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July 9, 2021

The Controller of Patents
The Patent Office
CP 2, CP Block,
Sector V, Bidhannagar
Kolkata, West Bengal 700091
India

Re: **REPRESENTATION u/s 25(1) of the Patent act – By THE DELHI NETWORK OF POSITIVE PEOPLE against Indian Patent Application No. 3158/KOLNP/2012 filed on 17/10/2012**
Applicant: **VERTEX PHARMACEUTICALS INCORPORATED**

Respected Sir,

We submit herewith Pre-Grant Opposition under Section 25(1) of the Patent Act, 2005 and Form 7A.

The Learned Controller is requested to take the documents on record and proceed further in the matter and keep the Petitioner advised of each and every step taken in the matter.

We crave the leave of the Learned Controller to submit additional documents or evidence or if necessary to support any of the averments in the representation as may be necessitated in the proceeding.

Lastly, we request the Learned Controller to grant an opportunity of being heard before the above representation is finally decided.

Thanking you,

Yours faithfully,

RAJESHWARI H. IN/PA - 0358
AGENT FOR THE OPPONENT
FOR RAJESHWARI AND ASSOCIATES

Encl: As stated

C.C.: ANAND AND ANAND
B-41, NIZAMUDDIN EAST
NEW DELHI – 110013
Email.: email@anandandanand.com

THE OFFICE OF THE CONTROLLER OF PATENTS, KOLKATA

IN THE MATTER OF:

The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005, and The Patents Rules, 2003, as amended by The Patents (Amendment) Rules, 2006
AND
IN THE MATTER of Pre-grant opposition under Section 25(1)
AND
IN THE MATTER of Indian Patent Application No. 3158/KOLNP/2012

IN THE MATTER OF:

THE DELHI NETWORK OF POSITIVE PEOPLE ..... OPPONENT

VS.

VERTEX PHARMACEUTICALS INCORPORATED. ....APPLICANT

PRE-GRANT OPPOSITION BY THE DELHI NETWORK OF POSITIVE PEOPLE

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9.	**Annexure 7:** Copy of Article Development of a rapidly dispersing tablet of a poorly wettable compound—formulation DOE and mechanistic study of effectof formulation excipients on wetting of celecoxib. Xiaorong He et al., International Journal of Pharmaceutics 353 (2008) 176–186	230-240
10.	**Annexure 8:** Copy of Article Effect of the Mode of Super Disintegrant Incorporation on Dissolution in Wet Granulated Tablets. Marc S. Gordon et al., Journal of Pharmaceutical Sciences, Vol. 82, No. 2, February 1993.	241-247
11.	**Annexure 9:** Copy of Article the Effect of Different Superdisintegrants and their Concentrations on the Dissolution of Topiramate Immediate Release Tablets. V A. Vamshi Priya et al., International Journal of Pharmaceutical Sciences and Nanotechnology Volume 2 • Issue 2 • July – September 2009	248-253
12.	Power of Attorney	Will follow

Dated this day 09th of July, 2021

RAJESHWARI H.
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

To,
The Controller of Patents
The Patent Office, Kolkata

FORM 7A
THE PATENTS ACT,
1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[See Rule 55]

We, **THE DELHI NETWORK OF POSITIVE PEOPLE,** having its office at A1-5, House No. 141 Gali No. 3, IGNOU Main Road, Neb Saral, New Delhi - 110068, hereby give Notice of opposition to the grant of patent in respect of Indian Patent Application No. 3158/KOLNP/2012 filed on 17/10/2012 made by VERTEX PHARMACEUTICALS INCORPORATED on the grounds.

(a) Section 25(1)(b): Lack of novelty
(b) Section 25(1)(e): Lack of inventive step
(c) Section 25(1)(f): Invention is not patentable under section 3 (d)
(d) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
(e) Section 25(1)(h): Failed to disclose to the Controller the information required by section 8.

(Detailed grounds are set out in the Opposition)

Our address for service in India is:

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Dated this 09th day of July, 2021

RAJESHWARI H. IN/PA – 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

To
The Controller of Patents
Patent Office, Kolkata

THE OFFICE OF THE CONTROLLER OF PATENTS, KOLKATA

In the matter of Section 25(1) of The Patents Act,1970 as amended by The Patents (Amendment) Act 2005;

AND

In the matter of Rule 55 of The Patents Rules 2003 as amended by thePatent (Amendment) Rules, 2006

AND

IN THE MATTER of Indian Patent Application **3158/KOLNP/2012 filed on 17/10/2012** in the name of **VERTEX PHARMACEUTICALS INCORPORATED.**

REPRESENTATION BY:

THE DELHI NETWORK OF POSITIVE PEOPLE ..... OPPONENT

VS.

