involves heating above the softening point of the polymer(s). The preparation of the melt can take place in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or be simultaneously mixed and melted. The melt can also be homogenized in order to disperse the active ingredient(s) efficiently. In addition, it may be convenient first to melt the polymer(s) and then to mix in and homogenize the active ingredient(s). In one example, all materials except surfactant(s) are blended and fed into an extruder, while the surfactant(s) is molten externally and pumped in during extrusion.

[0044] To start a melt-extrusion process, the active ingredient(s) (e.g., Compound 1, or a combination of Compound 1 and at least another anti-HCV agent) can be employed in their solid forms, such as their respective crystalline forms. The active ingredient(s) can also be employed as a solution or dispersion in a suitable liquid solvent such as alcohols, aliphatic hydrocarbons, esters or, in some cases, liquid carbon dioxide. The solvent can be removed, e.g. evaporated, upon preparation of the melt.

[0045] Various additives can also be included in the melt, for example, flow regulators (e.g., colloidal silica), binders, lubricants, fillers, disintegrants, plasticizers, colorants, or stabilizers (e.g., antioxidants, light stabilizers, radical scavengers, and stabilizers against microbial attack).

[0046] The melting and/or mixing can take place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders, intermeshing screw extruders or multiscrew extruders, preferably twin screw extruders, which can be corotating or counterrotating and, optionally, be equipped with kneading disks. It will be appreciated that the working temperatures will be determined by the kind of extruder or the kind of configuration within the extruder that is used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, the friction and shearing of the material in the extruder

may also provide a substantial amount of energy to the mixture and aid in the formation of a homogeneous melt of the components.

[0047] The melt can range from thin to pasty to viscous. Shaping of the extrudate can be conveniently carried out by a calender with two counter-rotating rollers with mutually matching depressions on their surface. The extrudate can be cooled and allow to solidify. The extrudate can also be cut into pieces, either before (hot-cut) or after solidification (cold-cut).

[0048] The solidified extrusion product can be further milled, ground or otherwise reduced to granules. The solidified extrudate, as well as each granule produced, comprises a solid dispersion, preferably a solid solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). Where the granules do not contain any surfactant, a pharmaceutically acceptable surfactant described above can be added to and blended with the granules. The extrusion product can also be blended with other active ingredient(s) and/or additive(s) before being milled or ground to granules. The granules can be further processed into suitable solid oral dosage forms.

[0049] The approach of solvent evaporation, via spray-drying, provides the advantage of allowing for processability at lower temperatures, if needed, and allows for other modifications to the process in order to further improve powder properties. The spray-dried powder can then be formulated further, if needed, and final drug product is flexible with regards to whether capsule, tablet or any other solid dosage form is desired.

[0050] Exemplary spray-drying processes and spray-drying equipment are described in K. Masters, *SPRAY DRYING HANDBOOK* (Halstead Press, New York, 4th ed., 1985). Non-limiting examples of spray-drying devices that are suitable for the present invention include spray dryers manufactured by Niro Inc. or GEA Process Engineering Inc., Buchi Labortechnik AG, and Spray Drying Systems, Inc. A spray-drying process generally involves breaking up a liquid mixture into small droplets and rapidly removing solvent from the droplets in a container (spray drying apparatus) where there is a strong driving force for evaporation of solvent from the droplets. Atomization techniques include, for example, two-fluid or pressure nozzles, or rotary atomizers. The strong driving force for solvent evaporation can be provided, for example, by maintaining the partial pressure of solvent in the spray drying apparatus well below the vapor pressure of the solvent at the temperatures of the drying droplets. This may be accomplished by either (1) maintaining the pressure in the spray drying apparatus at a partial vacuum; (2) mixing the liquid droplets with a warm drying gas (e.g., heated nitrogen); or (3) both.

[0051] The temperature and flow rate of the drying gas, as well as the spray dryer design, can be selected so that the droplets are dry enough by the time they reach the wall of the apparatus. This help to ensure that the dried droplets are essentially solid and can form a fine powder and do not stick to the apparatus wall. The spray-dried product can be collected by removing the material manually, pneumatically, mechanically or by other suitable means. The actual length of time to achieve the preferred level of dryness depends on the size of the droplets, the formulation, and spray dryer operation. Following the solidification, the solid powder may stay in the spray drying chamber for additional time (e.g., 5-60

seconds) to further evaporate solvent from the solid powder. The final solvent content in the solid dispersion as it exits the dryer is preferably at a sufficiently low level so as to improve the stability of the final product. For instance, the residual solvent content of the spray-dried powder can be less than 2% by weight. Highly preferably, the residual solvent content is within the limits set forth in the International Conference on Harmonization (ICH) Guidelines. In addition, it may be useful to subject the spray-dried composition to further drying to lower the residual solvent to even lower levels. Methods to further lower solvent levels include, but are not limited to, fluid bed drying, infra-red drying, tumble drying, vacuum drying, and combinations of these and other processes.

[0052] Like the solid extrudate described above, the spray dried product contains a solid dispersion, preferably a solid solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). Where the spray dried product does not contain any surfactant, a pharmaceutically acceptable surfactant described above can be added to and blended with the spray-dried product before further processing.

[0053] Before feeding into a spray dryer, the active ingredient(s) (e.g., Compound 1, or a combination of Compound 1 and at least another anti-HCV agent), the hydrophilic polymer(s), as well as other optional active ingredients or excipients such as the pharmaceutically acceptable surfactant(s), can be dissolved in a solvent. Suitable solvents include, but are not limited to, alkanols (e.g., methanol, ethanol, 1-propanol, 2-propanol or mixtures thereof), acetone, acetone/water, alkanol/water mixtures (e.g., ethanol/water mixtures), or combinations thereof. The solution can also be preheated before being fed into the spray dryer.

[0054] The solid dispersion produced by melt-extrusion, spray-drying or other techniques can be prepared into any suitable solid oral dosage forms. In one embodiment, the solid dispersion prepared by melt-extrusion, spray-drying or other techniques can be compressed into tablets. The solid dispersion can be either directly compressed, or milled or ground to granules or powders before compression. Compression can be done in a tablet press, such as in a steel die between two moving punches. When a solid composition of the present invention comprises Compound 1 and another anti-HCV agent, it is possible to separately prepare solid dispersions of each individual active ingredient and then blend the optionally milled or ground solid dispersions before compacting. Compound 1 and other active ingredient(s) can also be prepared in the same solid dispersion, optionally milled and/or blended with other additives, and then compressed into tablets.

[0055] At least one additive selected from flow regulators, binders, lubricants, fillers, disintegrants, or plasticizers may be used in compressing the solid dispersion. These additives can be mixed with ground or milled solid dispersion before compacting. Various other additives may also be used in preparing a solid composition of the present invention, for example dyes such as azo dyes, organic or inorganic pigments such as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

[0056] In any aspect, embodiment and example described herein, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered to an HCV patient in combination with another anti-HCV agent. Preferably, such a treatment does not include the use of interferon throughout the

treatment regimen. The treatment regimen can last, for example and without limitation, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9 or 8 weeks. Preferably, the treatment regimen last, for example and without limitation, 12 weeks. The treatment regimen may also last less than 12 weeks, such as 11, 10, 9 or 8 weeks.

[0057] Suitable anti-HCV agents that can be combined with Compound 1 (or a pharmaceutically acceptable salt thereof) include, but are not limited to, HCV polymerase inhibitors (e.g., nucleoside polymerase inhibitors or non-nucleoside polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, other HCV NS5A inhibitors, HCV entry inhibitors, cyclophilin inhibitors, CD81 inhibitors, internal ribosome entry site inhibitors, or any combination thereof. For instance, said another anti-HCV agent can be an HCV polymerase inhibitor. For another instance, said another anti-HCV agent can be an HCV protease inhibitor.

[0058] Said another anti-HCV agent can also include two or more HCV inhibitors. For instance, said another anti-HCV agent can be a combination of an HCV polymerase inhibitor and an HCV protease inhibitor. For another instance, said another anti-HCV agent can be a combination of two different HCV protease inhibitors. For another instance, said another anti-HCV agent can be a combination of two different HCV polymerase inhibitors (e.g., one is a nucleoside or nucleotide polymerase inhibitor and the other is a non-nucleoside polymerase inhibitor; or both are nucleoside or nucleotide polymerase inhibitors; or both are non-nucleoside polymerase inhibitor). In yet another example, said another anti-HCV agent can be a combination of another HCV NS5A inhibitor and an HCV polymerase inhibitor. In yet another example, said another anti-HCV agent can be a combination of another HCV NS5A inhibitor and an HCV protease inhibitor. In still another example, said another anti-HCV agent can be a combination of two other HCV NS5A inhibitors.

[0059] Specific examples of anti-HCV agents that are suitable for combination with Compound 1 (or a pharmaceutically acceptable salt thereof) in any aspect, embodiment or example described herein include, but are not limited to, PSI-7977 (Pharmasset/Gilead), PSI-7851 (Pharmasset/Gilead), PSI-938 (Pharmasset/Gilead), PF-00868554, ANA-598, IDX184, IDX102, IDX375, GS-9190, VCH-759, VCH-916, MK-3281, BCX-4678, MK-3281, VBY708, ANA598, GL59728, GL60667, BMS-790052, BMS-791325, BMS-650032, BMS-824393, GS-9132, ACH-1095, AP-H005, A-831 (Arrow Therapeutics), A-689 (Arrow Therapeutics), INX08189 (Inhibitex), AZD2836, telaprevir, boceprevir, ITMN-191 (Intermune/Roche), BI-201335, VBY-376, VX-500 (Vertex), PHX-B, ACH-1625, IDX136, IDX316, VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191 (Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), BI-201335 (Boehringer Ingelheim), R7128 (Roche), MK-3281 (Merck), MK-0608 (Merck), PF-868554 (Pfizer), PF-4878691 (Pfizer), IDX-184 (Novartis), IDX-375, PPI-461 (Presidio), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), CTS-1027 (Conatus), GS-9620 (Gilead), PF-4878691 (Pfizer), RO5303253 (Roche), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), GSK62336805 (GlaxoSmithKline), or any combinations thereof.

[0060] Non-limiting examples of HCV protease inhibitors that are suitable for combination with Compound 1 (or a pharmaceutically acceptable salt thereof) in any aspect,

embodiment or example described herein include ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BI-201335 (Boehringer Ingelheim), BMS-650032 (BMS), boceprevir, danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or any combination thereof. Non-limiting examples of HCV polymerase inhibitors that are suitable for combination with Compound 1 (or a pharmaceutically acceptable salt thereof) in any aspect, embodiment or example described herein include ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset/Gilead), PSI-938 (Pharmasset/Gilead), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or any combination thereof. A polymerase inhibitor may be a nucleotide polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset/Gilead), PSI-938 (Pharmasset/Gilead), RG7128 (Roche), TMC64912 (Medivir), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or any combination thereof. A polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or any combination thereof. Non-limiting examples of NS5A inhibitors that are suitable for combination with Compound 1 (or a pharmaceutically acceptable salt thereof) in any aspect, embodiment or example described herein include GSK62336805 (Glaxo SmithKline), ACH-2928 (Achillion), ACH-3102 (Achillion), AZD2836 (Astra-Zeneca), AZD7295 (Astra-Zeneca), BMS-790052 (BMS), BMS-824393 (BMS), EDP-239 (Enanta/Novartis), GS-5885 (Gilead), IDX-719 (Idenix), MK-8742 (Merck), PPI-1301 (Presidio), PPI-461 (Presidio), or any combination thereof. Non-limiting examples of cyclophilin inhibitors that are suitable for combination with Compound 1 (or a pharmaceutically acceptable salt thereof) in any aspect, embodiment or example described herein include alisporovir (Novartis & Debiopharm), NM-811 (Novartis), SCY-635 (Scynexis), or any combination thereof. Non-limiting examples of HCV entry inhibitors that are suitable for combination with Compound 1 (or a pharmaceutically acceptable salt thereof) in any aspect, embodiment or example described herein include ITX-4520 (iTherx), ITX-5061 (iTherx), or a combination thereof.

[0061] In any aspect, embodiment or example described herein, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered, for example and without limitation,

concurrently with said another anti-HCV agent. Compound 1 (or a pharmaceutically acceptable salt thereof) can also be administered, for example and without limitation, sequentially with said another anti-HCV agent. For instance, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered immediately before or after the administration of said another anti-HCV agent. The frequency of administration may be the same or different. For example, Compound 1 (or a pharmaceutically acceptable salt thereof) and said another anti-HCV agent can be administered once daily. For another example, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered once daily, and said another anti-HCV agent can be administered twice daily.

[0062] In any aspect, embodiment or example described herein, Compound 1 (or a pharmaceutically acceptable salt thereof) can be co-formulated with said another anti-HCV agent in a single dosage form. Non-limiting examples of suitable dosage forms include liquid or solid dosage forms. Preferably, the dosage form is a solid dosage form. More preferably, the dosage form is a solid dosage form in which Compound 1 (or a pharmaceutically acceptable salt thereof) is in amorphous form, or highly preferably molecularly dispersed in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. Said another anti-HCV agent can also be in amorphous form, or molecularly dispersed in the same matrix or a different matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. Said another anti-HCV agent can also be formulated in different form(s) (e.g., in a crystalline form).

[0063] As a non-limiting alternative, Compound 1 (or a pharmaceutically acceptable salt thereof) and said another anti-HCV agent can be formulated in different dosage forms. For instance, Compound 1 (or a pharmaceutically acceptable salt thereof) and said another anti-HCV agent can be formulated in different respective solid dosage forms.

[0064] In any aspect, embodiment or example described herein, Compound 1 or a pharmaceutically acceptable salt thereof may be administered in a suitable amount such as, for example, in doses of from about 0.1 mg/kg to about 200 mg/kg body weight, or from about 0.25 mg/kg to about 100 mg/kg, or from about 0.3 mg/kg to about 30 mg/kg. As another non-limiting example, Compound 1 (or a pharmaceutically acceptable salt thereof) may be administered in a total daily dose amount of from about 5 mg to about 300 mg, or from about 25 mg to about 200 mg, or from about 25 mg to about 50 mg or an amount there between. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

[0065] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the disease undergoing therapy. It will also be understood that the total daily dosage of the compounds and compositions to be administered will be decided by the attending physician within the scope of sound medical judgment.

[0066] The following table lists non-limiting examples of a combination of Compound 1 (or a pharmaceutically acceptable salt thereof) and another anti-HCV agent that can be used

in any aspect, embodiment or example described herein. For each treatment, Compound 1 (or a pharmaceutically acceptable salt thereof) and said another anti-HCV agent can be administered daily to an HCV patient. Each treatment can be interferon-free. Administration of ribavirin can be included in each regimen. However, the present invention contemplates that each treatment regimen can be both interferon- and ribavirin-free. In addition, interferon and/or ribavirin can be included in each treatment regimen if needed. Each treatment regimen may also optionally comprise administering one or more other anti-HCV agents to the patient. The duration of each treatment regimen may last, for example and without limitation, 8-48 weeks, depending on the patient's response. In any given regimen described in Table 1, the drugs can be, for example and without limitation, co-formulated in a single solid dosage form. For instance, all drugs used in a regimen can be co-formulated in amorphous forms or molecularly dispersed in a matrix comprising a pharmaceutically acceptable water-soluble polymer and optionally a pharmaceutically acceptable surfactant; for another instance, Compound 1 is formulated in amorphous form or molecularly dispersed in a matrix comprising a pharmaceutically acceptable water-soluble polymer and optionally a pharmaceutically acceptable surfactant, and the other drug is in crystalline form(s) and combined with amorphous Compound 1 in a single solid dosage form. For yet another instance, Compound 1 is formulated in a different dosage form than that of the other drug.

TABLE 1

Non-Limiting Examples of Interferon-free Treatment Regimens (with or without ribavirin)		
Regimen	Drugs used in the treatment	
1	Compound 1 (or its salt)	ACH-1095 (Achillion)
2	Compound 1 (or its salt)	ACH-1625 (Achillion)
3	Compound 1 (or its salt)	ACH-2684 (Achillion)
4	Compound 1 (or its salt)	ACH-2928 (Achillion)
5	Compound 1 (or its salt)	aliporivir (Debio 025; Novartis)
6	Compound 1 (or its salt)	ALS-2158
7	Compound 1 (or its salt)	ALS-2200
8	Compound 1 (or its salt)	ANA-598 (setrobuvir, Anadys)
9	Compound 1 (or its salt)	ANA-773 (Anadys)
10	Compound 1 (or its salt)	AVL-181 (Avila)
11	Compound 1 (or its salt)	AVL-192 (Avila)
12	Compound 1 (or its salt)	AZD2836 (Astra-Zeneca)
13	Compound 1 (or its salt)	AZD7295 (Astra-Zeneca)
14	Compound 1 (or its salt)	BCX-4678 (BioCryst)
15	Compound 1 (or its salt)	BI-201335 (Boehringer Ingelheim)
16	Compound 1 (or its salt)	BI-207127 (Boehringer Ingelheim)
17	Compound 1 (or its salt)	BILB-1941 (Boehringer Ingelheim)
18	Compound 1 (or its salt)	BMS-650032 (BMS)
19	Compound 1 (or its salt)	BMS-790052 (BMS)
20	Compound 1 (or its salt)	BMS-791325 (BMS)
21	Compound 1 (or its salt)	BMS-824393 (BMS)
22	Compound 1 (or its salt)	boceprevir
23	Compound 1 (or its salt)	CTS-1027 (Conatus)
24	Compound 1 (or its salt)	danoprevir
25	Compound 1 (or its salt)	VX-985 (Vertex)
26	Compound 1 (or its salt)	filibuvir (PF-00868554, Pfizer)
27	Compound 1 (or its salt)	GL59728 (Glaxo)
28	Compound 1 (or its salt)	GL60667 (Glaxo)
29	Compound 1 (or its salt)	GS-5885 (Gilead)
30	Compound 1 (or its salt)	GS-6620 (Gilead)
31	Compound 1 (or its salt)	GS-9132 (Gilead)
32	Compound 1 (or its salt)	GS-9256 (Gilead)
33	Compound 1 (or its salt)	GS-9451 (Gilead)
34	Compound 1 (or its salt)	GS-9620 (Gilead)
35	Compound 1 (or its salt)	GS-9669 (Gilead)
36	Compound 1 (or its salt)	GSK62336805
37	Compound 1 (or its salt)	GSK625433 (GlaxoSmithKline)

TABLE 1-continued

Non-Limiting Examples of Interferon-free Treatment Regimens (with or without ribavirin)		
Regimen	Drugs used in the treatment	
38	Compound 1 (or its salt)	IDX-102 (Idenix)
39	Compound 1 (or its salt)	IDX-136 (Idenix)
40	Compound 1 (or its salt)	IDX-184 (Idenix)
41	Compound 1 (or its salt)	IDX-316 (Idenix)
42	Compound 1 (or its salt)	IDX-320 (Idenix)
43	Compound 1 (or its salt)	IDX-375 (Idenix)
44	Compound 1 (or its salt)	INX-189 (Inhibitex)
45	Compound 1 (or its salt)	ITX-4520 (iTherx)
46	Compound 1 (or its salt)	ITX-5061 (iTherx)
47	Compound 1 (or its salt)	MK-0608 (Merck)
48	Compound 1 (or its salt)	MK-3281 (Merck)
49	Compound 1 (or its salt)	MK-5172 (Merck)
50	Compound 1 (or its salt)	narlaprevir
51	Compound 1 (or its salt)	NM-811 (Novartis)
52	Compound 1 (or its salt)	PF-4878691 (Pfizer)
53	Compound 1 (or its salt)	PHX-1766 (Phenomix)
54	Compound 1 (or its salt)	PPI-1301 (Presidio)
55	Compound 1 (or its salt)	PPI-461 (Presidio--)
56	Compound 1 (or its salt)	PSI-7977 (Pharmasset/Gilead)
57	Compound 1 (or its salt)	PSI-938 (Pharmasset/Gilead)
58	Compound 1 (or its salt)	mericitabine (RG7128; Roche)
59	Compound 1 (or its salt)	RO5303253 (Roche)
60	Compound 1 (or its salt)	SCY-635 (/Scynexis/)
61	Compound 1 (or its salt)	tegobuvir
62	Compound 1 (or its salt)	telaprevir
63	Compound 1 (or its salt)	TMC-435 (Tibotec)
64	Compound 1 (or its salt)	TMC-647055 (Tibotec)
65	Compound 1 (or its salt)	TMC64912 (Medivir)
66	Compound 1 (or its salt)	vaniprevir
67	Compound 1 (or its salt)	VBY708 (Virobay)
68	Compound 1 (or its salt)	VCH-759 (Vertex & ViraChem)
69	Compound 1 (or its salt)	VCH-916 (ViraChem)
70	Compound 1 (or its salt)	VX-222 (VCH-222) (Vertex & ViraChem)
71	Compound 1 (or its salt)	VX-500 (Vertex)
72	Compound 1 (or its salt)	VX-759 (Vertex)
73	Compound 1 (or its salt)	VX-813 (Vertex)
74	Compound 1 (or its salt)	TMC649128 (Medivir)
75	Compound 1 (or its salt)	tegobuvir (GS-9190; Gilead)
76	Compound 1 (or its salt)	GI-5005 (GlobeImmune)
77	Compound 1 (or its salt)	IMO-2125 (Idera//)
78	Compound 1 (or its salt)	ITX-5061 (iTherx)
79	Compound 1 (or its salt)	miR-122 (Regulus)
80	Compound 1 (or its salt)	Miravirsen (SPC3649; Santaris)
81	Compound 1 (or its salt)	ACH-3102
82	Compound 1 (or its salt)	EDP-239
83	Compound 1 (or its salt)	IDX-719
84	Compound 1 (or its salt)	MK-8742
85	Compound 1 (or its salt)	

[0067] It should be understood that the above-described embodiments and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

Example 1

Antiviral Activity of Compound 1 in HCV Replicon Cell Culture Assays

[0068] The inhibitory activities of Compound 1 can be evaluated using the following protocol. Two genotype 1 stable subgenomic replicon cell lines can be used for compound characterization in cell culture: one derived from genotype 1a-H77 and the other derived from genotype 1b-Con1. The replicon constructs can be bicistronic subgenomic replicons. The genotype 1a replicon construct contains NS3-

NS5B coding region derived from the H77 strain of HCV (1a-H77). The replicon also has a firefly luciferase reporter and a neomycin phosphotransferase (Neo) selectable marker. These two coding regions, separated by the FMDV 2a protease, comprise the first cistron of the bicistronic replicon construct, with the second cistron containing the NS3-NS5B coding region with addition of adaptive mutations E1202G, K1691R, K2040R, and S2204I. The 1b-Con1 replicon construct is identical to the 1a-H77 replicon, except that the HCV 5' UTR, 3' UTR, and NS3-NS5B coding region are derived from the 1b-Con1 strain, and the adaptive mutations are K1609E, K1846T, and Y3005C. In addition, the 1b-Con1 replicon construct contains a poliovirus IRES between the HCV IRES and the luciferase gene. Replicon cell lines can be maintained in Dulbecco's modified Eagles medium (DMEM) containing 10% (v/v) fetal bovine serum (FBS), 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen), and 200 mg/ml G418 (Invitrogen). The inhibitory effects of Compound 1 on HCV replication can be determined by measuring the luciferase reporter activity. For example, replicon-containing cells can be seeded into 96-well plates at a density of 5000 cells per well in 100 μ l DMEM containing 5% FBS. The following day Compound 1 can be diluted in dimethyl sulfoxide (DMSO) to generate a 200 \times stock in a series of eight half-log dilutions. The dilution series can then be further diluted 100-fold in the medium containing 5% FBS. Medium with the inhibitor is added to the overnight cell culture plates already containing 100 μ A of DMEM with 5% FBS. The cells can be incubated for three days in the tissue culture incubators after which time 30 μ l of Passive Lysis buffer (Promega) can be added to each well, and then the plates are incubated for 30-45 minutes with rocking to lyse the cells. Luciferin solution (100 μ l, Promega) can be added to each well, and luciferase activity can be measured with a Victor II luminometer (Perkin-Elmer). The percent inhibition of HCV RNA replication can be calculated for each compound concentration and the EC₅₀ value can be calculated using nonlinear regression curve fitting to the 4-parameter logistic equation and GraphPad Prism 4 software.

[0069] The ability of Compound 1 to inhibit NS5A from non-genotype 1 HCV can be evaluated according to the following. A number of stable subgenomic 1b-Con1 replicon cell lines containing a portion of NS5A from genotype 2a, 2b, 3a, 4a, 5a or 6a HCV are created. The replicon construct contains a NotI restriction site upstream of NS5A, and a BlnI restriction site just after NS5A amino acid 214. HCV RNA from infected subjects is isolated (see Middleton et al., *JVIROL METHODS* 145:137-145 (2007), and Tripathi et al., *ANTIVIRAL RES* 73:40-49 (2007)), and RT-PCR is conducted on the RNA to generate a DNA fragment encoding HCV NS5A amino acids 1-214. The PCR fragment incorporates NotI and BlnI compatible ends, and this fragment is ligated into a plasmid containing the 1b-Con1 replicon. Stable cell lines containing these chimeric replicons are generated by introducing these constructs into Huh-7 cells. The inhibitory effect of Compound 1 on HCV replication in these replicons can be determined by measuring activity of the luciferase reporter gene as described above.

[0070] Using the above-described assays or similar cell-based replicon assays, Compound 1 showed significantly inhibitory activities against replication of HCV replicons with NS5A from genotype 1-6 (Table 2).

TABLE 2

HCV Replicon Subtype	Mean EC ₅₀ \pm Std. Dev. (pM)
Genotype 1a-H77	1.8 \pm 0.9
Genotype 1b-Con1	4.3 \pm 1.7
Genotype 2a	2.3 \pm 0.7
Genotype 2b	1.9 \pm 0.6
Genotype 3a	2.1 \pm 0.7
Genotype 4a	1.9 \pm 0.6
Genotype 5a	1.4 \pm 0.4
Genotype 6a	2.8 \pm 0.7

Example 2

Antiviral Potency of Compound 1 Against HCV
Non-Genotype 1 Wild Type and Variants as
Compared to Other HCV NS5a Inhibitors

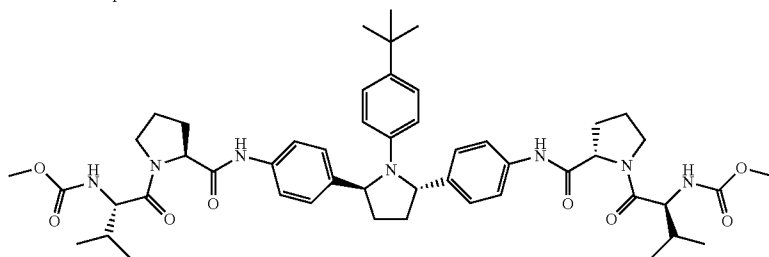
[0071] Compound 1 was tested against mutants resistant to other NS5A inhibitors, including the reference compound shown in Table 3. Transiently replicating chimeric replicons containing NS5A from genotype 2-6 wild types or replicons containing variants within NS5A were constructed in the 1b-Con1 background. These replicons also contained a firefly luciferase reporter gene. Variants were introduced by site-directed mutagenesis using the Change-IT Multiple Mutation Site Directed Mutagenesis Kit (USB). After the mutagenesis was confirmed by sequence analysis, the plasmids were linearized with ScaI restriction enzyme. The TranscriptAid T7 High Yield Transcription Kit (Fermentas) was used to transcribe the HCV subgenomic RNA from the plasmids. The RNA was transfected via electroporation into a Huh-7 derived cell line as described (see Middleton et al. and Tripathi et al., *supra*) except that 3×10^6 cells were electroporated with 15 μ g of template RNA and the 96 well plate was seeded with 7.5×10^3 cells per well. Four hours post-transfection, the wells from one plate were harvested for luciferase measurement. This plate provided a measure of the amount of translatable input RNA, and therefore transfection efficiency. To the wells of the remaining plates, a half-log dilution series of the test compound in culture medium (0.5% DMSO final concentration) was added, and plates were incubated at 37° C., 5% CO₂ in a humidified incubator for 4 days. After this period, the media was removed and the plates were washed with 100 μ l phosphate-buffered saline per well. Luciferin solution (50 μ l, Promega) was added to each well, and luciferase activity was measured with a Victor II luminometer (Perkin-Elmer). The percent inhibition of HCV RNA replication was calculated for each compound concentration and the EC₅₀ value was calculated using nonlinear regression curve fitting to the 4-parameter logistic equation and GraphPad Prism 4 software.

[0072] Using the above-described assays or similar cell-based replicon assays, Compound 1 showed significant inhibitory activities against replication of HCV replicons containing non-genotype 1 wild type NS5A as well as NS5A with resistant variants (Table 3).

TABLE 3

Genotype	Mutant	Average EC ₅₀ (pM) (Compound 1)	Average EC ₅₀ (pM) (reference compound*)
2a	WT	1.3	3.4
	T24A	1.3	92
2b	WT	1.0	1.1
	L28F	1.1	39
	L31V	0.9	427
	WT	1.8	7.2
3a	M28T	0.8	3030
	Y93H	4.3	>100,000
	WT	0.9	0.4
4a	L28V	0.8	5.3
	L30H	1.0	0.8
	WT	1.1	0.9
5a	L28I	1.0	72
	L31F	1.9	263
	L31V	0.9	221
	WT	1.4	80
6a	T58N	2.5	8468
	L31V	1.0	5035
	T58A	1.5	1145

*Reference compound is



[0073] The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

1. A method of treatment for HCV, comprising administering an effective amount of Compound 1 or a pharmaceutically acceptable salt thereof to an HCV patient, wherein said patient is not genotyped for said treatment.

2. The method of claim 1, wherein said patient is infected with HCV genotype 2.

3. The method of claim 1, wherein said patient is infected with HCV genotype 3.

4. The method of claim 1, wherein said patient is infected with HCV genotype 4.

5. The method of claim 1, wherein said patient is infected with HCV genotype 5.

6. The method of claim 1, wherein said patient is infected with HCV genotype 6.

7. The method according to one of claims 1-6, where said Compound 1 or the salt thereof is co-administered with another anti-HCV agent.

8. The method according to one of claims 1-6, wherein said Compound 1 is co-administered with an HCV protease inhibitor or an HCV polymerase inhibitor.

9. The method according to one of claims 1-6, wherein said Compound 1 is co-administered with an HCV protease inhibitor and an HCV polymerase inhibitor.

10. The method according to one of claims 1-6, wherein said treatment lasts for less than 24 weeks and does not include administration of interferon to said patient.

11. The method according to one of claims 1-6, wherein said treatment lasts for no more than 12 weeks and does not include administration of interferon to said patient.

12. The method according to one of claims 1-6, wherein said Compound 1 is co-administered with an HCV protease inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, and wherein said treatment lasts for less than 24 weeks and does not include administration of interferon to said patient.

13. The method according to one of claims 1-6, wherein said Compound 1 is co-administered with an HCV protease inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, and wherein said treatment lasts for no more than 12 weeks and does not include administration of interferon to said patient.

14. A method of treatment for HCV, comprising administering an effective amount of Compound 1 or a pharmaceutically acceptable salt thereof to an HCV patient, wherein said patient is infected with HCV genotype 2, 3, 4, 5, or 6.

15. The method of claim 13, wherein said patient is infected with HCV genotype 2.

16. The method of claim 13, wherein said patient is infected with HCV genotype 3.

17. The method of claim 13, wherein said patient is infected with HCV genotype 4.

18. The method of claim 13, wherein said patient is infected with HCV genotype 5.

19. The method of claim 13, wherein said patient is infected with HCV genotype 6.

20. The method according to one of claims **14-19**, wherein said Compound 1 is co-administered with an HCV protease inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, and wherein said treatment lasts for less than 24 weeks and does not include administration of interferon to said patient.

21. The method according to one of claims **14-19**, wherein said Compound 1 is co-administered with an HCV protease inhibitor or a combination of an HCV protease inhibitor and an HCV polymerase inhibitor, and wherein said treatment lasts for no more than 12 weeks and does not include administration of interferon to said patient.

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reduce prevalence by half by 2030, 880 patients have to be treated annually if treatment is restricted to fibrosis \geq F2 starting in 2016. Due to the undiagnosed population, annual treatment numbers of \geq F3 patients cannot be increased beyond about 700 after 4–5 year of treatment

Conclusions: If the aim is to reduce liver related mortality, HCC and decompensated cirrhosis, the strategy of prioritizing treatment for patients with \geq F3 is effective but does little by way of reducing prevalence. Finding undiagnosed patients with severe fibrosis and cirrhosis is essential to further reduce liver related morbidity and mortality.

P0715

STEADY-STATE PHARMACOKINETICS AND SAFETY OF COADMINISTRATION OF PAN-GENOTYPIC, DIRECT ACTING PROTEASE INHIBITOR, ABT-493 WITH PAN-GENOTYPIC NS5A INHIBITOR, ABT-530, IN HEALTHY ADULT SUBJECTS

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Background and Aims: A next generation direct acting antiviral (DAA) combination of ABT-493 (NS3/4A protease inhibitor discovered by AbbVie and Enanta) + ABT-530 (NS5A inhibitor) is being developed for the treatment of chronic hepatitis C (HCV) genotype 1–6 infection. Each compound demonstrated potent antiviral activity following 3-day monotherapy (AASLD 2014). The purpose of this study was to evaluate pharmacokinetics (PK) and safety of several different dose levels of ABT-493 and ABT-530 when given in combination.

Methods: Open-label 5-arm, cohort study in 72 healthy subjects with assessment of steady-state PK and safety of ABT-493 (100, 400, 700 or 1200 mg QD) combined with ABT-530 (40, 120, 160 or 200 mg QD). Intensive blood sampling for determination of ABT-493 and ABT-530 concentrations was performed. Safety and tolerability were assessed throughout the study.

ABT-530 dose	ABT-493 dose	Results
40 mg	100 mg	ABT-530 had minimal impact on ABT-493 ABT-493 increased ABT-530 to 1.5×
40 mg	400 mg	ABT-530 had minimal impact on ABT-493 ABT-493 increased ABT-530 to 6×
120 mg	400 mg	ABT-530 slightly increased ABT-493 exposures ABT-493 increased ABT-530 to 3–4×
160 mg	700 mg	ABT-530 slightly increased ABT-493 exposures ABT-493 increased ABT-530 to 5–7×
200 mg	1200 mg	Arm was prematurely discontinued, no steady state data were available

Results: ABT-493 exposures increased in a greater than dose proportional manner across the 100 mg to 1200 mg dose range. In the presence of ABT-530 (120 and 160 mg), geometric mean ABT-493 exposures were higher (41% to 83%) compared with ABT-493 administered alone. ABT-530 exposures increased in a greater than dose-proportional manner across the 40 mg to 120 mg dose range and approximately dose-proportionally from 120 mg to 200 mg. Co-administration with 400 mg ABT-493 increased ABT-530 120 mg exposures to 3- to 4-fold and 40 mg ABT-530 exposures to 6-fold compared with ABT-530 administered alone (Table). In contrast, 100 mg ABT-493 increased 40 mg ABT-530 exposures to 1.5-fold (Table). The ABT-493 1200 mg + ABT-530 200 mg arm was prematurely discontinued due to ABT-493 exposures exceeding the pre-specified upper exposure limit by the protocol. Two subjects discontinued prematurely, one was due to a Grade 2 adverse event of allergic dermatitis after a single dose of ABT-493, and the other was due to an asymptomatic Grade 3 ALT elevation after 7 days of 1200 mg ABT-493. One subject developed asymptomatic,

isolated, Grade 3 total bilirubin elevation. Described laboratory abnormalities were observed with 1200 mg or 700 mg ABT-493, and improved/normalized after conclusion of dosing.

Conclusions: ABT-530 at doses of 120 or 160 mg QD, but not 40 mg QD, slightly increased ABT-493 exposures (\leq 83%). ABT-493 dose-dependently increased the exposures of ABT-530. Both ABT-530 and ABT-493 were well tolerated and not associated with clinically significant/relevant laboratory abnormalities when the ABT-493 dose was less than 700 mg QD.

P0716

THE SIGNIFICANCE OF PLATELET MICROPARTICLES IN PATIENTS WITH CHRONIC HEPATITIS C AND THEIR ASSOCIATION WITH ANTIVIRAL TREATMENT AND SMOKING

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Background and Aims: Platelet-microparticles (PMPs) are platelet-derived membrane vesicles generated by cell activation and apoptosis which have been involved in cardiovascular diseases and atherosclerosis. Chronic hepatitis C (CHC) is associated with increased atherosclerosis, but the effect of antiviral treatment on the atherogenic potential of CHC has not been adequately studied so far. The aim of this study was to evaluate PMPs levels before and after antiviral treatment in CHC patients.

Methods: 28 CHC patients (13 G1/G4, 15 G3) were included, whereas 20 healthy volunteers (HV) and 20 patients with non-alcoholic fatty liver disease (NAFLD) were used as controls. Patients with cardiovascular diseases, diabetes, anticoagulant and antiplatelet treatment were excluded. All CHC patients were treated with pegylated-interferon/ribavirin. Twenty-four (86%) achieved sustained virological response (SVR). PMPs levels were determined by flow-cytometry (CD61-Annexin V) at baseline in all CHC patients and controls as well as at end of treatment (EOT) and 24 weeks post-treatment (SVR24) in all CHC patients.

Results: PMPs levels at baseline were higher in CHC compared to NAFLD patients ($P < 0.001$) and HV ($P = 0.007$). Higher PMPs levels at baseline were observed in smokers ($n = 18$) compared to non smokers ($n = 10$) with CHC ($P = 0.006$). Among smokers from all groups, CHC patients had higher PMPs at baseline compared to NAFLD ($P = 0.001$) and HV ($P = 0.024$). During antiviral treatment in all CHC patients, PMPs levels declined from baseline to both EOT ($P = 0.035$) and SVR24 ($P = 0.006$). PMPs levels decline during treatment was mainly observed in smokers [PMPs declined significantly from baseline to EOT ($P = 0.004$) and SVR24 ($P = 0.009$)]. Only patients achieving SVR had a significant decline in PMPs from baseline to SVR24 ($P = 0.018$), while those without SVR did not experience any significant change. Patients with G1/G4 experienced a higher decline in PMPs compared to G3 patients. PMPs levels at EOT and SVR24 in all CHC patients as well as in smokers became similar to those in control groups.

Conclusions: The higher PMPs levels in CHC patients and particularly in smokers further support the atherosclerotic potential of CHC and suggest a potentially synergistic effect of smoking and CHC on the atherosclerotic process. Since PMPs levels in CHC patients with SVR do not differ from those in controls, the atherosclerotic potential of CHC seems to be abolished by effective antiviral treatment.

POSTERS

Serum NGAL is a biomarker for renal tubular cell injury and red blood cell production suppressant, while Cystatin C is a biomarker of glomerular function. Thus could NGAL and Cystatin C predict renal function decline and anaemia severity in cirrhotic and non-cirrhotic patients on PI therapy.

Methods: 33 patients with HCV genotype 1 undergoing PI (bocepravir or telaprevir) based therapy had serum NGAL and Cystatin C measurements at the following time points: treatment initiation (TW0), TW12, end of treatment (EOT) (median 41 weeks) and 24 weeks post treatment (FUW24), using commercially available Quantikine ELISA kits from R&D systems. Absorbance measured at 450 nm on a microplate reader. Renin, creatinine, eGFR and Hb measurements were also made at these time points. Statistical analysis was performed using SPSS.

Results: Of the 33 patients (median age 50.32 years), 22 had cirrhosis, with 9 having renal risk factors (diabetes and hypertension). The remainder were neither cirrhotic nor had renal risk factors. Sustained virologic response (SVR) rates were comparable between the telaprevir and bocepravir groups (75% and 70.5% respectively). Serum NGAL levels showed no significant differences based on PI, SVR or level of fibrosis. However, in cirrhotics regardless of PI, a statistically significant rise in NGAL levels from TW0 until EOT with subsequent resolution was observed. TW0 NGAL levels >70 ng/ml were associated with >4 g/dl Hb decline at TW12 (PPV 89%) necessitating erythropoietin initiation.

Cystatin C levels were higher at TW0 in cirrhotics vs. non-cirrhotics (933 vs. 791, $p=0.04$) but only increased during therapy in cirrhotic patients. Baseline Cystatin C levels (>900 ng/ml) were linked to >20% decline in eGFR by TW12 (PPV 86%). Renin and creatinine levels did not correspond to Cystatin C levels, thus suggesting dehydration was not a contributory factor to these changes.

Conclusions: TW0 Cystatin C levels (>900 ng/ml) can determine which patients will have significant renal dysfunction during therapy, whilst serum NGAL levels >70 ng/ml identifies those requiring EPO support, regardless of cirrhosis, thus facilitating safer delivery of PI based therapy.

P0854

ESTIMATING THE COST OFFSETS AND IMPACT ON QUALITY-ADJUSTED LIFE EXPECTANCY ASSOCIATED WITH INCREASING SVR IN UK PATIENTS WITH HEPATITIS C-RELATED ADVANCED LIVER DISEASE

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Background and Aims: Most health economic models for hepatitis C consider the value of treating chronically infected patients; however, few have been designed to model treatment in those with advanced liver disease (ALD). Described herein is an adaptation to the MONARCH model to allow modeling of those with ALD with significantly more granularity, including pre- and post-transplant stages. MONARCH ALD was used to estimate the potential benefit of increased efficacy associated with novel direct-acting antivirals (DAAs) over conventional treatment with pegylated interferon- α plus ribavirin (PR) when treating patients from the following disease stages: compensated cirrhosis (CC); decompensated cirrhosis (DC); and post-liver transplant fibrosis stage F2 (pLTx-F2).

Methods: A systematic literature review informed the structural framework of the model and key parameters for modeling patients with ALD. Transition rates between health states were obtained from published sources. Costs and mortality estimates were obtained from UK-specific sources. Baseline sustained virologic response (SVR) rates of 30.0%, 14.3% and 45.6% for PR (extracted from published sources) were utilised, with future costs and health

benefits discounted at 3.5%. An SVR of 90% was used for comparison to a hypothetical novel DAA. Total complication costs and quality-adjusted life expectancy (QALE) of patients aged 55 with HCV therapy commencing from CC, DC or pLTx-F2 were estimated.

Results: Predicted complication costs and QALEs utilising base case and improved SVR rates are presented in Table 1.

Table 1.

Stage of treatment initiation	Cost of complications (£)			QALE		
	PR	DAA	Cost-offset	PR	DAA	Incremental QALE
CC	32,444	7,801	24,642	8.28	11.23	2.95
DC	104,949	93,230	11,719	7.31	7.96	0.65
pLTx-F2	81,352	47,035	34,317	10.56	12.2	1.63

Conclusions: With the introduction of new therapies with higher rates of SVR, it is likely that significant benefits, in terms of reducing complication costs and increasing QALEs, over conventional therapies will be realised. The greatest cost offset due to the increase in SVR was observed in those that initiated treatment from the pLTx-F2 health state. The greatest improvement in QALE was observed in patients that initiated treatment from the CC health state.

P0855

PHARMACOKINETICS OF ABT-493 AND ABT-530 IS SIMILAR IN HEALTHY CAUCASIAN, CHINESE, AND JAPANESE ADULT SUBJECTS

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Background and Aims: A next generation direct acting antiviral (DAA) combination of ABT-493 (NS3/4A protease inhibitor discovered by AbbVie and Enanta) + ABT-530 (NS5A inhibitor) is being developed for the treatment of chronic hepatitis C infection. This study assessed pharmacokinetics (PK) and safety of multiple oral doses of ABT-493 and ABT-530 administered alone and in combination in healthy Han Chinese, Japanese, and Caucasian subjects.

Methods: This Phase 1, single center, multiple-dose, open-label study consisted of 11 Han Chinese, 12 Japanese, and 12 Caucasian subjects randomized into 2 cohorts with stratification by race (Figure). Intensive PK assessments were performed on Days 1, 7, 8 and 14. PK parameters were estimated by noncompartmental analyses. Safety [adverse events (AEs), clinical labs, vital signs, ECG] was assessed throughout the study.

Results: ABT-493 and ABT-530 exposures (difference $\leq 32\%$ and $\leq 58\%$, respectively) were comparable in Japanese, Chinese and Caucasians when administered alone. When taking DAAs in combination, three ethnic groups also had similar ABT-493 and ABT-530 exposures: the geometric means for ABT-493 C_{max} were 15300, 13900, and 16700 ng/mL, and for AUC were 66000, 49400, and 67500 ng·h/mL, respectively in Caucasian, Chinese, and Japanese; for ABT-530 C_{max} were 289, 288, and 326 ng/mL, and for AUC were 2910, 2570, and 3070 ng·h/mL, respectively in Caucasian, Chinese, and Japanese. Interaction between ABT-493 and ABT-530 were also comparable among ethnicities: on average ABT-493 AUC and C_{max} were increased by 17–61% and 16–30%, respectively, in presence of steady-state ABT-530; ABT-530 AUC and C_{max} were increased to 5.1- to 7.5-fold and 3.1- to 5.0-fold, respectively in presence of steady-state ABT-493. Elimination half-lives of ABT-493 and ABT-530 were similar among Japanese, Chinese, and Caucasian.

Asymptomatic Grade 3 ALT and Grade 2 AST elevation (without concurrent bilirubin elevations) were observed in a Caucasian subject, and 2 additional subjects (Chinese and Caucasian) developed isolated asymptomatic Grade 3 total bilirubin elevations with predominantly indirect fraction. Overall the regimens were well tolerated. There were no serious AEs, premature discontinuations and described laboratory abnormalities normalized/improved following completion of dosing.

	Days 1 to 7	Days 8 to 14
Cohort 1 (N = 18)	ABT-493 700 mg QD	ABT-493 700 mg QD ABT-530 160 mg QD
Cohort 2 (N = 17)	ABT-530 160 mg QD	ABT-493 700 mg QD ABT-530 160 mg QD

Conclusions: Ethnicity does not have much impact on the exposures, safety and tolerability of ABT-493 or ABT-530 alone, or ABT-493 + ABT-530 combination.

P0856

OMBITASVIR/PARITAPREVR/RITONAVIR AND DASABUVIR WITH RIBAVIRIN (RBV) HAS MILD IMPACT ON HEALTH-RELATED QUALITY OF LIFE (HRQOL) COMPARED WITH PLACEBO DURING 12-WEEK TREATMENT IN TREATMENT-EXPERIENCED ADULTS WITH CHRONIC HEPATITIS C (CHC)

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Background and Aims: Interferon can negatively impact patient HRQoL during CHC treatment. We assessed the HRQoL impact of an interferon-free all-oral CHC therapy – ombitasvir/paritaprevir (identified by AbbVie and Enanta)/ritonavir and dasabuvir with RBV (3D+RBV) – compared with placebo in treatment-experienced, non-cirrhotic, Genotype 1 (GT1) adults during 12 weeks of treatment in the Phase 3 trial SAPPHERE-II.

Methods: Patients were randomized in a 3:1 ratio to 3D+RBV or placebo and treated during a 12-week double-blind period. HRQoL was assessed using the SF-36 v2 Health Survey (SF-36) which was administered at baseline, during treatment, and at end of treatment (EOT) for both treatment groups, and at post-treatment (PT) visits for the 3D+RBV group only. Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were calculated for the SF-36. Summary statistics of change from baseline, including mean and standard deviation (SD), were generated for each visit by treatment group. A repeated measures analysis of covariance (RM-ANCOVA) was carried out for PCS and MCS, respectively, to determine the mean difference in adjusted scores between treatment groups during the 12-week treatment period. The factors in the RM-ANCOVA analysis were treatment group and visit and covariates were baseline PCS score, MCS score, and patient characteristics.

Table: Mean baseline (SD) and change from baseline (SD) HRQoL scores by treatment group

		Baseline	Wk 4	Wk 8	EOT	PT Wk 4	PT Wk 12
PCS	3D+RBV	50.7 (8.46)	-2.2 (6.67)	-3.0 (7.47)	-2.8 (7.74)	0.0 (6.46)	0.8 (6.36)
	Placebo	50.7 (8.03)	-1.2 (4.59)	-0.6 (5.26)	-1.3 (6.27)	n.a.	n.a.
MCS	3D+RBV	50.0 (9.86)	-2.4 (7.91)	-3.9 (9.37)	-3.7 (9.74)	-0.3 (8.41)	0.8 (8.54)
	Placebo	48.6 (11.08)	0.5 (7.55)	-0.5 (7.78)	-0.6 (9.04)	n.a.	n.a.

Results: The analysis included 297 patients on 3D+RBV and 97 on placebo. HRQoL results are summarized in Table. At EOT, greater changes from baseline PCS and MCS scores were observed in the 3D+RBV group (-2.8 in PCS and -3.7 in MCS) compared with the placebo group (-1.3 for PCS and -0.6 for MCS). At PT Wk 12 visit, PCS and MCS scores for 3D+RBV patients were improved over baseline (PCS: +0.8 and MCS: +0.8). Results from RM-ANCOVA demonstrated that the adjusted mean decrements in PCS and MCS scores over the 12 week treatment period in the 3D+RBV group were greater than in the placebo group, and both differences were statistically significant – 1.57 greater decrement in PCS (95%CI, 0.31 to 2.84) and 2.45 greater decrement in MCS (95%CI, 0.83 to 4.07).

Conclusions: During the 12-week treatment period in SAPPHERE-II, the interferon-free all-oral 3D+RBV regimen had mild impact on patient HRQoL compared with placebo. Post-treatment scores for 3D+RBV showed improvement over baseline.

P0857

98% SVR12 IN KOREAN AND TAIWANESE PATIENTS WITH CHRONIC GENOTYPE 1 HCV INFECTION RECEIVING 12 WEEKS OF LEDIPASVIR/SOFOSBUVIR: RESULTS FROM AN INTERNATIONAL, MULTICENTER PHASE 3 STUDY

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Background and Aims: Approximately half of the patients with chronic hepatitis C virus (HCV) infection in Korea and Taiwan are infected with HCV genotype (GT) 1. The majority of these patients have often failed to respond to prior interferon (IFN)-based therapy. Frequently, patients may be ineligible for, or intolerant of current treatment options. Highly effective, safe and well-tolerated IFN- and ribavirin-free therapies are needed to address the burden of HCV-related liver disease in Korea and Taiwan.

Methods: An open-label, Phase 3 study was conducted to evaluate the efficacy and safety of the ledipasvir (LDV) 90 mg/sofosbuvir (SOF) 400 mg fixed-dose combination (FDC) tablet administered orally, once daily for 12 weeks in Korean and Taiwanese adults with chronic GT1 HCV infection, with and without cirrhosis. There was no upper age limit, we included patients with cirrhosis, no entry restriction applied for neutrophils and the minimum platelet count was 50,000/ μ L. NS5A and NS5B resistance associated variants (RAVs) were evaluated by deep sequencing. The primary efficacy endpoint was SVR12.

Table 1. SVR12 rates in GT 1-infected patients and difficult-to-treat subgroups

	Korea (N = 93)	Taiwan (N = 85)	Overall (N = 178)
Virologic response (ITT):			
Overall, SVR12, n (%)	92 (99)	83 (98)	175 (98)
On-treatment failure, n (%)	0	0	0
Relapse, n (%)	1 (1)	1 (1)	2 (1)
Withdrew consent, n (%)	0	1 (1)	1 (<1)
SVR12 by subgroup:			
Treatment-experienced (TE), n/N (%)	46/47 (98)	41/43 (95)	87/90 (97)
Cirrhotic, n/N (%)	17/17 (100)	9/9 (100)	26/26 (100)
TE with cirrhosis, n/N (%)	13/13 (100)	4/4 (100)	17/17 (100)

Results: 178 patients were enrolled. The mean (range) age was 54 (20–75) years old, BMI 24 (18–38) kg/m², and baseline HCV RNA 6.7 (3.7–7.6) log₁₀ IU/mL. The majority of patients were treatment-experienced (51%), non-cirrhotic (85%), GT1b infected (93%), female (56%), and had IL28B CC genotype (72%). Table 1 shows the overall SVR12 rates. A total of 38 subjects were identified as having baseline NS5A RAVs, of which 37/38 (97%) achieved SVR12. Three (2%) patients failed to achieve SVR12: 2 patients relapsed and 1 patient withdrew consent. Both relapse patients had detectable NS5A RAVs, but no detectable S282T at the time of relapse. Headache was the only adverse event (AE) reported in \geq 10% of patients. Five patients (3%) had treatment-emergent SAEs all unrelated to study drug. Two patients (1%) discontinued therapy due to an AE. No AE leading to

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(54) Title: SOLID PHARMACEUTICAL DOSAGE FORM

(57) Abstract: A solid pharmaceutical dosage form providing improved oral bioavailability is disclosed for inhibitors of HIV protease. In particular, the dosage form comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C. Preferably, the pharmaceutically acceptable surfactant has an HLB value of from about 4 to about 10.



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SOLID PHARMACEUTICAL DOSAGE FORM

5 The present invention is directed to a solid pharmaceutical dosage form comprising at least one HIV protease inhibitor, and a process for preparing same.

 The virus causing acquired immunodeficiency syndrome (AIDS) is known by different names, including T-lymphocyte virus III (HTLV-III) or lymphadenopathy-
10 associated virus (LAV) or AIDS-related virus (ARV) or human immunodeficiency virus (HIV). Up until now, two distinct families have been identified, i. e., HIV-1 and HIV-2.

 One of the critical pathways in a retroviral life cycle is the processing of polyprotein precursors by aspartic protease. For instance with the HIV virus the gag-pol protein is
15 processed by HIV protease. The correct processing of the precursor polyproteins by the aspartic protease is required for the assembly of infectious virions, thus making the aspartic protease an attractive target for antiviral therapy. In particular for HIV treatment, the HIV protease is an attractive target.

20 A measure of the potential usefulness of an oral dosage form of a pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength and first pass effect. Aqueous solubility is one of the most important of these factors.
25 Unfortunately, HIV protease inhibiting compounds typically are characterized by having poor aqueous solubility.

 For a variety of reasons, such as patient compliance and taste masking, a solid dosage form is usually preferred over a liquid dosage form. In most instances however, oral solid
30 dosage forms of a drug provide a lower bioavailability than oral solutions of the drug.

There have been attempts to improve the bioavailability provided by solid dosage forms by forming solid solutions of the drug. The term "solid solution" defines a system in a solid state wherein the drug is molecularly dispersed throughout a matrix such that the system is chemically and physically uniform or homogenous throughout. Solid solutions are preferred physical systems because the components therein readily form liquid solutions when contacted with a liquid medium such as gastric juice. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of the components from a crystalline or microcrystalline solid phase. If, however, the drug absorption in the gastrointestinal tract is slow the drug released from the solid solution may result in a high supersaturation and precipitate in the aqueous fluids of the gastrointestinal tract.

There is a continuing need for the development of improved oral solid dosage forms for HIV protease inhibitors which have suitable oral bioavailability and stability and which do not necessitate high vehicle volumes.

The present invention provides a solid pharmaceutical dosage form comprising a solid dispersion of at least one HIV protease inhibitor in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant. In one embodiment, the pharmaceutically acceptable water-soluble polymer has a glass transition temperature (T_g) of at least about 50 °C.

The term "solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed evenly throughout the other component or components. For example, the active ingredient or combination of active ingredients is dispersed in a matrix comprised of the pharmaceutically acceptable water-soluble polymer(s) and pharmaceutically acceptable surfactant(s). The term "solid dispersion" encompasses systems having small particles, typically of less than 1 μm in diameter, of one phase dispersed in another phase. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion will be called a

"solid solution" or a "glassy solution". A glassy solution is a homogeneous, glassy system in which a solute is dissolved in a glassy solvent. Glassy solutions and solid solutions of HIV protease inhibitors are preferred physical systems. These systems do not contain any significant amounts of active ingredients in their crystalline or microcrystalline state, as evidenced by thermal analysis (DSC) or X-ray diffraction analysis (WAXS).

In one embodiment of the present invention, the pharmaceutical dosage form is comprising from about 5 to about 30 % by weight of the total dosage form (preferably from about 10 to about 25 % by weight of the total dosage form) of an HIV protease inhibitor or a combination of HIV protease inhibitors, from about 50 to about 85 % by weight of the total dosage form (preferably from about 60 to about 80 % by weight of the total dosage form) of a water-soluble polymer (or any combination of such polymers), from about 2 to about 20 % by weight of the total dosage form (preferably from about 3 to about 15 % by weight of the total dosage form) of the surfactant (or combination of surfactants), and from about 0 to about 15 % by weight of the total dosage form of additives.

HIV protease inhibiting compounds suitable for use in the present invention include for example, but are not limited thereto:

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]-amino-1,6-diphenylhexane (ABT-378; lopinavir);

N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginy]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-*t*-butylamide;

[1S-[1R-(R-),2S*]]-N¹ [3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;

amprenavir (VX-478); DMP-323; DMP-450; AG1343 (nelfinavir);

atazanavir (BMS 232,632);

tipranavir;

palinavir;

TMC-114;

RO033-4649;

fosamprenavir (GW433908);

P-1946;

BMS 186,318; SC-55389a; BILA 1096 BS; and U-140690, or combinations thereof.

In one embodiment, ritonavir (Abbott Laboratories, Abbott Park, IL, USA) is an HIV protease inhibitor which may be formulated into the dosage form of the invention. This and other compounds as well as methods for preparing same are disclosed in U. S. Patent Nos. 5,542,206 and 5,648,497, the disclosures of which are herein incorporated by reference. In a further embodiment, the present invention provides a dosage form wherein said HIV protease inhibitor is ritonavir or a combination of ritonavir and at least one other HIV protease inhibitor, the dosage form showing a dose-adjusted AUC of ritonavir plasma concentration in dogs of at least about 9 µg.h/ml/100 mg.

In another embodiment, lopinavir (Abbott Laboratories, Abbott Park, IL, USA) is an HIV protease inhibitor which may be formulated into the dosage form of the invention. This and other compounds, as well as methods for preparing same, are identified in U. S. Patent No. 5,914,332, the disclosure of which is herein incorporated by reference. In a further embodiment, the present invention provides a dosage form wherein said HIV protease inhibitor is lopinavir or a combination of lopinavir and at least one other HIV protease inhibitor, the dosage form showing a dose-adjusted AUC of lopinavir plasma concentration in

dogs of at least about 20 $\mu\text{g.h/ml/100 mg}$ (preferably at least about 22.5 $\mu\text{g.h/ml/100 mg}$, most preferred at least about 35 $\mu\text{g.h/ml/100 mg}$).

In yet another embodiment, nelfinavir mesylate (marketed under the tradename Viracept by Agouron Pharmaceuticals, Inc. in La Jolla, CA) is an HIV protease inhibitor which may be formulated into the dosage form of the invention.

The dosage forms of the present invention exhibit a release and absorption behaviour that is characterized by high attainable AUC, high attainable C_{max} (maximum plasma concentration), and low T_{max} (time to reach maximum plasma concentration).

In still another embodiment, the present invention provides a dosage form wherein said HIV protease inhibitor is a combination of ritonavir and lopinavir, the dosage form showing a dose-adjusted AUC of ritonavir plasma concentration in dogs of at least about 15 $\mu\text{g.h/ml/100 mg}$ and a dose-adjusted AUC of lopinavir plasma concentration of at least about 20 $\mu\text{g.h/ml/100 mg}$ (preferably at least about 22.5 $\mu\text{g.h/ml/100 mg}$, most preferred at least about 35 $\mu\text{g.h/ml/100 mg}$).

The term "AUC" means "Area Under the Curve" and is used in its normal meaning, i. e. as the area under the plasma concentration-time curve from 0 to 24 hours, where the dosage form has been administered orally to dogs (beagle) under non-fasting conditions. "Non-fasting condition" means that the dogs receive a nutritionally balanced daily ration during the pre-test period and the whole test period. The AUC has units of concentration times time. Once the experimental concentration-time points have been determined, the AUC may conveniently be calculated, e. g. by a computer program or by the trapezoidal method. All AUC data herein were dose adjusted to the 100 mg dose level. For the purposes herein, the AUC is determined within a dose range where the AUC increases proportionally with dose. Administration of 50 mg ritonavir or 200 mg lopinavir, respectively, to dogs is considered suitable for determining the AUC values as used herein.

The dosage forms according to the invention are characterized by an excellent stability and, in particular, exhibit high resistance against recrystallization or decomposition of the active ingredient(s). Thus, upon storage for 6 weeks at 40 °C and 75% humidity (e.g., when kept in high density polyethylene (HDPE) bottles without desiccant), the dosage forms according to the present invention usually do not exhibit any sign of crystallinity (as evidenced by DSC or WAXS analysis) and contain at least about 98 % of the initial active ingredient content (as evidenced by HPLC analysis).

The term "pharmaceutically acceptable surfactant" as used herein refers to a pharmaceutically acceptable non-ionic surfactant. In one embodiment, the dosage form is comprising at least one surfactant having an hydrophilic lipophilic balance (HLB) value of from about 4 to about 10, preferably from about 7 to about 9. The HLB system (Fiedler, H.B., Encyclopedia of Excipients, 5th ed., Aulendorf: ECV-Editio-Cantor-Verlag (2002)) attributes numeric values to surfactants, with lipophilic substances receiving lower HLB values und hydrophilic substances receiving higher HLB values. Surfactants having an HLB value of from about 4 to about 10 suitable for use in the present invention include for example, but are not limited thereto:

polyoxyethylene alkyl ethers, e.g. polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether; polyoxyethylene alkylaryl ethers, e.g. polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether;

polyethylene glycol fatty acid esters, e.g. PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate;

alkylene glycol fatty acid mono esters, e.g. propylene glycol monolaurate (Lauroglycol®);

sucrose fatty acid esters, e.g. sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate; or

sorbitan fatty acid mono esters such as sorbitan mono laurate (Span® 20), sorbitan monooleate, sorbitan monopalmitate (Span® 40), or sorbitan stearate, or

mixtures of one or more thereof.

The sorbitan mono fatty acid esters are preferred, with sorbitan mono laurate and sorbitan monopalmitate being particularly preferred.

Besides the surfactant having an HLB value of from about 4 to about 10, the dosage form may comprise additional pharmaceutically acceptable surfactants such as polyoxyethylene castor oil derivates, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethylenglycol 40 hydrogenated castor oil (Cremophor® RH 40) or polyethylenglycol 60 hydrogenated castor oil (Cremophor® RH 60); or block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene polypropyleneglycol, such as Poloxamer® 124, Poloxamer® 188, Poloxamer® 237, Poloxamer® 388, Poloxamer® 407 (BASF Wyandotte Corp.); or a mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), polyoxyethylene (20) sorbitan monolaurate (Tween® 20).

Where such additional surfactants are used, the surfactant having an HLB value of from about 4 to about 10 generally accounts for at least about 50 % by weight, preferably at least about 60 % by weight, of the total amount of surfactant used.

The water-soluble polymer employed in the present invention has a Tg of at least about 50 °C, preferably at least about 60°C, most preferred from about 80 °C to about 180

°C. Methods for determining Tg values of the organic polymers are described in "Introduction to Physical Polymer Science", 2nd Edition by L.H. Sperling, published by John Wiley & Sons, Inc., 1992. The Tg value can be calculated as the weighted sum of the Tg values for homopolymers derived from each of the individual monomers, i.e., that make up the polymer: $T_g = \sum W_i X_i$ where W is the weight percent of monomer i in the organic polymer, and X is the Tg value for the homopolymer derived from monomer i. Tg values for the homopolymers may be taken from "Polymer Handbook", 2nd Edition by J. Brandrup and E.H. Immergut, Editors, published by John Wiley & Sons, Inc., 1975.

Water-soluble polymers having a Tg as defined above allow for the preparation of solid dispersions that are mechanically stable and, within ordinary temperature ranges, sufficiently temperature stable so that the solid dispersions may be used as dosage forms without further processing or be compacted to tablets with only a small amount of tableting aids.

The water-soluble polymer comprised in the dosage form is a polymer that preferably has an apparent viscosity, when dissolved at 20 °C in an aqueous solution at 2 % (w/v), of about 1 to about 5000 mPa.s. more preferably of about 1 to about 700 mPa.s, and most preferred of about 5 to about 100 mPa.s. Water-soluble polymers suitable for use in the present invention include for example, but are not limited thereto:

homopolymers and copolymers of N-vinyl lactams, especially homopolymers and copolymers of N-vinyl pyrrolidone, e.g. polyvinylpyrrolidone (PVP), copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate,

cellulose esters and cellulose ethers, in particular methylcellulose and ethylcellulose, hydroxyalkylcelluloses, in particular hydroxypropylcellulose, hydroxyalkylalkylcelluloses, in particular hydroxypropylmethylcellulose, cellulose phthalates or succinates, in particular cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate or hydroxypropylmethylcellulose acetate succinate;

and more preferably, in particular, hydroxypropylmethylcellulose.

high molecular polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide,

polyacrylates and polymethacrylates such as methacrylic acid/ethyl acrylate
5 copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates),
poly(hydroxyalkyl methacrylates),

polyacrylamides,

10 vinyl acetate polymers such as copolymers of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate (also referred to as partially saponified "polyvinyl alcohol"),

polyvinyl alcohol,

15 oligo- and polysaccharides such as carrageenans, galactomannans and xanthan gum, or mixtures of one or more thereof.

Of these, homopolymers or copolymers of N-vinyl pyrrolidone, in particular a
20 copolymer of N-vinyl pyrrolidone and vinyl acetate, are preferred. A particularly preferred polymer is a copolymer of about 60 % by weight of the copolymer, N-vinyl pyrrolidone and about 40 % by weight of the copolymer, vinyl acetate.

The dosage forms of the invention may contain at least one conventional additive,
25 such as flow regulators, lubricants, bulking agents (fillers) and disintegrants. In general, the additive is contained in an amount of about 0.01 to about 15 % by weight relative to the weight of the dosage form.

Various methods can be used for manufacturing the solid dosage forms according to
30 the invention. These methods comprise the preparation of a solid solution of the HIV protease inhibitor or the combination of HIV protease inhibitors in a matrix of the water-soluble

polymer and the surfactant, and shaping into the required tablet form. Alternatively, the solid solution product may be subdivided to granules, e.g. by grinding or milling, and the granules may subsequently be compacted to tablets.

5 Various techniques exist for preparing solid solutions including melt-extrusion, spray-drying and solution-evaporation with melt-extrusion being preferred.

10 The melt-extrusion process comprises the steps of preparing a homogeneous melt of the HIV protease inhibitor or the combination of HIV protease inhibitors, the water-soluble polymer and the surfactant, and cooling the melt until it solidifies. "Melting" means a transition into a liquid or rubbery state in which it is possible for one component to get embedded homogeneously in the other. Typically, one component will melt and the other components will dissolve in the melt thus forming a solution. Melting usually involves heating above the softening point of the water-soluble polymer. The preparation of the melt
15 can take place in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or be simultaneously mixed and melted. Usually, the melt is homogenized in order to disperse the active ingredients efficiently. Also, it may be convenient first to melt the water-soluble polymer and then to mix in and homogenize the active ingredients.

20

 Usually, the melt temperature is in the range of about 70 to about 250 °C, preferably from about 80 to about 180 °C, most preferred from about 100 to about 140 °C.

25 The active ingredients can be employed as such or as a solution or dispersion in a suitable solvent such as alcohols, aliphatic hydrocarbons or esters. Another solvent which can be used is liquid carbon dioxide. The solvent is removed, e.g. evaporated, upon preparation of the melt.

30 Various additives may be included in the melt, for example flow regulators such as colloidal silica; lubricants, fillers, disintegrants, plasticizers, stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

The melting and/or mixing takes place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders, intermeshing screw extruders or else multiscrew extruders, preferably twin screw
5 extruders, which can be corotating or counterrotating and, optionally, be equipped with kneading disks. It will be appreciated that the working temperatures will also be determined by the kind of extruder or the kind of configuration within the extruder that is used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, the friction and shearing of the material in the extruder may
10 also provide a substantial amount of energy to the mixture and aid in the formation of a homogeneous melt of the components.

The melt ranges from pasty to viscous. Shaping of the extrudate conveniently is carried out by a calender with two counter-rotating rollers with mutually matching
15 depressions on their surface. A broad range of tablet forms can be attained by using rollers with different forms of depressions. Alternatively, the extrudate is cut into pieces, either before (hot-cut) or after solidification (cold-cut).

Optionally, the resulting solid solution product is milled or ground to granules. The
20 granules may then be compacted. Compacting means a process whereby a powder mass comprising the granules is densified under high pressure in order to obtain a compact with low porosity, e.g. a tablet. Compression of the powder mass is usually done in a tablet press, more specifically in a steel die between two moving punches. Where a solid dosage form of the invention comprises a combination of more than one HIV protease inhibitor (or a
25 combination of an HIV protease inhibitor with one or more other active ingredients) it is of course possible to separately prepare solid solution products of the individual active ingredients and to blend the milled or ground products before compacting.

At least one additive selected from flow regulators, disintegrants, bulking agents
30 (fillers) and lubricants is preferably used in compacting the granules. Disintegrants promote a rapid disintegration of the compact in the stomach and keeps the granules which are liberated

separate from one another. Suitable disintegrants are crosslinked polymers such as crosslinked polyvinyl pyrrolidone and crosslinked sodium carboxymethylcellulose. Suitable bulking agents (also referred to as "fillers") are selected from lactose, calcium hydrogenphosphate, microcrystalline cellulose (Avicell®), silicates, in particular silicium dioxide, magnesium oxide, talc, potato or corn starch, isomalt, polyvinyl alcohol.

Suitable flow regulators are selected from highly dispersed silica (Aerosil®), and animal or vegetable fats or waxes.

A lubricant is preferably used in compacting the granules. Suitable lubricants are selected from polyethylene glycol (e.g., having a Mw of from 1000 to 6000), magnesium and calcium stearates, sodium stearyl fumarate, and the like.

Various other additives may be used, for example dyes such as azo dyes, organic or inorganic pigments such as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

Dosage forms according to the invention may be provided as dosage forms consisting of several layers, for example laminated or multilayer tablets. They can be in open or closed form. "Closed dosage forms" are those in which one layer is completely surrounded by at least one other layer. Multilayer forms have the advantage that two active ingredients which are incompatible with one another can be processed, or that the release characteristics of the active ingredient(s) can be controlled. For example, it is possible to provide an initial dose by including an active ingredient in one of the outer layers, and a maintenance dose by including the active ingredient in the inner layer(s). Multilayer tablets types may be produced by compressing two or more layers of granules. Alternatively, multilayer dosage forms may be produced by a process known as "coextrusion". In essence, the process comprises preparation of at least two different melt compositions as explained above, and passing these molten compositions into a joint coextrusion die. The shape of the coextrusion die depends on the

required drug form. For example, dies with a plain die gap, called slot dies, and dies with an annular slit are suitable.

In order to facilitate the intake of such a dosage form by a mammal, it is advantageous to give the dosage form an appropriate shape. Large tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape.

A film coat on the tablet further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. If desired, the film-coat may be an enteric coat. The film-coat usually includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. a Tween® type, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. The film coat usually accounts for less than about 5 % by weight of the dosage form.

The exact dose and frequency of administration depends on the particular condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art.

Exemplary compositions of the present invention for combined administration of ritonavir/ lopinavir are shown below in Table 1, and the values are % by weight.

25

Table 1. Exemplary compositions of the present invention

Ritonavir	18	4.17	4.17
Lopinavir	– 22.5 in total	16.67	16.67

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Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40)	65 - 75	71.16	70.12
Span 20 (Sorbitan monolaurate)	4 - 10	7.0	5.02
Cremophor RH40 (polyoxyethyleneglycerol oxystearate)	0 - 10	-	3.02
Colloidal silica	0 - 3	1.0	1.0

Exemplary compositions of the invention for administration of ritonavir only are shown below in Table 2. The values are % by weight.

5

Ritonavir	18 - 22.5	20.8
Lopinavir	-	-
Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40)	60 - 75	63.15
Span 20 (Sorbitan monolaurate)	5 -15	-
Cremophor RH40 (polyoxyethyleneglycerol oxystearate)	in total	10.00
PEG 6000	0 - 8	5.00
Colloidal silica	0 - 3	1.04

The above compositions are processed by melt extrusion. The resulting extrudates may be used as such or milled and compressed into tablets, preferably by the use of suitable
5 tableting aids such as sodium stearyl fumarate, colloidal silica, lactose, isomalt, calcium silicate, and magnesium stearate, cellulose or calcium hydrogenphosphate.

The following examples will serve to further illustrate the invention without limiting
it.

10

Protocol for the oral bioavailability studies

Dogs (beagle dogs, mixed sexes, weighing approximately 10 kg) received a balanced diet with 27 % fat and were permitted water ad libitum. Each dog received a 100 µg/kg
15 subcutaneous dose of histamine approximately 30 minutes prior to dosing. A single dose corresponding to about 200 mg lopinavir, about 50 mg ritonavir, or about 200 mg lopinavir and about 50 mg ritonavir, respectively, was administered to each dog. The dose was followed by approximately 10 milliliters of water. Blood samples were obtained from each animal prior to dosing and 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after drug
20 administration. The plasma was separated from the red cells by centrifugation and frozen (-30 °C) until analysis. Concentrations of HIV protease inhibitors were determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The area under the curve (AUC) was calculated by the trapezoidal method over the time course of the study. Each dosage form was evaluated in a group containing 8
25 dogs; the values reported are averages for each group of dogs.

Comparative example

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 78.17 parts by
30 weight) was mixed with ritonavir (4.16 parts by weight), lopinavir (16.67 parts by weight) and colloidal silica (1.0 part by weight). The powdery mixture was then fed into a twin-screw

extruder (screw diameter 18 mm) at a rate of 2.0 kg/h and a melt temperature of 133 °C. The clear, fully transparent melt was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1080 mg were thus obtained. DSC and WAXS analysis did not reveal any evidence of crystalline drug material in the formulation.

The dose-adjusted AUC in dogs was 0.52 µg.h/ml/100 mg for ritonavir and 4.54 µg.h/ml/100 mg for lopinavir. This example shows that solid solutions of HIV protease inhibitors without added surfactant yield a very poor bioavailability.

Example 1

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 68.17 parts by weight) was blended with Cremophor RH40 (polyoxyethyleneglycerol oxystearate; 10.00 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (4.17 parts by weight), lopinavir (16.67 parts by weight) and colloidal silica (1.00 parts by weight). The powdery mixture was then fed into a Leistritz Micro 18 twin-screw extruder at a rate of 2.3 kg/h and a melt temperature of 126 °C. The extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled using a high impact universal mill. The milled material (86.49 parts by weight) was blended in a bin blender with lactose monohydrate (6.00 parts by weight), crosslinked PVP (6.00 parts by weight), colloidal silica (1.00 part by weight) and magnesium stearate (0.51 parts by weight). The powdery blend was compressed to tablets of 1378.0 mg on a Fette E 1 single punch tablet press. The tablets were then film-coated in a coating pan by spraying an aqueous dispersion for film coating (Opadry, available from Colorcon) at a temperature of 60 °C.

The dose-adjusted AUC in dogs was 0.60 µg.h/ml/100 mg for ritonavir and 7.43 µg.h/ml/100 mg for lopinavir. This example shows that inclusion of a surfactant into solid solutions of HIV protease inhibitors improves the bioavailability attained.

Example 2

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 853.8 parts by weight) was blended with Span 20 (Sorbitan monolaurate; 83.9 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (50 parts by weight),
5 lopinavir (200 parts by weight) and colloidal silica (12 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 119 °C. The extrudate was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1120 mg were thus obtained.

10 The dose-adjusted AUC in dogs was 10.88 µg.h/ml/100 mg for ritonavir and 51.2 µg.h/ml/100 mg for lopinavir. This example shows that inclusion of a surfactant having an HLB of 4 to 10 into solid solutions of HIV protease inhibitors markedly improves the bioavailability attained.

15 Example 3

Example 2 was repeated, however, the extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled to a particle size of about 250 µm, using a high
20 impact universal mill. The milled material was blended in a bin blender with sodium stearyl fumarate (12.3 parts by weight) and colloidal silica (8.0 parts by weight) for 20 min. The powdery blend was compressed on a rotary tablet machine with 3 punches (6500 tablets/h). The tablets were then film-coated in a coating pan by spraying an aqueous dispersion for film coating (Opadry) at a temperature of 60 °C.

25 The dose-adjusted AUC in dogs was 14.24 µg.h/ml/100 mg for ritonavir and 52.2 µg.h/ml/100 mg for lopinavir.

30 Example 4

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 841.3 parts by weight) was blended with Cremophor RH40 (polyoxyethyleneglycerol oxystearate; 36.2 parts by weight), Span 20 (Sorbitan monolaurate; 60.2 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (50 parts by weight), lopinavir (200 parts by weight) and colloidal silica (12 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 114 °C. The extrudate was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1120 mg were thus obtained.

The dose-adjusted AUC in dogs was 10.96 µg.h/ml/100 mg for ritonavir and 46.5 µg.h/ml/100 mg for lopinavir. This example shows that a combination of a surfactant having an HLB of 4 to 10 and a further surfactant can successfully be used.

Example 5

Example 4 was repeated, however, the extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled to a particle size of about 250 µm, using a high impact universal mill. The milled material was blended in a bin blender with sodium stearyl fumarate (13.9 parts by weight), colloidal silica (7.0 parts by weight), isomalt DC100 (159.4 parts by weight) and calcium silicate (7.0 parts by weight) for 20 min. The blend was compressed and film-coated as described in example 1.

The dose-adjusted AUC in dogs was 10.38 µg.h/ml/100 mg for ritonavir and 42.7 µg.h/ml/100 mg for lopinavir.

Example 6

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 683.3 parts by weight) was blended with Span 40 (sorbitan monopalmitate; 67.2 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with lopinavir (200 parts by

weight) and colloidal silica (9.6 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 119 °C. The extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled using a high impact universal mill. The milled material was blended in a bin blender
5 with sodium stearyl fumarate (7.9 parts by weight), colloidal silica (11.3 parts by weight), isomalt DC100 (129.1 parts by weight) and sodium dodecyl sulfate (15.6 parts by weight). The blend was compressed and film-coated as described in example 1.

Tablets corresponding to 200 mg lopinavir were coadministered to dogs together with
10 50 mg ritonavir. The dose-adjusted AUC of lopinavir was 38.8 µg.h/ml/100 mg.

Example 7

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 151.5 parts by
15 weight) was blended with Cremophor RH40 (24 parts by weight) and PEG 6000 (12 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (50 parts by weight) and colloidal silica (2.4 parts by weight). The powdery mixture was then fed into a twin-screw extruder and was melt-extruded. The extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled using a high impact universal mill. The
20 milled material was blended in a bin blender with colloidal silica (1.4 parts by weight), isomalt DC100 (31.9 parts by weight) and calcium silicate (4.2 parts by weight). The blend was compressed and film-coated as described in example 1.

The dose-adjusted AUC_x in dogs was 9.98 µg.h/ml/100 mg.

We claim:

1. A solid pharmaceutical dosage form which comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C.
2. The dosage form of claim 1 comprising a glassy solution or solid solution of said HIV protease inhibitor.
3. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant has an HLB value of from about 4 to about 10.
4. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant is a combination of at least one pharmaceutically acceptable surfactant having an HLB value of from about 4 to about 10 and at least one further pharmaceutically acceptable surfactant.
5. The dosage form of Claim 1 wherein said pharmaceutically acceptable surfactant is a sorbitan fatty acid ester.
6. The dosage form of Claim 1 which comprises, relative to the weight of the dosage form, from about 5 to about 30 % by weight of said HIV protease inhibitor, from about 50 to about 85 % by weight of said water-soluble polymer, from about 2 to about 20 % by weight of said surfactant, and from about 0 to about 15 % by weight of additives.
7. The dosage form of claim 1, wherein said HIV protease inhibitor is selected from the group consisting of: 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir); (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydropyrimidin-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir); N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-

pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);
 N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginy]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);
 5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;
 1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4t-butylamide;
 5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;
 [1S-[1R-(R-),2S*])-N'-[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;
 amprenavir (VX-478); DMP-323; DMP-450; AG1343 (nelfinavir);
 atazanavir (BMS 232,632)
 tipranavir
 palinavir
 TMC-114
 RO033-4649
 fosamprenavir (GW433908)
 P-1946,
 BMS 186,318; SC-55389a; BILA 1096 BS; U-140690,
 or combinations thereof.

8. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).
9. The dosage form of Claim 8 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of ritonavir plasma concentration of at least about 9 µg.h/ml/100 mg.

10. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)-amino-3-hydroxy-5-[2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl]amino-1,6-diphenylhexane (lopinavir).
11. The dosage form of claim 10 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of lopinavir plasma concentration of at least about 20 $\mu\text{g.h/ml/100 mg}$.
12. The dosage form of claim 1 wherein said HIV protease inhibitor is a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydropyrimid-2-onyl)-3-methylbutanoyl] amino-1,6-diphenylhexane (lopinavir).
13. The dosage form of claim 12 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of ritonavir plasma concentration of at least 9 about $\mu\text{g.h/ml/100 mg}$ and a dose-adjusted AUC of lopinavir plasma concentration of at least about 20 $\mu\text{g.h/ml/100 mg}$.
14. The solid dosage form of Claim 1 wherein said water-soluble polymer has a Tg of from about 80 to about 180 °C.
15. The solid dosage form of Claim 1 wherein said water-soluble polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.
16. The solid dosage form of Claim 1 wherein said water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate.
17. The solid dosage form of Claim 1 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

18. The solid dosage form of Claim 1 which contains, upon storage for about 6 weeks at about 40 °C and about 75% humidity, at least about 98 % of the initial content of HIV protease inhibitor.
19. A method of preparing a solid dosage form of claim 1 which comprises:
- preparing a homogeneous melt of said HIV protease inhibitor(s), said water-soluble polymer(s) and said surfactant(s), and
 - allowing the melt to solidify to obtain a solid dispersion product.
20. The method of claim 19 additionally comprising grinding said solid dispersion product and compressing said solid dispersion product into a tablet.
21. A method of treating an HIV infection comprising administering the solid dosage form of claim 1 to a mammal in need of such treatment.
22. A solid pharmaceutical dosage form comprising,
- (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);
- a homopolymer of N-vinyl pyrrolidone; and
- a sorbitan fatty acid ester.
23. The solid dosage form of Claim 22 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.
24. A solid pharmaceutical dosage form comprising,
- (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir);
- a copolymer of N-vinyl pyrrolidone; and
- a sorbitan fatty acid ester.

25. The solid dosage form of Claim 24 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

26. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir);

a copolymer of N-vinyl pyrrolidone and vinyl acetate; and

a sorbitan fatty acid ester.

27. The solid dosage form of Claim 26 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

28. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) from about 5 % to about 30 % by weight of the dosage form;

a homopolymer of N-vinyl pyrrolidone from about 50 % to about 85 % by weight of the dosage form; and

a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

29. The solid dosage form of Claim 28 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

30. The solid dosage form of claim 29 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight.

31. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir) from about 5 % to about 30 % by weight of the dosage form;

a copolymer of N-vinyl pyrrolidone from about 50 % to about 85 % by weight of the dosage form; and

a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

32. The solid dosage form of Claim 31 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

33. The solid dosage form of claim 32 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight.

34. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir) present in an amount from about 5 % to about 30 % by weight of the dosage form;

a copolymer of N-vinyl pyrrolidone and vinyl acetate from about 50 % to about 85 % by weight of the dosage form; and

a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

35. The solid dosage form of Claim 34 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

36. The solid dosage form of claim 35 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight of the dosage form.

37. A method of treating an HIV infection comprising administering the solid dosage form of any one of claims 22-36 to a mammal in need of such treatment.

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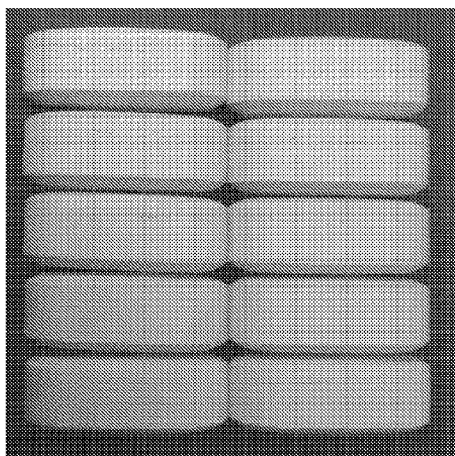


Figure 1A

(57) Abstract: The present invention features tablet dosage forms comprising two or more different active ingredients. In one embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises polymer-based solid dispersion particles having a mean particle size of no more than 200 μm .

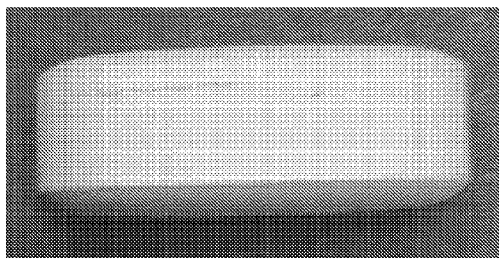


Figure 1B

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TABLET DOSAGE FORMS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to United States Provisional Application Serial No. 61/767,101, filed February 20, 2013, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to tablet dosage forms comprising two or more different active ingredients.

BACKGROUND

[0003] Kaletra[®] (marketed as Aluvia[®] in certain developing countries) is one of the most affordable and successful HIV protease inhibitors in the world. Kaletra contains co-formulated lopinavir and ritonavir, in which lopinavir is the primary HIV protease inhibitor, and ritonavir functions as a pharmacokinetic booster. Upon administration, ritonavir suppresses the CYP3A4-mediated lopinavir metabolism, thereby increasing the plasma concentration of lopinavir.

[0004] Prior to 2005, Kaletra was only available in liquid forms in which lopinavir and ritonavir were dissolved in organic solvents. These liquid formulations are unstable at high temperatures and therefore often require refrigerated storage conditions. Moreover, these formulations need to be taken with food in order to provide adequate bioavailability. For patients residing in economically challenged or developing countries, these requirements represent a particularly challenging dilemma.

[0005] After intensive research and major formulation breakthroughs, a heat-stable Kaletra tablet was developed and approved in 2005. This heat-stable Kaletra tablet contains 200 mg of lopinavir and 50 mg of ritonavir, and provides critically important advantages for patients in developing countries, including storage without refrigeration, no dietary restrictions, and lower pill burden.

[0006] Lamivudine (3TC) is a potent nucleoside analog reverse transcriptase inhibitor, and is commercially available as Epivir[®] tablet. One form of Epivir tablet contains 150 mg of crystalline lamivudine. Lamivudine is often given in combination with zidovudine, with which it is highly synergistic. Zidovudine (AZT) is another nucleoside analog reverse-transcriptase inhibitor. Combivir[®] tablet is a fixed dose combination containing 150 mg of crystalline lamivudine and 300 mg of crystalline zidovudine.

SUMMARY OF THE INVENTION

[0007] It has been particularly challenging to compress another layer of an active ingredient(s) to the Kaletra tablet core to make a bilayer tablet. Lopinavir and ritonavir are among the most difficult

to be formulated in solid dosage forms. In order to provide sufficient bioavailability to lopinavir/ritonavir, a significant amount of polymers is used to form an amorphous solid dispersion in which lopinavir and ritonavir are molecularly dispersed. When prepared using melt extrusion, the extrudate, which comprises the amorphous solid dispersion of lopinavir and ritonavir, is often milled, and the milled solid dispersion particles are then compressed, together with other additives, to form a tablet core. The use of the solid dispersion technology leads to a large tablet size. For instance, a Kaletra tablet containing 200 mg lopinavir and 50 mg ritonavir has a weight of at least 1,200 mg.

[0008] A bilayer tablet often requires the two layers of active ingredients to be of similar sizes in order to provide manufacturability and/or physical stability. For a bilayer tablet that contains a Kaletra tablet core, this would require that the other layer of active ingredient(s) have a weight comparable to 1,200 mg. This would create a bilayer tablet that is too large to be orally administered.

[0009] On the other hand, reducing the size of the other layer of active ingredient(s) has led to less manufacturability and/or physical stability. For instance, multiple attempts to compress 200-300 mg of another layer of active ingredient(s) against a 1,200 mg lopinavir/ritonavir tablet core have failed to produce a physically stable bilayer tablet. The bilayer tablets so prepared often showed severe cracking. See, for example, Figure 1.

[0010] It was surprisingly found that when the mean particle size of the solid dispersion particles used to prepare the lopinavir/ritonavir tablet core is reduced to less than 215 μm , the cracking in the bilayer tablets can be eliminated or significantly reduced. See, for example, Figure 2.

[0011] Accordingly, in one aspect, the present invention features a tablet dosage form comprising a first layer and a second layer. The first layer comprises compressed solid dispersion particles each of which comprises ritonavir and lopinavir formulated in a solid dispersion, said solid dispersion comprising a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant. The mean particle size of the solid dispersion particles is no more than 200 μm . Preferably, the mean particle size of the solid dispersion particles is no more than 190 μm . Also preferably, the mean particle size of the solid dispersion particles is no more than 180 μm . Also preferably, the mean particle size of the solid dispersion particles is from 120 to 200 μm . Also preferably, the mean particle size of the solid dispersion particles is from 120 to 190 μm . Also preferably, the mean particle size of the solid dispersion particles is from 120 to 180 μm . Also preferably, the mean particle size of the solid dispersion particles is from 140 to 160 μm . Also preferably, the mean particle size of the solid dispersion particles is from 160 to 180 μm . The second layer comprises another therapeutic agent, such as lamivudine or a combination of lamivudine and zidovudine.

[0012] The tablet dosage form preferably is a coated bilayer tablet.

[0013] The weight ratio of the second layer to the first layer preferably is no more than 1:2. More preferably, the weight ratio of the second layer to the first layer is no more than 1:3. Highly preferably, the weight ratio of the second layer to the first layer is no more than 1:4. Also highly preferably, the weight ratio of the second layer to the first layer is no more than 1:5. For example, the weight ratio of the second layer to the first layer is 1:5. For another example, the weight ratio of the second layer to the first layer is 1:6. For yet another example, the weight ratio of the second layer to the first layer is from 1:5 to 1:6.

[0014] The tablet dosage form preferably is no more than 1.6 g, and the first layer preferably is at least 1 g. For instance, the dosage form is no more than 1.6 g, and the first layer can be at least 1.1 g. For another instance, the dosage form is no more than 1.6 g, and the first layer can be at least 1.2 g. Preferably, the dosage form is from 1.4 to 1.6 g, and the first layer is from 1.1 to 1.3 g.

[0015] The first layer can constitute, for example, at least 60% by weight of the tablet dosage form. Preferably, the first layer constitutes at least 70% by weight of the tablet dosage form. More preferably, the first layer constitutes at least 75% by weight of the tablet dosage form. Also preferably, the first layer constitutes at least 85% by weight of the tablet dosage form.

[0016] Lopinavir and ritonavir in the first layer preferably are molecularly dispersed in the solid dispersion. Also preferably, the solid dispersion is an amorphous solid dispersion. More preferably, the solid dispersion is solid solution or glassy solution.

[0017] Lopinavir and ritonavir can, for example, be formulated in the same solid dispersion, solid solution or glassy solution. Lopinavir and ritonavir can also, for example, be separately formulated in different solid dispersions, solid solutions or glassy solutions, and then milled to the desired particle sizes and combined and compressed.

[0018] Suitable pharmaceutically acceptable polymers for use in the solid dispersion of the first layer preferably have a T_g of at least 50 °C. The first layer preferably contains at least 50% by weight of such a pharmaceutically acceptable polymer or a combination of such polymers. Preferably, the first layer contains from 50 to 80% by weight of such a polymer or a combination of such polymers. Also preferably, the first layer contains from 60 to 80% by weight of such a polymer or a combination of such polymers. Highly preferably, the first layer contains from 70 to 75% by weight of such a polymer or a combination of such polymers. As used herein, the term “% by weight”, when used in describing the amount of a component in a tablet layer, refers to the weight percentage of that component in that layer. Preferred polymers include, but are not limited to, copovidone.

[0019] Suitable pharmaceutically acceptable surfactants for use in the solid dispersion of the first layer include non-ionic surfactants which preferably have an HLB value of from 4 to 10. The first layer preferably contains from 2 to 20% by weight of such a surfactant, or a combination of such

surfactants, which has an HLB value of from 4 to 10. More preferably, the first layer contains from 5 to 15% by weight of such a surfactant, or a combination of such surfactants, which has an HLB value of from 4 to 10. Highly preferably, the first layer contains from 5 to 10% by weight of such a surfactant, or a combination of such surfactants, which has an HLB value of from 4 to 10. For example, the first layer can contain less than 10% by weight of such a surfactant, or a combination of such surfactants, which has an HLB value of from 4 to 10. Preferred surfactants include, but are not limited to, sorbitan monolaurate.

[0020] The second layer in a tablet dosage form of the invention comprises another therapeutic agent which is preferably mixed with other excipients. The therapeutic agent in the second layer can be formulated in solid dispersion, or in non-solid dispersion forms such as granules or physical mixtures with suitable excipients. The therapeutic agent in the second layer can be, for example and without limitation, in an amorphous form. The therapeutic agent can also be, for example and without limitation, in a crystalline form.

[0021] The therapeutic agent in the second layer can be, for example, an anti-HIV agent, such as a nucleoside reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, an integrase inhibitor, an entry or fusion inhibitor, or a combination thereof. Non-limiting examples of suitable anti-HCV agents include atazanavir, darunavir, amprenavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir, lamivudine, abacavir, stavudine, didanosine, zidovudine, emtricitabine, tenofovir, delavirdine, efavirenz, rilpivirine, etravirine, nevirapine, enfuvirtide, maraviroc, raltegravir, and pharmaceutically acceptable salts thereof, and any combinations thereof. The therapeutic agent in the second layer preferably comprises lamivudine. Also preferably, the therapeutic agent in the second layer comprises lamivudine and zidovudine. Other therapeutic agents, such as anti-HCV agents, can also be used and formulated in the second layer. In one example, the second layer comprises (1) from 0% to 75% by weight of microcrystalline cellulose, (2) from 0% to 50% by weight of lactose, (3) from 0.5% to 5% by weight of sodium starch glycolate, (4) from 0.1% to 2% by weight of sodium stearyl fumarate,; (5) from 0.2% to 3% by weight of colloidal silicon dioxide, and (6) from 0% to 75% by weight of hydroxypropyl cellulose.

[0022] In one embodiment, the first layer is 1.2 g, and the second layer is from 0.2 to 0.3 g.

[0023] In another embodiment, the first layer contains 200 mg lopinavir and 50 mg ritonavir, and the second layer preferably comprises 75 mg lamivudine.

[0024] In still another embodiment, the first layer contains 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 75 mg lamivudine and 150 mg zidovudine.

[0025] In yet another embodiment, the first layer comprises 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 200 mg raltegravir (or the corresponding amount of raltegravir salt, e.g., 217.2 mg raltegravir potassium).

[0026] In yet another embodiment, the first layer of a tablet dosage form of the invention comprises 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 75 mg lamivudine. With respect to lopinavir and lamivudine, the tablet dosage form is bioequivalent to a combination of a Kaletra tablet (200 mg lopinavir and 50 mg ritonavir per tablet) and one half of an Epivir tablet (150 mg lamivudine per tablet). Thus, with respect to lopinavir and lamivudine, two tablet dosage forms of this embodiment are bioequivalent to a combination of two Kaletra tablet (containing 200 mg lopinavir and 50 mg ritonavir per tablet) and one Epivir tablet (150 mg lamivudine per tablet). As used herein, a first dosage form is bioequivalent to a second dosage form (or a combination of dosage forms) with respect to an active ingredient if the 90% confidence intervals around the AUC_{∞} point estimate of the active ingredient in the first dosage form, relative to the second dosage form (or the combination of dosage forms), is within the range of from 80% to 125% when tested in a single dose study. A first dosage form is also considered bioequivalent to a second dosage form (or a combination of dosage forms) with respect to an active ingredient if the 90% confidence intervals around the AUC_t point estimate of the active ingredient in the first dosage form, relative to the second dosage form (or the combination of dosage forms), is within the range of from 80% to 125% when tested in a single or multiple dose study. In a single dose study, t can be from 24 to 36 hours, such as 24 or 36 hours. In a multiple dose study, t is one complete dosing interval. AUC_{∞} or AUC_t point estimates can be tested in either humans or dogs (e.g., beagles); preferably AUC_{∞} or AUC_t point estimates are determined in humans.

[0027] In yet another embodiment, the first layer of a tablet dosage form of the invention comprises 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 75 mg lamivudine and 150 mg zidovudine. With respect to lopinavir, lamivudine and zidovudine, the tablet dosage form is bioequivalent to a combination of a Kaletra tablet (200 mg lopinavir and 50 mg ritonavir per tablet) and one half of a Combivir tablet (150 mg lamivudine and 300 mg zidovudine per tablet). Thus, two tablet dosage forms of this embodiment are bioequivalent to a combination of two Kaletra tablets (200 mg lopinavir and 50 mg ritonavir per tablet) and one Combivir tablet (150 mg lamivudine and 300 mg zidovudine per tablet).

[0028] In yet another embodiment, the first layer comprises 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 200 mg raltegravir (or the corresponding amount of raltegravir salt, e.g., 217.2 mg raltegravir potassium). With respect to lopinavir and raltegravir, the tablet dosage form is bioequivalent to a combination of a Kaletra tablet (200 mg lopinavir and 50 mg

ritonavir per tablet) and one half of an Isentress[®] tablet (400 mg) (containing 434.4 mg raltegravir potassium per tablet). Thus, two tablet dosage forms of this embodiment are bioequivalent to a combination of two Kaletra tablets (200 mg lopinavir and 50 mg ritonavir per tablet) and one Isentress tablet (400 mg) (containing 434.4 mg raltegravir potassium per tablet).

[0029] Throughout this disclosure, features of a tablet dosage form of the invention may be described separately or in different examples, embodiments or preferences, e.g., the preferred mean particles sizes, the preferred weight ratios of the second layer over the first layer, the preferred pharmaceutically acceptable polymers or surfactants or their preferred amounts. The present invention contemplates tablet dosage forms with any combination of these separately described features.

[0030] In another aspect, the present invention features tablet dosage forms suitable for administration to pediatric patients. These pediatric tablet dosage forms often have the same composition as a tablet dosage form described herein, except that the amount of each ingredient is proportionally reduced. Preferably, the amount of each ingredient is reduced by half. For instance, the first layer of a pediatric tablet dosage form can comprise 100 mg lopinavir and 25 mg ritonavir, and the second layer comprises 37.5 mg lamivudine. For another instance, the first layer of a pediatric tablet dosage form can comprise 100 mg lopinavir and 25 mg ritonavir, and the second layer comprises 37.5 mg lamivudine and 75 mg zidovudine. Accordingly, each tablet dosage form of the invention can have a corresponding pediatric tablet dosage form in which the amount of each ingredient is reduced by half.

[0031] In yet another aspect, the present invention feature processes of making a tablet dosage form of the invention. The processes comprise compressing the first layer and the second layer into a bilayer.

[0032] In one embodiment, a process of the invention comprise (1) solidifying a homogeneous melt which comprises lopinavir, ritonavir, a pharmaceutically acceptable hydrophilic polymer as described herein and a pharmaceutically acceptable surfactant as described herein; (2) milling the solidified melt to a desired mean particle size as described herein; (3) adding the milled melt, optionally with other excipients, to a bilayer tablet press; (4) adding another pharmaceutical preparation comprising another therapeutic agent to the bilayer tablet press; and (5) compressing the milled melt and the other pharmaceutical preparation to form a bilayer tablet. The milled melt, optionally with the other excipients, forms the first layer of a tablet dosage form of the invention as described herein, while the other pharmaceutical preparation forms the second layer as described herein. Any tablet dosage form of the invention can be prepared according to this process. If needed, another layer(s) of active ingredient(s) can be further added.

[0033] In still another aspect, the present invention features a bottle of tablets of the invention, wherein no more than 10% of the tablets in the bottle show cracking. Preferably, no more than 5% of the tablets in the bottle show cracking. More preferably, no more than 2% of the tablets in the bottle show cracking. Highly preferably, no more than 1% of the tablets in the bottle show cracking. Most preferably, no tablet in the bottle shows cracking.

[0034] The present invention further features methods of treating HIV infection. The methods comprise administering a tablet dosage form of the invention to a HIV patient in need thereof.

[0035] In any aspect, preference, example or embodiment described herein, lopinavir and ritonavir in the first layer of a tablet dosage form of the invention can be readily replaced with another therapeutic agent(s). Therefore, the present invention also features such tablet dosage forms as well as their corresponding pediatric tablet dosage forms.

[0036] Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] The drawings are provided for illustration, not limitation.

[0038] Figure 1A illustrates the severe crack in the coated bilayer tablets. Each of the tablets comprises a lopinavir/ritonavir layer and a lamivudine layer and is coated with Color Yellow. The lopinavir/ritonavir layer comprises 200 mg lopinavir and 50 mg ritonavir which are dispersed in amorphous solid dispersion composed of copovidone and sorbitan monolaurate. The mean particle size of the lopinavir/ritonavir solid dispersion is about 210 μm . The total weight of the lopinavir/ritonavir layer is about 1,200 mg. The lamivudine layer comprises 75 mg lamivudine and has a total weight of about 200 mg. At least 50% of such coated tablets showed severe cracks. X-ray tomography showed that these cracks were not the bilayer interface. Instead, they started under the bilayer interface and extended into the lopinavir/ritonavir layer.

[0039] Figure 1B is an enlarged view of a tablet prepared as described in Figure 1A. Cracking was shown, which extended into the lopinavir/ritonavir layer.

[0040] Figure 2A shows coated bilayer tablets with the same composition as described in Figure 1A, except that the mean particle size of the lopinavir/ritonavir solid dispersion was no more than 180 μm . No cracking showed in these tablets.

[0041] Figure 2B is an enlarged view of a table prepared according to Figure 2A. No cracking was observed.

DETAILED DESCRIPTION

[0042] Combining lopinavir/ritonavir with another therapeutic agent (e.g., lamivudine, or lamivudine/zidovudine) in a solid, fixed-dose combination formulation that is bioequivalent or substantially similar in pharmacokinetic profiles to their respective individual tablet forms have not been successful. For instance, Epivir and Combivir tablets are immediate release formulations and can be prepared by blending crystalline lamivudine and zidovudine with other excipients. In contrast, Kaletra tablet is an erosion-based formulation and is prepared by dispersing lopinavir and ritonavir in a polymer-based matrix to form an amorphous solid dispersion. Therefore, when these two formulations are mixed together, the release profile of each active ingredient is expected to be significantly altered, thereby producing a composition that is unlikely bioequivalent or substantially similar to a combination of the respective individual tablet forms.

[0043] Combining Epivir or Combivir with Kaletra into a single, bilayer tablet has also been found exceedingly difficult. Kaletra tablet has a large tablet size due to the use of a large amount of polymers in order to confer adequate bioavailability to lopinavir and ritonavir. For instance, a Kaletra tablet containing 200 mg lopinavir and 50 mg ritonavir has a weight of at least 1,200 mg. A bilayer tablet often requires the two layers of active ingredients to be of similar sizes in order to provide manufacturability and/or physical stability. This would require the lamivudine or lamivudine/zidovudine layer to have a weight comparable to 1,200 mg, which would make the final product too large to be orally administered.

[0044] On the other hand, reducing the size of the lamivudine or lamivudine/zidovudine layer would lead to less manufacturability and/or physical stability. For instance, many attempts to compress a 200-300 mg lamivudine layer (containing 75 mg lamivudine) against a 1,200 mg lopinavir/ritonavir tablet core (containing 200 mg lopinavir and 50 mg ritonavir) have failed to produce a stable bilayer tablet.

[0045] It was unexpectedly found that when the mean particle size of the solid dispersion particles used to prepare the lopinavir/ritonavir tablet core is reduced to 200 μm or less, the cracking in the bilayer tablets can be eliminated or significantly reduced. Cf. Example 3 of U.S. Patent No. 8,025,899, which describes a post-extrusion process comprising milling the extrudates (which include a solid dispersion of lopinavir and ritonavir) to a particle size of about 250 μm , followed by compressing the milled extrudates into a tablet.

[0046] Accordingly, in one aspect, the present invention features a tablet dosage form comprising a first layer and a second layer. The first layer comprises compressed solid dispersion particles, each of which comprises ritonavir and lopinavir formulated in a solid dispersion, and said solid dispersion comprising a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant. The mean particle size of these solid dispersion particles is no more than 200 μm . Preferably, the mean particle size of these solid dispersion particles is no more than 190 μm . More preferably, the mean particle size of these solid dispersion particles is no more than 180 μm . Also preferably, the mean particle size of the solid dispersion particles is from 100 to 190 μm , such as from 110 to 190 μm , from 120 to 190 μm , from 130 to 190 μm , from 140 to 190 μm , from 150 to 190 μm , or from 160 to 190 μm . Also preferably, the mean particle size of the solid dispersion particles is from 100 to 180 μm , such as from 110 to 180 μm , from 120 to 180 μm , from 130 to 180 μm , from 140 to 180 μm , from 150 to 180 μm , or from 160 to 180 μm . Also preferably, the mean particle size of the solid dispersion particles is from 100 to 170 μm , such as from 110 to 170 μm , from 120 to 170 μm , from 130 to 170 μm , from 140 to 170 μm , or from 150 to 170 μm . Also preferably, the mean particle size of the solid dispersion particles is from 100 to 160 μm , such as from 110 to 160 μm , from 120 to 160 μm , from 130 to 160 μm , or from 140 to 160 μm .

[0047] The particle size distribution can be determined by sieve analysis or other means as appreciated by those skilled in the art. An exemplary sieve analysis involves the use of sieves with different opening sizes. The sieves can be assembled into a column with the top sieve having the widest openings and each lower sieve in the column having smaller openings than the one above. The column can be placed in a mechanical shaker. The shaker shakes the column for a pre-determined amount of time. After the shaking is complete, the material on each sieve is weighed. The weight of the sample of each sieve is then divided by the total weight to give a percentage retained on each sieve. The mean particle size (MPS) can be calculated using the following equation:

$$MPS = \frac{C_1 - 50\%}{C_1 - C_2} \times (S_2 - S_1) + S_1$$

where C_1 is the accumulated percentage of particles just larger than 50%; C_2 is the accumulated percentage of particles just smaller than 50%; S_1 is the size of particles which has an accumulated percentage just larger than 50%, and S_2 is the size of the particles which have an accumulated percentage just smaller than 50%.

[0048] The second layer in a tablet dosage form of this aspect of the invention comprises another therapeutic agent, such as lamivudine or a combination of lamivudine and zidovudine. The therapeutic agent preferably is mixed with suitable excipients. The therapeutic agent in the second layer can be formulated in solid dispersion, or in non-solid dispersion forms such as granules or

physical mixtures with other excipients. The therapeutic agent in the second layer can be, for example and without limitation, in an amorphous form. The therapeutic agent can also be, for example and without limitation, in a crystalline form.

[0049] A tablet dosage form of this aspect of the invention preferably is a coated bilayer tablet. The tablet dosage form can also include a third layer of yet another active ingredient, or two or more layers of other active ingredients.

[0050] The weight ratio of the second layer to the first layer according to this aspect of the invention preferably is no more than 1:2. More preferably, the weight ratio of the second layer to the first layer is no more than 1:3. Highly preferably, the weight ratio of the second layer to the first layer is no more than 1:4. Also highly preferably, the weight ratio of the second layer to the first layer is no more than 1:5. For example, the weight ratio of the second layer to the first layer is 1:5. For another example, the weight ratio of the second layer to the first layer is 1:6. For yet another example, the weight ratio of the second layer to the first layer is from 1:3 to 1:6. For yet another example, the weight ratio of the second layer to the first layer is from 1:4 to 1:6. For yet another example, the weight ratio of the second layer to the first layer is from 1:5 to 1:6.

[0051] A tablet dosage form of this aspect of the invention can be, for example and without limitation, from 1.3 g to 1.7 g, and the first layer can be, for example and without limitation, from 0.9 g to 1.2 g. For instance, the tablet dosage form can be from 1.3 g to 1.5 g, and the first layer is from 1.0 g to 1.2 g. For instance, the tablet dosage form can be from 1.4 g to 1.6 g, and the first layer is from 1.1 g to 1.3 g. In one example, the tablet dosage form is no more than 1.7 g, and the first layer is at least 1 g. In another example, the tablet dosage form can be no more than 1.6 g, and the first layer is at least 1 g. In another yet example, the tablet dosage form can be no more than 1.5 g, and the first layer is at least 1 g. In yet another example, the tablet dosage form is no more than 1.7 g, and the first layer is at least 1.1 g. In yet another example, the tablet dosage form is no more than 1.6 g, and the first layer is at least 1.1 g. In yet another example, the tablet dosage form is no more than 1.5 g, and the first layer is at least 1.1 g. In yet another example, the tablet dosage form is no more than 1.7 g, and the first layer is at least 1.2 g. In yet another example, the tablet dosage form is no more than 1.6 g, and the first layer is at least 1.2 g. In yet another example, the tablet dosage form is no more than 1.5 g, and the first layer is at least 1.2 g. In yet another example, the tablet dosage form is no more than 1.7 g, and the first layer is from 1.0 g to 1.3 g. In another example, the tablet dosage form is no more than 1.7 g, and the first layer is at from 1.0 g to 1.2 g. In yet another example, the tablet dosage form is no more than 1.7 g, and the first layer is from 1.0 g to 1.1 g. In yet another example, the tablet dosage form is no more than 1.7 g, and the first layer is from 1.1 g to 1.3 g. In yet another example, the tablet dosage form is no more than 1.7 g, and the first layer is from 1.1 g to 1.2 g. In yet

another example, the tablet dosage form is no more than 1.6 g, and the first layer is from 1.0 g to 1.3 g. In another example, the tablet dosage form is no more than 1.6 g, and the first layer is at from 1.0 g to 1.2 g. In yet another example, the tablet dosage form is no more than 1.6 g, and the first layer is from 1.0 g to 1.1 g. In yet another example, the tablet dosage form is no more than 1.6 g, and the first layer is from 1.1 g to 1.3 g. In yet another example, the tablet dosage form is no more than 1.6 g, and the first layer is from 1.1 g to 1.2 g. In yet another example, the tablet dosage form is no more than 1.5 g, and the first layer is from 1.0 g to 1.3 g. In another example, the tablet dosage form is no more than 1.5 g, and the first layer is at from 1.0 g to 1.2 g. In yet another example, the tablet dosage form is no more than 1.5 g, and the first layer is from 1.0 g to 1.1 g. In yet another example, the tablet dosage form is no more than 1.5 g, and the first layer is from 1.1 g to 1.3 g. In yet another example, the tablet dosage form is no more than 1.5 g, and the first layer is from 1.1 g to 1.2 g.

[0052] Preferably, the dosage form is from 1.4 to 1.6 g, and the first layer is from 1.1 to 1.3 g. Also preferably, the dosage form is from 1.4 to 1.6 g, and the first layer is from 1.2 to 1.3 g.

[0053] The first layer can comprise, for example, at least 60% by weight of the tablet dosage form. Preferably, the first layer comprises at least 70% by weight of the tablet dosage form. More preferably, the first layer comprises at least 75% by weight of the tablet dosage form. Also preferably, the first layer comprises at least 85% by weight of the tablet dosage form. In one example, the first layer comprises from 60 to 90% by weight of the tablet dosage form. In another example, the first layer comprises from 70 to 90% by weight of the tablet dosage form. In another example, the first layer comprises from 80 to 90% by weight of the tablet dosage form. In another example, the first layer comprises from 60 to 80% by weight of the tablet dosage form. In another example, the first layer comprises from 70 to 80% by weight of the tablet dosage form.

[0054] Lopinavir and ritonavir in the first layer preferably are molecularly dispersed in the solid dispersion. Also preferably, the solid dispersion is an amorphous solid dispersion. More preferably, the solid dispersion is solid solution or glassy solution.

[0055] Lopinavir and ritonavir can, for example, be formulated in the same solid dispersion, solid solution or glassy solution. Lopinavir and ritonavir can also, for example, be separately formulated in different solid dispersions, solid solutions or glassy solutions, and then milled to the desired particle sizes and mixed.

[0056] In one embodiment, the first layer preferably includes a solid dispersion, where the solid dispersion comprises ritonavir, lopinavir, the pharmaceutically acceptable hydrophilic polymer, and the pharmaceutically acceptable surfactant.

[0057] In another embodiment, the first layer comprises a solid solution, where the solid solution comprises ritonavir, lopinavir, the hydrophilic polymer, and the surfactant.

[0058] In still another embodiment, the first layer comprises a glassy solution, where the glassy solution comprises ritonavir, lopinavir, the hydrophilic polymer, and the surfactant.

[0059] In yet another embodiment, the first layer comprises a first and second solid dispersions (i.e., a lopinavir solid dispersion and a ritonavir solid dispersion, respectively), wherein the first solid dispersion comprises lopinavir and a first pharmaceutically acceptable hydrophilic polymer, and the second solid dispersion comprises ritonavir and a second pharmaceutically acceptable hydrophilic polymer, and the first layer also contains a pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different.

[0060] In yet another embodiment, the first layer comprises a first and second solid dispersions (i.e., a lopinavir solid dispersion and a ritonavir solid dispersion, respectively), wherein the first solid dispersion comprises lopinavir, a first pharmaceutically acceptable hydrophilic polymer, and a first pharmaceutically acceptable surfactant, and the second solid dispersion comprises ritonavir, a second pharmaceutically acceptable hydrophilic polymer, and a second pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different; and the first and second surfactants can also be the same or different.

[0061] In yet another embodiment, the first layer comprises a first and second solid solutions (i.e., a lopinavir solid solution and a ritonavir solid solution, respectively), wherein the first solid solution comprises lopinavir and a first pharmaceutically acceptable hydrophilic polymer, and the second solid solution comprises ritonavir and a second pharmaceutically acceptable hydrophilic polymer, and the first layer also contains a pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different.

[0062] In yet another embodiment, the first layer comprises a first and second solid solutions (i.e., a lopinavir solid solution and a ritonavir solid solution, respectively), wherein the first solid solution comprises lopinavir, a first pharmaceutically acceptable hydrophilic polymer, and a first pharmaceutically acceptable surfactant, and the second solid solution comprises ritonavir, a second pharmaceutically acceptable hydrophilic polymer, and a second pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different; and the first and second surfactants can also be the same or different.

[0063] In still another embodiment, the first layer comprises a first and second glassy solutions (i.e., a lopinavir glassy solution and a ritonavir glassy solution, respectively), wherein the first glassy solution comprises lopinavir and a first pharmaceutically acceptable hydrophilic polymer, and the second glassy solution comprises ritonavir and a second pharmaceutically acceptable hydrophilic polymer, and the first layer also contains a pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different.

[0064] In yet another embodiment, the first layer comprises a first and second glassy solutions (i.e., a lopinavir glassy solution and a ritonavir glassy solution, respectively), wherein the first glassy solution comprises lopinavir, a first pharmaceutically acceptable hydrophilic polymer, and a first pharmaceutically acceptable surfactant, and the second glassy solution comprises ritonavir, a second pharmaceutically acceptable hydrophilic polymer, and a second pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different; and the first and second surfactants can also be the same or different.

[0065] A solid dispersion employed in this aspect of the invention preferably comprises or consists of a single-phase (defined in thermodynamics) in which lopinavir and/or ritonavir, together with the pharmaceutically acceptable hydrophilic polymer and/or the pharmaceutically acceptable surfactant, are molecularly dispersed. In such cases, thermal analysis of the solid dispersion using differential scanning calorimetry (DSC) typically shows only one single glass transition temperature (T_g), and the solid dispersion does not contain any detectable crystalline lopinavir or ritonavir as measured by X-ray powder diffraction spectroscopy.

[0066] In one embodiment of this aspect of the invention, the first layer contains 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 75 mg lamivudine.

[0067] In still another embodiment, the first layer contains 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 75 mg lamivudine and 150 mg zidovudine.

[0068] In yet another embodiment, the first layer comprises 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 200 mg raltegravir (or the corresponding amount of raltegravir salt, e.g., 217.2 mg raltegravir potassium).

[0069] In yet another embodiment, the first layer of a tablet dosage form of the invention comprises 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 75 mg lamivudine. With respect to lopinavir and lamivudine, the tablet dosage form is bioequivalent to a combination of a Kaletra tablet (200 mg lopinavir and 50 mg ritonavir per tablet) and one half of an Epivir tablet (150 mg lamivudine per tablet). Thus, with respect to lopinavir and lamivudine, two tablet dosage forms of this embodiment are bioequivalent to a combination of two Kaletra tablet (containing 200 mg lopinavir and 50 mg ritonavir per tablet) and one Epivir tablet (150 mg lamivudine per tablet).

[0070] In yet another embodiment, the first layer of a tablet dosage form of the invention comprises 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 75 mg lamivudine and 150 mg zidovudine. With respect to lopinavir, lamivudine and zidovudine, the tablet dosage form is bioequivalent to a combination of a Kaletra tablet (200 mg lopinavir and 50 mg ritonavir per tablet) and one half of a Combivir tablet (150 mg lamivudine and 300 mg zidovudine per tablet). Thus, two tablet dosage forms of this embodiment are bioequivalent to a combination of two Kaletra

tablets (200 mg lopinavir and 50 mg ritonavir per tablet) and one Combivir tablet (150 mg lamivudine and 300 mg zidovudine per tablet).

[0071] In yet another embodiment, the first layer comprises 200 mg lopinavir and 50 mg ritonavir, and the second layer comprises 200 mg raltegravir (or the corresponding amount of raltegravir salt, e.g., 217.2 mg raltegravir potassium). With respect to lopinavir and raltegravir, the tablet dosage form is bioequivalent to a combination of a Kaletra tablet (200 mg lopinavir and 50 mg ritonavir per tablet) and one half of an Isentress[®] tablet (400 mg) (containing 434.4 mg raltegravir potassium per tablet). Thus, two tablet dosage forms of this embodiment are bioequivalent to a combination of two Kaletra tablets (200 mg lopinavir and 50 mg ritonavir per tablet) and one Isentress tablet (400 mg) (containing 434.4 mg raltegravir potassium per tablet).

[0072] In another embodiment, a tablet dosage form comprises a first layer and a second layer, wherein the first layer comprises 200 mg lopinavir and 50 mg ritonavir and constitutes at least 70% by weight of the total dosage form, and the second layer comprises 75 mg lamivudine. The first layer comprises (i) at least 50% by weight a pharmaceutically acceptable hydrophilic polymer, and (ii) a pharmaceutically acceptable surfactant. The total weight of the tablet is no more than 1700 mg. Preferably, the tablet is no more than 1600 mg. More preferably, the tablet is no more than 1500 mg.

[0073] In yet another embodiment, a tablet dosage form comprises a first layer and a second layer, wherein the first layer comprises 200 mg lopinavir and 50 mg ritonavir and constitutes at least 70% by weight of the total dosage form, and the second layer comprises 75 mg lamivudine and 150 mg zidovudine. The first layer comprises (i) at least 50% by weight a pharmaceutically acceptable hydrophilic polymer, and (ii) a pharmaceutically acceptable surfactant. The total weight of the tablet is no more than 1700 mg. Preferably, the tablet is no more than 1600 mg.

[0074] A pharmaceutically acceptable salt of lopinavir or a pharmaceutically acceptable salt of ritonavir can be used, instead of lopinavir or ritonavir, respectively, in the first layer.

[0075] The other therapeutic agent in the second layer can be, for example and without limitation, an anti-HIV agent, an anti-HCV agent, or another anti-viral agent. Non-limiting examples of the other therapeutic agent include anti-HIV agents, such as lamivudine, zidovudine, didanosine, abacavir, efavirenz, emtricitabine, tenofovir, stavudine, delavirdine, rilpivirine, etravirine, nevirapine, enfuvirtide, maraviroc, raltegravir, dolutegravir, lersivirine, atazanavir, darunavir, amprenavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir, or a pharmaceutically acceptable salt thereof, or a combination of two or more of the above agents or their respective salts (e.g., a combination of lamivudine and zidovudine, a combination of abacavir, lamivudine and zidovudine, a combination of efavirenz, emtricitabine and tenofovir, a combination of emtricitabine and tenofovir, or a combination of emtricitabine, rilpivirine and tenofovi). Other non-limiting examples of the other

therapeutic agent in the second layer include anti-HCV agents, such as NM-811 (Novartis), SCY-635 (Scynexis), ITX-4520 (iTherx), ITX-5061 (iTherx), ANA-773 (Anadys), ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), setrobuvir, BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), ACH-2928 (Achillion), AZD2836 (Astra-Zeneca), AZD7295 (Astra-Zeneca), BMS-790052 (BMS), BMS-824393 (BMS), EDP-239 (Enanta), GS-5885 (Gilead), PPI-1301 (Presidio), PPI-461 (Presidio), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), ABT-450 (Abbott/Enanta), ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BI-201335 (Boehringer Ingelheim), BMS-650032 (BMS), boceprevir, danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), CTS-1027 (Conatus), GS-9620 (Gilead), PF-4878691 (Pfizer), RO5303253 (Roche), ALS-2200, ALS-2158, GSK62336805, or a pharmaceutically acceptable salt thereof, or a combination of two or more of the above agents or their respective salts.

[0076] The amount of the other therapeutic agent in the second layer can range, for example and without limitation, from 10 mg to 300 mg, such as from 50 mg to 200 mg.

[0077] Preferably, the other therapeutic agent in the second layer is a HIV reverse transcriptase inhibitors (e.g., lamivudine or zidovudine), a HIV integrase (e.g., raltegravir or dolutegravir), a HIV entry inhibitor (e.g., enfuvirtide or maraviroc), or a combination thereof (e.g., a combination of lamivudine and zidovudine, a combination of abacavir, lamivudine and zidovudine, a combination of efavirenz, emtricitabine and tenofovir, a combination of emtricitabine and tenofovir, or a combination of emtricitabine, rilpivirine and tenofovir). More preferably, the other therapeutic agent in the second layer comprises lamivudine. In one embodiment, the second layer comprises, in addition to the other therapeutic agent as described above, (1) from 0% to 75% by weight of microcrystalline cellulose, (2) from 0% to 50% by weight of lactose, (3) from 0.5% to 5% by weight of sodium starch glycolate, (4) from 0.1% to 2% by weight of sodium stearyl fumarate,; (5) from 0.2% to 3% by weight of colloidal silicon dioxide, and (6) from 0% to 75% by weight of hydroxypropyl cellulose.

[0078] A pharmaceutically acceptable hydrophilic polymers employed in the first layer of a tablet dosage form of the invention preferably have a T_g of at least 50 °C. More preferably, the hydrophilic

polymer has a T_g of at least 60 °C, such as at least 80 °C, at least 100 °C, or from 80 °C to 180 °C, or from 100 °C to 150 °C. Hydrophilic polymers with a T_g as described above allow for the preparation of solid dispersions that are mechanically stable and, within ordinary temperature ranges, sufficiently temperature stable. Hydrophilic polymers having a T_g of below 50 °C may also be included.

[0079] A pharmaceutically acceptable hydrophilic polymer employed in the first layer of a tablet dosage form of the invention preferably is water-soluble. The first layer may also include a poorly water-soluble or water-insoluble polymer, such as a cross-linked polymer. A hydrophilic polymer employed in the first layer preferably has an apparent viscosity, when dissolved at 20 °C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa·s, and more preferably of 1 to 700 mPa·s, and most preferably of 5 to 100 mPa·s.

[0080] Pharmaceutically acceptable hydrophilic polymers that are suitable for use in the first layer include, but are not limited to, homopolymers or copolymers of N-vinyl lactams, such as homopolymers or copolymers of N-vinyl pyrrolidone (e.g., polyvinylpyrrolidone (PVP), or copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate); cellulose esters or cellulose ethers, such as alkylcelluloses (e.g., methylcellulose or ethylcellulose), hydroxyalkylcelluloses (e.g., hydroxypropylcellulose), hydroxyalkylalkylcelluloses (e.g., hydroxypropylmethylcellulose), and cellulose phthalates or succinates (e.g., cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, or hydroxypropylmethylcellulose acetate succinate); high molecular polyalkylene oxides, such as polyethylene oxide, polypropylene oxide, and copolymers of ethylene oxide and propylene oxide; polyacrylates or polymethacrylates, such as methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), and poly(hydroxyalkyl methacrylates); polyacrylamides; vinyl acetate polymers, such as copolymers of vinyl acetate and crotonic acid, and partially hydrolyzed polyvinyl acetate (also referred to as partially saponified “polyvinyl alcohol”); polyvinyl alcohol; oligo- or polysaccharides, such as carrageenans, galactomannans, and xanthan gum; polyhydroxyalkylacrylates; polyhydroxyalkyl-methacrylates; copolymers of methyl methacrylate and acrylic acid; polyethylene glycols (PEGs); or any mixture thereof.

[0081] Non-limiting examples of suitable hydrophilic polymers include polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid

copolymer (Eudragit®) L100-55, Eudragit L100, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.

[0082] Of these, homopolymers or copolymers of N-vinyl pyrrolidone, such as copolymers of N-vinyl pyrrolidone and vinyl acetate, are preferred. A non-limiting example of a preferred polymer is a copolymer of 60 % by weight of N-vinyl pyrrolidone and 40 % by weight of vinyl acetate. Other preferred polymers include, without limitation, hydroxypropyl methylcellulose (HPMC, also known as hypromellose in USP), such as hydroxypropyl methylcellulose grade E5 (HPMC-E5); and hydroxypropyl methylcellulose acetate succinate (HPMC-AS).

[0083] Preferably, the first layer in a tablet dosage form of the invention comprises at least 50% by weight of a pharmaceutically acceptable hydrophilic polymer or polymers. More preferably, the first layer comprises at least 60% by weight of a pharmaceutically acceptable hydrophilic polymer or polymers. Highly preferably, the first layer comprises at least 70% weight of a pharmaceutically acceptable hydrophilic polymer or polymers. In one embodiment, the first layer comprises from 50 to 80% weight of a pharmaceutically acceptable hydrophilic polymer or polymers. In another embodiment, the first layer comprises from 60 to 80% weight of a pharmaceutically acceptable hydrophilic polymer or polymers. In another embodiment, the first layer comprises from 65 to 75% weight of a pharmaceutically acceptable hydrophilic polymer or polymers. In another embodiment, the first layer comprises from 70 to 75% weight of a pharmaceutically acceptable hydrophilic polymer or polymers.

[0084] In each aspect, example, embodiment and preference described herein, sugar alcohols or other binders may be used in addition to, or in lieu of, hydrophilic polymers in the first layer.

[0085] A pharmaceutically acceptable surfactant employed in the first layer of a tablet dosage form of the invention preferably is a non-ionic surfactant. More preferably, a pharmaceutically acceptable, non-ionic surfactant employed in the first layer has an HLB value of from 4 to 10. For instance, the surfactant can have an HLB value of from 7 to 9. A surfactant having an HLB value other than 4-10, such as a surfactant having an HLB value of below or above 10, may also be used. As used herein, a surfactant encompasses a mixture or combination of two or more different surfactants.

[0086] Pharmaceutically acceptable surfactants that are suitable for use in the first layer include, but are not limited to, polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester, and sorbitan fatty acid mono ester. Non-limiting examples of suitable surfactants include polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5)

stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate (e.g., Lauroglycol®);, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan mono laurate (e.g., Span® 20), sorbitan monooleate, sorbitan monopalmitate (e.g., Span® 40), sorbitan stearate, or mixtures of one or more thereof.

[0087] The sorbitan mono fatty acid esters are preferred, with sorbitan mono laurate and sorbitan mono palmitate being particularly preferred.

[0088] Other pharmaceutically acceptable surfactants that may be used in the first layer include, but are not limited to, polyoxyethylene castor oil derivatives, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethyleneglycol 40 hydrogenated castor oil (Cremophor® RH 40) or polyethyleneglycol 60 hydrogenated castor oil (Cremophor® RH 60); or block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene polypropyleneglycol, such as Poloxamer® 124, Poloxamer® 188, Poloxamer® 237, Poloxamer® 388, Poloxamer® 407 (BASF Wyandotte Corp.); or a mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan mono oleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan mono palmitate (Tween® 40), polyoxyethylene (20) sorbitan monolaurate (Tween® 20).

[0089] In one embodiment, the first layer comprises two or more surfactants, wherein the surfactant(s) having an HLB value of from 4 to 10 accounts for at least 50% by weight, preferably at least 60% by weight, of the total amount of surfactants used in the first layer.

[0090] The first layer preferably comprises at least 1% by weight of a pharmaceutically acceptable surfactant. More preferably, the first layer comprises at least 2% by weight of a pharmaceutically acceptable surfactant. Highly preferably, the first layer comprises at least 5% by weight of a pharmaceutically acceptable surfactant. In one embodiment, the first layer comprise from 2% to 20% by weight of a pharmaceutically acceptable surfactant. In another embodiment, the first layer comprise from 4% to 20% by weight of a pharmaceutically acceptable surfactant. In another embodiment, the first layer comprise from 5% to 15% by weight of a pharmaceutically acceptable surfactant. In another embodiment, the first layer comprise from 5% to 10% by weight of a pharmaceutically acceptable surfactant. In yet another embodiment, the first layer contains from 2 to 20% by weight of a pharmaceutically acceptable surfactant, or a combination of such surfactants, which has an HLB value of from 4 to 10. In another embodiment, the first layer contains from 5 to 15%

by weight of a pharmaceutically acceptable surfactant, or a combination of such surfactants, which has an HLB value of from 4 to 10. In another embodiment, the first layer contains from 5 to 10% by weight of a pharmaceutically acceptable surfactant, or a combination of such surfactants, which has an HLB value of from 4 to 10.

[0091] The first layer can, for example and without limitation, contain less than 10% by weight of a pharmaceutically acceptable surfactant, or a combination of such surfactants, which has an HLB value of from 4 to 10.

[0092] Features of a tablet dosage form of the invention may be described separately or in different aspects, examples, embodiments or preferences, e.g., the preferred mean particles sizes, the preferred weight ratios of the second layer over the first layer, the preferred pharmaceutically acceptable polymers or surfactants or their preferred amounts. However, the present invention contemplates tablet dosage forms with any combination of these features of different aspects, embodiments, examples or preferences.

[0093] In one embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.7 g, and the first layer is at least 1 g. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a T_g of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer).

[0094] In yet another embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.6 g, and the first layer is at least 1

g. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a T_g of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer).

[0095] In another embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.5 g, and the first layer is at least 1 g. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a T_g of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer).

[0096] In still another embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.5 g, and the first layer is at least 1.1 g. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution

comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a Tg of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer).

[0097] In yet another embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.6 g, and the weight ratio of the first layer over the second layer is no less than 3:1. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a Tg of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer). The first layer is also preferably at least 1.1 g.

[0098] In yet another embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.6 g, and the weight ratio of the first layer over the second layer is no less than 4:1. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a Tg of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the

surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer). The first layer is also preferably at least 1.1 g.

[0099] In yet another embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.6 g, and the weight ratio of the first layer over the second layer is no less than 5:1. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a Tg of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer). The first layer is also preferably at least 1.1 g.

[00100] In yet another embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.5 g, and the weight ratio of the first layer over the second layer is no less than 3:1. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a Tg of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the

hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer). The first layer is also preferably at least 1.1 g.

[0100] In yet another embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.5 g, and the weight ratio of the first layer over the second layer is no less than 4:1. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a Tg of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer). The first layer is also preferably at least 1.1 g.

[0101] In yet another embodiment, a tablet dosage form of the invention comprises a first layer and a second layer, wherein the first layer comprises a pharmaceutically acceptable hydrophilic polymer, a pharmaceutically acceptable surfactant, 50 mg ritonavir and 200 mg lopinavir, in solid dispersion particles with a desired mean particle size as described herein, and wherein the second layer comprises another therapeutic agent (e.g., 75 mg lamivudine, or a combination of 75 mg lamivudine and 150 mg zidovudine). The tablet is no more than 1.5 g, and the weight ratio of the first layer over the second layer is no less than 5:1. Preferably, lopinavir and ritonavir in the first layer are formulated in solid dispersion comprising the hydrophilic polymer and the surfactant; more preferably, lopinavir and ritonavir in the first layer are formulated in solid solution comprising the hydrophilic polymer and the surfactant; highly preferably, lopinavir and ritonavir in the first layer are formulated in glassy solution comprising the hydrophilic polymer and the surfactant. The hydrophilic polymer preferably has a Tg of at least 50 °C; and more preferably, the hydrophilic polymer is copovidone. The surfactant preferably has a HLB value of from 4 to 10; and more preferably, the surfactant is sorbitan mono laurate. The first layer preferably comprises at least 50% by weight of the hydrophilic polymer (e.g., from 65 to 75% by weight of the hydrophilic polymer). The first layer is also preferably at least 1.1 g.

[0102] Where the first layer comprises 200 mg lopinavir and the second layer comprises 75 mg lamivudine, the tablet dosage form preferably is bioequivalent, with respect to lopinavir and lamivudine, to a combination of a Kaletra tablet (200 mg lopinavir and 50 mg ritonavir per tablet) and one half of an Epivir tablet (150 mg lamivudine per tablet); or two such tablet dosage forms preferably are bioequivalent, with respect to lopinavir and lamivudine, to a combination of two Kaletra tablets (200 mg lopinavir and 50 mg ritonavir per tablet) and one Epivir tablet (150 mg lamivudine per tablet). Where the first layer comprises 200 mg lopinavir and the second layer comprise a combination of 75 mg lamivudine and 150 mg zidovudine, the tablet dosage form preferably is bioequivalent, with respect to lopinavir, lamivudine and zidovudine, to a combination of a Kaletra tablet (200 mg lopinavir and 50 mg ritonavir per tablet) and one half of an Combivir tablet (150 mg lamivudine and 300 mg zidovudine per tablet); or two such tablet dosage forms preferably are bioequivalent, with respect to lopinavir, lamivudine and zidovudine, to a combination of two Kaletra tablet (200 mg lopinavir and 50 mg ritonavir per tablet) and one Combivir tablet (150 mg lamivudine and 300 mg zidovudine per tablet).

[0103] The first and second layers of a tablet dosage form of the invention can be prepared by a variety of techniques such as, without limitation, granulation (e.g., wet or dry granulation), blending, melt-extrusion, spray-drying, co-precipitation, freeze drying, or other solvent evaporation or solid dispersion techniques, with melt-extrusion and spray-drying being preferred for the preparation of the first layer.

[0104] Melt-extrusion and spray-drying are non-limiting examples that are suitable for making solid dispersions. Powdery solid dispersions can be, for example, directly compressed to form the first layer of a tablet dosage form of the invention. Non-powdery solid dispersions can be, for example, milled or ground to small particles before being compressed. Additional ingredients or excipients may be mixed with the solid dispersions before grinding and/or compression.

[0105] The melt-extrusion process typically comprises (1) preparing a melt which includes the active ingredient(s) (e.g., lopinavir and/or ritonavir), a pharmaceutically acceptable hydrophilic polymer as described above, and preferably a pharmaceutically acceptable surfactant as described above, and (2) cooling the melt until it solidifies. Melting often involves a transition into a liquid or rubbery state in which it is possible for one component to get dissolved or embedded, preferably homogeneously dissolved or embedded, in the other component or components such as the pharmaceutically acceptable hydrophilic polymer. In many cases, the polymer component(s) will melt and the other components including the active ingredient(s) and surfactant will dissolve in the melt thereby forming a solution. In such a case, the polymer functions as a solvent. Melting often involves heating above the softening point of the polymer. The preparation of the melt can take place

in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or be simultaneously mixed and melted. The melt can also be homogenized in order to disperse the active ingredient(s) efficiently. In addition, it may be convenient first to melt the polymer and then to mix in and homogenize the active ingredient(s). In one example, all materials except the surfactant are blended and fed into an extruder, while the surfactant is molten externally and pumped in during extrusion.

[0106] The melt temperature may range, for example, from 70 to 250 °C, preferably from 80 to 180 °C, most preferred from 100 to 140 °C. Various additives may be included in the melt, for example, flow regulators such as colloidal silica; lubricants; fillers; disintegrants; plasticizers; or stabilizers such as antioxidants, light stabilizers, radical scavengers, or stabilizers against microbial attack.

[0107] In another example, the melt comprises lopinavir, ritonavir, or preferably both, as well as a pharmaceutically acceptable hydrophilic polymer as described above; and the melt temperature is in the range of from 100 to 170 °C, preferably from 120 to 150 °C, and highly preferably from 135 to 140 °C. The melt can also include a pharmaceutically acceptable surfactant as described above.

[0108] In still another example, the melt comprises lopinavir, ritonavir, and a pharmaceutically acceptable polymer as described above. The melt can also include a pharmaceutically acceptable surfactant as described above. The melt temperature can be in the range of from 100 to 170 °C, preferably from 120 to 150 °C, and highly preferably from 135 to 140 °C.

[0109] To start a melt-extrusion process, the active ingredient(s) (e.g., lopinavir and/or ritonavir) can be employed in their solid forms, such as their respective crystalline forms. The active ingredient(s) can also be employed as a solution or dispersion in a suitable liquid solvent such as alcohols, aliphatic hydrocarbons, esters or, in some cases, liquid carbon dioxide. The solvent can be removed, e.g. evaporated, upon preparation of the melt.

[0110] The melting and/or mixing can take place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders, intermeshing screw extruders or multiscrew extruders, preferably twin screw extruders, which can be corotating or counterrotating and, optionally, be equipped with kneading disks. It will be appreciated that the working temperatures will be determined by the kind of extruder or the kind of configuration within the extruder that is used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, the friction and shearing of the material in the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogeneous melt of the components.

[0111] The melt can range from thin to pasty to viscous. Shaping of the extrudate can be conveniently carried out, for example, by a calender with two counter-rotating rollers with mutually matching depressions on their surface. The extrudate can be cooled and allow to solidify. The extrudate can also be cut into pieces, either before (hot-cut) or after solidification (cold-cut).

[0112] The solidified extrusion product can be further milled, ground or otherwise reduced to granules or particles with desired sizes. The solidified extrudate, as well as each granule or particle produced, comprises a solid dispersion, preferably a solid solution or glassy solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer and optionally the surfactant. Where the granules/particles do not contain any surfactant, a pharmaceutically acceptable surfactant described above can be, for example, added to and blended with the granules/particles. The extrusion product can also be blended with other active ingredient(s) and/or additive(s) before being milled or ground to granules/particles. The granules/particles can be, for example, further processed and compressed to form the first layer of a tablet dosage form of the invention. The second layer material may be compressed simultaneously or sequentially with the first layer to form a bilayer tablet.

[0113] In some cases, direct-shaping techniques such as injection moulding can be used in combination with melt extrusion to prepare the first layer of a tablet dosage form of the invention.

[0114] In one example, copovidone and one or more surfactants are mixed and granulated, followed by the addition of aerosil and the active ingredient(s) (e.g., lopinavir, ritonavir, or preferably a combination of lopinavir and ritonavir). The mixture, which may contain for example at least 5% by weight of the active ingredient(s) is then milled. The mixture is then subject to extrusion, and the extrudate thus produced can be milled and sieved for further processing for the preparation of the first layer. Surfactant(s) employed in this example can also be added through liquid dosing during extrusion.

[0115] The approach of solvent evaporation, via spray-drying, may provide the advantage of allowing for processability at lower temperatures, if needed, and allow for other modifications to the process in order to further improve powder properties. In many cases, the spray-dried powder can be formulated further, if needed, and then compressed to form the first layer of a tablet dosage form of the invention.

[0116] Exemplary spray-drying processes and spray-drying equipment are described in K. Masters, *Spray Drying Handbook* (Halstead Press, New York, 4th ed., 1985). Non-limiting examples of spray-drying devices that are suitable for the present invention include spray dryers manufactured by Niro Inc. or GEA Process Engineering Inc., Buchi Labortechnik AG, and Spray Drying Systems, Inc. A spray-drying process generally involves breaking up a liquid mixture into small droplets and rapidly removing solvent from the droplets in a container (spray drying apparatus) where there is a

strong driving force for evaporation of solvent from the droplets. Atomization techniques include, for example, two-fluid or pressure nozzles, or rotary atomizers. The strong driving force for solvent evaporation can be provided, for example, by maintaining the partial pressure of solvent in the spray drying apparatus well below the vapor pressure of the solvent at the temperatures of the drying droplets. This may be accomplished by either (1) maintaining the pressure in the spray drying apparatus at a partial vacuum; (2) mixing the liquid droplets with a warm drying gas (e.g., heated nitrogen); or (3) both.

[0117] The temperature and flow rate of the drying gas, as well as the spray dryer design, can be selected so that the droplets are dry enough by the time they reach the wall of the apparatus. This help to ensure that the dried droplets are essentially solid and can form a fine powder and do not stick to the apparatus wall. The spray-dried product can be collected by removing the material manually, pneumatically, mechanically or by other suitable means. The actual length of time to achieve the preferred level of dryness can depend on the size of the droplets, the formulation, and spray dryer operation. Following the solidification, the solid powder may stay in the spray drying chamber for additional time (e.g., 5-60 seconds) to further evaporate solvent from the solid powder. The final solvent content in the solid dispersion as it exits the dryer is preferably at a sufficiently low level so as to improve the stability of the final product. For instance, the residual solvent content of the spray-dried powder can be less than 2% by weight. Highly preferably, the residual solvent content is within the limits set forth in the International Conference on Harmonization (ICH) Guidelines. In addition, it may be useful to subject the spray-dried composition to further drying to lower the residual solvent to even lower levels. Methods to further lower solvent levels include, but are not limited to, fluid bed drying, infra-red drying, tumble drying, vacuum drying, and combinations of these and other processes.

[0118] Like the solid extrudate described above, the spray dried product can contain a solid dispersion, preferably a solid solution and more preferably a glassy solution, of the active ingredient(s) in a matrix comprised of a pharmaceutically acceptable hydrophilic polymer as described above and optionally a pharmaceutically acceptable surfactant as described above. Where the spray dried product does not contain any surfactant, a pharmaceutically acceptable surfactant described above may be optionally added to and blended with the spray-dried product before further processing.

[0119] Before feeding into a spray dryer, the active ingredient(s) (e.g., lopinavir, ritonavir, or preferably a combination of ritonavir and lopinavir), a pharmaceutically acceptable hydrophilic polymer described above, and optionally a pharmaceutically acceptable surfactant described above can be dissolved in a solvent. Suitable solvents include, but are not limited to, water, alkanols (e.g.,

methanol, ethanol, 1-propanol, 2-propanol or mixtures thereof), acetone, acetone/water, alkanol/water mixtures (e.g., ethanol/water mixtures), or combinations thereof. The solution can also be preheated before being fed into the spray dryer.

[0120] A solid dispersion (preferably a solid solution or a glassy solution) prepared by melt-extrusion, spray-drying or other techniques may include both lopinavir and ritonavir. Ritonavir solid dispersion and lopinavir solid dispersion can also be separately prepared as described above, optionally milled, blended, and then compressed into the first layer. In one embodiment, ritonavir solid dispersion described above and lopinavir solid dispersion described above are separately prepared, and compressed into two different layers in the first layer of a tablet dosage form of the invention.

[0121] The first layer of a tablet dosage form of the invention can also comprise one or more additives, such as flow regulators, binders, lubricants, fillers, disintegrants, or plasticizers. These additives can be, for example, mixed with milled or powdery solid dispersions before compression. These additives can also be, for example, mixed with solid dispersions before milling. Disintegrants may promote a rapid disintegration of a tablet in the stomach and keep the liberated granules separate from one another. Non-limiting examples of suitable disintegrants are cross-linked polymers such as cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethylcellulose or sodium croscarmellose. Non-limiting examples of suitable fillers (also referred to as bulking agents) are lactose monohydrate, calcium hydrogenphosphate, microcrystalline cellulose (e.g., Avicell[®] or Emcocel[®]), silicates, in particular silicium dioxide, magnesium oxide, talc, potato or corn starch, isomalt, or polyvinyl alcohol. Non-limiting examples of suitable flow regulators include highly dispersed silica (e.g., colloidal silica such as Aerosil[®]). Non-limiting examples of suitable lubricants include those described above, such as magnesium and calcium stearates, sodium stearyl fumarate, and the like.

[0122] The second layer of a tablet dosage form of the invention can be prepared using techniques that are suitable for formulating the other therapeutic agent comprised in the second layer. Non-limiting examples of these techniques include blending, dry granulation, wet granulation, or solid dispersion. For instance, the other therapeutic agent (e.g., lamivudine, or a combination of lamivudine and zidovudine) can be blended with suitable excipients, milled, and then compressed with the first layer to form a bilayer tablet core. Other additives described above may also be included in the second layer.

[0123] Preferably, the weight ratio of the second layer to the first layer is no more than 1:3, such as no more than 1:4, 1:5, or 1:6. Techniques suitable for compressing two layers together in a tablet

are known in the art. In some cases, the first layer can be pre-compressed before the compression of the second layer.

[0124] In order to facilitate the intake of a tablet dosage form, it is advantageous to give the tablet an appropriate shape. Large tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape.

[0125] A film coat on the tablet core further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. The film-coat usually includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. polysorbates, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. Preferably, the film coat accounts for less than 5 % by weight of a tablet dosage form of the present invention. In one embodiment, a tablet dosage form of the invention (e.g., with a bilayer tablet core described herein) is coated with Opadry[®] HPMC based coating solution.

[0126] Various other additives may also be used in preparing a tablet dosage form of the invention, for example dyes such as azo dyes, organic or inorganic pigments such as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

[0127] In another aspect, the present invention features tablet dosage forms suitable for pediatric uses. Each tablet dosage form of the invention described hereinabove has a corresponding pediatric tablet dosage form, where the pediatric tablet has the same active ingredients and excipients as the regular tablet, as well as the same mean particle size, except that each component in the pediatric tablet is only one half of the amount of the same component in the regular tablet. For instance, a pediatric tablet dosage form of the invention can comprise a first layer and a second layer, wherein the first layer comprises (i) 100 mg lopinavir, (ii) 25 mg ritonavir, (iii) a pharmaceutically acceptable hydrophilic polymer as described above, and (iv) a pharmaceutically acceptable surfactant as described above; and the second layer comprises another therapeutic agent (e.g., 37.5 mg lamivudine, or a combination of 37.5 mg lamivudine and 75 mg zidovudine).

[0128] The weight ratio of the second layer to the first layer in a pediatric tablet dosage form of the invention can be, for example and without limitation, no more than 1:4. Preferably, the weight ratio of the second layer to the first layer is no more than 1:5; for example, the weight ratio of the second layer to the first layer can be 1:5, 1:6 or less. Also preferably, the first layer comprises at least 60% weight of the tablet dosage form. More preferably, the first layer comprises at least 70% weight

of the tablet dosage form. Highly preferably, the first layer comprises at least 80% weight of the tablet dosage form.

[0129] A pediatric tablet dosage form of the invention can be, for example and without limitation, from 0.55 g to 0.85 g, and the first layer can be, for example and without limitation, from 0.45 g to 0.65 g. For instance, the tablet dosage form can be from 0.55 g to 0.75 g, and the first layer is from 0.45 g to 0.65 g. For instance, the tablet dosage form can be from 0.6 g to 0.7 g, and the first layer is from 0.5 g to 0.6 g. In one example, the tablet dosage form is no more than 0.85 g, and the first layer is at least 0.5 g. In another example, the tablet dosage form can be no more than 0.8 g, and the first layer is at least 0.5 g. In another yet example, the tablet dosage form can be no more than 0.75 g, and the first layer is at least 0.5 g. In yet another example, the tablet dosage form is no more than 0.7 g, and the first layer is at least 0.5 g. In yet another example, the tablet dosage form is no more than 0.85 g, and the first layer is at least 0.55 g. In yet another example, the tablet dosage form is no more than 0.8 g, and the first layer is at least 0.55 g. In yet another example, the tablet dosage form is no more than 0.75 g, and the first layer is at least 0.55 g. In yet another example, the tablet dosage form is no more than 0.7 g, and the first layer is at least 0.55 g. In yet another example, the tablet dosage form is no more than 0.85 g, and the first layer is at least 0.6 g. In yet another example, the tablet dosage form is no more than 0.8 g, and the first layer is at least 0.6 g. In yet another example, the tablet dosage form is no more than 0.75 g, and the first layer is at least 0.6 g. In yet another example, the tablet dosage form is no more than 0.85 g, and the first layer is from 0.5 g to 0.65 g. In another example, the tablet dosage form is no more than 0.85 g, and the first layer is at from 0.5 g to 0.6 g. In yet another example, the tablet dosage form is no more than 0.85 g, and the first layer is from 0.5 g to 0.55 g. In yet another example, the tablet dosage form is no more than 0.85 g, and the first layer is from 0.55 g to 0.65 g. In yet another example, the tablet dosage form is no more than 0.85 g, and the first layer is from 0.55 g to 0.6 g. In yet another example, the tablet dosage form is no more than 0.8 g, and the first layer is from 0.5 g to 0.65 g. In another example, the tablet dosage form is no more than 0.8 g, and the first layer is at from 0.5 g to 0.6 g. In yet another example, the tablet dosage form is no more than 0.8 g, and the first layer is from 0.5 g to 0.55 g. In yet another example, the tablet dosage form is no more than 0.8 g, and the first layer is from 0.55 g to 0.65 g. In yet another example, the tablet dosage form is no more than 0.8 g, and the first layer is from 0.55 g to 0.6 g. In yet another example, the tablet dosage form is no more than 0.75 g, and the first layer is from 0.5 g to 0.65 g. In another example, the tablet dosage form is no more than 0.75 g, and the first layer is at from 0.5 g to 0.6 g. In yet another example, the tablet dosage form is no more than 0.75 g, and the first layer is from 0.5 g to 0.55 g. In yet another example, the tablet dosage form is no more than 0.75

g, and the first layer is from 0.55 g to 0.65 g. In yet another example, the tablet dosage form is no more than 0.75 g, and the first layer is from 0.55 g to 0.6 g.

[0130] The first layer in a pediatric tablet dosage form of the invention preferably includes a solid dispersion comprising ritonavir, lopinavir, a pharmaceutically acceptable hydrophilic polymer described above, and a pharmaceutically acceptable surfactant described above. More preferably, the first layer comprises a solid solution comprising ritonavir, lopinavir, a pharmaceutically acceptable hydrophilic polymer described above, and a pharmaceutically acceptable surfactant described above. Highly preferably, the first layer comprises a glassy solution comprising ritonavir, lopinavir, a pharmaceutically acceptable hydrophilic polymer described above, and a pharmaceutically acceptable surfactant described above.

[0131] In a pediatric tablet dosage form of the invention, lopinavir and ritonavir can also be formulated, for example, in different solid dispersions and then mixed and included in the first layer. In one example, the first layer comprises a first and second solid dispersions, wherein the first solid dispersion comprises lopinavir and a first pharmaceutically acceptable hydrophilic polymer, and the second solid dispersion comprises ritonavir and a second pharmaceutically acceptable hydrophilic polymer, and the first layer also contains a pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different. In another example, the first layer comprises a first and second solid dispersions, wherein the first solid dispersion comprises lopinavir, a first pharmaceutically acceptable hydrophilic polymer, and a first pharmaceutically acceptable surfactant, and the second solid dispersion comprises ritonavir, a second pharmaceutically acceptable hydrophilic polymer, and a second pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different; and the first and second surfactants can also be the same or different.

[0132] In yet another example, the first layer comprises a first and second solid solutions, wherein the first solid solution comprises lopinavir and a first pharmaceutically acceptable hydrophilic polymer, and the second solid solution comprises ritonavir and a second pharmaceutically acceptable hydrophilic polymer, and the first layer also contains a pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different. In another example, the first layer comprises a first and second solid solutions, wherein the first solid solution comprises lopinavir, a first pharmaceutically acceptable hydrophilic polymer, and a first pharmaceutically acceptable surfactant, and the second solid solution comprises ritonavir, a second pharmaceutically acceptable hydrophilic polymer, and a second pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different; and the first and second surfactants can also be the same or different.

[0133] In still another example, the first layer comprises a first and second glassy solutions, wherein the first glassy solution comprises lopinavir and a first pharmaceutically acceptable hydrophilic polymer, and the second glassy solution comprises ritonavir and a second pharmaceutically acceptable hydrophilic polymer, and the first layer also contains a pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different. In another example, the first layer comprises a first and second glassy solutions, wherein the first glassy solution comprises lopinavir, a first pharmaceutically acceptable hydrophilic polymer, and a first pharmaceutically acceptable surfactant, and the second glassy solution comprises ritonavir, a second pharmaceutically acceptable hydrophilic polymer, and a second pharmaceutically acceptable surfactant. The first and second hydrophilic polymers can be the same or different; and the first and second surfactants can also be the same or different.

[0134] Any other therapeutic agents that can be included in the second layer of a regular tablet dosage form of the invention can also be included in the second layer of a pediatric tablet dosage form of the invention. In one embodiment, the second layer of a pediatric tablet dosage form comprises 37.5 mg lamivudine. In another embodiment, the second layer of a pediatric tablet dosage form comprises 37.5 mg lamivudine and 75 mg zidovudine. In yet another embodiment, the second layer of a pediatric tablet dosage form comprises 100 mg raltegravir potassium (or the corresponding amount of raltegravir salt, e.g., 108.6 mg raltegravir potassium)..

[0135] In yet another aspect, the present invention features methods of using a tablet dosage form of the invention to treat HIV infection. The methods comprise administering a tablet dosage form of the invention to a patient in need thereof. Any tablet dosage form described herein (including a pediatric tablet dosage) can be used in a method of the invention.

[0136] In any aspect, example, embodiment or preference described herein, lopinavir and ritonavir in the first layer of a tablet dosage form of the invention can be readily replaced with another therapeutic agent(s). Therefore, the present invention also features such tablet dosage forms as well as their corresponding pediatric tablet dosage forms.

[0137] It should be understood that the above-described embodiments and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

EXAMPLE 1

[0138] Lopinavir/ritonavir extrudate was prepared according to the process described in Example 2 of U.S. Patent No. 8,025,899. The extrudate was milled to a mean particle size of 165 μm

using standard milling equipment (Fitzmill or Alpine mill). A portion or all of the milled extrudate was combined with sodium stearyl fumarate and colloidal silicon dioxide and passed through a screen or comill and the mixture was blended. 3TC, sodium starch glycolate, sodium stearyl fumarate, colloidal silicon dioxide and part or all of the microcrystalline cellulose were passed through a screen or comill and then blended. The lopinavir/ritonavir blend (1220 mg; the first layer) and the 3TC blend (210 mg; the second layer) are compressed into a bilayer tablet using an automated bilayer tablet press. The composition of the bilayer tablet so prepared is provided in Table 1. The tablets thus prepared showed no or significantly less cracking. The tablets were then dedusted and coated using an HPMC-based aqueous coating suspension.

Table 1

Lopinavir/Ritonavir (LPV/RTV) Layer	
Milled LPV/RTV Extrudate (mg)	1199.7 (200 mg lopinavir, 50 mg ritonavir))
Sodium Stearyl Fumarate (mg)	12.3
Silicon Dioxide Colloidal (mg)	8
Total LPV/RTV Layer (mg)	1220
Lamivudine (3TC) Layer	
3TC (mg)	75
Microcrystalline Cellulose (mg)	126.6
Sodium Starch Glycolate (mg)	6.3
Silicon Dioxide Colloidal (mg)	0.4
Sodium Stearyl Fumarate (mg)	1.7
Total 3TC Layer (mg)	210

EXAMPLE 2

[0139] Lopinavir/ritonavir extrudate was prepared according to the process described in Example 2 of U.S. Patent No. 8,025,899. The extrudate was milled to a mean particle size of 140 μm using standard milling equipment (Fitzmill or Alpine mill). A portion or all of the milled extrudate was combined with sodium stearyl fumarate and colloidal silicon dioxide and passed through a screen or comill and the mixture was blended. AZT, 3TC, sodium starch glycolate, sodium stearyl fumarate, colloidal silicon dioxide and the microcrystalline cellulose were screened and blended. The lopinavir/ritonavir blend (1220 mg; the first layer) and the AZT/3TC blend (300 mg; the second layer) are compressed into a bilayer tablet using an automated bilayer tablet press. The composition

of the bilayer tablet so prepared is provided in Table 2. The tablets thus prepared showed no or significantly less cracking. The tablets were then dedusted and coated using an HPMC-based aqueous coating suspension.

Table 2

Lopinavir/Ritonavir (LPV/RTV) Layer	
Milled LPV/RTV Extrudate (mg)	1199.7 (200 mg lopinavir, 50 mg ritonavir))
Sodium Stearyl Fumarate (mg)	12.3
Silicon Dioxide Colloidal (mg)	8
Total LPV/RTV Layer (mg)	1220
Zidovudine/Lamivudine (AZT/3TC) Layer	
AZT (mg)	150
3TC (mg)	75
Microcrystalline Cellulose (mg)	69.1
Sodium Starch Glycolate (mg)	2.3
Silicon Dioxide Colloidal (mg)	0.9
Sodium Stearyl Fumarate (mg)	2.7
Total AZT/3TC Layer (mg)	300

[0140] The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

1. A tablet dosage form comprising a first layer and a second layer, wherein the first layer comprises compressed solid dispersion particles each of which comprises ritonavir and lopinavir in a solid dispersion, said solid dispersion comprising a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant, and said solid dispersion particles having a mean particle size of no more than 200 μm , and wherein said second layer comprises another therapeutic agent.
2. The tablet dosage form of claim 1, wherein the weight ratio of the second layer to the first layer is no more than 1:2.
3. The tablet dosage form of claim 1, wherein the weight ratio of the second layer to the first layer is no more than 1:3.
4. The tablet dosage form of claim 1, wherein the weight ratio of the second layer to the first layer is no more than 1:4.
5. The tablet dosage form of claim 1, wherein the dosage form is no more than 1.6 g, and the first layer is at least 1 g.
6. The tablet dosage form of claim 1, wherein the dosage form is no more than 1.6 g, and the first layer is at least 1.1 g.
7. The tablet dosage form of claim 1, wherein the dosage form is no more than 1.6 g, and the first layer is at least 1.2 g.
8. The tablet dosage form of claim 1, wherein the dosage form is from 1.4 to 1.6 g, and the first layer is from 1.1 to 1.3 g.
9. The tablet dosage form of claim 8, wherein said first layer comprises 200 mg lopinavir and 50 mg ritonavir, and said second layer comprises 75 mg lamivudine.
10. The tablet dosage form of claim 9, wherein said second layer further comprises 150 mg zidovudine.

11. The tablet dosage form of claim 9, wherein said solid dispersion particles have a mean particle size of from 120 to 190 μm .
12. The tablet dosage form of claim 1, wherein said first layer comprises 100 mg lopinavir and 25 mg ritonavir, and said second layer comprises 37.5 mg lamivudine.
13. The tablet dosage form of claim 11, wherein said second layer further comprises 75 mg zidovudine.
14. A tablet dosage form according to claim 1, wherein said pharmaceutically acceptable hydrophilic polymer has a Tg of at least 50 $^{\circ}\text{C}$.
15. A tablet dosage form according to claim 1, wherein said solid dispersion is a solid solution.
16. A tablet dosage form according to claim 1, wherein said solid dispersion is a glassy solution.
17. A tablet dosage form according to claim 1, wherein said pharmaceutically acceptable hydrophilic polymer has a Tg of at least 50 $^{\circ}\text{C}$, and said pharmaceutically acceptable surfactant has an HLB value of from 4 to 10.
18. A tablet dosage form according to claim 1, wherein said pharmaceutically acceptable hydrophilic polymer is copovidone, and said pharmaceutically acceptable surfactant is sorbitan monolaurate.
19. A process of making a tablet dosage form according to claim 1, comprising compressing said first layer and said second layer.
20. A bottle of tablets according to claim 1, wherein no more than 10% of said tablets show cracking.
21. The bottle of claim 20, wherein no more than 5% of said tablets show cracking.

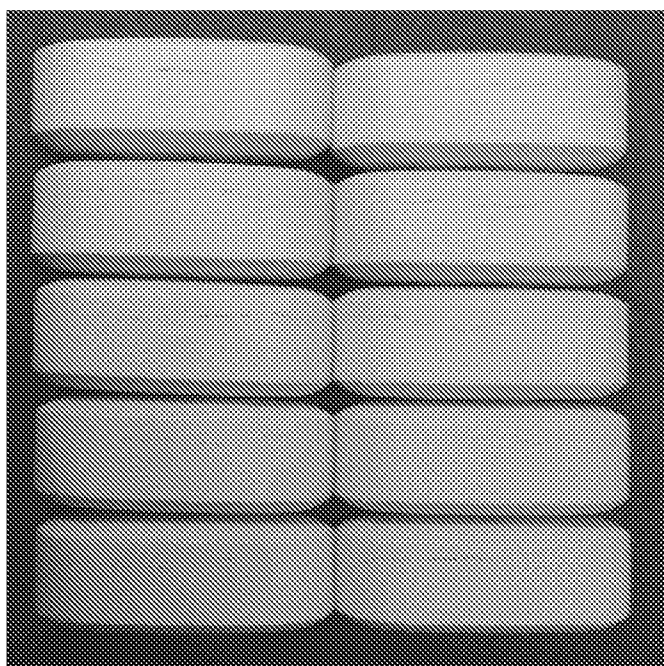


Figure 1A

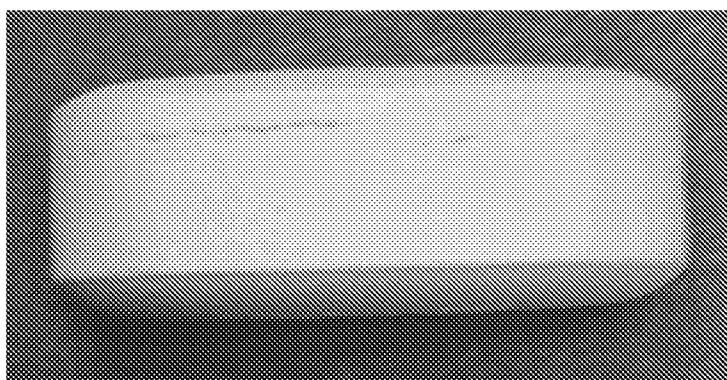


Figure 1B

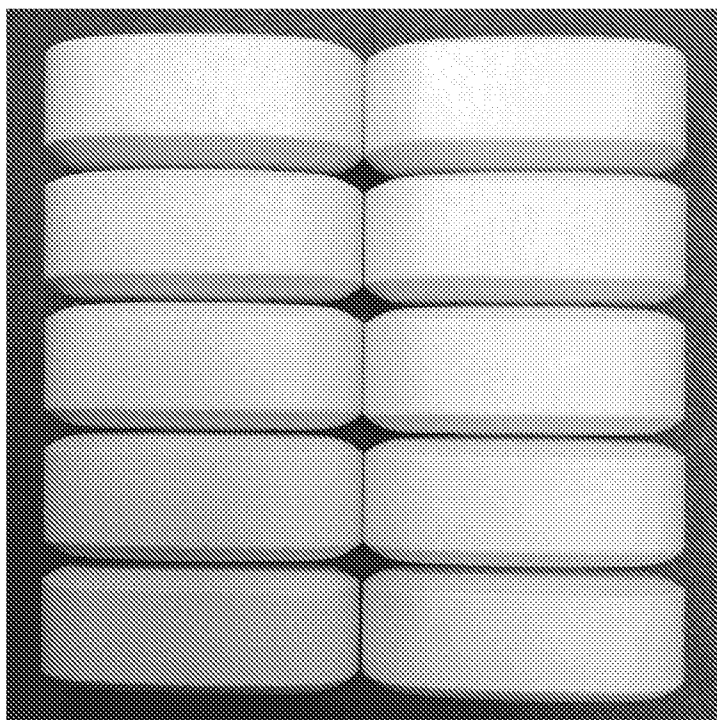


Figure 2A

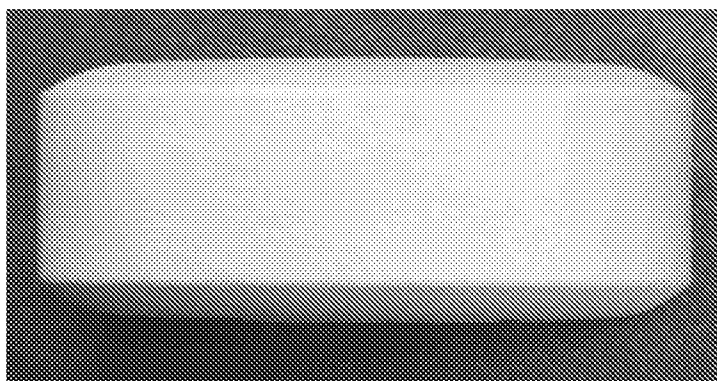


Figure 2B

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(54) Title: SOLID COMPOSITIONS

(57) Abstract: The present invention features solid compositions comprising amorphous Compound I. A solid dispersion of the present invention also contains a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant. Compound I may be formulated in an amorphous solid dispersion which comprises a pharmaceutically acceptable hydrophilic polymer and preferably a pharmaceutically acceptable surfactant.

SOLID COMPOSITIONS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional patent application Ser. No. 61/339,964, filed March 10, 2010, the contents of which are incorporated herein in its entirety by reference.

JOINT RESEARCH AGREEMENT

[0002] Inventions described in this application were made by or on behalf of Abbott Laboratories and Enanta Pharmaceuticals, Inc. whom are parties to a joint research agreement, that was in effect on or before the date such inventions were made and such inventions were made as a result of activities undertaken within the scope of the joint research agreement.

FIELD OF THE INVENTION

[0003] The present invention relates to solid compositions comprising anti-HCV compounds and methods of using the same to treat HCV infection.

BACKGROUND

[0004] The hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

[0005] HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon- alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often inadequate. Therefore, there is a need for new drugs to treat HCV infection.

SUMMARY OF THE INVENTION

[0006] The present invention features solid compositions comprising (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide (hereinafter Compound I) or a pharmaceutical acceptable salt thereof. Compound I is a potent HCV inhibitor. The solid compositions of the invention comprise (1) Compound I (or a pharmaceutically acceptable salt thereof) in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant.

[0007] In one aspect, the present invention features a solid composition comprising a solid dispersion, wherein the solid dispersion comprises Compound I (or a pharmaceutically acceptable salt thereof) in an amorphous form and a pharmaceutically acceptable hydrophilic polymer, and the solid composition further comprises a pharmaceutically acceptable surfactant. The surfactant can be, without limitation, either formulated in the solid dispersion or separately combined or mixed with the solid dispersion. Preferably, the hydrophilic polymer has a T_g of at least 50 °C. More preferably, the hydrophilic polymer has a T_g of at least 80 °C. Highly preferably, the hydrophilic polymer has a T_g of at least 100 °C. Also preferably, the surfactant has a HLB value of at least 10. Hydrophilic polymers with T_g of at least 25 °C can also be used.

[0008] In one embodiment of this aspect of the invention, the hydrophilic polymer is selected from homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide, or polysaccharide. Non-limiting examples of suitable hydrophilic polymers include homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl

acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan, or xanthan gum.

[0009] In another embodiment of this aspect of the invention, the surfactant is selected from polyoxyethylene castor oil derivatives, mono fatty acid ester of polyoxyethylene sorbitan, polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester, or sorbitan fatty acid mono ester. Non-limiting examples of suitable surfactants include polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethyleneglycol 40 hydrogenated castor oil (Cremophor® RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate) or polyethyleneglycol 60 hydrogenated castor oil (Cremophor® RH 60), mono fatty acid ester of polyoxyethylene sorbitan, such as mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40) or polyoxyethylene (20) sorbitan monolaurate (Tween® 20), polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan mono laurate, sorbitan monooleate, sorbitan monopalmitate, or sorbitan stearate.

[0010] In yet another embodiment, the solid dispersion is an amorphous solid dispersion. In still another embodiment, the solid dispersion is an amorphous solid dispersion which comprises Compound I (or a pharmaceutically acceptable salt thereof), the hydrophilic polymer, and the surfactant. In a further embodiment, the solid dispersion is a solid solution comprising Compound I (or a pharmaceutically acceptable salt thereof) and the hydrophilic polymer. In yet another embodiment, the solid dispersion is a solid solution comprising Compound I (or a pharmaceutically acceptable salt thereof), the hydrophilic polymer and the surfactant.

[0011] In yet another embodiment of this aspect of the invention, the hydrophilic polymer is a homopolymer or copolymer of N-vinyl pyrrolidone. Preferably, the hydrophilic polymer is copovidone.

[0012] In still another embodiment, the surfactant is propylene glycol laurate (e.g., lauroglycol FCC from Gattefosse). The solid composition may further comprise another pharmaceutically acceptable surfactant such as D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS).

[0013] In still yet another embodiment, the surfactant is a polysorbate. Preferably, the surfactant is polysorbate 80 (Tween 80).

[0014] In yet another embodiment, a solid composition of the invention comprises an amorphous solid dispersion or a solid solution which comprises Compound I (or a pharmaceutically acceptable salt thereof), copovidone, and a surfactant selected from polysorbate (preferably polysorbate 80), vitamin E TPGS or a combination of vitamin E TPGS and propylene glycol laurate (e.g., lauroglycol FCC).

[0015] A solid composition of the present invention may further include ritonavir, preferably a solid dispersion of ritonavir. Ritonavir and Compound I (or a pharmaceutically acceptable salt thereof) may be formulated in the same solid dispersion or solid solution; they may be also formulated in different solid dispersions or solid solutions.

[0016] In another aspect, the present invention features processes of making a solid composition of the present invention. In one embodiment, the process comprises drying a solvent in a liquid solution, wherein said solution comprises: (1) Compound I or a pharmaceutically acceptable salt thereof; (2) a pharmaceutically acceptable hydrophilic polymer; and optionally (3) a pharmaceutically acceptable surfactant. The drying process can be carried out using any suitable solvent evaporation techniques including but not limited to spray-drying techniques.

[0017] In another embodiment, the process comprises solidifying a melt which comprises: (1) Compound I or a pharmaceutically acceptable salt thereof; (2) a pharmaceutically acceptable hydrophilic polymer; and optionally (3) a pharmaceutically acceptable surfactant.

[0018] A solid composition of the invention may also contain other additives or ingredients, such as coloring agents, flavoring agents, lubricants or preservatives. A solid composition of the invention can be prepared into any suitable dosage forms, such as capsule, dragee, granule, powder, or tablet.

[0019] A solid composition of the invention may further comprise another anti-HCV agent, for example, an agent selected from HCV helicase inhibitors, HCV polymerase inhibitors, HCV protease inhibitors, HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors.

[0020] The present invention further features methods of using a solid composition of the present invention to treat HCV infection. The methods comprise administering a solid composition of the present invention to a patient in need thereof, thereby reducing the blood or tissue level of HCV virus in the patient.

[0021] Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description.

DETAILED DESCRIPTION

[0022] The present invention features solid compositions comprising amorphous Compound I (or a pharmaceutically acceptable salt thereof), a pharmaceutically acceptable hydrophilic polymer, and a pharmaceutically acceptable surfactant. Compound I has low aqueous solubility, and its *in vivo* absorption is expected to be dissolution-rate limited. Formulating Compound I in an amorphous form can increase the inherent drug solubility and dissolution rate, thereby enhancing the bioavailability of the compound. A solid composition of the invention can also include ritonavir. Ritonavir is a potent inhibitor of cytochrome P450 3A4 enzyme (CYP3A4), and CYP3A4 is believed to be involved in the metabolism of Compound I. Therefore, co-administering Compound I with ritonavir can reduce the metabolism of Compound I, thereby improving the bioavailability of Compound I.

[0023] A non-limiting way to form an amorphous form of Compound I or a combination of Compound I and ritonavir is through the formation of solid dispersions with a polymeric carrier. The presence of hydrophilic polymer(s) and surfactant(s), as well as the dispersion of Compound I in an amorphous form in a matrix containing the polymer(s), can significantly enhance the dissolution rate of the poorly soluble Compound I. In many cases, a solid dispersion formulation can also effectively maintain Compound I in its supersaturation state to allow for better absorption.

[0024] As used herein, the term "solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed throughout the other component or components. For example, an active ingredient or a combination of active ingredients can be dispersed in a matrix comprised of a pharmaceutically acceptable hydrophilic polymer(s) and a pharmaceutically acceptable surfactant(s). The term "solid dispersion" encompasses systems having small

particles of one phase dispersed in another phase. These particles are often of less than 400 μm in size, such as less than 100, 10, or 1 μm in size. When a solid dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion is called a "solid solution." A glassy solution is a solid solution in which a solute is dissolved in a glassy solvent.

[0025] The term " AUC_{∞} " refers to the area under the plasma concentration time curve (AUC) extrapolated to infinity.

[0026] The terms "weight percent" or "percent by weight" or "% by weight" or "wt %" denote the weight of an individual component in a composition or mixture as a percentage of the weight of the composition or mixture.

[0027] In one aspect, the present invention features a solid composition comprising Compound I (or a pharmaceutically acceptable salt thereof) in an amorphous form, a pharmaceutically acceptable hydrophilic polymer, and a pharmaceutically acceptable surfactant. The Compound I (or the salt thereof) and the polymer are formulated in a solid dispersion. The surfactant may also be formulated in the same solid dispersion; or the surfactant can be separately combined or mixed with the solid dispersion.

[0028] In one embodiment, a solid composition of the invention comprises an amorphous solid dispersion which comprises Compound I (or a pharmaceutically acceptable salt thereof), a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant. In another embodiment, a solid composition of the invention comprises a solid solution which comprises Compound I (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable hydrophilic polymer. In still another embodiment, a solid composition of the invention comprises a solid solution which comprises Compound I (or a pharmaceutically acceptable salt thereof), a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant. In yet another embodiment, a solid composition of the invention comprises a glassy solution which includes Compound I (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable hydrophilic polymer. In a further embodiment, a solid composition of the invention comprises a glassy solution which includes Compound I (or a pharmaceutically acceptable salt thereof), a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant.

[0029] A solid composition of the invention can further comprise a solid dispersion of ritonavir. Preferably, the solid composition comprises a solid solution of ritonavir. More

preferably, the solid composition comprises a glassy solution of ritonavir. Compound I (or a pharmaceutically acceptable salt thereof) and ritonavir can be formulated in the same solid dispersion or solid solution. They may also be formulated in separate solid dispersions or solid solutions, which can then be combined or mixed to form a solid composition of the present invention.

[0030] In yet another embodiment, a solid composition of the invention comprises an amorphous solid dispersion which includes Compound I (or a pharmaceutically acceptable salt thereof), ritonavir and a pharmaceutically acceptable hydrophilic polymer. In another embodiment, a solid composition of the invention comprises an amorphous solid dispersion which includes Compound I (or a pharmaceutically acceptable salt thereof), ritonavir, a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant. In still another embodiment, a solid composition of the invention comprises a solid solution which includes Compound I (or a pharmaceutically acceptable salt thereof), ritonavir and a pharmaceutically acceptable hydrophilic polymer. In still yet another embodiment, a solid composition of the invention comprises a solid solution which includes Compound I (or a pharmaceutically acceptable salt thereof), ritonavir, a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant.

[0031] In yet another embodiment, a solid composition of the invention comprises a first amorphous solid dispersion which includes Compound I (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable hydrophilic polymer, and a second amorphous solid dispersion comprising ritonavir. In another embodiment, a solid composition of the invention comprises a first amorphous solid dispersion which includes Compound I (or a pharmaceutically acceptable salt thereof), a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant, and a second amorphous solid dispersion comprising ritonavir. In still another embodiment, a solid composition of the invention comprises a first solid solution which includes Compound I (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable hydrophilic polymer, and a second solid solution comprising ritonavir. In another embodiment, a solid composition of the invention comprises a first solid solution which includes Compound I (or a pharmaceutically acceptable salt thereof), a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant, and a second solid solution comprising ritonavir.

[0032] Preferably, a solid dispersion or solid solution that contains ritonavir also includes a pharmaceutically acceptable surfactant to improve the dissolution and/or bioavailability of ritonavir.

[0033] The weight ratio of Compound I over ritonavir in a solid composition of the invention may range, without limitation, from 1:1 to 5: 1. Preferably, the weight ratio of Compound I over ritonavir is 2:1, 3:1, or 4:1.

[0034] A solid composition of the invention can contain, for example, from 1 to 50% by weight of Compound I. For instance, a solid composition of the invention can contain from 5 to 30% by weight of Compound I. Preferably, a solid composition of the invention contains from 10 to 25% by weight of Compound I.

[0035] A solid dispersion of the invention may contain at least 30% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. Preferably, the solid dispersion contains at least 40% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. More preferably, the solid dispersion contains at least 50% (including, e.g., at least 60%, 70% or 80%) by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers. A solid dispersion of the invention may also contain at least 1% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. Preferably, the solid dispersion contains at least 2% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. More preferably, the solid dispersion contains from 4% to 20% by weight of the surfactant(s), such as from 5% to 10% by weight of the surfactant(s).

[0036] In one embodiment, a solid dispersion of the invention comprises at least 30% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and at least 1% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In another embodiment, a solid dispersion of the invention comprises at least 50% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 2% to 20% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In yet another embodiment, a solid dispersion of the invention comprises from 50% to 90% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 3% to 15% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In yet another embodiment, a solid dispersion of the invention comprises from 60% to 80% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 5% to 10% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants.

[0037] Preferably, a hydrophilic polymer employed in the present invention has a T_g of at least 50 °C, more preferably at least 60 °C, and highly preferably at least 80 °C including, but not limited to from, 80 °C to 180 °C, or from 100 °C to 150 °C. Methods for determining T_g values of organic polymers are described in INTRODUCTION TO PHYSICAL POLYMER SCIENCE (2nd Edition by L.H. Sperling, published by John Wiley & Sons, Inc., 1992). The T_g value can be calculated as the weighted sum of the T_g values for homopolymers derived from each of the individual monomers, i.e., the polymer $T_g = \sum W_i \cdot X_i$ where W_i is the weight percent of monomer i in the organic polymer, and X_i is the T_g value for the homopolymer derived from monomer i . T_g values for the homopolymers may be taken from POLYMER HANDBOOK (2nd Edition by J. Brandrup and E.H. Immergut, Editors, published by John Wiley & Sons, Inc., 1975). Hydrophilic polymers with a T_g as described above may allow for the preparation of solid dispersions that are mechanically stable and, within ordinary temperature ranges, sufficiently temperature stable so that the solid dispersions may be used as dosage forms without further processing or be compacted to tablets with only a small amount of tableting aids. Hydrophilic polymers having a T_g of below 50°C may also be used.

[0038] Preferably, a hydrophilic polymer employed in the present invention is water-soluble. A solid composition of the present invention can also comprise poorly water-soluble or water-insoluble polymer or polymers, such as cross-linked polymers. A hydrophilic polymer comprised in a solid composition of the present invention preferably has an apparent viscosity, when dissolved at 20 °C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa-s., and more preferably of 1 to 700 mPa-s, and most preferably of 5 to 100 mPa-s.

[0039] Hydrophilic polymers suitable for use in a solid composition of the invention include, but are not limited to, homopolymers or copolymers of N-vinyl lactams, such as homopolymers or copolymers of N-vinyl pyrrolidone (e.g., polyvinylpyrrolidone (PVP), or copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate); cellulose esters or cellulose ethers, such as alkylcelluloses (e.g., methylcellulose or ethylcellulose), hydroxyalkylcelluloses (e.g., hydroxypropylcellulose), hydroxyalkylalkylcelluloses (e.g., hydroxypropylmethylcellulose), and cellulose phthalates or succinates (e.g., cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, or hydroxypropylmethylcellulose acetate succinate); high molecular polyalkylene oxides, such as polyethylene oxide, polypropylene oxide, and copolymers of ethylene oxide and propylene oxide; polyacrylates or polymethacrylates, such as methacrylic acid/ethyl

acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), and poly(hydroxyalkyl methacrylates); polyacrylamides; vinyl acetate polymers, such as copolymers of vinyl acetate and crotonic acid, and partially hydrolyzed polyvinyl acetate (also referred to as partially saponified "polyvinyl alcohol"); polyvinyl alcohol; oligo- or polysaccharides, such as carrageenans, galactomannans, and xanthan gum; polyhydroxyalkylacrylates; polyhydroxyalkyl-methacrylates; copolymers of methyl methacrylate and acrylic acid; polyethylene glycols (PEGs); or any mixture thereof.

[0040] Non-limiting examples of preferred hydrophilic polymers for the invention include polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) L100-55, Eudragit L100, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.

[0041] Of these, homopolymers or copolymers of N-vinyl pyrrolidone, such as copolymers of N-vinyl pyrrolidone and vinyl acetate, are preferred. A non-limiting example of a preferred polymer is a copolymer of 60 % by weight of N-vinyl pyrrolidone and 40 % by weight of vinyl acetate. Other preferred polymers include, without limitation, hydroxypropyl methylcellulose (HPMC, also known as hypromellose in USP), such as hydroxypropyl methylcellulose grade E5 (HPMC-E5); and hydroxypropyl methylcellulose acetate succinate (HPMC-AS).

[0042] A pharmaceutically acceptable surfactant employed in the present invention is preferably a non-ionic surfactant. More preferably, a solid composition of the present invention comprises a pharmaceutically acceptable surfactant having an HLB value of at least 10. A solid composition of the present invention can also include a mixture of pharmaceutically acceptable surfactants, with at least one surfactant having an HLB value of no less than 10 and at least another surfactant having an HLB value of below 10. In one example, each surfactant comprised in a solid composition of the invention has an HLB value of at least 10. In another example, each surfactant comprised in a solid composition of the invention has an HLB value of below 10. In yet another example, a solid composition of the

present invention includes at least two pharmaceutically acceptable surfactants, one having an HLB value of at least 10 and the other having an HLB value of below 10. The HLB system (Fiedler, H.B., *ENCYCLOPEDIA OF EXCIPIENTS*, 5th ed., Aulendorf: ECV-Editio-Cantor-Verlag (2002)) attributes numeric values to surfactants, with lipophilic substances receiving lower HLB values and hydrophilic substances receiving higher HLB values.

[0043] Non-limiting examples of pharmaceutically acceptable surfactants that are suitable for the present invention include polyoxyethylene castor oil derivatives, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethyleneglycol 40 hydrogenated castor oil (Cremophor® RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate) or polyethyleneglycol 60 hydrogenated castor oil (Cremophor® RH 60); or a mono fatty acid ester of polyoxyethylene sorbitan, such as a mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), or polyoxyethylene (20) sorbitan monolaurate (Tween® 20). Other non-limiting examples of suitable surfactants include polyoxyethylene alkyl ethers, e.g. polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether; polyoxyethylene alkylaryl ethers, e.g. polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether; polyethylene glycol fatty acid esters, e.g. PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate; alkylene glycol fatty acid mono esters, e.g. propylene glycol monolaurate (Lauroglycol®); sucrose fatty acid esters, e.g. sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate; sorbitan fatty acid mono esters such as sorbitan mono laurate (Span® 20), sorbitan monooleate, sorbitan monopalmitate (Span® 40), or sorbitan stearate. Other suitable surfactants include, but are not limited to, block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene polypropyleneglycol, such as Poloxamer® 124, Poloxamer® 188, Poloxamer® 237, Poloxamer® 388, or Poloxamer® 407 (BASF Wyandotte Corp.). As described above, a mixture of surfactants can be used in a solid composition of the present invention.

[0044] Non-limiting examples of preferred surfactants for the invention include to polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40,

Cremophor EL, Gelucire 44/14, Gelucire 50/13, D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, and sorbitan monolaurate.

[0045] In one embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or a solid solution which includes Compound I (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable hydrophilic polymer. The solid composition also includes a pharmaceutically acceptable surfactant which preferably is formulated in the amorphous solid dispersion or solid solution. The hydrophilic polymer can be selected, for example, from the group consisting of homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide, and polysaccharide. As a non-limiting example, the hydrophilic polymer is selected from the group consisting of homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan, and xanthan gum. Preferably, the hydrophilic polymer is selected from polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) L100-55, Eudragit L100, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, or poloxamer 407. More preferably, the hydrophilic polymer is selected from homopolymers of vinylpyrrolidone

(e.g., PVP with Fikentscher K values of from 12 to 100, or PVP with Fikentscher K values of from 17 to 30), or copolymers of 30 to 70% by weight of N-vinylpyrrolidone (VP) and 70 to 30% by weight of vinyl acetate (VA) (e.g., a copolymer of 60% by weight VP and 40% by weight VA). The surfactant can be selected, for example, from the group consisting of polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate, mono fatty acid ester of polyoxyethylene sorbitan, polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester, and sorbitan fatty acid mono ester. As a non-limited example, the surfactant is selected from the group consisting of polyethylenglycol 40 hydrogenated castor oil (Cremophor® RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate), polyethylenglycol 60 hydrogenated castor oil (Cremophor® RH 60), a mono fatty acid ester of polyoxyethylene (20) sorbitan (e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), or polyoxyethylene (20) sorbitan monolaurate (Tween® 20)), polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan mono laurate, sorbitan monooleate, sorbitan monopalmitate, and sorbitan stearate. Preferably, the surfactant is selected from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40, Cremophor EL, Gelucire 44/14, Gelucire 50/13, D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, or sorbitan monolaurate. More preferably, the surfactant is selected from Tween (e.g., Tween 80, 60, 40 or 20) or D-alpha-tocopheryl polyethylene glycol 1000 succinate. The solid composition may also comprise an amorphous solid dispersion or solid solution of ritonavir, and preferably, ritonavir and Compound I (or a pharmaceutically acceptable salt thereof) are formulated in the same amorphous solid dispersion or solid solution.

[0046] In another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes Compound I (or a pharmaceutically acceptable salt thereof) and a homopolymer or copolymer of N-vinyl

pyrrolidone (e.g., copovidone). The solid composition also comprises a pharmaceutically acceptable surfactant (e.g., vitamin E TPGS, or polysorbate such as polysorbate 80), wherein the surfactant preferably is formulated in the amorphous solid dispersion or solid solution. The solid composition may also comprise an amorphous solid dispersion or solid solution of ritonavir, and preferably, ritonavir and Compound I (or a pharmaceutically acceptable salt thereof) are formulated in the same amorphous solid dispersion or solid solution.

[0047] In yet another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes Compound I (or a pharmaceutically acceptable salt thereof), copovidone, and a pharmaceutically acceptable surfactant selected from vitamin E TPGS or polysorbate (e.g., polysorbate 80). The amorphous solid dispersion or solid solution may also include another pharmaceutically acceptable surfactant such as propylene glycol laurate (e.g., lauroglycol FCC). The solid composition may comprise an amorphous solid dispersion or solid solution of ritonavir, and preferably, ritonavir and Compound I (or a pharmaceutically acceptable salt thereof) are formulated in the same amorphous solid dispersion or solid solution.

[0048] A solid dispersion employed in the present invention preferably comprises or consists of a single-phase (defined in thermodynamics) in which the therapeutic agent (e.g., Compound I and/or ritonavir) and the pharmaceutically acceptable hydrophilic polymer are molecularly dispersed. In such cases, thermal analysis of the solid dispersion using differential scanning calorimetry (DSC) typically shows only one single T_g , and the solid dispersion does not contain any detectable crystalline Compound I or ritonavir as measured by X-ray powder diffraction spectroscopy.

[0049] Compound I can be prepared according to the procedures described in U.S. Patent Application No. 12/584,716, filed September 10, 2009. Boc-2(S)-amino-non-8-eoic acid dicyclohexylamine salt can be suspended in isopropyl acetate, washed several times with an aqueous citric acid solution and then once with water. The washed product, concentrated and then re-diluted in isopropyl acetate, can be reacted with HCl to produce 2(S)-amino-non-8-eoic acid HCl salt. 5-Methyl-2-pyrazinecarboxylic acid, N,N'-disuccinimidyl carbonate, and N,N-dimethylaminopyridine can be dissolved in N-methyl-2-pyrrolidone (NMP) and stirred. 2(S)-Amino-non-8-eoic acid HCl salt is subsequently added, followed by triethylamine, and stirred to produce (S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoic acid, which can be crystallized out by adding HCl followed by water. (2S,4R)-N-Boc-4-hydroxyproline can be reacted with 6-chlorophenanthridine in NMP, in the presence of sodium t-butoxide, to produce (2S,4R)-1-(tert-butoxycarbonyl)-4-(phenanthridin-6-

xyloxy)pyrrolidine-2-carboxylic acid. Methyl tertiary butyl ether (MTBE) and water can then be added. The aqueous layer is separated, washed, and then HCl is added, followed by extraction with MTBE. The extracted product can be mixed with diisopropylethylamine (DIPEA) and HATU (CAS # 148893-10-1), and then reacted with (1R,2S)-ethyl-1-amino-2-vinylcyclopropanecarboxylate tosylate salt in dimethylformide (DMF) and toluene. The reaction produces (2S,4R)-tert-butyl 2-((1R,2S)-1-(ethoxycarbonyl)-2-vinylcyclopropylcarbamoyl)-4-(phenanthridin-6-yloxy)pyrrolidine-1-carboxylate, which can be extracted with MTBE and washed with HCl, further extracted, washed, dried, and dissolved in 2-propanol.

[0050] HCl can be added to the 2-propanol solution to produce (1R,2S)-ethyl 1-((2S,4R)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, which can be crystallized out by neutralizing with NaOH. (1R,2S)-ethyl 1-((2S,4R)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, (S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoic acid, N-hydroxy-5-norbornene-2,3-dicarboximide, and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride can be mixed and stirred in DMF, followed by addition of N,N-dimethylethylene diamine. The reaction produces (1R,2S)-ethyl 1-((2S,4R)-1-((S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoyl)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, which can be dissolved in isopropyl acetate and extracted with aqueous H₃PO₄, and then extracted with aqueous K₂HPO₄. The product can be reacted with di-tert-butyl dicarbonate in the presence of dimethylaminopyridine, followed by extraction with a mixture of a citric acid solution and a sodium chloride solution, to produce (1R,2S)-ethyl-1-((2S,4R)-N-(tert-butoxycarbonyl)-1-((S)-2-(5-methylpyrazine-2-carboxamido)non-8-enoyl)-4-(phenanthridin-6-yloxy)pyrrolidine-2-carboxamido)-2-vinylcyclopropanecarboxylate, which can be subject to ring-closing metathesis in the presence of Zhan Catalyst-IB (Zannan Pharma Ltd., Shanghai, China) in toluene to produce (2R,6S,13aS,14aR,16aS,Z)-15-tert-butyl 14a-ethyl 6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-2,3,5,6,7,8,9,10,11,13a,14,14a,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a,15(IH)-dicarboxylate. The catalyst can be quenched with imidazole after the reaction.

[0051] The ring-closed product in toluene can be solvent switched to acetonitrile, followed by addition of hydrogen chloride in dioxane and heated to produce (2R,6S,13aS,14aR,16aS,Z)-ethyl-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-

hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate hydrochloride, which can then be isolated, mixed with tetrahydrofuran, water and $\text{LiOH}\cdot\text{H}_2\text{O}$, and then heated and stirred. The reaction mixture can be later cooled, added with aqueous H_3PO_4 , aqueous NaCl and 2-methyl tetrahydrofuran, and the organic layer is separated, washed and filtered. MeCN is added to the concentrated organic layer, heated and cooled, and then diethylamine is added. The slurry is heated and cooled to form (2R,6S,13aS,14aR,16aS,Z)-6-(5-Methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate diethylamine salt, which can be further washed and dried.

[0052] The diethylamine salt can be mixed with tetrahydrofuran, 2-methyl tetrahydrofuran and aqueous H_3PO_4 . The organic layer is separated, washed with aqueous NaCl , and then concentrated and/or purified. The product can be subsequently mixed with NMP, followed by addition of carbonyldiimidazole (CDI) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Cyclopropylsulfonamide can be subsequently added. The reaction mixture is stirred for hours. Isopropyl acetate can then be added, followed by aqueous KH_2PO_4 and then aqueous H_3PO_4 . The organic layer can be isolated, washed, and purified to produce Compound I, which can be further dissolved in isopropyl acetate and then the solution is diluted with ethanol. Water can be added to the resulting solution in portion-wise manner with adequate hold-times after each addition to ensure de-super-saturation. Water addition is terminated just as the ternary solvent system becomes bi-phasic due to the partial immiscibility of isopropyl acetate, ethanol, water solvent system. The slurry can be stirred for hours and then the solid is isolated via filtration and drying to produce the crystalline hydrate of Compound I.

[0053] A solid composition of the present invention can further include one or more other anti-HCV agents. These other anti-HCV agents can be, for example, HCV polymerase inhibitors (including nucleoside or non-nucleoside type of polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, internal ribosome entry site inhibitors, or HCV NS5A inhibitors. Specific examples of these other anti-HCV agents include, but are not limited to, ribavirin, oc-interferon, β -interferon, pegylated interferon- α , pegylated interferon-lambda, telaprevir, boceprevir, ITMN-191, BI-201335, TMC-435, MK-7009, VBY-376, VX-500 (Vertex), PHX-B, ACH-1625, IDX136, IDX316, VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191

(Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), BI-201335 (Boehringer Ingelheim), R7128 (Roche), PSI-7851 (Pharmasset), MK-3281 (Merck), PF-868554 (Pfizer), IDX-184 (Novartis), IDX-375 (Pharmasset), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), and Albuferon (Novartis).

[0054] A solid composition of the present invention preferably is a solid oral dosage form. Common solid oral dosage forms suitable for the present invention include, but are not limited to, capsules, dragees, granules, pills, powders and tablets, with capsules and tablets being preferred. A solid oral dosage form of the present invention can also include other excipients or inset diluents, such as sucrose, lactose or starch. Lubricants, coloring agents, releasing agents, coating agents, sweetening or flavoring agents, buffering agents, preservatives, or antioxidants can also be included in a solid oral dosage form of the present invention.

[0055] A solid composition of the present invention can be prepared by a variety of techniques such as, without limitation, melt-extrusion, spray-drying, co-precipitation, freeze drying, or other solvent evaporation techniques, with melt-extrusion and spray-drying being preferred. The melt-extrusion process typically comprises the steps of preparing a melt which includes the active ingredient(s), the hydrophilic polymer(s) and preferably the surfactant(s), and then cooling the melt until it solidifies. "Melting" means a transition into a liquid or rubbery state in which it is possible for one component to get embedded, preferably homogeneously embedded, in the other component or components. In many cases, the polymer component(s) will melt and the other components including the active ingredient(s) and surfactant(s) will dissolve in the melt thereby forming a solution. Melting usually involves heating above the softening point of the polymer(s). The preparation of the melt can take place in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or be simultaneously mixed and melted. The melt can also be homogenized in order to disperse the active ingredient(s) efficiently. In addition, it may be convenient first to melt the polymer(s) and then to mix in and homogenize the active ingredient(s). In one example, all materials except surfactant(s) are blended and fed into an extruder, while the surfactant(s) is molten externally and pumped in during extrusion.

[0056] In another example, the melt comprises Compound I and one or more hydrophilic polymers described above, and the melt temperature is in the range of from 100 to 170 °C, preferably from 120 to 150 °C, and highly preferably from 135 to 140 °C.

[0057] In yet another example, the melt comprises Compound I, ritonavir and one or more hydrophilic polymers described above. The melt can also include a pharmaceutically acceptable surfactant described above.

[0058] In still another example, the melt comprises Compound I, ritonavir, at least another HCV agent described above, and one or more hydrophilic polymers described above. The melt can also include a pharmaceutically acceptable surfactant described above.

[0059] To start a melt-extrusion process, the active ingredient(s) (e.g., Compound I, or a combination of Compound I and ritonavir, or a combination of Compound I, ritonavir and at least another anti-HCV agent) can be employed in their solid forms, such as their respective crystalline forms. The active ingredient(s) can also be employed as a solution or dispersion in a suitable liquid solvent such as alcohols, aliphatic hydrocarbons, esters or, in some cases, liquid carbon dioxide. The solvent can be removed, e.g. evaporated, upon preparation of the melt.

[0060] Various additives can also be included in the melt, for example, flow regulators (e.g., colloidal silica), binders, lubricants, fillers, disintegrants, plasticizers, colorants, or stabilizers (e.g., antioxidants, light stabilizers, radical scavengers, and stabilizers against microbial attack).

[0061] The melting and/or mixing can take place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders, intermeshing screw extruders or multiscrew extruders, preferably twin screw extruders, which can be corotating or counterrotating and, optionally, be equipped with kneading disks. It will be appreciated that the working temperatures will be determined by the kind of extruder or the kind of configuration within the extruder that is used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, the friction and shearing of the material in the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogeneous melt of the components.

[0062] The melt can range from thin to pasty to viscous. Shaping of the extrudate can be conveniently carried out by a calender with two counter-rotating rollers with mutually matching depressions on their surface. The extrudate can be cooled and allow to solidify. The extrudate can also be cut into pieces, either before (hot-cut) or after solidification (cold-cut).

[0063] The solidified extrusion product can be further milled, ground or otherwise reduced to granules. The solidified extrudate, as well as each granule produced, comprises a

solid dispersion, preferably a solid solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). Where the granules do not contain any surfactant, a pharmaceutically acceptable surfactant described above can be added to and blended with the granules. The extrusion product can also be blended with other active ingredient(s) and/or additive(s) before being milled or ground to granules. The granules can be further processed into suitable solid oral dosage forms.

[0064] In one example, copovidone and one or more surfactants are mixed and granulated, followed by the addition of aerosil, Compound I and ritonavir. The mixture is then milled. The weight ratio of Compound I over ritonavir can range, for example, from 1:1 to 5:1, such as 1:1, 2:1 or 4:1. For instance, the mixture can contain 10% Compound I and 5% ritonavir by weight. For another instance, the mixture can contain 15% Compound I and 7.5% ritonavir by weight. The mixture is then subject to extrusion, and the extrudate thus produced can be milled and sieved for further processing to make capsules or tablets. Surfactant(s) employed in this example can also be added through liquid dosing during extrusion.

[0065] In another example, copovidone and one or more surfactants are mixed and granulated, following by the addition of aerosil and Compound I. The mixture, which may contain for example 15% by weight of Compound I, is then milled and extruded. The extrudate thus produced can be further milled and sieved. Ritonavir extrudate can be similarly prepared. Compound I extrudate can be blended with ritonavir extrudate and then co-compressed to make tablets. Preferably, the weight ratio of Compound I over ritonavir in the blend can range, without limitation, from 1:1 to 1:5, such as 1:1, 2:1 or 4:1.

[0066] The approach of solvent evaporation, via spray-drying, provides the advantage of allowing for processability at lower temperatures, if needed, and allows for other modifications to the process in order to further improve powder properties. The spray-dried powder can then be formulated further, if needed, and final drug product is flexible with regards to whether capsule, tablet and/or co-formulation with ritonavir is desired.

[0067] Exemplary spray-drying processes and spray-drying equipment are described in K. Masters, SPRAY DRYING HANDBOOK (Halstead Press, New York, 4th ed., 1985). Non-limiting examples of spray-drying devices that are suitable for the present invention include spray dryers manufactured by Niro Inc. or GEA Process Engineering Inc., Buchi Labortechnik AG, and Spray Drying Systems, Inc. A spray-drying process generally involves breaking up a liquid mixture into small droplets and rapidly removing solvent from

the droplets in a container (spray drying apparatus) where there is a strong driving force for evaporation of solvent from the droplets. Atomization techniques include, for example, two-fluid or pressure nozzles, or rotary atomizers. The strong driving force for solvent evaporation can be provided, for example, by maintaining the partial pressure of solvent in the spray drying apparatus well below the vapor pressure of the solvent at the temperatures of the drying droplets. This may be accomplished by either (1) maintaining the pressure in the spray drying apparatus at a partial vacuum; (2) mixing the liquid droplets with a warm drying gas (e.g., heated nitrogen); or (3) both.

[0068] The temperature and flow rate of the drying gas, as well as the spray dryer design, can be selected so that the droplets are dry enough by the time they reach the wall of the apparatus. This help to ensure that the dried droplets are essentially solid and can form a fine powder and do not stick to the apparatus wall. The spray-dried product can be collected by removing the material manually, pneumatically, mechanically or by other suitable means. The actual length of time to achieve the preferred level of dryness depends on the size of the droplets, the formulation, and spray dryer operation. Following the solidification, the solid powder may stay in the spray drying chamber for additional time (e.g., 5-60 seconds) to further evaporate solvent from the solid powder. The final solvent content in the solid dispersion as it exits the dryer is preferably at a sufficiently low level so as to improve the stability of the final product. For instance, the residual solvent content of the spray-dried powder can be less than 2% by weight. Highly preferably, the residual solvent content is within the limits set forth in the International Conference on Harmonization (ICH) Guidelines. In addition, it may be useful to subject the spray-dried composition to further drying to lower the residual solvent to even lower levels. Methods to further lower solvent levels include, but are not limited to, fluid bed drying, infra-red drying, tumble drying, vacuum drying, and combinations of these and other processes.

[0069] Like the solid extrudate described above, the spray dried product contains a solid dispersion, preferably a solid solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). Where the spray dried product does not contain any surfactant, a pharmaceutically acceptable surfactant described above can be added to and blended with the spray-dried product before further processing.

[0070] Before feeding into a spray dryer, the active ingredient(s) (e.g., Compound I, or a combination of Compound I and ritonavir, or a combination of Compound I, ritonavir and at least another anti-HCV agent), the hydrophilic polymer(s), as well as other optional

active ingredients or excipients such as the pharmaceutically acceptable surfactant(s), can be dissolved in a solvent. Suitable solvents include, but are not limited to, alkanols (e.g., methanol, ethanol, 1-propanol, 2-propanol or mixtures thereof), acetone, acetone/water, alkanol/water mixtures (e.g., ethanol/water mixtures), or combinations thereof. The solution can also be preheated before being fed into the spray dryer.

[0071] The solid dispersion produced by melt-extrusion, spray-drying or other techniques can be prepared into any suitable solid oral dosage forms. In one embodiment, the solid dispersion prepared by melt-extrusion, spray-drying or other techniques (e.g., the extrudate or the spray-dried powder) can be compressed into tablets. The solid dispersion can be either directly compressed, or milled or ground to granules or powders before compression. Compression can be done in a tablet press, such as in a steel die between two moving punches. When a solid composition of the present invention comprises Compound I and ritonavir, or Compound I and another anti-HCV agent, it is possible to separately prepare solid dispersions of each individual active ingredient and then blend the optionally milled or ground solid dispersions before compacting. Compound I and other active ingredient(s) can also be prepared in the same solid dispersion, optionally milled and/or blended with other additives, and then compressed into tablets.

[0072] At least one additive selected from flow regulators, disintegrants, bulking agents (fillers) and lubricants may be used in compressing the solid dispersion. These additives can be mixed with ground or milled solid dispersion before compacting. Disintegrants promote a rapid disintegration of the compact in the stomach and keeps the liberated granules separate from one another. Non-limiting examples of suitable disintegrants are cross-linked polymers such as cross-linked polyvinyl pyrrolidone and cross-linked sodium carboxymethylcellulose. Non-limiting examples of suitable bulking agents (also referred to as "fillers") are lactose, calcium hydrogenphosphate, microcrystalline cellulose (e.g., Avicell), silicates, in particular silicium dioxide, magnesium oxide, talc, potato or corn starch, isomalt, or polyvinyl alcohol. Non-limiting examples of suitable flow regulators include highly dispersed silica (e.g., Aerosil), and animal or vegetable fats or waxes. Non-limiting examples of suitable lubricants include polyethylene glycol (e.g., having a molecular weight of from 1000 to 6000), magnesium and calcium stearates, sodium stearyl fumarate, and the like.

[0073] Various other additives may also be used in preparing a solid composition of the present invention, for example dyes such as azo dyes, organic or inorganic pigments such

as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

[0074] Solid compositions according to certain embodiments of the present invention may contain several layers, for example laminated or multilayer tablets. They can be in open or closed form. "Closed dosage forms" are those in which one layer is completely surrounded by at least one other layer.

[0075] In order to facilitate the intake of a solid dosage form, it is advantageous to give the dosage form an appropriate shape. Large tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape.

[0076] A film coat on the tablet further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. The film-coat usually includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. polysorbates, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. Preferably, the film coat accounts for less than 5 % by weight of a pharmaceutical composition of the present invention.

[0077] In another aspect, the present invention features methods of using solid compositions of the present invention to treat HIV infection. The methods comprise administering a solid composition of the present invention to a patient in need thereof. A solid composition of the present invention can be administered either alone, or in combination with one or more other anti-HCV agents, such as those described hereinabove. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the severity of the HCV infection; the activity of Compound I in the particular patient; the specific solid composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration and rate of excretion; the duration of the treatment; drugs used in combination or coincidental with Compound I; and like factors well known in the medical arts.

[0078] In one embodiment, a method of the present invention comprises administering to a patient in need thereof a solid composition of the present invention and at least another anti-HCV agent, wherein said another anti-HCV agent is selected from HCV polymerase inhibitors (e.g., nucleoside or non-nucleoside HCV polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, internal

ribosome entry site inhibitors, or HCV NS5A inhibitors. Preferably, said another anti-HCV agent is an HCV polymerase inhibitor (e.g., nucleoside or non-nucleoside HCV polymerase inhibitor) or an HCV NS5A inhibitor. The administration of a solid composition of the present invention and another anti-HCV agent(s) can be concurrent or sequential.

[0079] The present invention also features use of a solid composition of the present invention for the manufacture of medicaments for the treatment of HCV infection.

[0080] It should be understood that the above-described embodiments and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

Example 1

[0081] Pharmacokinetic (PK) parameters of Compound I and ritonavir were estimated using WinNonlin 5.2 (Pharsight, Mountain View, CA), using non-compartmental analysis. Values below limit of quantification were replaced by zero. Missing values were treated as if they were never drawn. Nominal blood sampling times and doses as specified in the protocol were used for PK analysis.

[0082] The following primary pharmacokinetic (PK) parameters were determined for Compound I and ritonavir:

AUC_∞ Area under the concentration versus time curve from time 0 to infinity calculated as $AUC_{\infty} = AUC_{i_{as},t} + (C_{i_{as},t}/K_e)$, where $C_{i_{as},t}$ is the last quantifiable concentration

Dose-normalized AUC_∞ Dose-normalized area under the concentration versus time curve from time 0 to infinity (AUC_∞ or AUC_(0-Inf)):

$$AUC_{(0-Inf) \text{ norm}} = AUC_{(0-Inf)} * \frac{\text{normalized dose}}{\text{actual dose}}$$

C_{max} Maximum observed plasma concentration

Dose-normalized C_{max} Dose-normalized maximum observed plasma concentration:

$$C_{\text{max norm}} = C_{\text{max}} * \frac{\text{normalized dose}}{\text{actual dose}}$$

T_{\max}

Time of maximum plasma concentration

Example 2

[0083] Compound **I** in crystalline monohydrate and dihydrate forms was mixed with hydrophilic polymers and pharmaceutically acceptable surfactants at various ratios, and dissolved in an organic solvent (acetone or ethanol/water mixtures). The solvent was then removed from the system under heat (75°C) and vacuum, using a Genevac rotary evaporatory or Buchi Rotavap. Solid dispersions of Compound **I** at various drug loading levels and using different surfactants or polymers were sieved through a 30 mesh screen to reduce particle size. The resultant solid dispersion samples were used for amorphous characterization by X-ray powder diffraction (PXRD), chemical stability, in-vitro dissolution test and dog bioavailability studies.

[0084] For dog bioavailability studies, the solid dispersion powder was filled into hard gelatin capsules to achieve target dose of 50 mg. The capsule was co-dosed with a 50 mg of ritonavir. For in-vitro dissolution studies, the release of Compound **I** was evaluated.

[0085] The hydrophilic polymers tested included copovidone, hydroxypropyl methylcellulose acetate succinate (HPMC-AS), and hydroxypropyl methylcellulose grade E5 (HPMC-E5). The surfactants tested included Vitamin E TPGS, polysorbate 20, polysorbate 80, poloxamer, propylene glycol laurate, and span 20. The amount of the surfactant(s) in each solid dispersion tested was no more than 10% by weight, and the amount of Compound **I** in each solid dispersion ranged from 10 to 40% by weight.

[0086] All solid dispersions tested showed that Compound **I** was in an amorphous form, as indicated by their PXRD patterns. Solid dispersions containing copovidone or HPMC-AS were tested for stability and showed chemical stability after 4 weeks at 40 °C and 75% relative humidity in open dish studies. These solid dispersions also exhibited rapid dissolution rate.

Example 3

[0087] Two tablet formulations were prepared using spray-drying to produce a solid dispersion powder of amorphous Compound **I** within a polymer matrix. For the 1st tablet formulation, the spray dried powder contained 17.5% by weight of Compound **I**, 72.5% by weight of copovidone, and 10% by weight of polysorbate 80. For the 2nd tablet formulation, the spray dried powder contained 17.5% by weight of Compound **I**, 72.5% by weight of

copovidone, 7% by weight of propylene glycol monolaurate, and 3% by weight of Vitamin E TPGS. For both formulations, acetone was used as a solvent for spray-drying.

[0088] The spray dried powder was further dried under vacuum to remove residual solvent. The vacuum dried powder was blended with microcrystalline cellulose, anhydrous dibasic calcium phosphate, pregelatinized starch, croscarmellose sodium, colloidal silicon dioxide, and sodium stearyl fumarate. This blend was optionally dry granulated via roller compaction and then milled to produce granules. The resulting granules were then blended with additional sodium stearyl fumarate prior to being compressed into the final tablet dosage form.

Example 4

[0089] Compound I and ritonavir were co-extruded using melt-extrusion. Four extrudates were prepared, and then milled and filled into capsules. The 1st extrudate contained Compound I, ritonavir, copovidone, lauroglycol FCC, and Vitamin E TPGS in a weight ratio of 10:5:77:5:3 (hereinafter Formulation 1). The 2nd extrudate contained Compound I, ritonavir, copovidone, and polysorbate 80 in a weight ratio of 15:7.5:67.5: 10 (hereinafter Formulation 2). The 3rd extrudate contained Compound I, ritonavir, copovidone, lauroglycol FCC, and Vitamin E TPGS in a weight ratio of 10:5:79:4:2 (hereinafter Formulation 3). The 4th extrudate contained Compound I, ritonavir, copovidone, lauroglycol FCC, and Vitamin E TPGS in a weight ratio of 15:7.5:69.5:5:3 (hereinafter Formulation 4). Each of these extrudate capsules contained 50 mg Compound I and 25 mg ritonavir.

[0090] Compound I and ritonavir were also separately extruded using melt-extrusion. The Compound I extrudate contained Compound I, copovidone, Lauroglycol FCC, Vitamin E TPGS and aerosol in a weight ratio of 15:76: 5:3:1. The ritonavir extrudate contained ritonavir, copovidone, span 20 and aerosol in a weight ratio of 15:74: 10:1. Both extrudates were milled, mixed together, and then co-compressed into tablets. Each tablet contained 100 mg Compound I and 50 mg ritonavir (hereinafter Formulation 5).

[0091] The bioavailability of the extrudate capsules and the co-compressed tablet was assessed in Beagle dogs after single oral administration. The administered doses were 100 mg Compound I and 50 mg ritonavir per animal. Four dogs (two male and two female dogs) were used in the study. Thirty minutes prior to dosing, each dog received a subcutaneous dose of histamine (100 µg/kg 0.05 ml/kg in water). See Kahlson *et al.* J PHYSIOL 174:400-416 (1964); and Akimoto *et al.* EUR J PHARM BIOPHARM 49:99-102 (2000). Each dogs was subjected to single oral doses of Formulations 1-5 in different weeks, each week with one

single dose administration. Plasma samples were collected at 0.33, 1, 2, 4, 6, 8, 12 and 24 hours post-dose administration, and were analyzed for Compound I and ritonavir by LC-MS/MS.

[0092] The mean dose-normalized AUC_{∞} values of Compound I for Formulations 1-5 were 183.6, 131.6, 188.9, 190.3, and 299.1 $\mu\text{g}\cdot\text{h}/\text{ml}$, respectively, at a 10 mg/kg dose. The mean dose-normalized C_{max} values of Compound I for Formulations 1-5 were 28.5, 24.5, 23.6, 26.8, and 43.3 $\mu\text{g}/\text{ml}$, respectively, at a 10 mg/kg dose.

[0093] The mean dose-normalized AUC_{∞} values of ritonavir for Formulations 1-5 were 3.9, 2.8, 2.4, 1.3, and 3.4 $\mu\text{g}\cdot\text{h}/\text{ml}$, respectively, at a 5 mg/kg dose. The mean dose-normalized C_{max} values of ritonavir for Formulations 1-5 were 1.1, 0.8, 0.7, 0.5, and 1.1 $\mu\text{g}/\text{ml}$, respectively, at a 5 mg/kg dose.

[0094] The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

1. A solid composition comprising
 - (1) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof, in an amorphous form;
 - (2) a pharmaceutically acceptable hydrophilic polymer; and
 - (3) a pharmaceutically acceptable surfactant.
2. The composition of claim 1, comprising a solid dispersion which includes:
 - (1) said (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or said pharmaceutically acceptable salt thereof, and
 - (2) said polymer.
3. The composition of claim 2, wherein said polymer has a T_g of at least 50 °C.
4. The composition of claim 3, wherein said surfactant has a HLB value of at least 10.
5. The composition of claim 4, further comprising another surfactant having a HLB value of below 10.
6. The composition of claim 3, wherein said solid dispersion is an amorphous solid dispersion which further comprises said surfactant.
7. The composition of claim 3, wherein said polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.
8. The composition of claim 2, wherein said polymer is copovidone.

9. The composition of claim 8, wherein said surfactant is propylene glycol laurate.
10. The composition of claim 9, further comprising D-alpha-tocopheryl polyethylene glycol 1000 succinate.
11. The composition of claim 8, wherein said surfactant is polysorbate.
12. The composition of claim 8, wherein said surfactant is polysorbate 80.
13. The composition of claim 8, wherein said solid dispersion is an amorphous solid dispersion.
14. The composition of claim 8, where said solid dispersion is a solid solution which comprises said surfactant.
15. The composition of claim 1, further comprising ritonavir.
16. The composition of claim 2, wherein said solid dispersion further comprises ritonavir.
17. The composition of claim 6, wherein said solid dispersion further comprises ritonavir.
18. The composition of claim 14, wherein said solid solution further comprises ritonavir.
19. A process of making the composition of claim 1, comprising drying a solvent in a liquid solution, wherein said solution comprises:
 - (1) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof;
 - (2) said polymer; and
 - (3) said surfactant.

20. A process of making the composition of claim 1, comprising solidifying a melt, wherein said melt comprises:

- (1) (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide, or a pharmaceutically acceptable salt thereof;
- (2) said polymer; and
- (3) said surfactant.

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(54) Title: SOLID COMPOSITIONS

(57) Abstract: The present invention features solid compositions comprising Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, in an amorphous form. In one embodiment, Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, is formulated in an amorphous solid dispersion which comprises a pharmaceutically acceptable hydrophilic polymer and preferably a pharmaceutically acceptable surfactant.



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SOLID COMPOSITIONS

The present application claims the benefit from and incorporates by reference the entire contents of U.S. Provisional Application Serial No. 61/353,553, filed June 10, 2010, and
 5 U.S. Patent Application Serial No. 12/813,301, filed June 10, 2010

FIELD OF THE INVENTION

The present invention relates to solid compositions comprising anti-HCV compounds and methods of using the same to treat HCV infection.

10

BACKGROUND

The hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The
 15 open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

HCV infection is associated with progressive liver pathology, including cirrhosis and
 20 hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often inadequate. Therefore, there is a need for new drugs to treat HCV infection.

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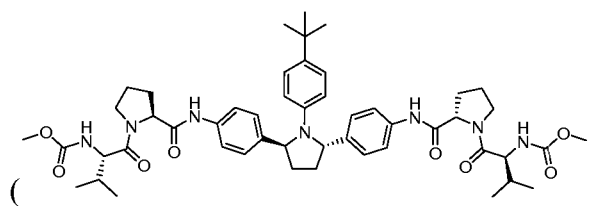
SUMMARY OF THE INVENTION

The present invention features solid compositions comprising a HCV inhibiting compound or a pharmaceutically acceptable salt thereof, wherein said HCV inhibiting compound is selected from the group consisting of:

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fer *t*-butylphenyl)pyrrolidine-
 30 2,5-diyl)bis(4, 1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2, 1-diyl))bis(3-

methyl-1-oxobutane-2,1-diyl)dicarbamate

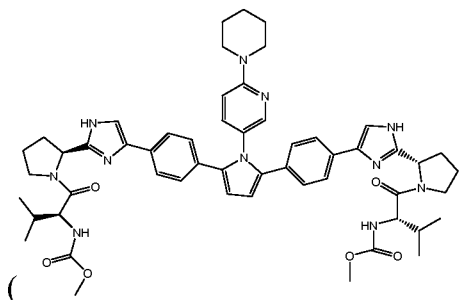
hereinafter Compound 1A),



methyl [(2S)-1-[(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-[(2S)-2-[(methoxycarbonyl)amino]-3-

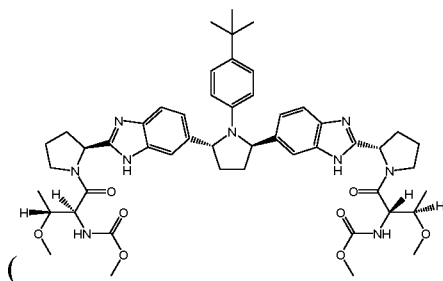
methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-4-yl}phenyl)-1-[6-(piperidin-1-yl)pyridin-3-yl]-

5 1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl] carbamate



, hereinafter Compound 1/2),

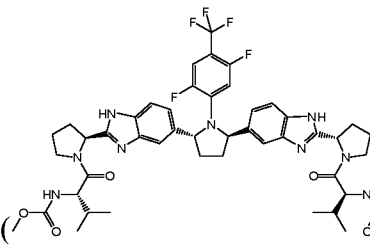
methyl {(2S,3R)-1-[(2S)-2-{6-[(2R,5R)-1-(4-tert-butylphenyl)-5-(2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl)-1 H-benzimidazol-6-yl]pyrrolidin-2-yl]-1 H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl} carbamate



10 (, hereinafter Compound 1c), and

methyl {(2S)-1-[(2S)-2-(5-[(2R,5R)-1-[2,5-difluoro-4-(trifluoromethyl)phenyl]-5-{2-[(2S)-1-[(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl]pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-

oxobutan-2-yl} carbamate (, hereinafter Compound 1D).



Compound IA, I_B, IC and I_D are potent HCV inhibitors. The solid compositions of the invention comprise (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and optionally (3) a pharmaceutically acceptable surfactant.

5 In one aspect, the present invention features a solid composition comprising a solid dispersion, wherein the solid dispersion comprises (1) a compound selected from Compound IA, I_B, IC or I_D (or a pharmaceutically acceptable salt thereof) in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant. The surfactant can be, without limitation, either formulated in the solid dispersion or
10 separately combined or mixed with the solid dispersion. Preferably, the hydrophilic polymer has a T_g of at least 50 °C. More preferably, the hydrophilic polymer has a T_g of at least 80 °C. Highly preferably, the hydrophilic polymer has a T_g of at least 100 °C. Also preferably, the surfactant has a HLB value of at least 10. Hydrophilic polymers with T_gs of below 50 °C, such as a polymer having a T_g of at least 25 °C, and/or surfactants having HLB values of below 10,
15 can also be used.

In one embodiment of this aspect of the invention, the hydrophilic polymer is selected from homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide, or polysaccharide. Non-limiting examples of suitable
20 hydrophilic polymers include homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, graft copolymer of polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate (e.g., Soluplus), polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose,
25 hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl
30 methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate,

carrageenan, galactomannan, or xanthan gum, or a combination thereof. In some cases, sugar alcohols can be used in addition to, or in lieu of, hydrophilic polymers.

In another embodiment of this aspect of the invention, the surfactant is selected from polyoxyethylene castor oil derivatives, mono fatty acid ester of polyoxyethylene sorbitan, polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester, or sorbitan fatty acid mono ester. Non-limiting examples of suitable surfactants include polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethyleneglycol 40 hydrogenated castor oil (Cremophor RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate) or polyethyleneglycol 60 hydrogenated castor oil (Cremophor RH 60), mono fatty acid ester of polyoxyethylene sorbitan, such as mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monopalmitate (Tween 40) or polyoxyethylene (20) sorbitan monolaurate (Tween 20), polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate (e.g., lauroglycol FCC), D₅-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan mono laurate, sorbitan monooleate, sorbitan monopalmitate, or sorbitan stearate, or a combination thereof. Other suitable ionic or non-ionic surfactants may also be used.

In yet another embodiment of this aspect of the invention, the solid dispersion is an amorphous solid dispersion. In still another embodiment, the solid dispersion is an amorphous solid dispersion which comprises (1) a compound selected from Compound IA, IB, IC or ID, or a pharmaceutically acceptable salt thereof, (2) the hydrophilic polymer, and (3) the surfactant. In a further embodiment, the solid dispersion is a solid solution comprising (1) a compound selected from Compound IA, IB, IC or ID, or a pharmaceutically acceptable salt thereof, and (2) the hydrophilic polymer. In yet another embodiment, the solid dispersion is a solid solution

comprising (1) a compound selected from Compound **IA**, **IB**, **IC** or **I_D**, or a pharmaceutically acceptable salt thereof, (2) the hydrophilic polymer, and (3) the surfactant.

In yet another embodiment of this aspect of the invention, the hydrophilic polymer is a homopolymer or copolymer of N-vinyl pyrrolidone. Preferably, the hydrophilic polymer is copovidone.

In still another embodiment, the surfactant is **D**-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS). In a further embodiment, the surfactant is lauroglycol FCC. In yet another embodiment, the surfactant is a combination of vitamin E TPGS and lauroglycol FCC. In still another embodiment, the surfactant is a sorbitan fatty acid ester, such as sorbitan mono laurate (Span 20). In another embodiment, the surfactant is selected from Tween 20, Tween 80, vitamin E TPGS, or lauroglycol FCC, or a combination thereof.

In yet another embodiment, a solid composition of the invention comprises an amorphous solid dispersion or a solid solution which comprises (1) a compound selected from Compound **IA**, **IB**, **IC** or **I_D**, or a pharmaceutically acceptable salt thereof, (2) copovidone, and (3) a surfactant selected from vitamin E TPGS, Span 20, or a combination thereof.

In another embodiment, a solid composition of the invention comprises an amorphous solid dispersion or a solid solution which comprises (1) a compound selected from Compound **IA**, **IB**, **IC** or **I_D**, or a pharmaceutically acceptable salt thereof, (2) copovidone, and (3) a combination of vitamin E TPGS and lauroglycol FCC.

In still another embodiment, a solid composition of the invention comprises an amorphous solid dispersion or a solid solution which comprises (1) a compound selected from Compound **IA**, **IB**, **IC** or **I_D**, or a pharmaceutically acceptable salt thereof, (2) copovidone, and (3) a surfactant selected from Tween 20 or Tween 80.

In another aspect, the present invention features processes of making a solid composition of the present invention. In one embodiment, the process comprises drying a solvent in a liquid solution, wherein said solution comprises: (1) a compound selected from Compound **IA**, **IB**, **IC** or **I_D**, or a pharmaceutically acceptable salt thereof; (2) a pharmaceutically acceptable hydrophilic polymer; and optionally (3) a pharmaceutically acceptable surfactant. The drying process can be carried out using any suitable solvent evaporation techniques including but not limited to spray-drying techniques.

In another embodiment, the process comprises solidifying a melt which comprises: (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof; (2) a pharmaceutically acceptable hydrophilic polymer; and optionally (3) a pharmaceutically acceptable surfactant.

5 A solid composition of the invention may also contain other additives or ingredients, such as coloring agents, flavoring agents, lubricants or preservatives. A solid composition of the invention can be prepared into any suitable dosage forms, such as capsule, dragee, granule, powder, or tablet.

10 A solid composition of the invention may further comprise another anti-HCV agent, for example, an agent selected from HCV helicase inhibitors, HCV polymerase inhibitors, HCV protease inhibitors, HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors.

15 The present invention further features methods of using a solid composition of the present invention to treat HCV infection. The methods comprise administering a solid composition of the present invention to a patient in need thereof, thereby reducing the blood or tissue level of HCV virus in the patient.

20 Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description.

DETAILED DESCRIPTION

25 The present invention features solid compositions comprising (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and optionally (3) a pharmaceutically acceptable surfactant. Formulating Compound IA, I_B, IC and I_D in an amorphous form can increase the inherent drug solubility and dissolution rate, thereby enhancing the bioavailability of the compound.

30 A non-limiting way to form an amorphous form of Compound IA, I_B, IC or I_D (or a pharmaceutically acceptable salt thereof) is through the formation of solid dispersions with a

polymeric carrier. The presence of hydrophilic polymer(s) and optional surfactant(s), as well as the dispersion of Compound IA, I_B, IC or I_D (or a pharmaceutically acceptable salt thereof) in an amorphous form in a matrix containing the polymer(s), can significantly enhance the dissolution rate of the compound. In some cases, a solid dispersion formulation can also effectively
5 maintain Compound IA, I_B, IC or I_D (or a pharmaceutically acceptable salt thereof) in its supersaturation state to allow for better absorption.

As used herein, the term "solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed throughout the other component or components. For example, an active
10 ingredient or a combination of active ingredients can be dispersed in a matrix comprised of a pharmaceutically acceptable hydrophilic polymer(s) and a pharmaceutically acceptable surfactant(s). The term "solid dispersion" encompasses systems having small particles of one phase dispersed in another phase. These particles are often of less than 400 μm in size, such as less than 100, 10, or 1 μm in size. When a solid dispersion of the components is such that the
15 system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion is called a "solid solution." A glassy solution is a solid solution in which a solute is dissolved in a glassy solvent.

The term AUC_{∞} or $\text{AUC}_{0-\infty}$ refers to the area under the plasma concentration time curve (AUC) extrapolated to infinity.

20 The terms "weight percent" or "percent by weight" or "% by weight" or "wt %" denote the weight of an individual component in a composition or mixture as a percentage of the weight of the composition or mixture.

In one aspect, the present invention features a solid composition comprising (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof,
25 in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant. The compound (or the salt thereof) and the polymer are formulated in a solid dispersion. The surfactant may be formulated in the same solid dispersion; or the surfactant can be separately combined or mixed with the solid dispersion.

In one embodiment, a solid composition of the invention comprises an amorphous
30 solid dispersion which comprises (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, (2) a pharmaceutically acceptable hydrophilic polymer,

and (3) a pharmaceutically acceptable surfactant. In another embodiment, a solid composition of the invention comprises a solid solution which comprises (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, and (2) a pharmaceutically acceptable hydrophilic polymer. In still another embodiment, a solid composition of the invention comprises a solid solution which comprises (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant. In yet another embodiment, a solid composition of the invention comprises a glassy solution which includes (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, and (2) a pharmaceutically acceptable hydrophilic polymer. In a further embodiment, a solid composition of the invention comprises a glassy solution which includes (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant.

A solid composition (or a solid dispersion) of the invention can contain, for example, at least 1% by weight of Compound IA, I_B, IC or I_D (or a pharmaceutically acceptable salt thereof), preferably at least 5%, including, e.g., at least 10%. For instance, a solid composition (or a solid dispersion) of the invention can contain from 1 to 50% by weight of the compound (or the salt thereof). For another instance, a solid composition (or a solid dispersion) of the invention can contain from 5 to 30% by weight of the compound (or the salt thereof). Preferably, a solid composition (or a solid dispersion) of the invention contains from 5 to 15% by weight of the compound (or the salt thereof).

A solid dispersion of the invention may contain at least 30% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. Preferably, the solid dispersion contains at least 40% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. More preferably, the solid dispersion contains at least 50% (including, e.g., at least 60%, 70%, 80% or 90%) by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers. A solid dispersion (or a solid composition) of the invention may also contain at least 1% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. Preferably, the solid dispersion (or solid composition) contains at least 2% by weight of a

pharmaceutically acceptable surfactant or a combination of such surfactants. More preferably, the solid dispersion (or solid composition) contains from 4% to 20% by weight of the surfactant(s), such as from 5% to 10% by weight of the surfactant(s).

In one embodiment, a solid dispersion (or a solid composition) of the invention
5 comprises at least 30% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and at least 1% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In another embodiment, a solid dispersion (or a solid composition) of the invention comprises at least 50% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 2% to 20% by
10 weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In yet another embodiment, a solid dispersion (or a solid composition) of the invention comprises from 50% to 90% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 3% to 15% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In yet another embodiment, a solid dispersion (or a solid
15 composition) of the invention comprises from 70% to 90% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 5% to 10% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants.

Preferably, a hydrophilic polymer employed in the present invention has a T_g of at least 50 °C, more preferably at least 60 °C, and highly preferably at least 80 °C including, but not
20 limited to from, 80 °C to 180 °C, or from 100 °C to 150 °C. Methods for determining T_g values of organic polymers are described in INTRODUCTION TO PHYSICAL POLYMER SCIENCE (2nd Edition by L.H. Sperling, published by John Wiley & Sons, Inc., 1992). The T_g value can be calculated as the weighted sum of the T_g values for homopolymers derived from each of the individual monomers, i.e., the polymer $T_g = \sum W_i \cdot X_i$ where W_i is the weight percent of monomer
25 i in the organic polymer, and X_i is the T_g value for the homopolymer derived from monomer i . T_g values for the homopolymers may be taken from POLYMER HANDBOOK (2nd Edition by J. Brandrup and E.H. Immergut, Editors, published by John Wiley & Sons, Inc., 1975). Hydrophilic polymers with a T_g as described above may allow for the preparation of solid dispersions that are mechanically stable and, within ordinary temperature ranges, sufficiently
30 temperature stable so that the solid dispersions may be used as dosage forms without further

processing or be compacted to tablets with only a small amount of tableting aids. Hydrophilic polymers having a T_g of below 50°C may also be used.

Preferably, a hydrophilic polymer employed in the present invention is water-soluble. A solid composition of the present invention can also comprise poorly water-soluble or water-insoluble polymer or polymers, such as cross-linked polymers. A hydrophilic polymer comprised in a solid composition of the present invention preferably has an apparent viscosity, when dissolved at 20 °C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa-s., and more preferably of 1 to 700 mPa-s, and most preferably of 5 to 100 mPa-s.

Hydrophilic polymers suitable for use in a solid composition of the invention include, but are not limited to, homopolymers or copolymers of N-vinyl lactams, such as homopolymers or copolymers of N-vinyl pyrrolidone (e.g., polyvinylpyrrolidone (PVP), or copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate); cellulose esters or cellulose ethers, such as alkylcelluloses (e.g., methylcellulose or ethylcellulose), hydroxyalkylcelluloses (e.g., hydroxypropylcellulose), hydroxyalkylalkylcelluloses (e.g., hydroxypropylmethylcellulose), and cellulose phthalates or succinates (e.g., cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, or hydroxypropylmethylcellulose acetate succinate); high molecular polyalkylene oxides, such as polyethylene oxide, polypropylene oxide, and copolymers of ethylene oxide and propylene oxide; polyacrylates or polymethacrylates, such as methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), and poly(hydroxyalkyl methacrylates); polyacrylamides; vinyl acetate polymers, such as copolymers of vinyl acetate and crotonic acid, and partially hydrolyzed polyvinyl acetate (also referred to as partially saponified "polyvinyl alcohol"); polyvinyl alcohol; oligo- or polysaccharides, such as carrageenans, galactomannans, and xanthan gum; polyhydroxyalkylacrylates; polyhydroxyalkyl-methacrylates; copolymers of methyl methacrylate and acrylic acid; polyethylene glycols (PEGs); graft copolymers of polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate, or any mixture or combination thereof. In some cases, sugar alcohols can be used in addition to, or in lieu of, hydrophilic polymers.

Non-limiting examples of preferred hydrophilic polymers for the invention include polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl

methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) L100-55, Eudragit L100, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, Soluplus, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.

Of these, homopolymers or copolymers of N-vinyl pyrrolidone, such as copolymers of N-vinyl pyrrolidone and vinyl acetate, are preferred. A non-limiting example of a preferred polymer is a copolymer of 60 % by weight of N-vinyl pyrrolidone and 40 % by weight of vinyl acetate. Other preferred polymers include, without limitation, hydroxypropyl methylcellulose (HPMC, also known as hypromellose in USP), such as hydroxypropyl methylcellulose grade E5 (HPMC-E5); and hydroxypropyl methylcellulose acetate succinate (HPMC-AS).

A pharmaceutically acceptable surfactant employed in the present invention is preferably a non-ionic surfactant. Ionic surfactants may also be used. More preferably, a solid composition of the present invention comprises a pharmaceutically acceptable surfactant having an HLB value of from 2-20. A solid composition of the present invention can also include a mixture of pharmaceutically acceptable surfactants, with at least one surfactant having an HLB value of no less than 10 and at least another surfactant having an HLB value of below 10. In one example, each surfactant comprised in a solid composition of the invention has an HLB value of at least 10. In another example, each surfactant comprised in a solid composition of the invention has an HLB value of below 10. In yet another example, a solid composition of the present invention includes at least two pharmaceutically acceptable surfactants, one having an HLB value of at least 10 and the other having an HLB value of below 10. The HLB system (Fiedler, H.B., *ENCYCLOPEDIA OF EXCIPIENTS*, 5th ed., Aulendorf: ECV-Editio-Cantor-Verlag (2002)) attributes numeric values to surfactants, with lipophilic substances receiving lower HLB values and hydrophilic substances receiving higher HLB values.

Non-limiting examples of pharmaceutically acceptable surfactants that are suitable for the present invention include polyoxyethylene castor oil derivatives, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor EL; BASF Corp.) or polyoxyethyleneglycerol

oxystearate such as polyethyleneglycol 40 hydrogenated castor oil (Cremophor RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate) or polyethyleneglycol 60 hydrogenated castor oil (Cremophor RH 60); or a mono fatty acid ester of polyoxyethylene sorbitan, such as a mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monopalmitate (Tween 40), or polyoxyethylene (20) sorbitan monolaurate (Tween 20). Other non-limiting examples of suitable surfactants include polyoxyethylene alkyl ethers, e.g. polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether; polyoxyethylene alkylaryl ethers, e.g. polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether; polyethylene glycol fatty acid esters, e.g. PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate; alkylene glycol fatty acid mono esters, e.g. propylene glycol monolaurate (lauroglycol, such as lauroglycol FCC); sucrose fatty acid esters, e.g. sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate; sorbitan fatty acid mono esters such as sorbitan mono laurate (Span 20), sorbitan monooleate, sorbitan monopalmitate (Span 40), or sorbitan stearate; D -alpha-tocopheryl polyethylene glycol 1000 succinate; or a combination or mixture thereof. Other suitable surfactants include, but are not limited to, block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene polypropyleneglycol, such as Poloxamer 124, Poloxamer 188, Poloxamer 237, Poloxamer 388, or Poloxamer 407 (BASF Wyandotte Corp.). As described above, a mixture of surfactants can be used in a solid composition of the present invention.

Non-limiting examples of preferred surfactants for the invention include to polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40, Cremophor EL, Gelucire 44/14, Gelucire 50/13, D -alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, and sorbitan monolaurate.

In one embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a compound selected from Compound IA, IB, IC or I_D, or a pharmaceutically acceptable salt thereof, and (2) a pharmaceutically acceptable hydrophilic polymer. The solid composition also includes a

pharmaceutically acceptable surfactant which preferably is formulated in the amorphous solid dispersion or solid solution. The hydrophilic polymer can be selected, for example, from the group consisting of homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide, and polysaccharide. As a non-limiting example, the hydrophilic polymer is selected from the group consisting of homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, graft copolymer of polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan, and xanthan gum. Preferably, the hydrophilic polymer is selected from polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) L100-55, Eudragit L100, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, Soluplus, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, or poloxamer 407. More preferably, the hydrophilic polymer is selected from homopolymers of vinylpyrrolidone (e.g., PVP with Fikentscher K values of from 12 to 100, or PVP with Fikentscher K values of from 17 to 30), or copolymers of 30 to 70% by weight of N-vinylpyrrolidone (VP) and 70 to 30% by weight of vinyl acetate (VA) (e.g., a copolymer of 60%> by weight VP and 40%> by weight VA). The surfactant can be selected, for

example, from the group consisting of polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate, mono fatty acid ester of polyoxyethylene sorbitan, polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester, and sorbitan fatty acid mono ester. As a non-limited example, the surfactant is selected from the group consisting of polyethyleneglycol 40 hydrogenated castor oil (Cremophor RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate), polyethyleneglycol 60 hydrogenated castor oil (Cremophor RH 60), a mono fatty acid ester of polyoxyethylene (20) sorbitan (e.g. polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monopalmitate (Tween 40), or polyoxyethylene (20) sorbitan monolaurate (Tween 20)), polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate, **D**-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, and sorbitan stearate. Preferably, the surfactant is selected from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40, Cremophor EL, Gelucire 44/14, Gelucire 50/13, **D**-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, or sorbitan monolaurate. More preferably, the surfactant is selected from sorbitan monolaurate, **D**-alpha-tocopheryl polyethylene glycol 1000 succinate, propylene glycol monolaurate, or a combination thereof (e.g., a combination of **D**-alpha-tocopheryl polyethylene glycol 1000 succinate and lauroglycol FCC).

In another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a compound selected from Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, and (2) a homopolymer or copolymer of N-vinyl pyrrolidone (e.g., copovidone). The solid composition also comprises a pharmaceutically acceptable surfactant (e.g., vitamin E TPGS, sorbitan monolaurate, or a

combination of vitamin E TPGS and lauroglycol FCC), wherein the surfactant preferably is formulated in the amorphous solid dispersion or solid solution.

In yet another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a compound selected from
5 Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, (2) copovidone, and (3) a pharmaceutically acceptable surfactant (e.g., vitamin E TPGS, sorbitan monolaurate, or a combination of vitamin E TPGS and lauroglycol FCC). The amorphous solid dispersion or solid solution may also include another pharmaceutically acceptable surfactant.

In still another embodiment, a solid composition of the present invention comprises an
10 amorphous solid dispersion or solid solution which includes (1) 10% by weight Compound IA, I_B, IC or I_D (or a pharmaceutically acceptable salt thereof) (2) 82% by weight copovidone, and (3) 5% by weight vitamin E TPGS and 2% by weight lauroglycol FCC. The solid composition can also include 1% by weight colloidal silica.

In a further embodiment, a solid composition of the present invention comprises an
15 amorphous solid dispersion or solid solution which includes (1) 10% by weight Compound IA, I_B, IC or I_D (or a pharmaceutically acceptable salt thereof) (2) 82% by weight copovidone, and (3) 7%, by weight propylene glycol monocaprylate (Capryol 90). The solid composition can also include 1% by weight colloidal silica.

A solid dispersion employed in the present invention preferably comprises or consists
20 of a single-phase (defined in thermodynamics) in which the therapeutic agent(s) (e.g., Compound IA, I_B, IC or I_D, or a pharmaceutically acceptable salt thereof, with or without another anti-HCV agent) is molecularly dispersed in a matrix containing the pharmaceutically acceptable hydrophilic polymer(s). In such cases, thermal analysis of the solid dispersion using differential scanning calorimetry (DSC) typically shows only one single T_g, and the solid dispersion does not
25 contain any detectable crystalline Compound IA, I_B, IC or I_D as measured by X-ray powder diffraction spectroscopy.

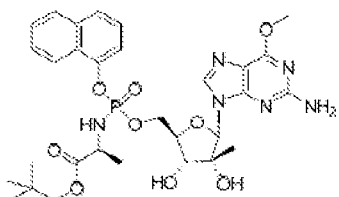
Compound IA, I_B, IC and I_D can be prepared according to the procedures described in Examples 37, 144, 250 and 237, respectively, of U.S. Patent Application Serial No. 12/813,301, filed June 10, 2010, now U.S. Patent Application Publication No. 2010/0317568, which is
30 incorporated herein by reference in its entirety.

A solid composition of the present invention can further include one or more other anti-HCV agents. These other anti-HCV agents can be, for example, HCV polymerase inhibitors (including nucleoside or non-nucleoside type of polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, internal ribosome entry site inhibitors, or HCV NS5A inhibitors. Specific examples of these other anti-HCV agents include, but are not limited to, ribavirin, α -interferon, β -interferon, pegylated interferon- α , pegylated interferon-lambda, PSI-7851 (Pharmasset) (nucleoside polymerase inhibitor), PSI-938 (Pharmasset) (nucleoside polymerase inhibitor), PF-00868554, ANA-598, IDX184 (nucleoside polymerase inhibitor), IDX102, IDX375 (non-nucleoside polymerase inhibitor), GS-9190 (non-nucleoside polymerase inhibitor), VCH-759, VCH-916, MK-3281, BCX-4678, MK-3281, VBY708, ANA598, GL59728, GL60667, BMS-790052 (NS5A inhibitor), BMS-791325 (protease Inhibitor), BMS-650032, BMS-824393, GS-9132, ACH-1095 (protease inhibitor), AP-H005, A-831 (Arrow Therapeutics) (NS5A inhibitor), A-689 (Arrow Therapeutics) (NS5A inhibitor), Γ NX08189 (Inhibitex) (polymerase inhibitor), AZD2836, telaprevir (protease Inhibitor), boceprevir (protease Inhibitor), ITMN-191 (Intermune/Roche), BI-201335 (protease Inhibitor), VBY-376, VX-500 (Vertex) (protease Inhibitor), PHX-B, ACH-1625, IDX136, IDX316, VX-813 (Vertex) (protease Inhibitor), SCH 900518 (Schering-Plough), TMC-435 (Tibotec) (protease Inhibitor), ITMN-191 (Intermune, Roche) (protease Inhibitor), MK-7009 (Merck) (protease Inhibitor), IDX-PI (Novartis), BI-201335 (Boehringer Ingelheim), R7128 (Roche) (nucleoside polymerase inhibitor), MK-3281 (Merck), MK-0608 (Merck) (nucleoside polymerase inhibitor), PF-868554 (Pfizer) (non-nucleoside polymerase inhibitor), PF-4878691 (Pfizer), IDX-184 (Novartis), IDX-375 (Pharmasset), PPI-461 (Presidio) (NS5A inhibitor), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), Albuferon (Novartis), ABT-333 (Abbott) (non-nucleoside polymerase inhibitor), and ABT-072 (Abbott) (non-nucleoside polymerase inhibitor).

In one embodiment, a solid composition of the invention comprises Compound IA, I_B, I_C or I_D (or a pharmaceutically acceptable salt thereof), and a HCV protease inhibitor. In another embodiment, a solid composition of the invention comprises Compound IA, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), and a HCV polymerase inhibitor (e.g., a non-nucleoside polymerase inhibitor, or preferably a nucleoside polymerase inhibitor). In yet another embodiment, a solid composition of the invention comprises (1) Compound IA, I_B, I_C or I_D (a

pharmaceutically acceptable salt thereof), (2) a HCV protease inhibitor, and (3) a HCV polymerase inhibitor (e.g., a non-nucleoside polymerase inhibitor, or preferably a nucleoside polymerase inhibitor). Non-limiting examples of protease and polymerase inhibitors are described above. For instance, the protease inhibitor can be selected from ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BI-201335 (Boehringer Ingelheim), BMS-650032 (BMS), boceprevir, danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof. And the HCV polymerase inhibitor can be selected from, without limitation, ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), or a combination thereof. The polymerase inhibitor may be a nucleotide polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), or a combination thereof. The polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof. The present invention also contemplates the inclusion of both a nucleotide polymerase inhibitor and a non-nucleoside polymerase inhibitor in a solid composition of the invention.

In yet another embodiment, a solid composition of the invention comprises (1) Compound 1A, 1_B, 1C or 1_D (a pharmaceutically acceptable salt thereof), and (2) INX-189



(Inhibitex;

). In still another embodiment, a solid composition of the

invention comprises (1) Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof),

and (2) RG7128, PSI-7977, PSI-938 or PSI-7851. In a further embodiment, a solid composition

of the invention comprises (1) Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt

thereof), (2) MK-5172, and optionally (3) RG7128. In another embodiment, a solid composition

of the invention comprises (1) Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt

thereof), (2) BMS-650032, and optionally (3) PSI-7977, PSI-938 or PSI-7851. In another

embodiment, a solid composition of the invention comprises (1) Compound IA, I_B, IC or I_D (a

pharmaceutically acceptable salt thereof), (2) danoprevir, and optionally (3) RG7128, PSI-7977,

PSI-938 or PSI-7851. In another embodiment, a solid composition of the invention comprises

(1) Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof), (2) TMC-435, and

optionally (3) RG7128, PSI-7977, PSI-938 or PSI-7851. In another embodiment, a solid

composition of the invention comprises (1) Compound IA, I_B, IC or I_D (a pharmaceutically

acceptable salt thereof), (2) BMS-650032, and optionally (3) BMS-790052. Compound I_A, I_B, I_C

or I_D (a pharmaceutically acceptable salt thereof), and BMS-790052, can be co-formulated in an

amorphous form, e.g., co-formulated in a solid dispersion or solid solution described herein. In

still another embodiment, a solid composition of the invention comprises (1) Compound IA, I_B, IC

or I_D (a pharmaceutically acceptable salt thereof), and (2) GS-9256, GS-9190, GS-9132, GS-

9451, GS-9669, or GS-6620.

Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof), and one or

more other anti-HCV agents described herein (e.g., MX-5172 or danoprevir), can be co-

formulated in amorphous forms, e.g., co-formulated in a solid dispersion or solid solution

described herein. Alternatively, Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt

thereof) can be co-administered with one or more other anti-HCV agents described herein, either

concurrently or sequentially, to a patient in need thereof for the treatment of HCV infection.

A solid composition of the present invention preferably is a solid oral dosage form.

Common solid oral dosage forms suitable for the present invention include, but are not limited

to, capsules, dragees, granules, pills, powders and tablets, with capsules and tablets being

preferred. A solid oral dosage form of the present invention can also include other excipients or inert diluents, such as sucrose, lactose or starch. Lubricants, coloring agents, releasing agents, coating agents, sweetening or flavoring agents, buffering agents, preservatives, or antioxidants can also be included in a solid oral dosage form of the present invention.

5 A solid composition of the present invention can be prepared by a variety of techniques such as, without limitation, melt-extrusion, spray-drying, co-precipitation, freeze drying, or other solvent evaporation techniques, with melt-extrusion and spray-drying being preferred. The melt-extrusion process typically comprises the steps of preparing a melt which includes the active ingredient(s), the hydrophilic polymer(s) and preferably the surfactant(s), and
10 then cooling the melt until it solidifies. Melting often involves a transition into a liquid state in which it is possible for one component to get dissolved or embedded, preferably homogeneously dissolved or embedded, in the other component or components. In many cases, the polymer component(s) will melt and the other components including the active ingredient(s) and surfactant(s) will dissolve in the melt thereby forming a solution. In such a case, the polymer
15 functions as a solvent. Melting usually involves heating above the softening point of the polymer(s). The preparation of the melt can take place in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or be simultaneously mixed and melted. The melt can also be homogenized in order to disperse the active ingredient(s) efficiently. In
20 addition, it may be convenient first to melt the polymer(s) and then to mix in and homogenize the active ingredient(s). In one example, all materials except surfactant(s) are blended and fed into an extruder, while the surfactant(s) is molten externally and pumped in during extrusion.

In another example, the melt comprises Compound IA, I_B, IC OR I_D (a pharmaceutically acceptable salt thereof), and one or more hydrophilic polymers described above; and the melt
25 temperature is in the range of from 100 to 170 °C, preferably from 120 to 150 °C, and highly preferably from 135 to 140 °C. The melt can also include a pharmaceutically acceptable surfactant described above.

In still another example, the melt comprises Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof), at least another anti-HCV agent described above, and
30 one or more hydrophilic polymers described above. The melt can also include a pharmaceutically acceptable surfactant described above.

To start a melt-extrusion process, the active ingredient(s) (e.g., Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof), or a combination of Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof) with at least another anti-HCV agent) can be employed in their solid forms, such as their respective crystalline forms. The active ingredient(s) can also
5 be employed as a solution or dispersion in a suitable liquid solvent such as alcohols, aliphatic hydrocarbons, esters or, in some cases, liquid carbon dioxide. The solvent can be removed, e.g. evaporated, upon preparation of the melt.

Various additives can also be included in the melt, for example, flow regulators (e.g., colloidal silica), binders, lubricants, fillers, disintegrants, plasticizers, colorants, or stabilizers
10 (e.g., antioxidants, light stabilizers, radical scavengers, and stabilizers against microbial attack).

The melting and/or mixing can take place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders, intermeshing screw extruders or multiscrew extruders, preferably twin screw extruders, which can be corotating or counterrotating and, optionally, be equipped with kneading
15 disks. It will be appreciated that the working temperatures will be determined by the kind of extruder or the kind of configuration within the extruder that is used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, the friction and shearing of the material in the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogeneous melt of the
20 components.

The melt can range from thin to pasty to viscous. Shaping of the extrudate can be conveniently carried out by a calender with two counter-rotating rollers with mutually matching depressions on their surface. The extrudate can be cooled and allow to solidify. The extrudate can also be cut into pieces, either before (hot-cut) or after solidification (cold-cut).

The solidified extrusion product can be further milled, ground or otherwise reduced to granules. The solidified extrudate, as well as each granule produced, comprises a solid dispersion, preferably a solid solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). Where the granules do not contain any surfactant, a pharmaceutically acceptable surfactant described above
25 can be added to and blended with the granules. The extrusion product can also be blended with
30

other active ingredient(s) and/or additive(s) before being milled or ground to granules. The granules can be further processed into suitable solid oral dosage forms.

In some cases, direct-shaping techniques such as injection moulding can be used in combination with melt extrusion to prepare suitable solid dosage forms.

5 In one example, copovidone and one or more surfactants are mixed and granulated, followed by the addition of aerosil and Compound **IA**, **IB**, **IC** or **I_D** (a pharmaceutically acceptable salt thereof). The mixture, which may contain for example at least 5% by weight of Compound **IA**, **IB**, **IC** or **I_D** (a pharmaceutically acceptable salt thereof) is then milled. The mixture is then subject to extrusion, and the extrudate thus produced can be milled and sieved for further
10 processing to make capsules or tablets. Surfactant(s) employed in this example can also be added through liquid dosing during extrusion.

The approach of solvent evaporation, via spray-drying, provides the advantage of allowing for processability at lower temperatures, if needed, and allows for other modifications to the process in order to further improve powder properties. The spray-dried powder can then
15 be formulated further, if needed, and final drug product is flexible with regards to whether capsule, tablet or any other solid dosage form is desired.

Exemplary spray-drying processes and spray-drying equipment are described in K. Masters, **SPRAY DRYING HANDBOOK** (Halstead Press, New York, 4th ed., 1985). Non-limiting examples of spray-drying devices that are suitable for the present invention include spray dryers
20 manufactured by Niro Inc. or GEA Process Engineering Inc., Buchi Labortechnik AG, and Spray Drying Systems, Inc. A spray-drying process generally involves breaking up a liquid mixture into small droplets and rapidly removing solvent from the droplets in a container (spray drying apparatus) where there is a strong driving force for evaporation of solvent from the droplets. Atomization techniques include, for example, two-fluid or pressure nozzles, or rotary atomizers.
25 The strong driving force for solvent evaporation can be provided, for example, by maintaining the partial pressure of solvent in the spray drying apparatus well below the vapor pressure of the solvent at the temperatures of the drying droplets. This may be accomplished by either (1) maintaining the pressure in the spray drying apparatus at a partial vacuum; (2) mixing the liquid droplets with a warm drying gas (e.g., heated nitrogen); or (3) both.

30 The temperature and flow rate of the drying gas, as well as the spray dryer design, can be selected so that the droplets are dry enough by the time they reach the wall of the apparatus.

This help to ensure that the dried droplets are essentially solid and can form a fine powder and do not stick to the apparatus wall. The spray-dried product can be collected by removing the material manually, pneumatically, mechanically or by other suitable means. The actual length of time to achieve the preferred level of dryness depends on the size of the droplets, the formulation, and spray dryer operation. Following the solidification, the solid powder may stay in the spray drying chamber for additional time (e.g., 5-60 seconds) to further evaporate solvent from the solid powder. The final solvent content in the solid dispersion as it exits the dryer is preferably at a sufficiently low level so as to improve the stability of the final product. For instance, the residual solvent content of the spray-dried powder can be less than 2% by weight. Highly preferably, the residual solvent content is within the limits set forth in the International Conference on Harmonization (ICH) Guidelines. In addition, it may be useful to subject the spray-dried composition to further drying to lower the residual solvent to even lower levels. Methods to further lower solvent levels include, but are not limited to, fluid bed drying, infra-red drying, tumble drying, vacuum drying, and combinations of these and other processes.

Like the solid extrudate described above, the spray dried product contains a solid dispersion, preferably a solid solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). Where the spray dried product does not contain any surfactant, a pharmaceutically acceptable surfactant described above can be added to and blended with the spray-dried product before further processing.

Before feeding into a spray dryer, the active ingredient(s) (e.g., Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof), or a combination of Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof) with at least another anti-HCV agent), the hydrophilic polymer(s), as well as other optional active ingredients or excipients such as the pharmaceutically acceptable surfactant(s), can be dissolved in a solvent. Suitable solvents include, but are not limited to, water, alkanols (e.g., methanol, ethanol, 1-propanol, 2-propanol or mixtures thereof), acetone, acetone/water, alkanol/water mixtures (e.g., ethanol/water mixtures), or combinations thereof. The solution can also be preheated before being fed into the spray dryer.

The solid dispersion produced by melt-extrusion, spray-drying or other techniques can be prepared into any suitable solid oral dosage forms. In one embodiment, the solid dispersion

prepared by melt-extrusion, spray-drying or other techniques (e.g., the extrudate or the spray-dried powder) can be compressed into tablets. The solid dispersion can be either directly compressed, or milled or ground to granules or powders before compression. Compression can be done in a tablet press, such as in a steel die between two moving punches. When a solid composition of the present invention comprises Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof) and another anti-HCV agent, it is possible to separately prepare solid dispersions of each individual active ingredient and then blend the optionally milled or ground solid dispersions before compacting. Compound IA, I_B, IC or I_D (a pharmaceutically acceptable salt thereof) and other active ingredient(s) can also be prepared in the same solid dispersion, optionally milled and/or blended with other additives, and then compressed into tablets.

At least one additive selected from flow regulators, binders, lubricants, fillers, disintegrants, or plasticizers may be used in compressing the solid dispersion. These additives can be mixed with ground or milled solid dispersion before compacting. Disintegrants promote a rapid disintegration of the compact in the stomach and keeps the liberated granules separate from one another. Non-limiting examples of suitable disintegrants are cross-linked polymers such as cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethylcellulose or sodium croscarmellose. Non-limiting examples of suitable fillers (also referred to as bulking agents) are lactose monohydrate, calcium hydrogenphosphate, microcrystalline cellulose (e.g., Avicell), silicates, in particular silicium dioxide, magnesium oxide, talc, potato or corn starch, isomalt, or polyvinyl alcohol. Non-limiting examples of suitable flow regulators include highly dispersed silica (e.g., colloidal silica such as Aerosil), and animal or vegetable fats or waxes. Non-limiting examples of suitable lubricants include polyethylene glycol (e.g., having a molecular weight of from 1000 to 6000), magnesium and calcium stearates, sodium stearyl fumarate, and the like.

Various other additives may also be used in preparing a solid composition of the present invention, for example dyes such as azo dyes, organic or inorganic pigments such as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

Solid compositions according to certain embodiments of the present invention may contain several layers, for example laminated or multilayer tablets. They can be in open or closed form. "Closed dosage forms" are those in which one layer is completely surrounded by at least one other layer.

In order to facilitate the intake of a solid dosage form, it is advantageous to give the dosage form an appropriate shape. Large tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape.

5 A film coat on the tablet further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. The film-coat usually includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. polysorbates, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-
10 coating may also comprise talc as anti-adhesive. Preferably, the film coat accounts for less than 5 % by weight of a pharmaceutical composition of the present invention.

In another aspect, the present invention feature methods of using solid compositions of the present invention to treat HIV infection. The methods comprise administering a solid composition of the present invention to a patient in need thereof. A solid composition of the
15 present invention can be administered either alone, or in combination with one or more other anti-HCV agents, such as those described hereinabove. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the severity of the HCV infection; the activity of the active ingredient(s) in the particular patient; the specific solid composition employed; the age, body weight, general health, sex and diet of the patient; the time
20 of administration and rate of excretion; the duration of the treatment; drugs used in combination or coincidental with Compound IA, I_B, IC or I_D; and like factors well known in the medical arts.

In one embodiment, a method of the present invention comprises administering to a patient in need thereof a solid composition of the present invention and at least another anti-HCV agent, wherein said another anti-HCV agent is selected from HCV polymerase inhibitors (e.g.,
25 nucleoside or non-nucleoside HCV polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, internal ribosome entry site inhibitors, or HCV NS5A inhibitors. Preferably, said another anti-HCV agent is an HCV polymerase inhibitor (e.g., nucleoside or non-nucleoside HCV polymerase inhibitor) or an HCV protease inhibitor. Also preferably, said another anti-HCV agent is interferon or ribavirin, or
30 preferably a combination thereof. The interferon preferably is a-interferon, and more preferably, pegylated interferon-a such as PEGASYS (peginterferon alfa-2a). The administration of a solid

composition of the present invention and another anti-HCV agent(s) can be concurrent or sequential.

The present invention also features use of a solid composition of the present invention for the manufacture of medicaments for the treatment of HCV infection.

It should be understood that the above-described embodiments and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

Example 1

Compound 1A was extruded using melt-extrusion. Two extrudates were prepared, and then milled and filled into capsules. The 1st extrudate contained Compound 1A, copovidone, and Vitamin E-TPGS in a weight ratio of 5:88:7 (hereinafter Formulation 1). The 2nd extrudate contained Compound 1A, copovidone and Sorbitan monolaurate in a weight ratio of 5:90:5 (hereinafter Formulation 2). The extrusion mixtures were prepared by use of mortar and pestle. Both formulations were extruded at 140°C. The obtained extruded strands were milled and the fractions of over 0.2 mm were combined with 100 mg mannite / colloidal silica (99:1) and then filled into capsules. Each of these extrudate capsules contained 5 mg Compound 1A-

Example 2

The pharmacokinetic profile of each formulation described in Example 1 was evaluated in dogs after single oral (PO) administration of the formulation. Four dogs (two male and two female dogs) were used in this study. The animals were fasted overnight and received food 30 min prior to dosing and throughout the duration of the study. Plasma samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post-dose administration. Plasma samples were analyzed for Compound 1A by LC-MS/MS. $AUC_{0-\infty}$ and C_{max} were normalized to a dose of 0.5 mg/kg Compound 1A-

Mean dose-normalized $AUC_{0-\infty}$ values of Compound 1A were 512.2 and 432.0 ng-h/ml, at a 0.5 mg/kg dose in Formulations 1 and 2, respectively. Mean dose-normalized C_{max} values of Compound 1A were 36.1 and 15.2 ng/ml at a 0.5 mg/kg dose in Formulations 1 and 2, respectively.

Example 3

Compound 1A was mixed with hydrophilic polymers and pharmaceutically acceptable surfactants at various ratios, and dissolved in an organic solvent (acetone or acetone/water mixtures). The solvent was then removed from the system under heat (~75°C) and vacuum, using a Genevac rotary evaporator or Buchi Rotavap. Solid dispersions of Compound 1A at various drug loading levels and using different surfactants or polymers were sieved through a 30 mesh screen to reduce particle size. The resultant solid dispersion samples were used for amorphous characterization by X-ray powder diffraction (PXRD), chemical stability, in-vitro dissolution test and dog bioavailability studies.

For dog bioavailability studies, the solid dispersion powder was mixed with other excipients and compressed into tablets to achieve strengths of 0.5 mg, 5.0 mg, and 25.0 mg. For in-vitro dissolution studies, the release of Compound 1A was evaluated.

The hydrophilic polymers employed were copovidone, Soluplus, hydroxypropyl methylcellulose phthalate (HPMCP), and hydroxypropyl methylcellulose grade E5 (HPMC-E5). The surfactants employed were Vitamin E TPGS and Cremophor RH40. The amount of the surfactant(s) in each solid dispersion was no more than 10% by weight, and the amount of Compound 1A in each solid dispersion ranged from 5 to 20% by weight.

All solid dispersions showed that Compound 1A was in an amorphous form, as indicated by their PXRD patterns. Solid dispersions containing copovidone were evaluated for stability and showed chemical stability after 4 weeks at 40 °C and 75% relative humidity in closed dish studies. These solid dispersions also exhibited rapid dissolution rate.

Example 4

One solid dispersion formulation was prepared using spray-drying to produce a solid dispersion powder of amorphous Compound 1A within a polymer matrix. The spray dried powder contained 10% by weight of Compound 1A, 85% by weight of copovidone, and 5% by weight of Vitamin E TPGS. Acetone and water in a 9:1 ratio was used as a solvent for spray-drying.

The spray dried powder was further dried under vacuum to remove residual solvent. The vacuum dried powder was blended with microcrystalline cellulose, lactose monohydrate,

colloidal silicon dioxide, sodium stearyl fumarate, and optionally croscarmellose sodium. This blend was then compressed into the final tablet dosage form.

Example 5

Compound I_B was formulated using melt-extrusion as well as spray-drying. Both formulations contained 10% Compound I_B, 82% copovidone, 2% Vitamin E TPGS, 5% lauroglycol FCC, and 1% Aerosil 200, and were processed further into compressed tablets. Both forms were tested in an accelerated stability test over 4 weeks. The pharmacokinetic study in dogs showed excellent bioavailability of Compound I_B.

Example 6

Compound I_c was mixed with Copovidone at drug loading of 10%>, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_c from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

The solid dispersion showed that Compound I_c was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_c in neat amorphous state.

Example 7

Compound I_c was mixed with Copovidone and Vitamin E TPGS at drug loading of 10%, and 20%>, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum (rotary evaporation or vacuum oven). Solid dispersion of Compound I_c at 10%> drug loading level was ground to fine particles using mortar and pestle, and was then characterized by X-ray powder diffraction (PXRD), DSC and TGA, and in vitro dissolution test. The resultant amorphous solid dispersion at 20% drug loading was also characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_c from above

amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound **Ic** was in an amorphous form, as indicated by PXRD, DSC or PLM. These solid dispersions exhibited rapid dissolution rate in comparison with Compound **Ic** in neat amorphous state.

Example 8

Compound **Ic** was mixed with Copovidone and Tween 80 or Cremophor RH40 at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound **Ic** from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

All four solid dispersions showed that Compound **Ic** was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound **Ic** in neat amorphous state.

Example 9

Compound **Ic** was mixed with Copovidone and Vitamin E TPGS and Lauroglycol FCC at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound **Ic** from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound **Ic** was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound **Ic** in neat amorphous state.

Example 10

Compound **Ic** was mixed with Soluplus and Vitamin E TPGS or Tween 80 or Cremophor RH40 at drug loading of 10% and 20%>, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound **Ic** from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

All six solid dispersions showed that Compound **Ic** was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound **Ic** in neat amorphous state.

Example 11

Compound **Ic** was mixed with Soluplus (a graft copolymer of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate) and Vitamin E TPGS and Lauroglycol FCC at drug loading of 10%> and 20%>, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound **Ic** from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound **Ic** was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound **Ic** in neat amorphous state.

Example 12

One solid dispersion formulation was prepared using spray-drying to produce a solid dispersion powder of amorphous Compound **Ic** within a polymer matrix. The spray dried powder contained 10%> by weight of Compound **Ic**, 85% by weight of Copovidone, and 5% by weight of Vitamin E TPGS. Methanol was used as a solvent for spray drying. The spray dried powder was further dried under vacuum to further remove residual solvent. The dried amorphous solid dispersion was characterized by X-ray powder diffraction (PXRD), DSC and TGA.

The solid dispersion showed that Compound Ic was in an amorphous form, as indicated by either PXRD and DSC.

Example 13

Compound I_D was mixed with Copovidone at drug loading of 10%, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

The solid dispersion showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 14

Compound I_D was mixed with Copovidone and Vitamin E TPGS or Tween 80 or Cremophor RH40 at drug loading of 10% and 20%>, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

All six solid dispersions showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 15

Compound I_D was mixed with Copovidone and Vitamin E TPGS and Lauroglycol FCC at drug loading of 10%> and 20%>, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from

above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 16

Compound I_D was mixed with Soluplus and Vitamin E TPGS or Tween 80 or Cremophor RH40 at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

All six solid dispersions showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 17

Compound I_D was mixed with Soluplus and Vitamin E TPGS and Lauroglycol FCC at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 18

Granulation of one formulation containing 15% Compound I_B, 7.1% Lauroglycol FCC, 2.9% Vitamin E TPGS and 75% copovidone was performed using a lab mill. Liquid excipients such as Lauroglycol FCC were granulated with the solid raw material, stored in the refrigerator over night for setting and mixed again. The resultant blends were used directly for
5 extrusion. Extrusion was carried out on a small-scale twin-screw extruder (rotation speed of 80 rpm) at a temperature of 140°C. Drug recovery and purity analysis after processing was evaluated by HPLC assay. The solid dispersion was characterized by DSC and polarized light microscopy (PLM). For in-vitro dissolution studies, the release of Compound I_B from above amorphous solid dispersion was evaluated in pH 6.8 phosphate buffer by HPLC assay.

10 DSC and PLM analysis of the solid dispersion revealed that Compound I_B was in an amorphous form and showed negligible degradation upon processing at high temperature. The solid dispersion exhibited rapid dissolution rate at pH 6.8.

It turned out that Compound I_B can be processed via melt extrusion at temperatures as high as about 170°C, which is far beyond the degradation temperature of the
15 drug substance of around 130°C without an increase in API degradation.

Example 19

Compound I_B was formulated using melt-extrusion as well as spray-drying. Both formulations included 10% Compound I_B, 82% copovidone, 5% Lauroglycol FCC, 2% Vitamin
20 E TPGS, and 1% Aerosil 200. Preparation of the granulate for melt extrusion was performed using a lab mill. Liquid excipients such as Lauroglycol FCC were granulated with the solid raw material, stored in the refrigerator over night for setting and mixed again. The resultant blends were used directly for extrusion. Extrusion was carried out on a small-scale twin-screw extruder (rotation speed of 80 rpm) at a temperature of 150°C. The resultant amorphous solid dispersion
25 was characterized by DSC and polarized light microscopy (PLM). For in-vitro dissolution studies, the release of Compound I_B from above amorphous solid dispersion was evaluated in pH 6.8 phosphate buffer by HPLC assay.

For spray drying, the same composition as applied for melt extrusion was dissolved in a isopropyl alcohol/water mixture, giving a feed solution formulation of 2 %
30 Compound I_B, 16.4% copovidone, 1% Lauroglycol FCC, 0.4% Vitamin E TPGS, 0.2% Aerosil 200, 70%, isopropyl alcohol and 10% DI water. The solid dispersion was manufactured using a

lab-scale spray drier at an inlet temperature of 110 °C and a rotavapor for post-drying at 40 °C and 40 mbar abs. to remove remaining solvents. The spray dried solid dispersion was tested for residual solvent content.

5 The yielded solid dispersions were compressed each into a 100 mg tablet by applying a direct-blend / direct-compression process of 50% solid dispersion, 28% Avicel 102, 14%, Di-CAFOS A, 5% croscarmellose sodium, 1% Aerosil 200 and 2% sodium stearyl fumarate.

10 The pharmacokinetic study in dogs showed excellent bioavailability of Compound I_B in the spray dried as well as in the melt extrusion tablet form compared to in vivo administration of a reference liquid formulation of compound I_B. Compressed tablets of both forms exhibited no degradation of compound I_B when stored at 40°C and 75% rel. humidity over 4 weeks. Dissolution behavior as well as the glass transition temperature remains constant.

Compound I_B was also formulated in solid dispersion with other surfactants such as Tween 80 or Cremophor RH40.

15 The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

1. A solid composition comprising

(1) a compound, or a pharmaceutically acceptable salt thereof, in an amorphous form,

(2) a pharmaceutically acceptable hydrophilic polymer; and

(3) optionally a pharmaceutically acceptable surfactant,

wherein said compound is selected from the group consisting of:

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fer *t*-butylphenyl)pyrrolidine-2,5-diyl)bis(4, 1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2, 1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (Compound IA),

methyl [(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(piperidin-1-yl)pyridin-3-yl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl] carbamate (Compound I_B),

methyl {(2S,3R)-1-[(2S)-2-{6-[(2R,5R)-1-(4-*tert*-butylphenyl)-5-(2-{(2S)-1-*N*-(methoxycarbonyl)-0-methyl-L-threonyl]pyrrolidin-2-yl}-1-*H*-benzimidazol-6-yl)pyrrolidin-2-yl]-1-*H*-benzimidazol-2-yl]pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl} carbamate (Compound I_C), and

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[2,5-difluoro-4-(trifluoromethyl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl} carbamate (Compound I_D).

2. The composition of claim 1, comprising a solid dispersion which includes:

(1) said compound or salt thereof, and

(2) said polymer.

3. The composition of claim 2, wherein said polymer has a T_g of at least 50 °C.

4. The composition of claim 3, further comprising said surfactant.

5. The composition of claim 4, wherein said solid dispersion comprises said surfactant.

6. The composition of claim 4, wherein said polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.

5

7. The composition of claim 4, wherein said polymer is copovidone.

8. The composition of claim 7, wherein said surfactant is D-alpha-tocopheryl polyethylene glycol 1000 succinate.

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9. The composition of claim 7, wherein said surfactant is a combination of D-alpha-tocopheryl polyethylene glycol 1000 succinate and propylene glycol monolaurate.

10. The composition of claim 7, wherein said surfactant is sorbitan mono laurate.

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11. The composition of claim 4, wherein said solid dispersion is an amorphous solid dispersion.

12. The composition of claim 4, where said solid dispersion is a solid solution which comprises said surfactant.

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13. The composition of claim 1, further comprising another anti-HCV agent.

14. The composition of claim 1, further comprising an HCV protease inhibitor.

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15. The composition of claim 1, further comprising an HCV polymerase inhibitor.

16. The composition of claim 4, wherein said compound is Compound IA.

17. The composition of claim 4, wherein said compound is Compound IB.

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18. The composition of claim 4, wherein said compound is Compound Ic.
19. The composition of claim 4, wherein said compound is Compound I_D.
- 5 20. A process of making the composition of claim 1, comprising dissolving said compound or salt in a solvent.
21. The process of claim 20, wherein said solvent is said polymer.
- 10 22. A method of treating HCV comprising administering the composition of claim 1 to a patient in need thereof.
23. The method of claim 22, comprising administering another anti-HCV agent to said patient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/039769

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/14 A61K9/16 A61K9/20 A61K31/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61K		
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal , CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2010/144646 A2 (ABBOTT LAB [US] ; DEGOEY DAVID A [US] ; KATI WARREN M [US] ; HUTCHINS CHA) 16 December 2010 (2010-12-16) cited in the applicati on exampl es 37, 144, 250, 237 page 407, line 19 - page 408, line 16 -----	1-8, 11, 12, 16-23
A	WO 2008/144380 A1 (SQUIBB BRISTOL MYERS CO [US] ; BACHAND CAROL [CA] ; BELEMA MAKONEN [US] ;) 27 November 2008 (2008-11-27) exampl es -----	1-23
A	WO 2008/021927 A2 (SQUIBB BRISTOL MYERS CO [US] ; BACHAND CAROL [CA] ; BELEMA MAKONEN [US] ;) 21 February 2008 (2008-02-21) exampl es ----- <div style="text-align: center;">-/- .</div>	1-23
<div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. </div> <div> <input checked="" type="checkbox"/> See patent family annex. </div> </div>		
* Special categories of cited documents : <div style="display: flex;"> <div style="flex: 1;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center;">26 September 2011</div>		Date of mailing of the international search report <div style="text-align: center;">06/10/2011</div>
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center;">SchLil e , Stefani e</div>

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/039769

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	wo 2010/017401 AI (SQUIBB BRISTOL MYERS CO [US] ; BELEMA MAKONEN [US] ; GOOD ANDREW C [US] ;) 11 February 2010 (2010-02-11) exampl es -----	1-23
A	DE FRANCESCO R ET AL: "Chal l enges and successes in devel opi ng new therapi es for hepati ti s C", NATURE, NATURE PUBLISHING GROUP, LONDON , GB, vol . 436, no. 7053 , 18 August 2005 (2005-08-18) , pages 953-960, XP002504755 , ISSN : 0028-0836, DOI : 10. 1038/NATURE04080 the whol e document -----	1-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/039769

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010144646 A2	16-12-2010	AR 077060 A1	27-07-2011
		AU 2010258769 A1	16-12-2010
		CA 2737601 A1	16-12-2010
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WO 2010017401 A1	11-02-2010	CN 102177141 A	07-09-2011
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(54) Title: SOLID COMPOSITIONS COMPRISING AN HCV INHIBITOR

(57) Abstract: The present invention features solid compositions comprising a selected HCV inhibitor in an amorphous form. In one embodiment, the selected HCV inhibitor is formulated in an amorphous solid dispersion which comprises a pharmaceutically acceptable hydrophilic polymer and preferably a pharmaceutically acceptable surfactant.



WO 2013/101550 A1

SOLID COMPOSITIONS COMPRISING AN HCV INHIBITOR

[0001] This application claims priority from U.S. Provisional Patent Application Serial No. 61/581,146, filed December 29, 2011, and U.S. Provisional Patent Application Serial No. 61/645,696, filed May 11, 2012, both of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention relates to solid compositions comprising anti-HCV compounds and methods of using the same to treat HCV infection.

BACKGROUND

[0003] The hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

[0004] HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often inadequate. Therefore, there is a need for new drugs to treat HCV infection.

SUMMARY OF THE INVENTION

[0005] The present invention features solid compositions comprising (1) an HCV inhibitor selected from telaprevir (VX-950), BI-201335, TMC-435 (TMC-435350), vaniprevir (MK-7009), MK-5172, asunaprevir (BMS-650032), daclatasvir (BMS-790052), danoprevir, simeprevir (ANA-598), tegobuvir (GS-333126 or GS-9190), GS-9451, mericitabine (R-4048), IDX-184, filibuvir (PF-00868554), PSI-7977, PSI-352938, BIT-225, boceprevir, GS-5885 or

GS-9256 (hereinafter a "selected HCV inhibitor"); (2) a pharmaceutically acceptable hydrophilic polymer; and optionally (3) a pharmaceutically acceptable surfactant.

[0006] In one aspect, the present invention features a solid composition comprising a solid dispersion, wherein the solid dispersion comprises (1) a selected HCV inhibitor in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant, wherein the selected HCV inhibitor is telaprevir (VX-950), BI-201335, TMC-435 (TMC-435350), vaniprevir (MK-7009), MK-5172, asunaprevir (BMS-650032), daclatasvir (BMS-790052), danoprevir, setrobuvir (ANA-598), tegobuvir (GS-333126 or GS-9190), GS-9451, mericitabine (RG-7128 or R-4048), IDX-184, filibuvir (PF-00868554), PSI-7977, PSI-352938, BIT-225, boceprevir, GS-5885 or GS-9256. The surfactant can be, without limitation, either formulated in the solid dispersion or separately combined or mixed with the solid dispersion. Preferably, the hydrophilic polymer has a T_g of at least 50 °C. More preferably, the hydrophilic polymer has a T_g of at least 80 °C. Highly preferably, the hydrophilic polymer has a T_g of at least 100 °C. Hydrophilic polymers with T_g s of below 50 °C, such as a polymer having a T_g of at least 25 °C, and/or surfactants having HLB values of below 10, can also be used.

[0007] In one embodiment of this aspect of the invention, the hydrophilic polymer is selected from homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide, or polysaccharide. Non-limiting examples of suitable hydrophilic polymers include homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, graft copolymer of polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate (e.g., Soluplus), polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate),

copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan, or xanthan gum, or a combination thereof. In some cases, sugar alcohols can be used in addition to, or in lieu of, hydrophilic polymers.

[0008] In another embodiment of this aspect of the invention, the surfactant is selected from polyoxyethylene castor oil derivatives, mono fatty acid ester of polyoxyethylene sorbitan, polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester, or sorbitan fatty acid mono ester. Non-limiting examples of suitable surfactants include polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethyleneglycol 40 hydrogenated castor oil (Cremophor RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate) or polyethyleneglycol 60 hydrogenated castor oil (Cremophor RH 60), mono fatty acid ester of polyoxyethylene sorbitan, such as mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monopalmitate (Tween 40) or polyoxyethylene (20) sorbitan monolaurate (Tween 20), polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate (e.g., lauroglycol FCC), D-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan mono laurate, sorbitan monooleate, sorbitan monopalmitate, or sorbitan stearate, or a combination thereof. Other suitable ionic or non-ionic surfactants may also be used.

[0009] In yet another embodiment of this aspect of the invention, the solid dispersion is an amorphous solid dispersion. In still another embodiment, the solid dispersion is an amorphous solid dispersion which comprises (1) the selected HCV inhibitor, (2) the hydrophilic polymer, and (3) the surfactant. In a further embodiment, the solid dispersion is a solid solution comprising (1) the selected HCV inhibitor, and (2) the hydrophilic polymer. In yet another

embodiment, the solid dispersion is a solid solution comprising (1) the selected HCV inhibitor, (2) the hydrophilic polymer, and (3) the surfactant.

[0010] In yet another embodiment of this aspect of the invention, the hydrophilic polymer is a homopolymer or copolymer of N-vinyl pyrrolidone. Preferably, the hydrophilic polymer is copovidone.

[0011] In still another embodiment, the surfactant is D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS). In a further embodiment, the surfactant is lauroglycol FCC. In yet another embodiment, the surfactant is a combination of vitamin E TPGS and lauroglycol FCC. In still another embodiment, the surfactant is a sorbitan fatty acid ester, such as sorbitan mono laurate (Span 20). In another embodiment, the surfactant is selected from Tween 20, Tween 80, vitamin E TPGS, lauroglycol FCC, or a combination thereof.

[0012] In yet another embodiment, a solid composition of the invention comprises an amorphous solid dispersion or a solid solution which comprises (1) the selected HCV inhibitor, (2) copovidone, and (3) a surfactant selected from vitamin E TPGS, Span 20, or a combination thereof.

[0013] In another embodiment, a solid composition of the invention comprises an amorphous solid dispersion or a solid solution which comprises (1) the selected HCV inhibitor, (2) copovidone, and (3) a combination of vitamin E TPGS and lauroglycol FCC.

[0014] In still another embodiment, a solid composition of the invention comprises an amorphous solid dispersion or a solid solution which comprises (1) the selected HCV inhibitor, (2) copovidone, and (3) a surfactant selected from Tween 20 or Tween 80.

[0015] In another aspect, the present invention features processes of making a solid composition of the present invention. In one embodiment, the process comprises drying a volatile solvent in a liquid solution, wherein said solution comprises: (1) the selected HCV inhibitor; (2) a pharmaceutically acceptable hydrophilic polymer; and optionally (3) a pharmaceutically acceptable surfactant. The drying process can be carried out using any suitable solvent evaporation techniques including but not limited to spray-drying techniques.

[0016] In another embodiment, the process comprises solidifying a melt which comprises: (1) the selected HCV inhibitor; (2) a pharmaceutically acceptable hydrophilic polymer; and optionally (3) a pharmaceutically acceptable surfactant.

[0017] A solid composition of the invention may also contain other additives or ingredients, such as coloring agents, flavoring agents, lubricants or preservatives. A solid composition of the invention can be prepared into any suitable dosage forms, such as capsule, dragee, granule, powder, or tablet.

[0018] A solid composition of the invention may further comprise another anti-HCV agent, for example, an agent selected from HCV helicase inhibitors, HCV polymerase inhibitors, HCV protease inhibitors, HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors.

[0019] The present invention further features methods of using a solid composition of the present invention to treat HCV infection. The methods comprise administering a solid composition of the present invention to a patient in need thereof, thereby reducing the blood or tissue level of HCV virus in the patient.

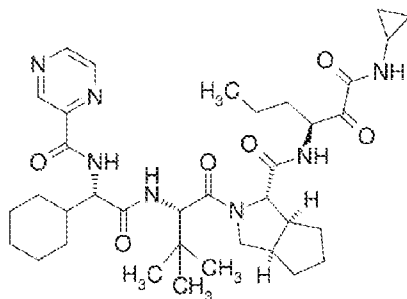
[0020] Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description.

DETAILED DESCRIPTION

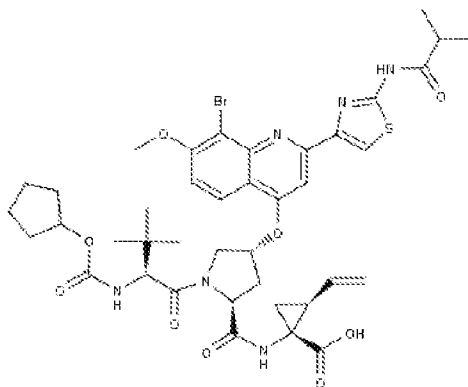
[0021] The present invention features solid compositions comprising (1) a selected HCV inhibitor, (2) a pharmaceutically acceptable hydrophilic polymer, and optionally (3) a pharmaceutically acceptable surfactant, wherein the selected inhibitor is telaprevir (VX-950), BI-201335, TMC-435 (TMC-435350), vaniprevir (MK-7009), MK-5172, asunaprevir (BMS-650032), daclatasvir (BMS-790052), danoprevir, setrobuvir (ANA-598), tegobuvir (GS-333126 or GS-9190), GS-9451, mericitabine (R-4048), IDX-184, filibuvir (PF-00868554), PSI-7977, PSI-352938, BIT-225, boceprevir, GS-5885 or GS-9256. Formulating the selected HCV inhibitor in an amorphous form can increase the inherent drug solubility and dissolution rate, thereby enhancing the bioavailability of the compound.

[0022] Telaprevir (VX-950), BI-201335, TMC-435 (TMC-435350), vaniprevir (MK-7009), MK-5172, asunaprevir (BMS-650032), danoprevir, GS-9451, boceprevir and GS-9256 are HCV protease inhibitors; daclatasvir (BMS-790052) and GS-5885 are HCV NS5A inhibitors;

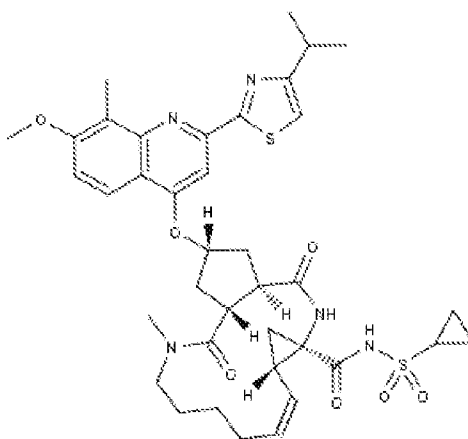
and setrobuvir (ANA-598), tegobuvir (GS-333126 or GS-9190), mericitabine (R-4048), IDX-184, filibuvir (PF-00868554), PSI-7977, PSI-352938 (PSI-938), and BIT-225 are polymerase inhibitors. The chemical structures of these selected HCV inhibitors are provided below:



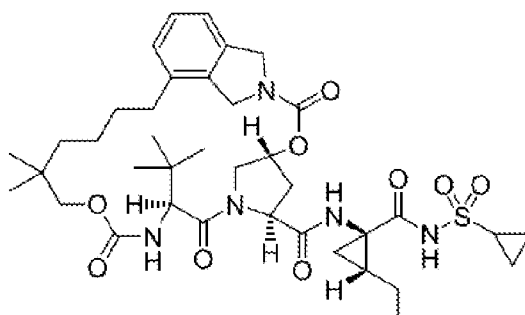
telaprevir



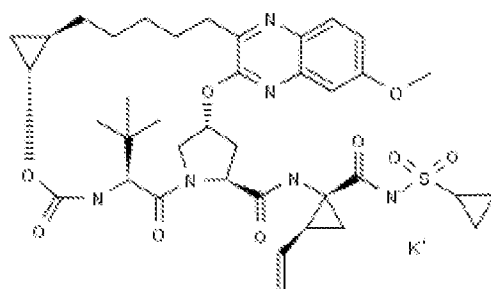
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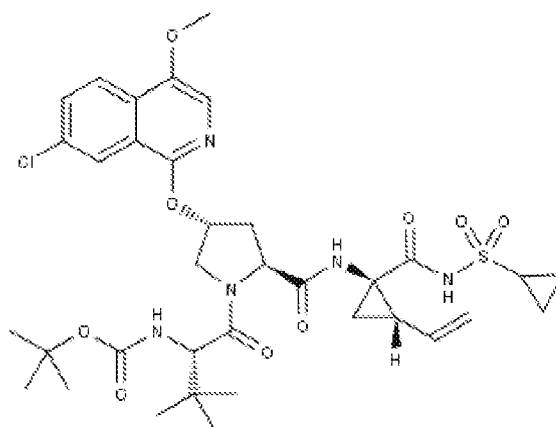
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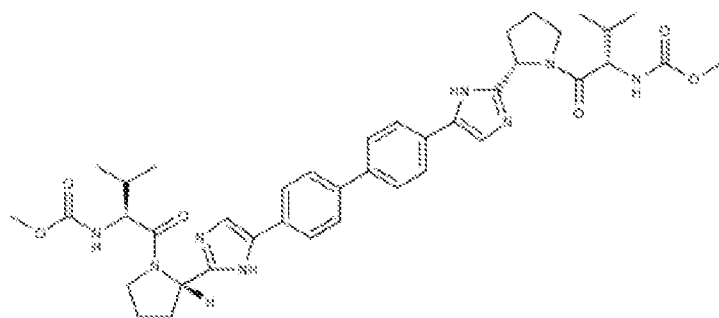
vaniprevir (MK-7009)



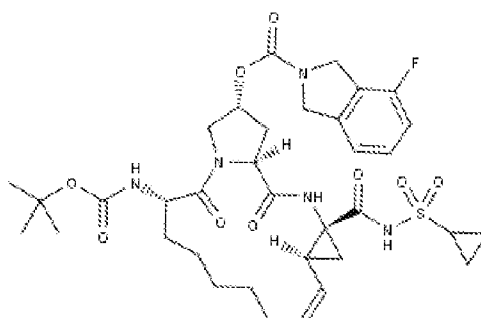
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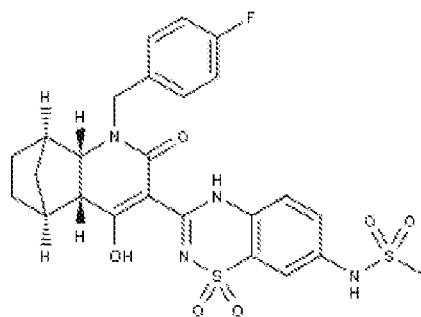
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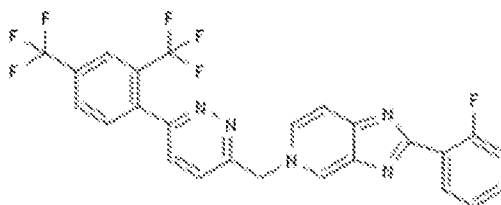
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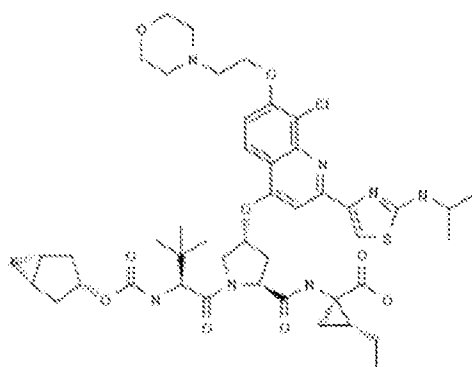
danoprevir



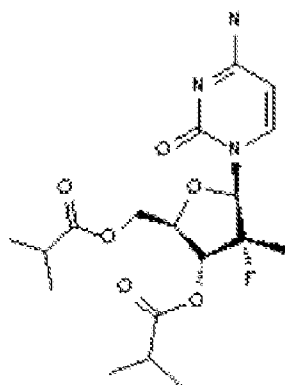
ANA-598 (Setrobuvir)



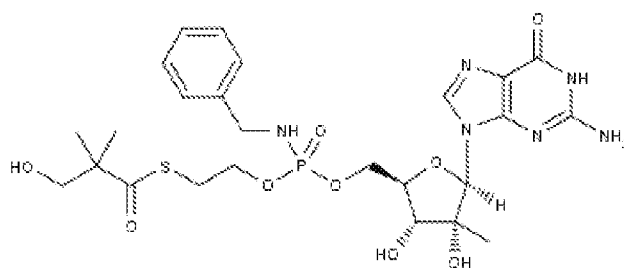
Tegobuvir



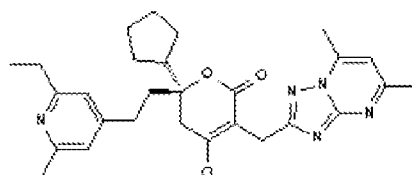
GS-9451



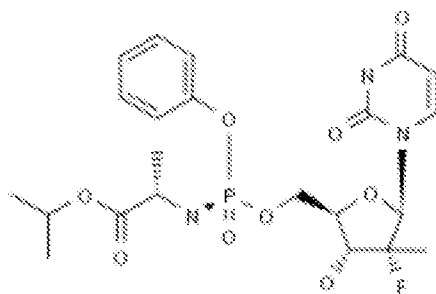
Mericitabine (R-4048)



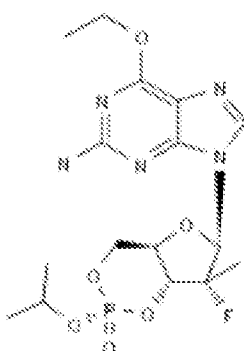
IDX-184



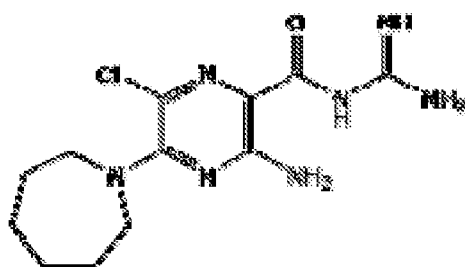
Filibuvir (PF-00868554)



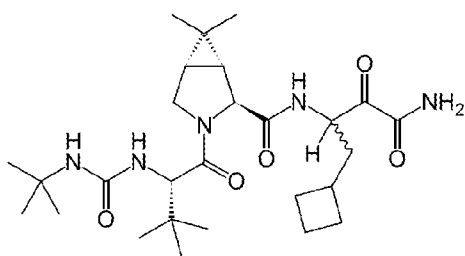
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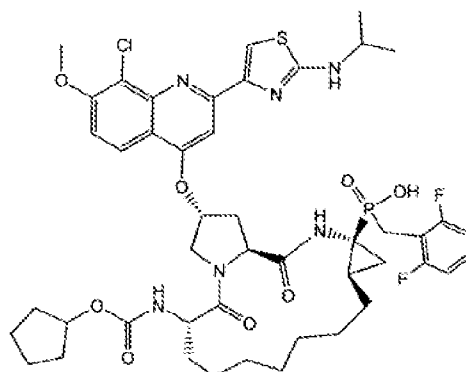
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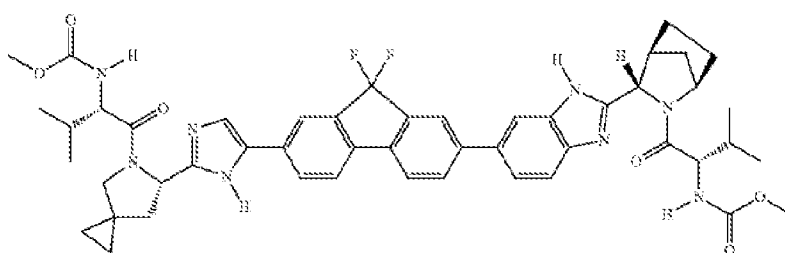
BIT-225



boceprevir



GS-9256



GS-5885

[0023] A non-limiting way to form an amorphous form of a selected HCV inhibitor described hereinabove is through the formation of solid dispersions with a polymeric carrier. The presence of hydrophilic polymer(s) and optional surfactant(s), as well as the dispersion of the selected HCV inhibitor in an amorphous form in a matrix containing the polymer(s), can significantly enhance the dissolution rate of the selected compound. In some cases, a solid dispersion formulation can also effectively maintain the selected HCV inhibitor in its supersaturation state to allow for better absorption.

[0024] As used herein, the term "solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed throughout the other component or components. For example, a selected HCV inhibitor described hereinabove can be dispersed in a matrix comprised of a pharmaceutically acceptable hydrophilic polymer(s) and a pharmaceutically acceptable surfactant(s). The term "solid dispersion" encompasses systems having small particles of one phase dispersed in another phase. These particles are often of less than 400 μm in size, such as less than 100, 10, or 1 μm in size. When a solid dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase

(as defined in thermodynamics), such a solid dispersion is called a "solid solution." A glassy solution is a solid solution in which a solute is dissolved in a glassy solvent.

[0025] The terms "weight percent" or "percent by weight" or "% by weight" or "wt %" denote the weight of an individual component in a composition or mixture as a percentage of the weight of the composition or mixture.

[0026] Modern new chemical entities tend to have higher molecular weight, greater lipophilicity and lower aqueous solubility, all of which negatively affect oral bioavailability. Despite formulation advances leading to the commercialization of enabling technologies such as lipid-based drug delivery systems (e.g. SEDDS) and nano-particles, the delivery of poorly water-soluble compounds remains challenging because of the limitations associated with each approach. Utilizing an amorphous solid dispersion (ASD) is attractive not only because it can increase the pharmacokinetic exposure of otherwise poorly absorbed drugs, but also because the final product may be delivered to the patient as a tablet or capsule, which may provide greater chemical stability and improved patient convenience compared to liquid dosage forms.

[0027] For all formulation approaches it is imperative to understand the intrinsic physicochemical and biopharmaceutical properties of the active drug substance prior to or at the onset of development. To that end, the biopharmaceutical classification system (BCS) has been routinely utilized to assess oral absorption and guide formulation development. For ASD formulations, the solubility/permeability of the active pharmaceutical ingredient (API) as well as the long term physical stability of the amorphous drug products are often considered. Conceptually, there are three major factors that influence the physical stability of an ASD: thermodynamic driving force (difference in drug loading and the solubility of drug in matrix), molecular mobility, and activation barrier for crystallization. The present invention relies on the use of an innovative assessment tool to rank the intrinsic physical stability of amorphous drug substances, e.g., crystallization tendency of amorphous API.

[0028] The molecular mobility of an amorphous material, which is often characterized by the relaxation time constant or its reciprocal, molecular mobility, is considered by many as a principal factor in determining its physical stability. Kinetic characterization of amorphous materials has been a subject of growing research in pharmaceutical field. The fact that crystallization of amorphous phases proceeds much faster in the supercooled liquid states compared to the glassy states demonstrates the importance of molecular mobility. However

significant differences in crystallization tendency have been observed across compounds that cannot be explained by mobility alone. For example, some amorphous phases crystallize almost immediately at the glass temperature, T_g (e.g., progesterone, parabens, acetaminophen), some crystallize below T_g in a relatively short time (e.g., griseofulvin, nifedipine), while others are quite stable. For some of the more stable amorphous phases, crystallization in the glassy state is often not observed and it does not proceed at a significant rate above T_g without seeding. Theoretically, T_g corresponds to the temperature of which the molecular relaxation time constant of the amorphous phase is equivalent to the experimental time scale. In light of these differences it has been postulated that, in addition to mobility, the thermodynamic driving force and activation barrier to crystallization contribute to the observed physical stability differences among these compounds.

[0029] Shamblin *et al*, **J. PHYS. CHEM. B** 103: 4113-4121 (1999), assessed molecular mobility of amorphous materials based on heat capacity measurements and the Adam-Gibbs model. This method allows calculation of molecular mobility using temperature-modulated differential scanning calorimetry (TMDSC) that is widely available in pharmaceutical laboratories together with the Adam-Gibbs model which has been used to characterize other materials, such as polymers and ceramics.

[0030] Using this method, the physical stability of pharmaceutically relevant compounds can be explored in an attempt to identify thermodynamic quantities critical to crystallization. Through this analysis, the calorimetric configurational entropy has been shown to be an important factor in determining crystallization tendency above the T_g .

[0031] The configurational entropy typically is a measure of the difference in the number of configurations between the amorphous and the crystalline phases. For molecules in the amorphous state to crystallize, they have to pack into a specific crystal lattice with defined configuration or orientation. Therefore, higher configurational entropy values suggest a lower probability that molecules are in the desirable orientation for packing into the crystal lattice. Hence, a meta-stable amorphous compound with larger configurational entropy tends to show greater physical stability. This is consistent with the observation that large molecules with numerous rotatable bonds are often more difficult to crystallize.

[0032] It has been hypothesized that the configurational entropy serves as a thermodynamic measurement of the probability of nucleation while the molecular mobility

dictates the rate at which a molecule can change its configurations and serves as a kinetic measurement of nucleation. Similar arguments may be applied to the rate of crystal growth as well. Therefore, these two quantities can be used to assess the intrinsic physical stability risk for the amorphous APIs.

[0033] Based on experimental crystallization observations of different compounds, Baird *et al*, **J. PHARM. SCI.** 99: 3787-3806 (2010); and Eerdenbrugh *et al*, **J. PHARM. SCI.** 99: 3826-3838 (2010) proposed a classification system for assessing the crystallization tendency of amorphous systems. However, crystallization experiments take relatively long time and the results are influenced by both intrinsic and extrinsic factors. The present invention utilizes the two above intrinsic properties and a different amorphous classification system (ACS) to assess the physical stability of amorphous drug candidates. The two intrinsic molecular properties can be calculated from a single convenient calorimetry measurement.

[0034] The structural flexibility and mobility of a molecule can be used to predict whether a compound will be kinetically stable as an amorphous phase. A physically stable amorphous API may play a role in the physical stability of a formulated ASD.

[0035] In the ACS used in the present invention, molecules can be categorized into four categories, as follows:

- Class I: Stable amorphous solid / poor crystallizer, and
High configurational entropy and low molecular mobility
(excellent candidates for developing ASD formulations)
- Class II: Intermediate amorphous stability / crystallizer, and
High configurational entropy but high molecular mobility
- Class III: Intermediate amorphous stability / crystallizer, and
Low molecular mobility but low configurational entropy
- Class IV: Unstable amorphous solid / good crystallizer, and
Low configurational entropy and high molecular mobility
(poor candidates for developing ASD formulations)

[0036] Mobility is highly dependent on the temperature but identical at the T_g for all glasses. Molecular mobility is usually represented by the VTF equation in the supercooled liquid state and by the AGV equation in the glassy state as follows:

$$\tau(T) = \tau_0 \exp\left(-\frac{DT_0}{T - T_0}\right) \quad (\text{VTF equation})$$

$$\tau(T, T_f) = \tau_0 \exp\left(-\frac{DT_0}{T - (T/T_f)T_0}\right) \quad (\text{AGV equation})$$

where τ is the relaxation time constant, τ_0 is a constant assumed to equal to 10^{-14} second, D is the strength parameter, and T_0 is the temperature with zero molecular mobility ($\tau = \infty$), which is called the Kauzmann temperature and is the temperature where the equilibrium supercooled liquid (i.e. ideal glass) has the same entropy as the crystalline state. T_f is the Active temperature, which is the temperature where the ideal glass has the same configurational entropy as a real glass at a given temperature (T). It is worth noting that, by definition, at T_g the relaxation time constants are the same for all amorphous systems (i.e. $\tau_g = 100$ sec). The strength parameter D can be used as a convenient representation of molecular mobility at $T < T_g$.

[0037] At the glass transition temperature, T_g , the following relationship holds, which can be obtained via the VTF equation:

$$\frac{T_g}{T_0} = \frac{D}{\ln(\tau_g / \tau_0)} + 1$$

where τ_g is the relaxation time constant at T_g . D and T_0 are not independent and that $T_g IT_0$ is a parameter associated with the strength parameter D . In many theoretical treatments, τ_0 is assumed to be 10^{-14} sec, therefore $\ln(x_g/x_0) = \ln(10^{16}) = 36.84$ is a constant.

[0038] Given that T_g is the temperature associated with a constant mobility (i.e. $\tau = 100$ sec) while T_0 is a temperature associated with zero mobility for ideal glasses, the ratio of $T_g IT_0$, and therefore the value D , represent how fast the molecular mobility of an ideal glass decreases with lowering temperature. The higher the D value, the slower the rate of decrease of molecular mobility with lowering temperature, thus favors crystallization.

[0039] It can be further shown for ideal glasses, that:

$$\ln[\tau_T / \tau_0] = \frac{DC(T_g / T)}{D + C(1 - T_g / T)}$$

Where $C = \ln(x_g / \tau_0) = 36.84$. Given $C > 0$, $T_g/T > 1$, hence at a common temperature represented on the scale of $T_g IT$, the molecular mobility of the ideal glass is expected to be

higher for a glass with larger D value. Opposite trend is true in the supercooled liquid state above T_g . Therefore the strength parameter serves a convenient indicator for molecular mobility in ideal glasses: the larger the D value, the higher the mobility (at identical T_g/T).

[0040] "Ideal freshly prepared glass" is one that is melt-quenched with sufficiently high cooling rates, such that no structural relaxation has occurred at temperatures below the glass transition temperature. In such "ideal freshly prepared glasses", the fictive temperature T_f equals its glass transition temperature, T_g . Therefore molecular relaxation time constant for an "ideal freshly prepared glass" may be derived based on the AGV equation:

$$\tau(T < T_g) = \tau_0 \exp\left(\frac{T_g}{T} \cdot \frac{DT_0}{T_g - T_0}\right) = \tau_0 \exp\left(\frac{T_g}{T} \cdot \ln(\tau_g / \tau_0)\right)$$

[0041] The above equation demonstrates the Arrhenius behavior with regard to the temperature dependence of molecular relaxation time constants in these systems. It is further noted that, at the same value of T_g/T , the molecular relaxation time constant or mobility is the same for all "ideal freshly prepared glasses", regardless of other characteristics of the system. At the first glance, the strength parameter does not appear to be relevant to the magnitude of molecular mobility.

[0042] However, configurations in real glasses are not fully arrested. Molecular motions do occur on a longer time scale which leads to structural relaxation or aging. As a result, molecular mobility of real glasses becomes a function of aging time. In reality, when a liquid is quench-cooled, structural relaxation has already occurred in any freshly prepared glass. During the process of aging, the strength parameter D plays a role in the evolution of molecular mobility, from the "ideal freshly prepared glass" where D is of no relevance, to the ideal glass where a higher D value is associated with a higher mobility. The evolution of the molecular mobility reveals a similar relationship between mobility and strength parameter, i.e. higher molecular mobility is dictated by a higher D value during this evolution process.

[0043] The configurational entropy at T_g would serve as a good indicator for this parameter for two reasons: (1) Amorphous pharmaceuticals are often practically stored below the glass transition temperature; (2) Configurational entropy for "ideal freshly prepared glass" is temperature independent at $T < T_g$.

[0044] During storage, the configurational entropy continuously decreases as structural relaxation occurs. However the decrease in entropy slows down with time and is far from the values in the ideal glass, even when considering the physical aging over the entire two year's of shelf-life.

[0045] To determine configurational entropy, instrument such as TMDSC can be calibrated to obtain accurate measurements of heat capacity. In addition, a conventional DSC scan may provide significant insight on this thermodynamic quantity. It has been observed that the change in configurational heat capacity at T_g or simply heat capacity change at T_g , $AC_p(T_g)$, shows a relatively good correlation with the configurational entropy and physical stability. Hence $AC_p(T_g)$, which can be obtained from a conventional DSC measurement, may serve as an approximate indicator or surrogate for configurational entropy. Heat capacity is a direct measurement on the modes by which a molecule can dissipate heat energies therefore is a physically meaningful measure of configurations. The heat capacity change at the glass transition temperature directly reflects the number of configurations that become available as a result of the glass-supercooled liquid transition. Because the temperature range of typical glass transition is relatively small, the contribution of anharmonic vibrations may be minimal. Therefore, such practices minimize the concerns on the true configurational origin of the excess entropy obtained via thermal analysis.

[0046] In addition, $AC_p(T_g)$ can be used to estimate the strength parameter D for a glass based on the Adam-Gibbs model and the assumption of hyperbolic temperature relationship of the configurational heat capacity, $C_{p^{conf}}$, at temperatures above T_g :

$$K = T \cdot C_{p^{conf}} \approx T_g \cdot \Delta C_p(T_g)$$

[0047] The entropy-based Kauzmann temperature is calculated as:

$$T_0 = \frac{T_m}{1 + \frac{\Delta H_m}{RT_m}}$$

where T_m and ΔH_m are the temperature and enthalpy of melting, respectively. Hence the strength parameter may be derived as:

$$D = \frac{T_g - T_0}{T_0} \cdot \ln(\tau_g / \tau_0)$$

[0048] The advantage of using $^A C_p(T_g)$ as an estimate of configurational entropy is that this quantity can be readily measured without laborious procedures such as those required for the determination of configuration entropy. In addition, the configurational entropy at T_g may be estimated based on $^A C_p(T_g)$ and other relevant parameters:

$$S_{\text{conf}}(T_g) = \Delta S_m - \int_{T_g}^{T_m} \frac{C_{p \text{ conf}}}{T} dT \approx \Delta S_m - K \left(\frac{1}{T_g} - \frac{1}{T_m} \right)$$

where ΔS_m is the entropy of melting.

[0049] The strength parameter D can therefore be used to represent the molecular mobility of an amorphous material, and the configurational entropy can be represented by its quantity at the glass transition temperature, or more conveniently, it can be represented by the change in heat capacity at T_g , $^A C_p(T_g)$. The high-low criterion for each quantity can then be defined to be used in the ACS assignment.

[0050] The criterion for stability is different across different fields of applications. Pharmaceutical products often concern the stability during the typical shelf lives, e.g., 2-3 years. A benchmarking approach may be adopted by surveying a number of pharmaceutical compounds with known physical stability, including those whose ASD formulations have been successfully commercialized. These compounds encompass a wide variety of structural features and a broad spectrum ranging from rapid crystallizers (such as acetaminophen, griseofulvin, phenobarbital, and sulfathiazole) to some that form kinetically stable amorphous phases (such as itraconazole, ketoconazole, saquinavir, ritonavir and lopinavir). These compounds include ritonavir, acetaminophen, fenofibrate, sucrose, nifedipine, griseofulvin, lopinavir, lovastatin, felodipine, indomethacin, itraconazole, ketoconazole, phenobarbital, flopropione, celecoxib, etoricoxib, rofecoxib, Valdecoxib, tolbutamide, quinidine, phenylbutazone, sulfathiazole, hydrochlorthiazide, glibenclamide, cimetidine, atropine, rac-Ibuprofen, salicin, santonin, simvastatin, and saquinavir.

[0051] Based on the assessments of mobility and configurational entropy, and the known physical stability for the above selected compounds in their amorphous states, the following criteria was developed:

- (1) $D \geq 9$ as the high molecular mobility criterion;

(2) $S_{\text{conf}}(T_g)/R \geq 6$ as the criterion for high configurational entropy. Alternatively high configurational entropy may be considered when ${}^A C_p(T_g)/R \geq 23$.

[0052] Choices of these criteria allow for categorization of the compounds into four categories in the context of physical stability or crystallization tendency. In many times, the configurational features of each molecule are reflected consistently by the simple measurement of ${}^A C_p(T_g)$ and information can be conveniently extracted to allow the ACS determination. The use of ${}^A C_p(T_g)$ allows the ACS assignment of a molecule even when no crystal form is identified, provided that the molecular mobility can be evaluated independently by other means such as viscosity measurement and the scanning rate dependence of the glass transition temperature.

[0053] Based on the above-described ACS model, it is believed that a selected HCV inhibitor described hereinabove is a good candidate for developing ASD formulations.

[0054] In one aspect, the present invention features a solid composition comprising (1) a selected HCV inhibitor, (2) a pharmaceutically acceptable hydrophilic polymer, and optionally (3) a pharmaceutically acceptable surfactant, wherein the selected HCV inhibitor is telaprevir (VX-950), BI-201335, TMC-435 (TMC-435350), vaniprevir (MK-7009), MK-5172, asunaprevir (BMS-650032), daclatasvir (BMS-790052), danoprevir, setrobuvir (ANA-598), tegobuvir (GS-333126 or GS-9190), GS-9451, mericitabine (R-4048), IDX-184, filibuvir (PF-00868554), PSI-7977, PSI-352938, BIT-225, boceprevir, GS-5885 or GS-9256. The selected HCV inhibitor and the polymer can be formulated in a solid dispersion. The surfactant may be formulated in the same solid dispersion; or the surfactant can be separately combined or mixed with the solid dispersion.

[0055] In one embodiment, a solid composition of the invention comprises an amorphous solid dispersion which comprises (1) the selected HCV inhibitor, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant. In another embodiment, a solid composition of the invention comprises a solid solution which comprises (1) the selected HCV inhibitor, and (2) a pharmaceutically acceptable hydrophilic polymer. In still another embodiment, a solid composition of the invention comprises a solid solution which comprises (1) the selected HCV inhibitor, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant. In yet another embodiment, a solid

composition of the invention comprises a glassy solution which includes (1) the selected HCV inhibitor, and (2) a pharmaceutically acceptable hydrophilic polymer. In a further embodiment, a solid composition of the invention comprises a glassy solution which includes (1) the selected HCV inhibitor, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant.

[0056] A solid composition (or a solid dispersion) of the invention can contain, for example, at least 1% by weight of the selected HCV inhibitor, preferably at least 5%, including, e.g., at least 10%. For instance, a solid composition (or a solid dispersion) of the invention can contain from 1 to 50% by weight of the selected HCV inhibitor. For another instance, a solid composition (or a solid dispersion) of the invention can contain from 5 to 30% by weight of the selected HCV inhibitor. Preferably, a solid composition (or a solid dispersion) of the invention contains from 5 to 15% by weight of the selected HCV inhibitor.

[0057] A solid dispersion of the invention may contain at least 30% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. Preferably, the solid dispersion contains at least 40% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. More preferably, the solid dispersion contains at least 50% (including, e.g., at least 60%, 70%, 80% or 90%) by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers. A solid dispersion (or a solid composition) of the invention may also contain at least 1% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. Preferably, the solid dispersion (or solid composition) contains at least 2% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. More preferably, the solid dispersion (or solid composition) contains from 4% to 20% by weight of the surfactant(s), such as from 5% to 10% by weight of the surfactant(s).

[0058] In one embodiment, a solid dispersion (or a solid composition) of the invention comprises at least 30% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and at least 1% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In another embodiment, a solid dispersion (or a solid composition) of the invention comprises at least 50% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 2% to 20% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In yet

another embodiment, a solid dispersion (or a solid composition) of the invention comprises from 50% to 90% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 3% to 15% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In yet another embodiment, a solid dispersion (or a solid composition) of the invention comprises from 70% to 90% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 5% to 10% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants.

[0059] Preferably, a hydrophilic polymer employed in the present invention has a T_g of at least 50 °C, more preferably at least 60 °C, and highly preferably at least 80 °C including, but not limited to from, 80 °C to 180 °C, or from 100 °C to 150 °C. Methods for determining T_g values of organic polymers are described in INTRODUCTION TO PHYSICAL POLYMER SCIENCE (2nd Edition by L.H. Sperling, published by John Wiley & Sons, Inc., 1992). The T_g value can be calculated as the weighted sum of the T_g values for homopolymers derived from each of the individual monomers, i.e., the polymer $T_g = \sum W_i \cdot X_i$ where W_i is the weight percent of monomer i in the organic polymer, and X_i is the T_g value for the homopolymer derived from monomer i . T_g values for the homopolymers may be taken from POLYMER HANDBOOK (2nd Edition by J. Brandrup and E.H. Immergut, Editors, published by John Wiley & Sons, Inc., 1975). Hydrophilic polymers with a T_g as described above may allow for the preparation of solid dispersions that are mechanically stable and, within ordinary temperature ranges, sufficiently temperature stable so that the solid dispersions may be used as dosage forms without further processing or be compacted to tablets with only a small amount of tableting aids. Hydrophilic polymers having a T_g of below 50°C may also be used.

[0060] Preferably, a hydrophilic polymer employed in the present invention is water-soluble. A solid composition of the present invention can also comprise poorly water-soluble or water-insoluble polymer or polymers, such as cross-linked polymers. A hydrophilic polymer comprised in a solid composition of the present invention preferably has an apparent viscosity, when dissolved at 20 °C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa-s., and more preferably of 1 to 700 mPa-s, and most preferably of 5 to 100 mPa-s.

[0061] Hydrophilic polymers suitable for use in a solid composition of the invention include, but are not limited to, homopolymers or copolymers of N-vinyl lactams, such as homopolymers or copolymers of N-vinyl pyrrolidone (e.g., polyvinylpyrrolidone (PVP), or

copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate); cellulose esters or cellulose ethers, such as alkylcelluloses (e.g., methylcellulose or ethylcellulose), hydroxyalkylcelluloses (e.g., hydroxypropylcellulose), hydroxyalkylalkylcelluloses (e.g., hydroxypropylmethylcellulose), and cellulose phthalates or succinates (e.g., cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, or hydroxypropylmethylcellulose acetate succinate); high molecular polyalkylene oxides, such as polyethylene oxide, polypropylene oxide, and copolymers of ethylene oxide and propylene oxide; polyacrylates or polymethacrylates, such as methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), and poly(hydroxyalkyl methacrylates); polyacrylamides; vinyl acetate polymers, such as copolymers of vinyl acetate and crotonic acid, and partially hydrolyzed polyvinyl acetate (also referred to as partially saponified "polyvinyl alcohol"); polyvinyl alcohol; oligo- or polysaccharides, such as carrageenans, galactomannans, and xanthan gum; polyhydroxyalkylacrylates; polyhydroxyalkyl-methacrylates; copolymers of methyl methacrylate and acrylic acid; polyethylene glycols (PEGs); graft copolymers of polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate, or any mixture or combination thereof. In some cases, sugar alcohols can be used in addition to, or in lieu of, hydrophilic polymers.

[0062] Non-limiting examples of preferred hydrophilic polymers for the invention include polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) LI00-55, Eudragit LI00, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, Soluplus, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.

[0063] Of these, homopolymers or copolymers of N-vinyl pyrrolidone, such as copolymers of N-vinyl pyrrolidone and vinyl acetate, are preferred. A non-limiting example of a preferred polymer is a copolymer of 60 % by weight of N-vinyl pyrrolidone and 40 % by weight

of vinyl acetate. Other preferred polymers include, without limitation, hydroxypropyl methylcellulose (HPMC, also known as hypromellose in USP), such as hydroxypropyl methylcellulose grade E5 (HPMC-E5); and hydroxypropyl methylcellulose acetate succinate (HPMC-AS).

[0064] A pharmaceutically acceptable surfactant employed in the present invention is preferably a non-ionic surfactant. Ionic surfactants may also be used. More preferably, a solid composition of the present invention comprises a pharmaceutically acceptable surfactant having an HLB value of from 2-20. In one example, a solid composition of the present invention includes a mixture of pharmaceutically acceptable surfactants, with at least one surfactant having an HLB value of no less than 10 and at least another surfactant having an HLB value of below 10. The HLB system (Fiedler, H.B., *ENCYCLOPEDIA OF EXCIPIENTS*, 5th ed., Aulendorf: ECV-Editio-Cantor-Verlag (2002)) attributes numeric values to surfactants, with lipophilic substances receiving lower HLB values and hydrophilic substances receiving higher HLB values.

[0065] Non-limiting examples of pharmaceutically acceptable surfactants that are suitable for the present invention include polyoxyethylene castor oil derivatives, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethylenglycol 40 hydrogenated castor oil (Cremophor RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate) or polyethylenglycol 60 hydrogenated castor oil (Cremophor RH 60); or a mono fatty acid ester of polyoxyethylene sorbitan, such as a mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monopalmitate (Tween 40), or polyoxyethylene (20) sorbitan monolaurate (Tween 20). Other non-limiting examples of suitable surfactants include polyoxyethylene alkyl ethers, e.g. polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether; polyoxyethylene alkylaryl ethers, e.g. polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether; polyethylene glycol fatty acid esters, e.g. PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate; alkylene glycol fatty acid mono esters, e.g. propylene glycol monolaurate (lauroglycol, such as lauroglycol FCC); sucrose fatty acid esters, e.g. sucrose monostearate,

sucrose distearate, sucrose monolaurate, sucrose dilaurate; sorbitan fatty acid mono esters such as sorbitan mono laurate (Span 20), sorbitan monooleate, sorbitan monopalmitate (Span 40), or sorbitan stearate; D-alpha-tocopheryl polyethylene glycol 1000 succinate; or a combination or mixture thereof. Other suitable surfactants include, but are not limited to, block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene polypropyleneglycol, such as Poloxamer 124, Poloxamer 188, Poloxamer 237, Poloxamer 388, or Poloxamer 407 (BASF Wyandotte Corp.). As described above, a mixture of surfactants can be used in a solid composition of the present invention.

[0066] Non-limiting examples of preferred surfactants for the invention include to polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40, Cremophor EL, Gelucire 44/14, Gelucire 50/13, D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, and sorbitan monolaurate.

[0067] In one embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a selected HCV inhibitor selected from telaprevir (VX-950), BI-201335, TMC-435 (TMC-435350), vaniprevir (MK-7009), MK-5172, asunaprevir (BMS-650032), daclatasvir (BMS-790052), danoprevir, setrobuvir (ANA-598), tegobuvir (GS-333126 or GS-9190), GS-9451, mericitabine (R-4048), IDX-184, filibuvir (PF-00868554), PSI-7977, PSI-352938, BIT-225, boceprevir, GS-5885 or GS-9256, and (2) a pharmaceutically acceptable hydrophilic polymer. The solid composition can also include a pharmaceutically acceptable surfactant which preferably is formulated in the amorphous solid dispersion or solid solution. The hydrophilic polymer can be selected, for example, from the group consisting of homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide, and polysaccharide. As a non-limiting example, the hydrophilic polymer is selected from the group consisting of homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate,

polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, graft copolymer of polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan, and xanthan gum. Preferably, the hydrophilic polymer is selected from polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) L100-55, Eudragit L100, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, Soluplus, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, or poloxamer 407. More preferably, the hydrophilic polymer is selected from homopolymers of vinylpyrrolidone (e.g., PVP with Fikentscher K values of from 12 to 100, or PVP with Fikentscher K values of from 17 to 30), or copolymers of 30 to 70% by weight of N-vinylpyrrolidone (VP) and 70 to 30% by weight of vinyl acetate (VA) (e.g., a copolymer of 60%> by weight VP and 40%> by weight VA). The surfactant can be selected, for example, from the group consisting of polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate, mono fatty acid ester of polyoxyethylene sorbitan, polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester, and sorbitan fatty acid mono ester. As a non-limited example, the surfactant is selected from the group consisting of polyethylenglycol 40 hydrogenated castor oil (Cremophor RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate), polyethylenglycol 60 hydrogenated castor oil (Cremophor RH 60), a mono fatty acid ester of polyoxyethylene (20) sorbitan (e.g. polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monopalmitate (Tween 40), or polyoxyethylene (20) sorbitan monolaurate (Tween 20)), polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl

ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate, **D**-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, and sorbitan stearate. Preferably, the surfactant is selected from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40, Cremophor EL, Gelucire 44/14, Gelucire 50/13, **D**-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, or sorbitan monolaurate. More preferably, the surfactant is selected from sorbitan monolaurate, **D**-alpha-tocopheryl polyethylene glycol 1000 succinate, propylene glycol monolaurate, or a combination thereof (e.g., a combination of **D**-alpha-tocopheryl polyethylene glycol 1000 succinate and lauroglycol FCC).

[0068] In another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a selected HCV inhibitor described hereinabove, and (2) a homopolymer or copolymer of N-vinyl pyrrolidone (e.g., copovidone). The solid composition also comprises a pharmaceutically acceptable surfactant (e.g., vitamin E TPGS, sorbitan monolaurate, or a combination of vitamin E TPGS and lauroglycol FCC), wherein the surfactant preferably is formulated in the amorphous solid dispersion or solid solution.

[0069] In yet another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a selected HCV inhibitor described hereinabove, (2) copovidone, and (3) a pharmaceutically acceptable surfactant (e.g., vitamin E TPGS, sorbitan monolaurate, or a combination of vitamin E TPGS and lauroglycol FCC). The amorphous solid dispersion or solid solution may also include another pharmaceutically acceptable surfactant.

[0070] In still another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) 10% by weight the selected HCV inhibitor, (2) 82% by weight copovidone, and (3) 5% by weight vitamin E TPGS

and 2% by weight lauroglycol FCC. The solid composition can also include 1% by weight colloidal silica.

[0071] In a further embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) 10% by weight the selected HCV inhibitor, (2) 82% by weight copovidone, and (3) 7% by weight propylene glycol monocaprylate (Capryol 90). The solid composition can also include 1% by weight colloidal silica.

[0072] A solid dispersion employed in the present invention preferably comprises or consists of a single-phase (defined in thermodynamics) in which the therapeutic agent(s) (e.g., a selected HCV inhibitor described hereinabove with or without another anti-HCV agent) is molecularly dispersed in a matrix containing the pharmaceutically acceptable hydrophilic polymer(s). In such cases, thermal analysis of the solid dispersion using differential scanning calorimetry (DSC) typically shows only one single T_g , and the solid dispersion does not contain any detectable crystalline HCV inhibitor as measured by X-ray powder diffraction spectroscopy.

[0073] A solid composition of the present invention can further include one or more other anti-HCV agents. These other anti-HCV agents can be, for example, HCV polymerase inhibitors (including nucleoside or non-nucleoside type of polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, internal ribosome entry site inhibitors, or HCV NS5A inhibitors.

[0074] In one embodiment, a solid composition of the invention comprises (1) a selected HCV inhibitor described hereinabove and (2) another HCV protease inhibitor. In another embodiment, a solid composition of the invention comprises (1) a selected HCV inhibitor described hereinabove, and (2) another HCV polymerase inhibitor (e.g., a non-nucleoside polymerase inhibitor, or preferably a nucleoside polymerase inhibitor). In yet another embodiment, a solid composition of the invention comprises (1) a selected HCV inhibitor described hereinabove, (2) another HCV protease inhibitor, and (3) another HCV polymerase inhibitor (e.g., a non-nucleoside polymerase inhibitor, or preferably a nucleoside polymerase inhibitor). In another embodiment, a solid composition of the invention comprises (1) a selected HCV inhibitor described hereinabove, and (2) another HCV NS5A inhibitor. In another embodiment, a solid composition of the invention comprises (1) a selected HCV inhibitor described hereinabove, (2) another HCV polymerase inhibitor (e.g., a non-nucleoside polymerase

inhibitor, or preferably a nucleoside polymerase inhibitor), and (3) another HCV NS5A inhibitor. In another embodiment, a solid composition of the invention comprises (1) a selected HCV inhibitor described hereinabove, (2) another HCV protease inhibitor, and (3) another HCV NS5A inhibitor.

[0075] Non-limiting examples of other protease inhibitors can be selected from ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BI-201335 (Boehringer Ingelheim), BMS-650032 (BMS), boceprevir, danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof. And non-limiting examples of other HCV polymerase inhibitors can be selected from ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), or a combination thereof. The polymerase inhibitor may be a nucleotide polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), or a combination thereof. The polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof. The present invention also contemplates the inclusion of both a nucleotide polymerase inhibitor and a non-nucleoside polymerase inhibitor in a solid composition of the invention. Non-limiting examples of other HCV NS5A inhibitors include ACH-2928 (Achillion), AZD2836 (Astra-Zeneca), AZD7295

(Astra-Zeneca), BMS-790052 (BMS), BMS-824393 (BMS), EDP-239 (Enanta), GS-5885 (Gilead), PPI-1301 (Presidio), PPI-461 (Presidio), GSK62336805, or a combination thereof.

[0076] A solid composition of the present invention preferably is a solid oral dosage form. Common solid oral dosage forms suitable for the present invention include, but are not limited to, capsules, dragees, granules, pills, powders and tablets, with capsules and tablets being preferred. A solid oral dosage form of the present invention can also include other excipients or inset diluents, such as sucrose, lactose or starch. Lubricants, coloring agents, releasing agents, coating agents, sweetening or flavoring agents, buffering agents, preservatives, or antioxidants can also be included in a solid oral dosage form of the present invention.

[0077] A solid composition of the present invention can be prepared by a variety of techniques such as, without limitation, melt-extrusion, spray-drying, co-precipitation, freeze drying, or other solvent evaporation techniques, with melt-extrusion and spray-drying being preferred. The melt-extrusion process typically comprises the steps of preparing a melt which includes the active ingredient(s), the hydrophilic polymer(s) and preferably the surfactant(s), and then cooling the melt until it solidifies. Melting often involves a transition into a liquid state in which it is possible for one component to get dissolved or embedded, preferably homogeneously dissolved or embedded, in the other component or components. In many cases, the polymer component(s) will melt and the other components including the active ingredient(s) and surfactant(s) will dissolve in the melt thereby forming a solution. In such a case, the polymer functions as a solvent. Melting usually involves heating above the softening point of the polymer(s). The preparation of the melt can take place in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or be simultaneously mixed and melted. The melt can also be homogenized in order to disperse the active ingredient(s) efficiently. In addition, it may be convenient first to melt the polymer(s) and then to mix in and homogenize the active ingredient(s). In one example, all materials except surfactant(s) are blended and fed into an extruder, while the surfactant(s) is molten externally and pumped in during extrusion.

[0078] In another example, the melt comprises a selected HCV inhibitor described hereinabove, and one or more hydrophilic polymers described above; and the melt temperature is in the range of from 100 to 170 °C, preferably from 120 to 150 °C, and highly preferably from

135 to 140 °C. The melt can also include a pharmaceutically acceptable surfactant described above.

[0079] In still another example, the melt comprises a selected HCV inhibitor described hereinabove, at least another anti-HCV agent described above, and one or more hydrophilic polymers described above. The melt can also include a pharmaceutically acceptable surfactant described above.

[0080] To start a melt-extrusion process, the active ingredient(s) (e.g., a selected HCV inhibitor described hereinabove) can be employed in their solid forms, such as their respective crystalline forms. The active ingredient(s) can also be employed as a solution or dispersion in a suitable liquid solvent such as alcohols, aliphatic hydrocarbons, esters or, in some cases, liquid carbon dioxide. The solvent can be removed, e.g. evaporated, upon preparation of the melt.

[0081] Various additives can also be included in the melt, for example, flow regulators (e.g., colloidal silica), binders, lubricants, fillers, disintegrants, plasticizers, colorants, or stabilizers (e.g., antioxidants, light stabilizers, radical scavengers, and stabilizers against microbial attack).

[0082] The melting and/or mixing can take place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders, intermeshing screw extruders or multiscrew extruders, preferably twin screw extruders, which can be corotating or counterrotating and, optionally, be equipped with kneading disks. It will be appreciated that the working temperatures will be determined by the kind of extruder or the kind of configuration within the extruder that is used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, the friction and shearing of the material in the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogeneous melt of the components.

[0083] The melt can range from thin to pasty to viscous. Shaping of the extrudate can be conveniently carried out by a calender with two counter-rotating rollers with mutually matching depressions on their surface. The extrudate can be cooled and allow to solidify. The extrudate can also be cut into pieces, either before (hot-cut) or after solidification (cold-cut).

[0084] The solidified extrusion product can be further milled, ground or otherwise reduced to granules. The solidified extrudate, as well as each granule produced, comprises a

solid dispersion, preferably a solid solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). Where the granules do not contain any surfactant, a pharmaceutically acceptable surfactant described above can be added to and blended with the granules. The extrusion product can also be blended with other active ingredient(s) and/or additive(s) before being milled or ground to granules. The granules can be further processed into suitable solid oral dosage forms.

[0085] In some cases, direct-shaping techniques such as injection moulding can be used in combination with melt extrusion to prepare suitable solid dosage forms.

[0086] In one example, copovidone and one or more surfactants are mixed and granulated, followed by the addition of aerosil and a selected HCV inhibitor described hereinabove. The mixture, which may contain for example at least 5% by weight of the selected HCV inhibitor is then milled. The mixture is then subject to extrusion, and the extrudate thus produced can be milled and sieved for further processing to make capsules or tablets. Surfactant(s) employed in this example can also be added through liquid dosing during extrusion.

[0087] The approach of solvent evaporation, via spray-drying, provides the advantage of allowing for processability at lower temperatures, if needed, and allows for other modifications to the process in order to further improve powder properties. The spray-dried powder can then be formulated further, if needed, and final drug product is flexible with regards to whether capsule, tablet or any other solid dosage form is desired.

[0088] Exemplary spray-drying processes and spray-drying equipment are described in **K. Masters, SPRAY DRYING HANDBOOK** (Halstead Press, New York, 4th ed., 1985). Non-limiting examples of spray-drying devices that are suitable for the present invention include spray dryers manufactured by Niro Inc. or GEA Process Engineering Inc., Buchi Labortechnik AG, and Spray Drying Systems, Inc. A spray-drying process generally involves breaking up a liquid mixture into small droplets and rapidly removing solvent from the droplets in a container (spray drying apparatus) where there is a strong driving force for evaporation of solvent from the droplets. Atomization techniques include, for example, two-fluid or pressure nozzles, or rotary atomizers. The strong driving force for solvent evaporation can be provided, for example, by maintaining the partial pressure of solvent in the spray drying apparatus well below the vapor pressure of the solvent at the temperatures of the drying droplets. This may be accomplished by either (1)

maintaining the pressure in the spray drying apparatus at a partial vacuum; (2) mixing the liquid droplets with a warm drying gas (e.g., heated nitrogen); or (3) both.

[0089] The temperature and flow rate of the drying gas, as well as the spray dryer design, can be selected so that the droplets are dry enough by the time they reach the wall of the apparatus. This help to ensure that the dried droplets are essentially solid and can form a fine powder and do not stick to the apparatus wall. The spray-dried product can be collected by removing the material manually, pneumatically, mechanically or by other suitable means. The actual length of time to achieve the preferred level of dryness depends on the size of the droplets, the formulation, and spray dryer operation. Following the solidification, the solid powder may stay in the spray drying chamber for additional time (e.g., 5-60 seconds) to further evaporate solvent from the solid powder. The final solvent content in the solid dispersion as it exits the dryer is preferably at a sufficiently low level so as to improve the stability of the final product. For instance, the residual solvent content of the spray-dried powder can be less than 2% by weight. Highly preferably, the residual solvent content is within the limits set forth in the International Conference on Harmonization (ICH) Guidelines. In addition, it may be useful to subject the spray-dried composition to further drying to lower the residual solvent to even lower levels. Methods to further lower solvent levels include, but are not limited to, fluid bed drying, infra-red drying, tumble drying, vacuum drying, and combinations of these and other processes.

[0090] Like the solid extrudate described above, the spray dried product contains a solid dispersion, preferably a solid solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). Where the spray dried product does not contain any surfactant, a pharmaceutically acceptable surfactant described above can be added to and blended with the spray-dried product before further processing.

[0091] Before feeding into a spray dryer, the active ingredient(s) (e.g., a selected HCV inhibitor described hereinabove), the hydrophilic polymer(s), as well as other optional active ingredients or excipients such as the pharmaceutically acceptable surfactant(s), can be dissolved in a solvent. Suitable solvents include, but are not limited to, water, alkanols (e.g., methanol, ethanol, 1-propanol, 2-propanol or mixtures thereof), acetone, acetone/water, alkanol/water mixtures (e.g., ethanol/water mixtures), or combinations thereof. The solution can also be preheated before being fed into the spray dryer.

[0092] The solid dispersion produced by melt-extrusion, spray-drying or other techniques can be prepared into any suitable solid oral dosage forms. In one embodiment, the solid dispersion prepared by melt-extrusion, spray-drying or other techniques (e.g., the extrudate or the spray-dried powder) can be compressed into tablets. The solid dispersion can be either directly compressed, or milled or ground to granules or powders before compression. Compression can be done in a tablet press, such as in a steel die between two moving punches. When a solid composition of the present invention comprises a selected HCV inhibitor described hereinabove and another anti-HCV agent, it is possible to separately prepare solid dispersions of each individual active ingredient and then blend the optionally milled or ground solid dispersions before compacting. A selected HCV inhibitor described hereinabove and other active ingredient(s) can also be prepared in the same solid dispersion, optionally milled and/or blended with other additives, and then compressed into tablets.

[0093] At least one additive selected from flow regulators, binders, lubricants, fillers, disintegrants, or plasticizers may be used in compressing the solid dispersion. These additives can be mixed with ground or milled solid dispersion before compacting. Disintegrants promote a rapid disintegration of the compact in the stomach and keeps the liberated granules separate from one another. Non-limiting examples of suitable disintegrants are cross-linked polymers such as cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethylcellulose or sodium croscarmellose. Non-limiting examples of suitable fillers (also referred to as bulking agents) are lactose monohydrate, calcium hydrogenphosphate, microcrystalline cellulose (e.g., Avicell), silicates, in particular silicium dioxide, magnesium oxide, talc, potato or corn starch, isomalt, or polyvinyl alcohol. Non-limiting examples of suitable flow regulators include highly dispersed silica (e.g., colloidal silica such as Aerosil), and animal or vegetable fats or waxes. Non-limiting examples of suitable lubricants include polyethylene glycol (e.g., having a molecular weight of from 1000 to 6000), magnesium and calcium stearates, sodium stearyl fumarate, and the like.

[0094] Various other additives may also be used in preparing a solid composition of the present invention, for example dyes such as azo dyes, organic or inorganic pigments such as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

[0095] Solid compositions according to certain embodiments of the present invention may contain several layers, for example laminated or multilayer tablets. They can be in open or

closed form. "Closed dosage forms" are those in which one layer is completely surrounded by at least one other layer.

[0096] In order to facilitate the intake of a solid dosage form, it is advantageous to give the dosage form an appropriate shape. Large tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape.

[0097] A film coat on the tablet further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. The film-coat usually includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. polysorbates, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. Preferably, the film coat accounts for less than 5 % by weight of a pharmaceutical composition of the present invention.

[0098] In another aspect, the present invention feature methods of using solid compositions of the present invention to treat HIV infection. The methods comprise administering a solid composition of the present invention to a patient in need thereof. A solid composition of the present invention can be administered either alone, or in combination with one or more other anti-HCV agents, such as those described hereinabove. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the severity of the HCV infection; the activity of the active ingredient(s) in the particular patient; the specific solid composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration and rate of excretion; the duration of the treatment; drugs used in combination or coincidental with the selected HCV inhibitor described hereinabove; and like factors well known in the medical arts.

[0099] In one embodiment, a method of the present invention comprises administering to a patient in need thereof a solid composition of the present invention and at least another anti-HCV agent, wherein said another anti-HCV agent is selected from HCV polymerase inhibitors (e.g., nucleoside or non-nucleoside HCV polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, internal ribosome entry site inhibitors, or HCV NS5A inhibitors. Preferably, said another anti-HCV agent is an HCV polymerase inhibitor (e.g., nucleoside or non-nucleoside HCV polymerase inhibitor) or an HCV

protease inhibitor. Also preferably, said another anti-HCV agent is interferon or ribavirin, or preferably a combination thereof. The interferon preferably is a-interferon, and more preferably, pegylated interferon-a such as PEGASYS (peginterferon alfa-2a). The administration of a solid composition of the present invention and another anti-HCV agent(s) can be concurrent or sequential.

[0100] The present invention also features use of a solid composition of the present invention for the manufacture of medicaments for the treatment of HCV infection.

[0101] In one embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is telaprevir (VX-950).

[0102] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is BI-201335.

[0103] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is TMC-435 (TMC-435350).

[0104] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is vaniprevir (MK-7009).

[0105] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is MK-5172.

[0106] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is asunaprevir (BMS-650032).

[0107] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is daclatasvir (BMS-790052).

[0108] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is danoprevir. Preferably, danoprevir is used together with ritonavir to improve the pharmacokinetics of danoprevir. More preferably, danoprevir is co-formulated with ritonavir in a solid composition of the invention. For instance, danoprevir and ritonavir in a solid composition of the invention can be formulated in the same solid dispersion or different solid dispersions.

[0109] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is setrobuvir (ANA-598).

[0110] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is tegobuvir (GS-333126 or GS-9190).

Preferably, a solid composition of this embodiment further comprises GS-9256, GS-9451 or GS-5885. Also preferably, a solid composition of this embodiment further comprises GS-9451 and GS-5885.

[0111] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is GS-9451. Preferably, a solid composition of this embodiment further comprises tegobuvir or GS-5855. Also preferably, a solid composition of this embodiment further comprises tegobuvir and GS-5885.

[0112] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is mericitabine (R-4048).

[0113] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is IDX-184.

[0114] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is filibuvir (PF-00868554).

[0115] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is PSI-7977. Preferably, a solid composition of this embodiment further comprises GS-5885 or daclatasvir.

[0116] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is PSI-352938.

[0117] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is BIT-225.

[0118] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is boceprevir.

[0119] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is GS-5885. Preferably, a solid composition of this embodiment further comprises PSI-7977, GS-9451 or tegobuvir. Also preferably, a solid composition of this embodiment further comprises GS-9451 and tegobuvir.

[0120] In another embodiment, the selected HCV inhibitor used in any aspect, embodiment, example or feature described hereinabove is GS-9256. Preferably, a solid composition of this embodiment further comprises tegobuvir.

[0121] Other formulation approaches, such as liquid-based formulations, simple solutions, nanoparticles, crystalline solids, salts or co-crystals, and conventional immediate

release formulations, can also be employed to formulate the selected HCV inhibitors, either alone or in combination with other anti-HCV agents.

[0122] The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

1. A solid composition comprising
an HCV inhibitor selected from telaprevir, BI-201335, TMC-435, vaniprevir, MK-5172, asunaprevir, daclatasvir, danoprevir, setrobuvir, tegobuvir, GS-9451, mericitabine, IDX-184, filibuvir, PSI-7977, PSI-352938, BIT-225, boceprevir, GS-5885 or GS-9256,
a pharmaceutically acceptable hydrophilic polymer, and
optionally a pharmaceutically acceptable surfactant.
2. The composition of claim 1, comprising a solid dispersion which includes:
said HCV inhibitor and
said polymer.
3. The composition of claim 2, wherein said polymer has a T_g of at least 50 °C.
4. The composition of claim 3, further comprising said surfactant.
5. The composition of claim 4, wherein said solid dispersion comprises said surfactant.
6. The composition of claim 4, wherein said polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.
7. The composition of claim 4, wherein said polymer is copovidone.
8. The composition of claim 7, wherein said surfactant is D-alpha-tocopheryl polyethylene glycol 1000 succinate.
9. The composition of claim 3, wherein said solid dispersion is an amorphous solid dispersion.
10. The composition of claim 3, where said solid dispersion is a solid solution.

11. The composition of claim 4, wherein said solid dispersion is an amorphous solid dispersion.
12. The composition of claim 4, where said solid dispersion is a solid solution.
13. The composition of claim 1, further comprising another anti-HCV agent.
14. The composition of claim 1, further comprising an HCV protease inhibitor.
15. The composition of claim 1, further comprising an HCV polymerase inhibitor.
16. A process of making the composition of claim 1, comprising dissolving said HCV inhibitor in a solvent.
17. The process of claim 16, wherein said solvent is said polymer.
18. A method of treating HCV comprising administering the composition of claim 1 to a patient in need thereof.
19. The method of claim 18, comprising administering another anti-HCV agent to said patient.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/070349

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K9/16 A61K31/497 A61P31/14
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal , BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	wo 2005/123076 A2 (VERTEX PHARMA [US] ; MURPHY MAURA [US] ; DINEHART KI RK [US] ; HURTER PATR) 29 December 2005 (2005-12-29) exampl e 6 -----	1-19
X	US 2007/218138 AI (BITTORF KEVIN J [US] ET AL) 20 September 2007 (2007-09-20) paragraph [0008] ; exampl es -----	1-19
X	wo 2011/156578 AI (ABBOTT LAB [US] ; LI EPOLD BERND [DE] ; JUNG TINA [DE] ; HOLIG PETER [DE] ;) 15 December 2011 (2011-12-15) page 16; exampl es -----	1-19
X	wo 2009/050289 A2 (ABBOTT GMBH & CO KG [DE] ; SCHR0EDER RUDOLF [DE] ; HEITERMANN TANJA [DE]) 23 April 2009 (2009-04-23) page 1 -----	1-19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

6 February 2013

Date of mailing of the international search report

14/05/2013

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Zimmer, Barbara

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/070349

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos. :

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos. :

I-19 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor telaprevir and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

2. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor BI-201335 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

3. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor TMC-435 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

4. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor vaniprevir and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

5. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor MK-5172 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

6. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor asunaprevir and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

7. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor daclatasvir and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

8. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor danoprevir

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

9. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor setrobuvir and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

10. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor tegobuvir and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

11. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor GS-9451 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

12. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor mericitabine and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

13. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor IDX-184 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

14. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor filibuvir and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

15. claims: I-19 (partially)

Solid composition comprising the HCV inhibitor PSI-7977 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

16. claims: I-19 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Solid composition comprising the HCV inhibitor PSI-352938 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

17. claims: 1-19 (partially)

Solid composition comprising the HCV inhibitor BIT-225 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

18. claims: 1-19 (partially)

Solid composition comprising the HCV inhibitor boceprevir and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

19. claims: 1-19 (partially)

Solid composition comprising the HCV inhibitor GS-5885 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

20. claims: 1-19 (partially)

Solid composition comprising the HCV inhibitor GS-9256 and a pharmaceutically acceptable hydrophilic polymer, its process of making and therapeutic use

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/070349

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005123076	A2	29-12-2005	AR 049297 AI 12-07 -2006
			AU 2005253957 AI 29-12 -2005
			BR PI0511900 A 22-01 -2008
			CA 2569310 AI 29-12 -2005
			CN 1988885 A 27-06 -2007
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			JP 2008501802 A 24-01-2008
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			EP 2579854 AI 17-04 -2013
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			CO 6270303 A2 20-04 -2011
			CR 11441 A 25-10 -2010
			DO P2010000114 A 15-05 -2010
			EC SP10010184 A 29-06 -2010
			EP 2197426 A2 23-06 -2010
			GT 201000095 A 03-04 -2012
			JP 2011500647 A 06-01 -2011
			KR 20100090689 A 16-08 -2010

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/070349

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		PE 10412009 A1	22-08-2009
		RU 2010119924 A	27-11-2011
		TW 200922549 A	01-06-2009
		US 2009143423 A1	04-06-2009
		UY 31406 A1	29-05-2009
		W0 2009050289 A2	23-04-2009

**The Patents Act, 1970
(AS AMENDED)
(Section 15)**

**In the matter of the application for
Patent Application No. 1554/CHENP/2013 filed on 26/02/2013.
Regeneron Pharmaceuticals, INC - Applicant.**

Hearing fixed on – 06/10/2020

Present: S. Anitha Shirmila Elizabeth of De Penning & De Penning, Chennai through video conference - On behalf of Regeneron Pharmaceuticals, INC

Decision

The application (1554/CHENP/2013) was filed by Arindam Paul of De Penning & De Penning, Chennai on 26/02/2013 on behalf of Regeneron Pharmaceuticals, INC. The application was published under section 11A on 10/10/2014 and request for examination (Form 18) was filed on 01/08/2014. The application was examined and First Examination Report (FER) was issued on 30/05/2018.

On examination of the amended documents received on 27/02/2019 it was found that the application was not put in order as per The Patents Act, 1970 and some objections were still pending for this application. As the last date was already over, the objections were communicated to De Penning & De Penning, Chennai through hearing notice and a hearing was fixed on 06/10/2020.

The hearing was held as per schedule and the same was attended by the agent through video conference. In the hearing, the agent had submitted their observations to overcome the objections as raised in the hearing letter. As per the office practice and subsequent request, the agent was allowed to submit the written note of arguments and the agent submitted the same on 21/10/2020.

Agent's submission:

To overcome the objections raised in the hearing notice the applicant has submitted that We respectfully disagree with the Controller's objection that claims amended in response to First Examination Report (FER) are not in compliance with Section 59 of Patents Act, 1970, as the amendments do not fall wholly within the scope of claims of the specification before the amendment. We bring to the notice of the Controller that the original PCT claims on file and specification specifically description on paragraph [0126] (describing modifying a mouse totipotent cell) indeed support claims towards a method for making a genetically modified mouse. In view of non-patentability objections raised against original PCT claims directed

towards a mouse, applicants have in fact limited the scope of these PCT claims to a method performed on the cells, rather than the animal *per se*. We submit that amendment to claims on file from a mouse to a method of modifying a mouse totipotent cell is indeed limiting. In this regard, we wish to rely on *Edwards Vs Acme Signs* (1990) RPC 621 at 640, wherein it was stated that in a pre-grant amendment it is not material whether that amended claim had the effect of widening or narrowing the monopoly claim. What is important is that the amended claim should not relate to a different invention from that which was disclosed in the application. Furthermore, Aldous, J. in *Bonzle vs Intervention* (No. 3) (1991) RPC 553 at 574, gave the correct approach for deciding the question whether the application for amendment is extending beyond that disclosed in the application as filed. The test of added matter is whether a skilled man would, upon looking at the amended specification, learn anything about the invention which he could not learn from the unamended specification. Thus from the reading of the Patents Act and various precedents set down by Courts, it is evident that Section 59 of the Act should be given wider interpretation while amending the application before grant. The expression “*specification before the amendment*” should be construed broadly and amendment to claims during prosecution should be allowed as long as the amended claims are within the scope of the original disclosure. Because such amendments are necessary to afford to the Applicant the benefit of the invention which has been disclosed in the complete specification ought to be available to the Applicant. The Applicant should not be deprived of its rights to amend claims during the prosecution of the application, in order to address various objections raised under the Indian Patent Law.

The amended claims are still within the scope of the original PCT claims as required under Section 59 of the Act. The applicants submits that both claims are directed to the novel concept of making a genetically modified mouse comprising in its germline

A) an unrearranged immunoglobulin light chain variable region (VL) gene segment and an unrearranged immunoglobulin light chain joining (JL) gene segment operably linked with a heavy chain constant region nucleic acid sequence, and B) a human light chain V segment and a human light chain J segment operably linked to a light chain constant gene. It should be noted that though the claims were limited to a method of modifying a rodent cell during the previous amendments in response to FER, the crux of the invention still remains the same.

The Applicant further relies upon *Bonzel v. Intervention Ltd* ([1991] RPC 553) which provides, on page 574, the correct approach in determining whether the amended claims fall within the scope of the original claims as envisaged by Section 59, namely:

- a. “*To ascertain through the eyes of the skilled addressee what is disclosed, both explicitly and impliedly in the application as filed.*”
- b. *To do the same in respect of the application as sought to be amended.*
- c. *To compare the two disclosures and decide whether any subject matter relevant to the invention would have been added, whether by deletion or addition. The comparison must be strict in the sense that subject matter would have been added unless such matter was clearly and unambiguously disclosed, either explicitly or implicitly in the application as filed.”*

The applicant therefore submits that the amended claims fall well within the scope of the originally filed product claims. The method of making a genetically modified mouse claims indeed provide the same scope of protection that the applicant requires. The claims have been amended only since the previous claims were objected as non-patentable in India. If such claims were only patentable under the Patents Act, the scope of protection rendered by the original product claims under Section 48 of the Act, would have been broader to that of the amended method claims which are restricted to modification made to a cell of a mouse. We therefore submit that the claims currently on file are in compliance with the requirement under Section 59(1) of the Act and are also patent eligible under the Indian Patent Law. Accordingly, a favorable reconsideration of this objection is humbly solicited.

Invention u/s 2(1)(j):

Applicants respectfully disagree with the Controller's objection that the claimed invention lacks novelty in view of *D1: WO 2009/143472 A2* and lacks inventive step in view of the cited documents – *D1: WO 2009/143472 A2, D2: US 2006/015957 A1, D3: US 2002/026036 A1, D4: US 2003/217373 A1, D5: US 6 596 541 B2, D6: US 2007/280945 A1 and D7: WO 2008/054606 A2.*

Applicants note that the Examiner has merely reiterated the comments of FER without providing his rationale behind maintaining this objection even after highlighting the novelty and inventiveness of the present invention over these citations in the response to the FER. Applicants understand that the FER was issued based on the original PCT claims. However, it should be noted that the original PCT claims were amended in response to the FER. For the reasons detailed above the claims on file, i.e. claims amended in response to the FER, comply with the requirement under Section 59(1) of the Act and are also patent eligible under the Indian Patent Law. Thus, the claims on file are indeed novel and inventive over the documents D1–D7. Accordingly, applicants wish to rely on their submission made in the response to the FER dated 27 February 2019.

Novelty

The original PCT Claim 11, which was considered novel over D1, is incorporated into the independent claims, which renders the rejection no longer applicable.

Inventive Step

Present Claims

Prior to addressing the specific objections raised, it may be useful to outline the contribution made by the claimed method. Claim 1 refer to a method of making a non-human animal comprising in its germ line:

A) an unrearranged immunoglobulin light chain variable region (VL) gene segment and an unrearranged immunoglobulin light chain joining (JL) gene segment operably linked with a heavy chain constant region nucleic acid sequence, and

B) a human light chain V segment and a human light chain J segment operably linked to a light chain constant gene.

The result of (a) and (b) is a non-human animal that can express antibodies where all the variable regions in the four chains of the antibody are light chain variable regions, but which has normal light and heavy chain constant regions. Such an antibody structure is a radical departure from conventional antibodies, which have light chain variable regions in the light chain and heavy chain variable regions in the heavy chain.

It has to be remembered that antibody light and heavy chains play an important role in B cell development. Typically, B cell development begins by rearrangement of the heavy chain locus. The B cell then "tests" the functionality of the heavy chain produced by incorporating the heavy chain into a receptor (pre-B cell receptor) that can signal its successful production. This "test" takes place in the presence of a "surrogate" light chain. Signalling through a pre-B cell receptor containing the rearranged heavy chain and the surrogate light chain halts rearrangement of the heavy chain locus and initiates the transition to the stage at which light chain rearrangement begins. Subsequent light chain rearrangement and expression of both the light and heavy chain on the cell surface as a B Cell Receptor is also necessary for B cell development. Subsequent affinity maturation further involves the B cell receptor.

Given that the production of antibodies, where all the variable regions are light chain variable regions, is so different from the natural antibody structure, it was therefore unexpected that the engineered made according to the claimed methods would rearrange light chain variable segments to form a functional heavy chain forming part of a pre-B cell receptor and give rise to B cells expressing such antibodies.

The present invention makes the surprising further demonstration that not only are antibodies containing only light chain variable domains made, but they are functional and indeed can display particularly high affinity as illustrated by the Examples of the present application. For instance, the Examples of the present specification, using mice as an illustrative non-human animal, show:

□□ in Examples I to III the generation of mice carrying a modified heavy chain locus where the heavy chain V, D and J gene segments have been removed and light chain V and J segments are introduced;

□□ in Example III that mice heterozygous for the modification express antibodies comprising the light chain variable region - heavy chain constant region hybrid chains meaning that B cells expressing the modified antibody can actually develop (see Table 2 on page 47 - the modified heavy chain allele is of IgMa haplotype, so can be distinguished from the unmodified allele which has a IgMb haplotype);

□□ in Example III, Figures 6 and 7 and Table 4 that mice homozygous for the modified heavy chain locus show similar staining patterns and B cells in the spleen, blood and bone marrow and also express a variety of light chain V and J gene segments from the modified heavy chain locus;

□□ in Example IV and Table 5 that mice homozygous for the modification use a variety of different V and J segment pairings in the hybrid chain and the light chain; and

□□ in Example V that the antibodies with only light chain variable regions display high affinity, with all of the antibodies analysed displaying a K_D in the nanomolar range, a large majority displaying single digit nanomolar affinity and six lower than 3 nm affinity (see in particular paragraph [00252]).

The mice made according to the claimed methods and the antibodies they produce are therefore unexpectedly effective, despite being such a departure in structure from normal antibodies. The claimed methods therefore represent a substantial advance. As discussed further below, the cited art neither discloses, nor suggests such methods.

Prior Arts

D1 is cited as the closest prior art. What D1 is concerned with is summarized in the "BRIEF SUMMARY" Section of D1 at page 5, first full paragraph, which states that: *"The present invention discloses novel chimeric single chain antibodies that contain a variable region of a human immunoglobulin light chain and a nonhuman heavy chain constant region. In particular, the chimeric antibodies of the present invention are devoid of the first constant domain CH1"* [emphasis added.]

The crux of D1 is therefore to try and generate single chain antibodies with a light chain variable region and heavy chain constant region, where the latter is modified by the deletion of CH1 to stop the single chain antibody forming the normal four chain antibody structure.

Starting from D1:

□□ the technical problem to be solved may be formulated as the provision of a non-human animal capable of expressing improved antibodies; and

□□ the solution to that technical problem is to generate the non-human animal specified by claim 1 which expresses a hybrid light chain variable-heavy chain constant region polypeptide and a light chain comprising a human variable region and a constant region.

As outlined above, the solution to the technical problem results in a non-human animal that does not just have surprisingly normal B cell development, but produces particularly high affinity binding proteins comprising only VL domains. D1 neither discloses nor suggests such a non-human animal, nor the unexpected technical advantages it displays.

The Solution to the Technical Problem was not obvious from D1

D1 is focused entirely on generating single chain antibodies. That is illustrated by the above cited passage of D1 at page 5, by the claims of D1 being limited to single chain antibodies and by the repeated references to single chain antibodies in the document, with D1 referring over 100 times to single chain antibodies.

The skilled person, starting from D1, would simply have carried on with the teaching of D1 to employ single chain antibodies. D1 even teaches to employ the deletion of the CH1 region, so you can only ever obtain single chain antibodies and nothing else.

D1 provides no teaching nor motivation to do anything other than that and certainly no suggestion of expressing an antibody with two heavy and two light chains, where all the variable regions are light chain variable regions.

The claimed non-human animals, that can express four chain antibodies with only light chain variable regions, represent a conceptual leap from what is disclosed in D1 or anywhere else, as none of the cited art considers such a structure, let alone actually generates it. The demonstration in the application as filed that not only can the claimed non-human animals display normal B cell development, but produce the VL binding proteins with particularly high affinity was therefore unexpected.

D1 does not even generate the antibodies it is focused on, let alone mice expressing them, still less does it consider generating antibodies with four chains, where all the variable regions are VL regions. The Examples of D1 are all "paper" Examples describing possible experiments, rather than actual experiments done.

D1 teaches directly away from non-human animals that produce such antibodies by its emphasis on wanting single chain antibodies and actually teaching to modify the single chain antibodies so they cannot form the four chain structure, with two light and two heavy chains that the claims are based around. The message of D1 is simple, if you are going to express a light chain/heavy chain hybrid, then it should be done as a single chain. D1 directs away from the invention. D1 therefore teaches away from the invention and the resulting unexpected advantages displayed by the claimed non-human animals and they antibodies they produce. The subject matter of the claims is therefore inventive over D1.

(D2 to D5 add nothing to the teaching of D1)

The WO-ISA also cites D2 to D5. However, D2 to D5 are concerned with various types of transgenic mice which express wholly or partially human antibodies. None of D2 to D5 discloses or suggests the specific structure antibodies that the claimed nonhuman animals will express. Those documents do not contemplate producing a hybrid light chain variable/heavy chain constant region polypeptide.

The skilled person would not have combined D1 with any of D2 to D5 and, even if they had, would have gained nothing by doing so. That is because the only document referring to hybrid light chain variable/heavy chain constant region polypeptide specifically teaches to introduce a modification that prevents assembly into the normal four chain antibody structure. That reflects how much of a departure the invention is, given D1 considers it necessary to actually prevent assembly into the normal antibody structure and away from the claimed non-human animals.

Applicants would like to rely upon the decision of Hon'ble High Court of Delhi as passed in the matter of *BristolMyers Squibb Holdings Ireland Unlimited Company &Ors. vs BDR Pharmaceuticals International Pvt. Ltd. & Anr.*; CS(COMM) 27/2020, wherein it has been categorically held that:

"38. As noted above, it is thus well settled that in case prior art document show a concept of teaching away from the inventive step, the said prior art document cannot be used to demonstrate that the invention is obvious and thus not liable to be patented."

Therefore none of the cited art suggested the claimed non-human antibodies and the resulting technical advantages, with the main document, D1, actually teaching directly away from what is claimed and the non-human animals capable of express an antibody comprising

four chains, where all the variable regions are light chain variable regions. The skilled person would have been no closer to the invention by combining D1 with any of the other cited documents, because D1 directs that if a heavy chain/light chain is expressed, it should be as a single antibody chain. The subject matter of the claims is therefore inventive over cited arts as a whole. Further, as per the established criterion for determination of obviousness, whether a prior art would have motivated a person skilled in art to arrive at the claimed invention with reasonable expectation of successes should be viewed in the light of the prior art. Hindsight analysis is not permissible.

Applicant would like to rely on the Hon'ble Delhi High Court decision in **CS(OS) 586/2013 of Merck Vs Glenmark** in the order dated 7th October 2015, wherein the Court held as follows:

"Onus to prove that invention in the suit patent was obvious to a person skilled in the art was on the defendant, which, in my view, defendant has failed to discharge by leading a positive evidence on record. Mere comparison of chemical structure is not sufficient, in as much as, picking up parts of chemical structures of different patents and clubbing them will also not be sufficient, as it appears to have been done, keeping in mind the molecule structure of the suit patent, as a hindsight analysis. A direct question was put to DW2 that the methodology followed by him was typically referred to a hindsight analysis and is a prohibited methodology in patent law to which he answered thus : "I have no comments". He has not denied this suggestion. Instead has given a vague answer which is deemed admission on this point. Hindsight analysis is not permissible". Applicant would also like to refer to the judgment given in case **CS (OS) No.89/2008 and C.C. 52/2008 of F. Hoffmann-La Roche Ltd vs. Cipla Ltd., (2012)** by the Division Bench of Delhi High Court wherein the Court has ruled that mere presence of a feature in each of the cited document is not sufficient to prove that the invention is obvious/lack inventive step. In the absence of any specific teaching, motivation and suggestion, the claimed invention cannot be rendered as obvious over the cited documents.

Further, Applicant would like to remark that in *Janssen Pharmaceutica N.V. & Amr. Vs. Mylan Pharmaceuticals, Inc. – 456 F. Supp. 2d 644*; it was held that *"It is not enough for a party seeking to defeat a patent on obviousness grounds to merely identify each element of the invention, in the prior art. Id. at 986. This can be done for nearly all inventions. Id. Instead, a prima facie case of obviousness requires the party to "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious". [page 8]*

There is no disclosure or suggestion in any of the cited documents that would motivate a person skilled in art to modify the documents or to combine their teachings so as to arrive at the present invention.

It has been clearly shown in the above discussion that none of the cited documents either alone or in combination make the present invention obvious. Also the present invention is inventive over the documents D1–D7 alone and/or in combination.

Furthermore, the above view is supported by the Examiners in other jurisdictions who have acknowledged the novelty, inventiveness of the present invention and accordingly patent

applications have been matured into a patent in many countries like Australia, China, Europe, Israel, Japan, Korea, Mexico, New Zealand, Russian Federation, Singapore, South Africa and United States of America.

The cited documents neither teach nor suggest nor motivate a person skilled in art to arrive at the present invention. Thus, it is submitted that the claimed invention is novel and inventive in view of D1–D7, thereby constituting an invention under Section 2(1)(j) & (ja) of the Indian Patents Act, 1970. Accordingly, a favourable reconsideration of this objection is humbly solicited.

Non-Patentability u/s 3:

Applicants respectfully disagree with the Controller's allegation that the claimed invention attracts the provision of Section 3(d), 3(j) and 3(b) of the Patents Act, 1970. Applicants understand that the Controller has maintained his non-patentability objections under Section 3 of the Patents Act, 1970, against the original PCT claims. However, it should be noted that the original PCT claims were amended in response to the FER. For the reasons detailed above the claims on file, i.e. claims amended in response to the FER, comply with the requirement under Section 59(1) of the Act and are also patent eligible under the Indian Patent Law.

Applicants submit that the claimed method is not a mere use of a known process rather as demonstrated above it is novel and thus, do not fall within the scope of Section 3(d) of the Act. Similarly, the claimed method uses totipotent mouse cell and thus, the present claims are not in contravention of Section 3(j) of the Act. Furthermore, merely for the reason that the claimed method is for making a genetically modified mouse, the claims should not blankly attract an objection under Section 3(b) of the Act. The claimed subject matter is actually beneficial to humanity in terms of medical research. Also the subject matter is limited to only mouse. Thus, the present claims do not attract the provision of Section 3(b) of the Act. In view of the foregoing, applicant respectfully submit that the present claims are not in contravention of Section 3 of the Act. Accordingly, a favorable reconsideration of this objection is humbly solicited.

The title has been suitably revised to read as "METHOD OF MAKING GENETICALLY MODIFIED MOUSE" so as to be consistent with the principal Claim 1 on file as directed by the Controller during hearing. Accordingly, we submit herewith a formal request on Form-13 along with highlighted & fresh Form-1, Form-2 and Abstract indicating the revised title. The prescribed fee of **Rs.4000/-** has been paid. Kindly take the same on record and allow our request at an early date. In view of the above, applicants believe that all objections which have been raised in respect of this application till date have been overcome. We also wish to place on record that no further objections were raised or maintained by the learned Controller during the hearing.

In view of the foregoing remarks, applicants trust that the application is in condition for allowance. Hence, we respectfully request the Learned Controller to proceed the application to grant. We look forward to receiving a favorable decision in this regard in due course.

Findings and Analysis:

After carefully considering the submission made by the applicant's agent in response to first examination report, submission made during hearing and in the written note of arguments and the amended claims submitted on 21/10/2020, I find that observations, submission made by the agent is not satisfactory with respect to the objections communicated in the hearing notice.

I observed that original set of claims (1-27) filed at international phase and while entering the national phase were directed to a mouse, cell and use of the mouse. The claims were as follows:

1. A mouse, comprising in its germline an unrearranged light chain V segment and an unrearranged J segment operably linked with a heavy chain constant region nucleic acid sequence.
2. The mouse of claim 1, wherein the unrearranged light chain V segment is selected from a human K segment, a human 'A segment, and a combination thereof.
3. The mouse of claim 1, wherein the heavy chain constant region nucleic acid sequence is selected from the group consisting of a CH1 sequence, a hinge sequence, ac sequence, a c H3 sequence, and a combination thereof.
4. The mouse of claim 1, wherein the unrearranged light chain V segment and the unrearranged J segment replace an endogenous mouse heavy chain V segment and an endogenous mouse heavy chain J segment at the endogenous mouse heavy chain locus.
5. The mouse of claim 4, wherein the unrearranged light chain V segment replaces all or substantially all functional mouse heavy chain V segments of the endogenous mouse heavy chain locus.
6. The mouse of claim 4, wherein the unrearranged J segment comprises a light chain J segment, and the light chain J segment replaces all or substantially all functional mouse heavy chain J segments of the endogenous mouse heavy chain locus.
7. The mouse of claim 6, wherein the unrearranged light chain V segment and the unrearranged light chain J segment are operably linked and the mouse lacks a functional D segment between the unrearranged light chain V segment and the unrearranged light chain J segment.
8. The mouse of claim 7, wherein the unrearranged light chain V segment is a human K segment and the unrearranged light chain J segment is a human K segment.
9. The mouse of claim 1, comprising a B cell that comprises in its genome a rearranged immunoglobulin gene that comprises a human K variable region operably linked to a mouse constant region gene.

10. The mouse of claim 1, wherein the rearranged immunoglobulin gene is at an endogenous mouse immunoglobulin heavy chain locus.
11. The mouse of claim 1, further comprising in its germline a human light chain V segment and a human light chain J segment operably linked to a light chain constant gene.
12. The mouse of claim 11, wherein the light chain constant gene is a mouse light chain constant gene.
13. The mouse of claim 12, wherein the human light chain V segment is a human K V segment.
14. The mouse of claim 13, wherein the mouse light chain constant gene is a mouse K light chain constant gene.
15. A mouse that expresses from its germline an immunoglobulin comprising a first polypeptide comprising a first human light chain variable region sequence fused with an immunoglobulin heavy chain constant region, and a second polypeptide comprising a second human light chain variable region fused with an immunoglobulin light chain constant region.
16. The mouse of claim 15, wherein the first human light chain variable region sequence comprises a human K variable region sequence, and the second human light chain variable region is selected from a human K variable region and a human λ variable region.
17. The mouse of claim 16, wherein the immunoglobulin heavy chain constant region is selected from a human heavy chain constant region and a mouse heavy chain constant region.
18. The mouse of claim 16, wherein the immunoglobulin light chain constant region is selected from a human light chain constant region and a mouse light chain constant region.
19. The mouse of claim 16, wherein the first polypeptide is expressed from a modified endogenous mouse immunoglobulin heavy chain locus that lacks a functional endogenous heavy chain V gene segment.
20. The mouse of claim 19, wherein the second polypeptide is expressed from a modified endogenous mouse immunoglobulin light chain locus that lacks a functional endogenous light chain V gene segment.
21. A mouse, comprising a replacement in the germline of the mouse at an endogenous mouse immunoglobulin heavy chain locus of all or substantially all functional endogenous mouse heavy chain variable gene segments with at least six or more unrearranged light chain V gene segments and one or more unrearranged J gene segments, wherein the unrearranged light chain V gene segments and the J gene segments are operably linked, wherein the mouse is incapable of expressing an immunoglobulin heavy chain derived from a heavy chain V gene segment, and wherein the mouse comprises a splenic 8 cell population (8220+/IgM +) that is at least about 75% the size of a splenic 8 cell population (8220 +J μ M +) of a wild-type mouse.
22. Use of a mouse according to any of the preceding claims to produce a binding protein that comprises a human light chain variable domain.
23. Use of a mouse according to any of claims 1-21 to produce an antibody.
24. The use according to claim 23, wherein the antibody is a human antibody.
25. Use of a mouse according to any one of claims 1-21 to produce a bispecific antibody.
26. A cell or tissue derived from a mouse according to any one of claims 1-21 .

27. A cell according to claim 26, wherein the cell is selected from an ES cell, a B cell, and a hybridoma.

On 01/08/2014 form 13 was filed for amendment in claims. The sets of claims (1-28) filed with form 13 were directed to “A method of making a genetically modified mouse, An antigen binding protein, A targeting vector, A nucleic acid construct”. The claims were as follows:

1. A method of making a genetically modified mouse comprising in its germline an unarranged immunoglobulin light chain variable region (VL) gene segment and an unarranged immunoglobulin light chain joining (JL) gene segment operably linked with a heavy chain constant region nucleic acid sequence, the method comprising:
 - (a) modifying a totipotent mouse cell to include an immunoglobulin locus comprising one or more unarranged VL gene segments and at least one unarranged JL gene segment operably linked to an immunoglobulin heavy chain constant region nucleic acid sequence;
 - (b) maintaining the totipotent mouse cell under suitable conditions to develop into a genetically modified mouse comprising in its germline an unarranged light chain V segment and an unarranged J segment operably linked with a heavy chain constant region nucleic acid sequence.
2. The method of claim 1, wherein the one or more unarranged VL gene segments comprise one or more human Vk gene segments, one or more human Vl gene segments, or a combination thereof, and optionally, wherein the at least one unarranged JL gene segment is a human JL gene segment, a human Jk gene segments, or a combination thereof.
3. The method of claim 1, wherein the immunoglobulin heavy chain constant region nucleic acid sequence is selected from the group consisting of a CH1 sequence, a hinge sequence, a CH2 sequence, a CH3 sequence, and a combination thereof.
4. The method of claim 1, wherein the immunoglobulin locus is an endogenous mouse immunoglobulin heavy chain locus, and wherein the one or more unarranged light chain VL gene segments and the at least one unarranged JL gene segment replace one or more endogenous mouse heavy chain variable region (VH) gene segments and one or more endogenous mouse heavy chain joining (JH) gene segments, respectively, of the endogenous mouse heavy chain locus.
5. The method of claim 4, wherein the one or more unarranged VL gene segments replace all or substantially all functional mouse VH gene segments of the endogenous mouse immunoglobulin heavy chain locus.
6. The method of claim 4, wherein the at least one unarranged JL gene replaces all or substantially all functional mouse JH gene segments of the endogenous mouse heavy chain locus.
7. The method of one of claims 4-6, wherein the one or more unarranged VL gene segment and the at least one unarranged JL gene segment are operably linked and the mouse lacks a

functional D segment between the one or more unrearranged VL gene segments and the at least one unrearranged JL gene segment.

8. The method of claim 7, wherein the one or more unrearranged VL gene segments are human Vk gene segments and the at least one unrearranged JL gene segment is a human Jk segment.

9. An antigen binding protein comprising a first polypeptide comprising a first human light chain variable region sequence fused with an first immunoglobulin heavy chain constant region.

10. The antigen binding protein of claim 9, further comprising a second polypeptide comprising a second light chain variable region fused with an immunoglobulin light chain constant region.

11. The antigen binding protein of claim 10, wherein the first human light chain variable region sequence comprises a human k variable region sequence, and the second human light chain variable region is selected from a human k variable region and a human l variable region.

12. The antigen binding protein of claim 11, wherein the immunoglobulin heavy chain constant region is selected from a human heavy chain constant region and a mouse heavy chain constant region.

13. The antigen binding protein of claim 11, wherein the immunoglobulin light chain constant region is selected from a human light chain constant region and a mouse light chain constant region.

14. The antigen binding protein of claim 11, further comprising a third polypeptide comprising a third human light chain variable region sequence fused with a second immunoglobulin heavy chain constant region, wherein the first and second immunoglobulin heavy chain constant regions are identical, and wherein the first, second, and third polypeptides associate to form a bispecific antigen binding protein.

15. The antigen binding protein of claim 14, wherein the first and third human light chain variable region sequences each comprise a human k variable region sequence, and the second human light chain variable region is selected from a human k variable region and a human l variable region.

16. The antigen binding protein of claim 15, wherein each of the first and second immunoglobulin heavy chain constant region is selected from a human heavy chain constant region and a mouse heavy chain constant region.

17. A method of making a genetically modified mouse comprising

(a) replacing all or substantially all functional endogenous mouse heavy chain variable gene segments at an endogenous immunoglobulin heavy chain locus of a totipotent mouse cell with at least six or more unrearranged light chain VL gene segments and one or more unrearranged JL gene segments, wherein the at least six or more unrearranged light chain VL gene segments and the one or more unrearranged JL gene segments are operably linked,

(b) maintaining the cell under suitable conditions to develop into a genetically modified mouse comprising in its germline endogenous immunoglobulin heavy chain locus at least six or more unrearranged light chain VL gene segments operably linked to one or more unrearranged JL gene segments; wherein the mouse is incapable of expressing an immunoglobulin heavy chain derived from a heavy chain VH gene segment, and wherein the mouse comprises a splenic B

cell population (B220+/IgM+) that is at least about 75% the size of a splenic B cell population (B220+/IgM+) of a wild-type mouse.

18. The method according to any one of claims 1-8 and 17, wherein the step of maintaining the totipotent mouse cell under suitable conditions to develop into a genetically modified mouse comprises the steps of culturing the pluripotent/totipotent mouse cell; introducing the cultured pluripotent/totipotent cell into a host embryo to form a chimeric embryo; and introducing the chimeric embryo into a suitable host mouse to develop into a genetically modified mouse.

19. The method according to one of claims 1-8 and 17-18, wherein the totipotent cell is a pluripotent mouse cell, a mouse embryonic stem (ES) cell or an induced pluripotent mouse cell.

20. A targeting vector comprising (a) a first targeting arm and a second targeting arm, wherein the first and second targeting arms are independently selected from human and mouse targeting arms, wherein the targeting arms direct the vector to an endogenous or modified immunoglobulin V region gene locus; and, (b) a contiguous sequence of human VL gene segments.

21. The targeting vector of claim 20, wherein the contiguous sequence comprises human VL gene segments and at least one Jk gene segment.

22. The targeting vector of claim 21, wherein the contiguous sequence is selected from the group consisting of (i) hVk4-1 through hVk1-6 and Jk1, (ii) hVk4-1 through hVk1-6 and Jk1 through Jk2, (iii) hVk4-1 through hVk1-6 and Jk1 through Jk3, (iv) hVk4-1 through hVk1-6 and Jk1 through Jk4, (v) hVk4-1 through hVk1-6 and Jk1 through Jk5, (vi) hVk3-7 through hVk1-16, (vii) hVk1-17 through hVk2-30, (viii) hVk3-31 through hVk2-40, and (ix) a combination thereof.

23. The targeting vector of claim 20, wherein the first and second targeting arms are identical to a sequence at the endogenous or modified immunoglobulin locus.

24. A nucleic acid construct encoding a VL binding protein, the construct comprising a modified immunoglobulin locus comprising gene segments encoding an immunoglobulin light chain variable domain, or portions thereof, operably linked to heavy chain constant region gene segments, wherein the gene segments encoding immunoglobulin light chain variable domains are capable of rearranging to form a rearranged nucleotide sequence comprising a first sequence encoding a light chain variable domain fused with a second sequence encoding a heavy chain constant region, wherein the rearranged nucleotide sequence encodes a polypeptide that has an immunoglobulin light chain variable domain fused with a heavy chain constant region.

25. An antigen binding protein made by a method comprising (a) immunizing a mouse made according to any one of claims 1-8 and 17-19 with and antigen of interest, and (b) recovering a cell from the immunized animal, wherein the cell produces an antigen-binding protein that comprises light chain variable (VL) domain fused to a heavy chain constant region.

26. The antigen binding protein of claim 26, wherein the VL domain is a human VL domain.

27. The antigen binding protein of claim 26, further comprising (c) obtaining a nucleotide sequence encoding the human VL domain; (d) cloning the nucleotide sequence encoding the VL region sequence in frame with a gene encoding a human CH region to form a human binding protein sequence, and (e) expressing the human binding protein sequence in a suitable cell.

28. A high-affinity antigen binding protein made by a method comprising (a) immunizing a mouse made according to any one of claims 1-8, and 17-19 with an antigen of interest, (b) allowing the mouse to develop an immune response to the antigen of interest, and (c) isolating a somatically mutated, class-switched human VL domain from the mouse that specifically binds the antigen of interest with high affinity.

On 27/02/2019 at the time of submitting a response to the first examination report (FER) the claims were amended. The sets of claims (1-10) filed in response to the FER were directed to “A method of making a genetically modified mouse”. The claims were as follows:

1. A method of making a genetically modified mouse comprising in its germline A) an unrearranged immunoglobulin light chain variable region (VL) gene segment and an unrearranged immunoglobulin light chain joining (JL) gene segment operably linked with a heavy chain constant region nucleic acid sequence, and B) a human light chain V segment and a human light chain J segment operably linked to a light chain constant gene; the method comprising:

(i) modifying a totipotent mouse cell to include

a) a first plurality of light chain gene segments comprising at least one VL gene segment and at least one unrearranged JL gene segment, wherein the first plurality is operably linked to an immunoglobulin heavy chain constant region nucleic acid sequence, and

b) a second plurality of light chain gene segments comprising at least one VL gene segment and at least one unrearranged JL gene segment, wherein the second plurality is operably linked to an immunoglobulin light chain constant region nucleic acid sequence; and

(ii) maintaining the totipotent mouse cell under suitable conditions to develop into a genetically modified mouse comprising in its germline A) an unrearranged immunoglobulin light chain variable region (VL) gene segment and an unrearranged immunoglobulin light chain joining (JL) gene segment operably linked with a heavy chain constant region nucleic acid sequence, and B) a human light chain V segment and a human light chain J segment operably linked to a light chain constant gene.

2. The method of claim 1, wherein the first plurality of light chain gene segments comprises a human Vk segment, a human Vl segment, or a combination thereof.

3. The method of claim 1, wherein the heavy chain constant region nucleic acid sequence comprises a CH1 sequence, a CH2 sequence, and a CH3 sequence.

4. The method of claim 1, wherein modifying comprises replacing at an endogenous mouse heavy chain locus an endogenous mouse heavy chain V segment, an endogenous mouse heavy chain D segment, and an endogenous mouse heavy chain J segment at the endogenous mouse heavy chain locus with the first plurality of light chain gene segments.

5. The method of claim 4, comprising replacing all functional mouse heavy chain V segments, all functional mouse heavy chain D segments, and all functional mouse heavy chain J segments of the endogenous mouse heavy chain locus.

6. The method of claim 5, wherein the first plurality of light chain gene segments comprises a human Vk segment and a human Jk segment.
7. The method of claim 1, wherein the rearranged immunoglobulin gene is at an endogenous mouse immunoglobulin heavy chain locus.
8. The method of claim 1, wherein the light chain constant gene is a mouse light chain constant gene.
9. The method of claim 8, wherein the second plurality of light chain gene segments comprises a human Vk segment.
10. The method of claim 9, wherein the mouse light chain constant gene is a mouse k light chain constant gene.

On 21/10/2020 at the time of submitting written submission form 13 was filed for amendment of the title of invention to “Method of making genetically modified mouse”.

Section 59(1) states that “No amendment of an application for a patent or a complete specification or any document relating thereto shall be made except by way of disclaimer, correction or explanation, and no amendment thereof shall be allowed, except for the purpose of incorporation of actual fact, and no amendment of a complete specification shall be allowed, the effect of which would be that the specification as amended would claim or describe matter not in substance disclosed or shown in the specification before the amendment, or that any claim of the specification as amended would not fall wholly within the scope of a claim of the specification before the amendment.” I observed that original sets of claims (1- 27) were directed to to a mouse, cell and use of the mouse. On 01/08/2014 form 13 was filed for amendment in claims. The amended claims were directed to “A method of making a genetically modified mouse, An antigen binding protein, A targeting vector, A nucleic acid construct” where the entire scope of the invention has been changed. In response to First Examination Report, the applicant had reworded the claims. The claims were directed to “A method of making a genetically modified mouse”. It is pertinent to mention here that the applicant reworded the claims, where the entire scope of the invention has been changed when compared with the claims filed in international phase or while entering the national phase. The applicant reworded the claims, where the entire scope of the invention has been changed. In the present case, neither in the international phase, nor at national phase entry the application had a claim for A method of making a genetically modified mouse. So from the above discussion, it is amply clear that the claim which is not claimed at the time of filing is disclaimed and such amendments of claims are not allowable under section 59(1) of the Act. So the Agent’s submission is not convincing to me and so this amendment of claims are not allowable.

Further, boundary of the protection is well defined in Patent Law by P. Narayanan, Third Edition 1998, page 88, para 5-19, *Guide lines to construction* “Guide Line 1: The words of the claims (when themselves correctly construed) provides the prima facie boundary of protection”. *Lord Russell in EMI v Lissen (1939)56 RPC 23 at 39 and 41* said: “The function of

Exhibit-J

the claims is to define clearly and with precision the monopoly claimed, so that others may know the exact boundaries of the area within which they will be trespassers. Their primary object is to limit and not to extend the monopoly. What is not claimed is disclaimed....”

Therefore, according to my consideration the method for preparing an expanded liver stromal cell culture, by culturing liver stromal cells in a culture medium are beyond the scope of the claims as originally filed and not allowable under Section 59(1) of the Patent Act 1970.

I observed that the present invention claims for a process for making a genetically modified mouse with modification in its germline. The present invention claims for a process for making a transgenic mouse with modification in its germline. The present invention claims for a process for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical or other benefit to man or animal. The claimed processes resulting in modification of the genetic identity of animals influences or has a deep impact upon the human or animal or involve serious questions about morality. This can lead to serious prejudice to the human and animal life or health, contrary to public order, morality. Hence these claims attract section 3(b) of the Act.

In view of the above findings and upon consideration to the submission to FER, observation in the written note of arguments, I find the alleged invention as claimed in revised claims is beyond scope of invention as originally filed and claims are not allowable under section 59(1) of the Patents Act. I find the alleged invention as claimed in revised claims fall within the scope of such clause (b) of Section 3 of the Act. Hence, I hereby order to refuse the instant application no. 1554/CHENP/2013 for grant of patent.

16/12/2020

(Dr. Abhijit Das)

Assistant Controller of Patents & Designs.

(Section 15)

In the matter of Application no. **2978/DELNP/2007** filed in India on 20/04/2007 for Grant of Patent;
Corresponding International Patent Application No. PCT/EP2005/011596 dated 29/10/2005, Claiming Priority
Date 05/11/2004 of EP;

Applicants:- M/S **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**

Applicants Attorneys: M/S REMFRY & SAGAR, GURGAON, INDIA

ATTORNEY'S PRESENT FOR ARGUMENT: MR AMIT SAINI

EXAMINER: DR ROHIT RATHORE, EXAMINER, PATENT OFFICE, NEW DELHI, INDIA

Date of Hearing: 25/06/2014

DECISION

[A] Above detailed application with title as "**BILAYER TABLET**" was filed in the patent office on 20/4/2007 for Grant of the Patent. On filing of the Request for the Examination the application was Examined and a first examination report was issued on with the following major objections:

Major objections of the FER:-

The last date for filing of the reply with all the compliance was and the same was received well within the time limit i.e. on .

The application was reexamined for if all the objections of the first examination report was complied with or not. On such scrutiny the Ld Examiner found the application still suffering with some shortcomings and as a result the matter came up for hearing U/S 14 with the said following pending issues . The applicant was heard in detail on 25/06/2014:-

[B] PENDING ISSUES:

S.NO	OBJECTIONS
1	Claim-1 does not sufficiently define the invention w.r.t. the expressions "water soluble diluent" and "tablet matrix disintegrating or eroding in a physiological aqueous medium"
2	Subject matter of the claims does not constitute an invention u/s 2(1) (j) (a) as the claims lack inventive step in view of cited documents: D1: WO 00/27397 discloses a pharmaceutical combination of telmisartan and lacidipine, which is a calcium antagonist particularly useful for treating hypertension. Preferably, the combination is administered as a single combined formulation in the form of a unit dosage form for the treatment and/or prophylaxis of hypertension (see cf. claims 3, 6 and 8; page 11, lines 24-25). In particular, bilayer tablets comprising telmisartan and lacidipine are prepared by a conventional procedure, e.g. by separately compressing two blends in a suitable tableting machine (page 10, lines 5-7). Example 2 of D1 is directed to a bilayer tablet prepared by separately compressing a blend comprising spray-dried telmisartan granules mixed with sorbitol and magnesium stearate and a blend comprising lacidipine granules mixed with sorbitol and magnesium stearate (page 12, line 15 to page 13, line 9). Consequently, just as the tablet according to claim 1 of the present application, D1 relates to a bilayer

tablet comprising a first layer containing telmisartan and a second layer comprising a calcium channel blocker as well as the use of such a combination formulation for the treatment of hypertension. The bilayer tablet according to Example 2 of D1 comprises telmisartan in a sorbitol matrix. Sorbitol is a suitable and even the preferred dissolving matrix former according to the present application (cf. page 6, lines 10-13). Hence, a first layer of telmisartan in a dissolving matrix is already disclosed by Example 2 of D1. Moreover, also the claim limitation of a "disintegrating or eroding tablet matrix" is disclosed by said example. The second layer of the bilayer tablets according to Example 2 of D1 comprises sorbitol and magnesium stearate which are preferred filler and lubricant of the second layer composition according to the present application. Sorbitol is soluble in aqueous medium. Hence, at least sorbitol is removed, i.e. eroded, from the second layer tablet matrix resulting in that the tablet matrix breaks down, i.e. disintegrates. It follows that also a second layer disintegrating or eroding tablet matrix is already disclosed by Example 2 of D1

D2: WO0243807 discloses a pharmaceutical combination of an angiotensin receptor blocker (which includes telmisartan) with either an anti-hypertensive drug (which includes amlodipine) or an HMG-CoA reductase inhibitor. The said pharmaceutical combination can be in a fixed combination as a solid oral dosage form like tablets. Further it discloses the amount of ARB i.e. 40, 80 or 160 mgs and of amlodipine i.e. 2.5, 5 or 10 mgs to be administered which is overlapping with the amount present in the claimed tablet.

D3: US6162802 discloses a synergistic combination therapy using benazepril and amlodipine for the treatment of cardiovascular disorders and compositions therefor. D2 discloses a bilayer tablet of amlodipine and benazepril for treating cardiovascular disorders (column 3 lines 13-23, and 48-62). D2 further specifically discloses that two physically incompatible active agents can be used and prepared in the art by combining two pill formulations together into a single tablet with methods common to the art, such as bilayered tablets. Example 1 discloses a bilayer tablet in which the amlodipine layer is comprised of the filler dibasic calcium phosphate, the disintegrant sodium starch glycolate, the lubricant magnesium stearate, the binder micro crystalline cellulose, and the flow control agent talc is used in a coating on the core, and other excipients and adjuvants. D2 clearly teaches that if amlodipine and the angiotensin converting enzyme inhibitor benazepril are incorporated into a single dosage form, they must be kept physically separated by e.g. the use of bi-layer tablet technology (column 3, lines 48-5

D4: Stangier, J. Et Al: "Pharmacokinetics Of Repeated Oral Doses Of Amlodipine And Amlodipine Plus Telmisartan In Healthy Volunteers" Journal Of Clinical Pharmacology, vol. 40, no. 12, PART 1, December 2000 (2000-12) pages 1347-1354 discloses (cf. page 1349, left-hand column, lines 10-13; page 1353, left-hand column, paragraph 2- right-hand column, last paragraph) the concomitant use of tablets of telmisartan with tablets of amlodipine.

D5: WO03/059327 discloses a bilayer pharmaceutical tablet comprises a first layer formulated for immediate release of the angiotensin II receptor antagonist telmisartan from a dissolving tablet matrix which contains telmisartan in substantially amorphous form, and a second layer formulated for immediate release of a diuretic like hydrochlorothiazide from a fast disintegrating tablet matrix. A method of producing the bilayer tablet is also disclosed. D5 teaches that the bi-layer tablet structure overcomes stability problems caused by the incompatibility of the second antihypertensive drug with the excipients of the telmisartan formulation.

D6: Calvo, C et al., "A comparative evaluation of amlodipine and

	<u>hydrochlorothiazide as monotherapy in the treatment of isolated systolic hypertension in the elderly”, Clinical Drug investigation, 19 May 2000</u> teaches that amlodipine is more effective than hydrochlorothiazide as monotherapy for treatment of hypertension. In the light of cited documents D1-D6 it is obvious for a person skilled in the art to arrive at the claimed invention.
3	Claims 1-13 fall within the scope of such clause (d) of section 3 of Indian Patents Act as claimed tablet is considered to be mere new form i.e. bilayer tablet having combination of two known substances with no enhancement in their known therapeutic efficacy. Claims 1-13 fall within the scope of such clause (e) of section 3 of Indian Patents Act as claimed tablet appears to be mere admixture of two known substances.
4	Extraneous matter should be deleted from left top of the pages of complete specification and fresh retyped pages should be filed.
5	Pages of the complete specification should be renumbered.
6	Fees should be filed for two extra pages as total pages of complete specification is 34 but fees filed only for 32 pages.

[C] The above mentioned issues were pending on the following set of the Claims:

Claim no	Claim
1	A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix and a second layer of amlodipine in a disintegrating or eroding tablet matrix.
2	The tablet of claim 1 wherein telmisartan is in a substantially amorphous form.
3	The tablet of claim 1 wherein the dissolving tablet matrix has instant release characteristics.
4	The tablet of claim 1 wherein the dissolving tablet matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.
5	The tablet of claim 4, wherein the basic agent is selected from alkali metal hydroxides, basic amino acids and meglumine.
6	The tablet of claim 4, wherein the water-soluble diluent is selected from saccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, and xylitol.
7	The tablet of claim 4, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.
8	The tablet of claim 1 wherein the first tablet layer composition of telmisartan is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent to obtain a spray-dried granulate, mixing said spray-dried granulate with a water-soluble diluent to obtain a premix and mixing said premix with a lubricant to obtain a final blend.
9	The tablet of claim 1 wherein the disintegrating or eroding tablet matrix of the second layer comprises one or more fillers, a disintegrant, a lubricant and, optionally, a binder, a flow control agent or other excipients and adjuvants.
10	The tablet of claim 9, wherein the second tablet layer composition of amlodipine is manufactured by direct compression, wet granulation or a roller compaction process.
11	The tablet of claim 1 wherein the first layer contains preferably 20-80 mg or 40-80 mg telmisartan.
12	The tablet of claim 1 wherein the second layer contains mg, preferably 2.5-10 mg amlodipine.

13	The tablet of claim 1 packaged in a moisture proof packaging materials such as a aluminum foil blister packs, or polypropylene tubes and HDPE bottles.
14	A method for the manufacture of a tablet of claim 1 to treat hypertension either alone or in combination with the treatment or prevention of a condition selected from the group consisting of chronic stable angina, vasospastic angina, stroke, myocardial infarction, transient ischemic attack, congestive heart failure, cardiovascular disease, diabetes, insulin resistance, impaired glucose tolerance, pre-diabetes, type 2 diabetes mellitus, diabetic nephropathy, metabolic syndrome (syndrome X), obesity, dyslipidemia, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentration of homocysteine, elevated serum concentration of low-density lipoprotein (LDL)-cholesterol, elevated serum concentration of lipoprotein-associated phospholipase (A2), reduced serum concentration of high density lipoprotein (HDL)-cholesterol, reduced serum concentration of HDL (2b)-cholesterol, reduced serum concentration of adiponectin, cognitive decline and dementia.
15	The method of claim 14 wherein the condition treated or prevented is chronic stable angina, vasospastic angina, stroke, myocardial infarction, congestive heart failure, diabetes, dyslipidemia or dementia.

[D] In view of the pending objections the applicant was offered an opportunity to be heard and accordingly the date of hearing was 25/06/2014 which was duly attended by the applicant's attorney. During hearing the applicant's attorney attended and argued the case thoroughly and offered some amendments in the claim. The amended set of the claims (total 9 claims) have been reproduced herein below;

No	Claim
1	A pharmaceutical tablet comprising a first layer of telmisartan in a dissolving tablet matrix comprising a basic agent selected from alkaline metal hydroxides, basic amino acids and meglumine; a water-soluble diluent selected from monosaccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, and xylitol; optionally other excipients and adjuvants and a second layer of amlodipine in a tablet matrix disintegrating or eroding in a physiological aqueous medium comprising one or more fillers, a disintegrant, a lubricant and, optionally, a binder, a flow control agent or other excipients and adjuvants.
2	The tablet as claimed in claim 1, wherein telmisartan is in a substantially amorphous form.
3	The tablet as claimed in claim 1, wherein the dissolving tablet matrix has instant release characteristics.
4	The tablet as claimed in claim 1, wherein the other excipients and adjuvants are selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers.
5	The tablet as claimed in claim 1, wherein the first tablet layer composition of telmisartan is produced by spray-drying an aqueous solution comprising telmisartan and a basic agent to obtain a spray-dried granulate, mixings aids spray-

	driedgranulatewithawater-solublediluenttoobtainapremixandmixingsaidpremixwithalubricant to obtainafinalblend.
6	Thetabletasclaimedinclaim1,whereinthesecondtabletlayercompositionofamlodipineismanufacturedbydirectcompression,wetgranulationorarollercompactionprocess
7	Thetabletasclaimedinclaim1,whereinonilayercontains1-20mg preferably2.5-10mgamlodipine.
8	Thetabletasclaimedinclaim1,wherein thefirstlayercontains 10-169 mg preferably20-80mgor40-80mgtelmisartan.
9	The tablet of claim 1 packaged in a moisture proof packaging material such as aluminiumfoilblisterpacks,orpolypropylenetubesandHDPEbottles

[E] The applicant offered arguments in favour of their revised 9 claims which are being reproduced hereinbelow

ARGUMENTS OF THE LD ATTORNEY:

Regarding paragraph 1, the applicant humbly submits that the claims have been suitably amended. The expressions "water soluble diluent" and "tablet matrix medium" have been clearly defined in amended claim 1. Accordingly, the learned Controller is respectfully requested to waive the objection.

Regarding paragraph 2, the applicant resists the Controller's objection and submits that the subject matter of claims is inventive over the cited prior art documents. In this regard, the applicant submits the following:

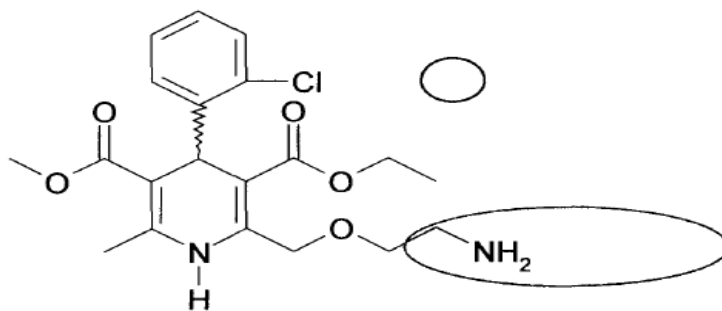
It is pointed out that the antihypertensive effect of the combination is not an essential feature of the claimed subject matter but evidence for its industrial applicability. The essential technical feature of the claimed invention is the unexpected combinability of an "amlodipine" – containing tablet layer with a "basic" telmisartan tablet matrix, which is neither taught nor suggested in D 1 to D 6.

D1(W000/27397)

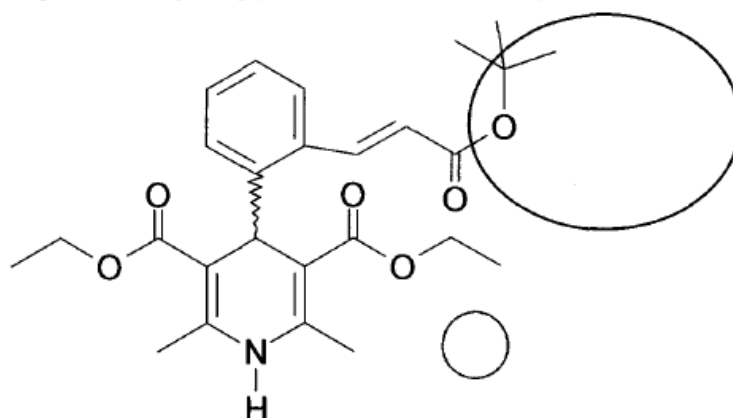
D1 does not mention amlodipine let alone bilayer tablets with amlodipine;

D 1 teaches away from the present invention. It is limited to lacidipine, does not mention amlodipine and primarily teaches capsule dosage forms. For bilayer tablets no incompatibility problem is recognized in respect of lacidipine. Further, lacidipine and amlodipine are not comparable CCBs. The chemical differences of both structures are indicated in the following formulae: . •

Amlodipine (2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid, 3-ethyl 5-methyl ester)



Lacidipine (3,5-diethyl4-{2-[(1E)-3-(tert-butoxy)-3-oxoprop-1-en-1-yl]phenyl}-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate)



Compared to lacidipine

- the pyridyl element of amlodipine carries in the 2 position a (2-aminoethoxy)methyl substituent instead of a small methyl group and
- the phenyl element of amlodipine carries in the 2 position a simple chlorine substituent instead of a 3-oxoprop-1-en-1-yl group.

Consequently, Lacidipine is a highly lipophilic calcium channel blocker (a solubility of about 84mg in a liter of water) while Amlodipine is a hydrophilic calcium channel blocker (with a solubility of about 7.5mg in a liter of water). And this was well known to the person skilled in the art (see Zwieten and Pfaffendorf in the Journal of Hypertension 11 (suppl 6): S3-S8, 1993, a copy whereof is enclosed as **Annexure A**). The said reference proves that the skilled artisan did not inevitably consider a technical teaching specific for a pharmaceutical composition comprising the lipophilic compound lacidipine as applicable to a pharmaceutical composition comprising the hydrophilic compound amlodipine. Instead, Zwieten and Pfaffendorf point out, that lacidipine and amlodipine represent compounds with very different physico-chemical properties. Thus, lacidipine is described as being preferable to a hydrophilic calcium channel blocker ("The slow onset of action of lacidipine therefore readily explains the lack of reflex tachycardia, which is an advantage", page S7, first sentence of the penultimate paragraph). Therefore, the applicant strongly disagrees that the person skilled in the art would have inevitably replaced the lipophilic calcium channel blocker lacidipine of exhibit 4 with the hydrophilic calcium channel blocker amlodipine.

D2(w00243807)

The essential feature of D2 is the treatment of SD and teaches separate co-administration, while D2 does not disclose co-administration of telmisartan and amlodipine let alone corresponding bilayer tablets;

D2 is restricted to combinations for the treatment of sexual dysfunction (SD) associated with hypertension and another condition by administering a pharmaceutical combination of an angiotensin receptor blocker with either an anti-hypertensive drug or an HMG-CoA reductase inhibitor. The applicant submits that sexual dysfunction is not a therapeutic condition according to the present invention. Moreover, valsartan is taught to be the "most preferred" ARB of the disclosed combinations, while lacidipine is not mentioned at all.

The present invention is pertains to a bilayer tablet of telmisartan and amlodipine which is nowhere disclosed or suggested in the cited reference.

D3 (US 6162802)

D3 teaches the specific combination of amlodipine with the ACE inhibitor benazepril, i.e. a compound structurally AND functionally very different from the angiotensin receptor blocker telmisartan.

D4 (Stangier, J et al; Pharmacokinetics of Repeated Oral Dose of Amlodipine and Amlodipine plus Telmisartan in Health Volunteers; Journal of Clinical Pharmacology vol. 40, no. 12, part 1; December 2000, pp 1347-1354)

D4 teaches that separate co-administration of telmisartan and amlodipine is safe, but does NOT disclose their combinability in a bilayer tablet;

D4 shows, that telmisartan and amlodipine when used together to improve blood pressure reduction, do not interact with each other. D4, however, does not teach any dosage form of a combined telmisartan plus amlodipine combination.

D5 (W02003/059327)

D5 is restricted to the combination partner HCTZ which is structurally very different to amlodipine. Further, HCTZ belongs to the diuretic class of compounds whereas amlodipine belongs to calcium channel blocker class of antihypertensives. Accordingly, HCTZ is both structurally and functionally very different from amlodipine. Therefore, incompatibility of HCTZ with basic constituents of the telmisartan formulation is not predictive for an incompatibility of amlodipine.

Further, since Hydrochlorothiazide was known as a diuretic while amlodipine was known as a calcium channel blocker. If a person skilled in the art would have considered to replace hydrochlorothiazide he would have considered to replace it with an alternative diuretic, for which a number of embodiments were available, because diuretics were the first drugs used to treat hypertension. A very prominent diuretic was chlorthalidone, for which more clinical trial data were available than for hydrochlorothiazide. Thus, if a person skilled in the art considered to replace

the diuretic hydrochlorothiazide taught in W003/059327 he would have replaced it with another diuretic and most likely with chlorthalidone. Replacing the diuretic of W003/059327 with a calcium channel blocker was not an obvious alternative.

Therefore, replacing the diuretic hydrochlorothiazide with the calcium channel blocker amlodipine constitutes an inventive approach in itself.

D6 (Calvo et al; "A Comparative Evaluation of Amlodipine and Hydrochlorothiazide as Monotherapy in the treatment of Isolated Systolic Hypertension in the Elderly" from Clinical Investigation dated on May 19, 2000)

D6 does not teach to combine amlodipine with hydrochlorothiazide let alone with another antihypertensive agent; instead on the bottom of the first column of page 325 D6 teaches that *"The dosages of hydrochlorothiazide studied in this trial were higher than currently recommended. and they might explain the observed unfavorable metabolic effects"*.

D6 is limited to monotherapy and does not insinuate combinations at all, leave alone a bilayer tablet comprising telmisartan and amlodipine as disclosed in the subject application.

Altogether neither of the documents D 1 to D6 nor any combination thereof inevitably teaches to combine telmisartan and amlodipine in a bilayer tablet.

In this regard, it would not be irrelevant to invite the learned Controller's attention towards the fact that various corresponding foreign applications (viz. AU, CA, EA, EP, ID, NZ, NZ, SG, TW, UA and VN), having claims similar to the subject application have proceeded to grant after a strict novelty and inventive step search. A copy of EP Patent 1814527 B1 IS enclosed for the ready reference.

In view of aforesaid submissions and amendments carried out to the claims, the learned Controller is respectfully requested to waive the objection.

Regarding paragraph 3, the applicant humbly submits that claims have been suitably amended and do not fall under the prohibition of Section 3(d) and Section 3(e).

The applicant submits that the claims pertain to a bilayer tablet which comprises two or more substance (such as telmisartan, amlodipine, etc) which are not derivatives/forms of each other.

As clarified by the Hon'ble IPAB in the matter of *Ajantha Pharma Limited Vs. Allergan Inc. & Ors.*, ORA/21/2011/PT/KOL (hereinafter referred to as *Ajantha Pharma Limited Case*) (copy enclosed as Annexure B), the claimed composition does not fall within the embargo of Section 3 (d) of the Act. In this regard, the learned Controller's attention is invited to paragraph 84 of the said judgment wherein it was observed that : *"The section explained that a mere discovery of which is not to be considered as an invention if it is a new form of a known substance, new property of new use of known substance or a known process or the use of a known process, machine or apparatus. But this discovery would be considered as an invention if the new form results in enhancement of known efficacy of that substance and so on as described in the section. The explanation to the section enumerates various derivatives of the known substance which shall be*

considered to be the same substance unless, there is significantly different in therapeutic efficacy. Therefore all the forms of the known substance that are mentioned are derivatives of the known substance which could be salts, esters, ethers and so on. Combination is also mentioned here. The respondent had argued that this cannot be considered as a form of a known substance. The respondent is right. This is invention is a combination of Brimonidine and Timolol. The applicant perhaps wants us to consider it either as a derivative of Brimonidine or as a derivative of Timolol. It is not a derivative. The combination mentioned in the Explanation can be only mean a combination of two or more of the derivatives mentioned in the Explanation or combination of one or more of the derivatives with the known substance which may result in a significant difference with regard to the efficacy. A combination of two active drugs like Brimonidine and Timolol cannot be considered derivatives of each other. This ground is rejected.

"[Emphasis supplied]

Accordingly, Section 3(d) is not applicable to the subject invention.

Further, the applicant submits that the claimed tablet is not a mere admixture as the combination of telmisartan and amlodipine is an synergistic combination and the same is well documented in the prior art documents (for e.g. please refer to WO 2005/070462). Furthermore, not only is the combination of telmisartan and amlodipine a synergistic combination in respect of blood pressure reduction but also contributes the interaction of telmisartan with the PP AR gamma receptor which is particularly beneficial for patients affected by the metabolic syndrome (for e.g. please refer to WO 2005/011680).

However, amlodipine is incompatible with the basic agent (such as sodium hydroxide, meglumine, etc) which must essentially be present in a formulation comprising telmisartan. The present invention overcomes this incompatibility provides a stable tablet comprising telmisartan and amlodipine.

Accordingly, the present invention does not fall under the prohibition of Section 3(e).

In view of the submissions presented above, waiver of the present objection is respectfully requested.

Regarding paragraphs 4 and 5, the requirements raised in these paragraphs have been complied with.

Regarding paragraph 6, we have the honour to submit fees for two additional pages. Waiver of the objection is respectfully requested.

[G] PreGrant opposition filed: two Pregrant oppositions were filed against the grant of the Patent as per the following details:

SNO.	OPPONENTU/ S 25(1)	Date of filing of oppositi	GROUNDS TAKEN	Citations used in opposition	Status of opposition
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		on			
1	M/S MEDITAB SPECIALITIES PVT LTD, MUMBAI, THRU M/S S. MAJUMDAR CO.		1. PRIOR CLAIMING 25(1)(c); 2. obviousness 3. Not Patentable U/S 3 4. NOT PATENTABLE Eany claim of Section 25(1)(f); 5. INSUFFICIENT DESCRIPTION 6 NON COMPLIANCE OF SEC 8		
2	M/S MYLAN LABORATORIES LIMITED, an Indian Company, Medak District, 502 325 ON 4 TH AUG 2014 THRU G. NATRAJ CO, NEW DELHI		1. That the invention is not Patentable under – Section 25(1)(c); 2. That the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive 3. That the subject of any claim of the complete specification is not an invention within the meaning of this Act, 4. That the complete specification does not sufficiently and clearly describe the invention and the method by which it is to be performed- Section 25(1) 5. That the patentee has failed to disclose to the Controller the information required by Section 8 or has furnished the information which in any material particular was false to this knowledge- Section 25(1)(h).		

[H] (i) Hearing u/s 25(1) or sec 14?

The applicants attorneys did not raise this issue at any time. Further the decision dated ... of the Hon'ble High court of Delhi in Gilead Pharmassetcase ,Patent application no 6087/DELNP/2007, that if the hearing U/s 14 is intended to be given to decide the Patentibility of any subject matter and the Ld Examiner has used any citation from the opposition filed prior to the date of issuance of hearing letter , the hearing must be given U/s 14 and 25(1) simultaneously ,does not apply in this case as the hearing in the application under considerations took place prior to the said decision of the hon'ble High Court of Delhi.

(ii) sec 2[1(j)]:

Amendments carried out in the Claim appears to be within the permissible limits of the Patents Act, hence allowed.

Objections no 1, 4 ,5 and 6 have been complied with hence no discussion required.

Further the objection relating to the novelty and Inventive step in respect of the claimed invention

also need not to be considered now as the Patents by major jurisdictions on this invention has already been issued considering various citations in addition to the citations raised by the Ld Indian Examiner. I also find that the cited documents in the light of the analysis by the Ld Examiner, the counter statement of rebuttal by the applicant's attorney are not sufficient to break the novelty and Inventive step of the invention under question. Hence the said objection is waived off.

[iii] Application of Section 3(d): Section 3 of the Indian Patent Act list out the Inventions that are not Patentable in India. That is to say the claimed invention in order to be Patentable need to pass the test of sec 3 after qualifying U/S 2(1{j}).

Sec 3(d)..the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance.....is not Patentable.....EXPLANATION:

For the purpose of this clause salts, esters, ethers.....combinations and other derivatives of known substance shall be considered to be same substance, unless they differ significantly in properties with regard to efficacy..

And according to the judgement of the hon'ble Chennai High court and the hon'ble Supreme Court of India the efficacy in the pharmaceutical cases may be measured by the results of the clinical trials.....

In the present case the novelty and inventive step of the claimed bilayer tablet lies in its unexpected combinability of an amlodipine containing tablet layer with a basic telmisartan tablet matrix.- Pages 4 and 9 of the instant specification states that the claimed tablet provides a pH-independent dissolution of the poorly water-soluble telmisartan, thereby facilitating dissolution of the drug (at least 70% dissolved after 30 minutes and complete release occurring within less than 60 minutes) at a physiological pH level, and adequate stability and drug release of amlodipine.

D1 (WO2000/27397) is the closest prior art. D1 teaches bilayer tablets useful for treatment of hypertension comprising telmisartan and lacidipine. Lacidipine is functionally and structurally similar to amlodipine. Both are dihydropyridine molecule and acts as calcium channel antagonist. The degradation mechanism is same for both lacidipine and amlodipine.

The amlodipine (calcium antagonists/calcium channel blockers) and telmisartan (angiotensin II receptor blockers), either alone or in combination, are commonly recommended to treat high blood pressure (hypertension). Amlodipine relaxes (widens) the blood vessels and telmisartan keeps blood vessels from narrowing, which improves blood flow thereby lowering the blood pressure.

At the time of hearing the agent submitted annexure A (Pieter A van Zwieten et al.) to show that lacidipine and amlodipine are not comparable compounds. The agent submitted that annexure A shows lacidipine is highly lipophilic calcium channel blocker (solubility of about 84 mg in 1 lit of water) whereas amlodipine is hydrophilic compound (solubility of about 75 mg in 1 lit of water). It is observed that this difference in hydrophilicity is not significant. Also the specification is silent regarding whether the hydrophilicity of amlodipine plays any role in telmisartan-amlodipine interaction in tablet form.

Even if it is presumed that hydrophilicity of amlodipine plays any significant role in therapeutic efficacy, then also the agents fail to demonstrate any data showing significant enhancement in therapeutic efficacy. Annexure A demonstrates that a slow onset and long duration of action of lacidipine are advantages in the chronic treatment of essential hypertension. A major advantage is the lack of reflex tachycardia, lower incidence of headaches and flushes. Therefore, it is observed that annexure A shows therapeutic efficacy for a highly lipophilic calcium channel blocker, Lacidipine and not for amlodipine which is a hydrophilic calcium channel blocker.

Although the instant claimed bilayer tablet shows structural stability (drug stability), however the said tablet does not show any significant enhancement in therapeutic efficacy. Page 2 of the specification states that amlodipine and telmisartan are considered to cooperate favorably in the treatment of hypertension particularly in patients where the target blood pressure cannot be achieved with one of the medications only. Therefore the instant application aims to prepare a fixed dose combination product comprising amlodipine and telmisartan by overcoming their incompatibility.

The specification does not show any data comparing the instant claimed tablet with the available comparator to know if the said tablet provides any significant health benefit. By reading the specification, a skilled artisan would not get any suggestion that the claimed bilayer tablet would be better than the existing ones.

Examples 1-13 of the specification shows the telmisartan/amlodipine 2-layer tablet in various dosages. Claims 7-8 recites the dosage ranges of telmisartan and amlodipine, respectively. However neither the specification nor the agents at the time of hearing showed any data to demonstrate that the specific dosage amounts contribute to therapeutic efficacy.

In *Novartis vs UOI & Others*, the Hon'ble Supreme Court decided that "efficacy" u/s 3(d) of the Patents Act would be interpreted as "therapeutic efficacy" because the subject matter of the patent is a compound of medicinal value. Novartis did not present evidence of a difference in therapeutic efficacy between the final form of Gleevec and the raw form of imatinib, and that therefore the patent application was properly rejected by the patent office and lower courts.

In the instant case, the claimed bilayer tablet shows drug stability and increased dissolution in lesser time. Therefore, it is observed that the physical efficacy of the claimed bilayer tablet is enhanced in comparison to other forms. However, as no data or evidence had been offered to indicate that the claimed bilayer tablet will produce an enhanced or superior therapeutic efficacy than what could be achieved with the other comparable forms. Therefore it is opined that the claimed bilayer tablet does not qualify the test of Section 3(d).

{ I } Hence in view of the above discussion the Patent on the present invention cannot be granted. Patent application is refused for the grant of the Patent.

DATED: 23/9/2016

Sd/-
(HARDEV KARAR)
DEPUTY CONTROLLER OF PATENTS & DESIGNS
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2250 2082
2250 2083
2250 2084

No. POC/DECISION/SEC.15 /2012/

Dated: 09/10/2012

To

Depenning & Depenning
31 South Bank Road
Chennai 600 028

Sub:Patent Application No. 3725/Chenp/2006- Reg.

Sir,

The above referred patent application filed by you has been refused U/S 15 of Patents Act, 1970 for not meeting requirements of Act. A copy of the order is enclosed herewith.

Thanking you,

Yours faithfully,


(PRIYADHARSINI RAJANBABU)

Asst. Controller of Patents & Designs.

Encl.: Copy of decision.

**THE PATENTS ACT, 1970
&
THE PATENTS RULES, 2003**

**In the matter of Application for Patent bearing the number as
3725/CHENP/2006
Filed by NOVARTIS AG**

And

**In the matter of Section 15 of the Patents
Act, 1970**

ORDER

1. A PCT national phase application for patent titled "AN ETHANOL FREE PHARMACEUTICAL COMPOSITION COMPRISING PIMECROLIMUS" was filed by NOVARTIS AG on 09.10.2006 at Patent office Chennai.

2. The said application was the national phase application of PCT international application PCT/EP05/03669 filed on 07.04.2005, which claimed priority from GB application 04-08070.1 and GB 0408076.8. A request for examination for this application was filed on 13.03.2008.

3. A FER was sent on 02.09.11, a reply was refiled on 29.05.12. Again a second examination report sent on 28.06.2012, a reply was refiled on 2.08.2012. As on the last date for putting the application in order for grant, the application was found to be not complying with certain requirements of act. Accordingly a hearing notice was issued with the following objections:

- a. Objection no.5 of FER, dated 2 September 2011 and Objection no.01 of Examination report dated 28 June 2012 stands maintained.
- b. Claims 1-2[amended] do not meet the requirements of Section 10(5)(c) of the Patents Act, 1970 ; as claims are not succinct.

4. Hearing has been fixed on 24/08/12 at 11.00Am. Agent for the applicant attended the hearing. And they refiled the documents on 31/08/12.

5. Objection number 5 of FER dated 2nd sep 2011 talks about section 3(e) of the patents act 1970 and objection no.1 of examination report dated 28th june 2012 speaks about novelty and inventive step.

6. Amended claims 1 and 2 are not allowable U/S 3(e) and 10(5)(c) of the patents act 1970.

Amended claims

1. A pharmaceutical foam composition substantially free of ethanol and comprising pimecrolimus in a carrier vehicle comprising a mixture of oily solvents amounting to at least 40% of the total weight of the composition and consisting of

- i. Hexylene glycol in the range of 1% to 10%
- ii. Optionally Oleyl alcohol in the range of 1% to 20% and
- iii. Dimethylisobornide in the range of 35% to 90% and medium chain triglycerides in the range of 5% to 20% and additionally:
- iv. Hydroxypropyl cellulose and /or stearyl alcohol in the range of 0.1% to 5%
- v. p-hydroxybenzoic acid ester with ethyleneglycol phenylether in the range of 0.1% to 0.5% and
- vi. glyceryl monostearate in the range of 1% to 3% and non-ionic sugar esters and butane/propane 80/20 as propellant gas for foaming.

2. A pharmaceutical foam composition substantially free of ethanol and comprising pimecrolimus in a carrier vehicle comprising a mixture of oily

solvents amounting to at least 40% of the total weight of the composition and consisting of

- i. Hexylene glycol in the range of 2% to 20%
- ii. medium chain triglycerides in the range of 50% to 80% and optionally Dimethyl lisosorbide in the range of 0% to 20% and additionally:
- iii. Water in an amount less than 25%
- iv. polyvinylpyrrolidone and stearyl alcohol in the range of 1% to 10%
- v. p-hydroxybenzoic acid ester with ethyleneglycol phenylether in the range of 0.1% to 0.5% and
- vi. glyceryl monostearate in the range of 1% to 3% and lecithin; and butane/propane 80/20 as propellant gas for foaming.

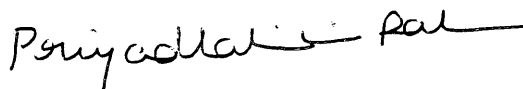
7. Amended claims is now limited to pharmaceutical foam composition with specific ingredients based on the formulation described in examples 1, 2 and 3. The pharmaceutical form of the present invention shows improved penetration properties and is particularly convenient in terms of ease of administration and patient compliance. Hence objection no.1 of examination report dated 28th Jun '12 is waived.

8. Claims 1 and 2 are not succinct and it doesn't fall under single inventive concept, because the components range and components as claimed in claim 1 and claim 2 are different. And hence they are not allowable u/s 10(5) (c) of the patents act 1970.

9. Applicant doesn't provide any supportive experimental data or comparative examples highlighting the surprising and or synergistic effect of the claimed formulation over the prior art compositions. Instead, examples 1, 2 and 3 provide only the amount of individual components in grams.

10. Hence in view of the above findings I hereby conclude that the application do not meet the requirements of section 3(e) and 10(5) (c) of the Patent Act. Therefore I refuse the application for patent 3725/CHENP/2006 U/S 15 of the Patents Act, 1970.

Dated 9th October, 2012



(PRIYADHARSINI RAJANBABU)

Assistant controller of Patents & Designs.



सत्यमेव जयते

INDIA NON JUDICIAL

Government of National Capital Territory of Delhi

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FORM 26
THE PATENTS ACT, 1970
&
THE PATENTS RULES, 2003
(Sections 127 and 132; Rule 135)

1. I, Henminlun, about 54 years of age, Indian resident, authorised signatory of Delhi Network of Positive People (DNP+) with address at C-197, Hari

Statutory Alert:

1. The authenticity of this Stamp certificate should be verified at 'www.shcilestamp.com' or using e-Stamp Mobile App of Stock Holding. Any discrepancy in the details on this Certificate and as available on the website / Mobile App renders it invalid.
2. The onus of checking the legitimacy is on the users of the certificate.
3. In case of any discrepancy please inform the Competent Authority.



Nagar, near Ghanta Ghar, New Delhi- 110064, hereby authorise Advocate- Ms. Priyam Lizmary Cherian having office at 309, Fourth Floor, Prakash Mohalla, Delhi 110065, to act on my behalf in connection with the pre-grant opposition under section 25(1) against patent Application No. **201817002543**, titled "Solid Pharmaceutical Compositions for Treating HCV" filed by Abbvie Inc. at the Delhi Office of the Patent Controller and request that all notices, requisitions and communication relating thereto may be sent to such persons at the above address unless otherwise specified.

2. I hereby revoke all previous authorisations, if any made, in respect of the same matter or proceeding.
3. I hereby assent to the action already taken by the said persons in the above matter.

Dated this the ___ day of September 2021



Mr. Henminlun

To
The Controller of Patents,
The Patent Office,
Delhi

ATTEST

NOTARY PUBLIC



81 OCT 2021