VERTEX PHARMACEUTICALS INCORPORATED. ....APPLICANT

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER SECTION 25(1) OF THE PATENTS ACT, 1970

We, **THE DELHI NETWORK OF POSITIVE PEOPLE** hereby submit our representation by way of oppostion to the grant of patent in respect of Indian Patent Application 3158/KOLNP/2012 filed on 17/10/2012 in the name of VERTEX PHARMACEUTICALS INCORPORATED entitled "PHARMACEUTICAL COMPOSITIONS OF 3-(6-(1-(2, 2-DIFLUOROBENZO[D][1, 3]DIOXOL-5-YL)CYCLOPROPANECARBOXAMIDO)-3-METHYLPYRIODIN-2-YL)BENZOICACID AND ADMINISTRATION THEREOF".

STATEMENT OF CASE OF OPPONENT

1. The Opponent has learnt that the Applicant has filed an Indian Patent Application No.3158/KOLNP/2012 (hereinafter "the Impugned Patent Application") on 17/10/2012. The Impugned patent application was published in the Official Journal of the patent office on 21/06/2013, which is currently pending before the Patent Office.

2. The Impugned application is entitled "PHARMACEUTICAL COMPOSITIONS OF 3-(6-(1-(2, 2-DIFLUOROBENZO[D] [1,3]DIOXOL-5-YL)CYCLOPROPANECARBOXAMIDO)-3-METHYLPYRIODIN-2-YL)BENZOICACID AND ADMINISTRATION THEREOF".

3. The Opponent by way of present pre-grant opposition submits that the claims currently pending on record are not patentable under the provisions provided in this Act. The claims as filed and currently on record are annexed herewith as **Annexure-1** and reproduced herein below for ready reference:

1. A tablet for oral administration comprising:

a. 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Compound 1) Form I wherein the Form I is characterized by one or more peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation, and wherein the Compound 1 Form I is present in an amount ranging from 25 mg to 250 mg;

b. a filler;

c. a diluent;

d. a disintegrant;

e. a surfactant;

f. a lubricant; and

g. a binder;

wherein the binder is polyvinylpyrrolidone.

2. A tablet for oral administration comprising:

a. Compound 1 Form I wherein the Form I is characterized by one or more peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation, and wherein the Compound 1 Form I is present in an amount ranging from 25 mg to 250 mg;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a lubricant; and

f. a binder;

wherein the disintegrant is croscarmellose sodium.

3. A tablet for oral administration comprising:

a. Compound 1 Form I wherein the Form I is characterized by one or more peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder

diffraction obtained using Cu K alpha radiation, and wherein the Compound 1 Form I is present in an amount ranging from 25 mg to 250 mg;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a lubricant; and

f. a binder;

wherein the surfactant is sodium lauryl sulfate and is present in an amount of 0.6 wt% to 2 wt% by weight of the tablet.

4. The tablet as claimed in claim 1,

wherein Compound 1 Form I is present in an amount of 30 to 70 wt% by weight of the tablet.

5. The tablet as claimed in claim 1,

wherein the disintegrant is croscarmellose sodium.

6. The tablet as claimed in claim 1,

wherein the surfactant is sodium lauryl sulfate and is present in an amount of 0.6 wt% to 2 wt% by weight of the tablet.

7. The tablet as claimed in claim 1,

wherein the tablet further comprises an additional therapeutic agent which is N-(5-hydroxy-2,4-ditert-butylphenyl)-4-oxo-1H-quinoline-3-carboxamide.

8. The tablet as claimed in claim 2,

wherein Compound 1 Form I is present in an amount of 30 to 70 wt% by weight of the tablet.

9. The tablet as claimed in claim 3,

wherein Compound 1 Form I is present in an amount of 30 to 70 wt% by weight of the tablet.

10. A tablet for oral administration comprising:

a. Compound 1 Form I wherein the Form I is characterized by one or more peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation, and wherein the Compound 1 Form I is present in an amount ranging from 25 mg to 250 mg;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a lubricant; and

f. a binder;

wherein Compound 1 Form I is present in an amount of 30 to 70 wt% by weight of the tablet; and

wherein the tablet further comprises an additional therapeutic agent which is N-(5-hydroxy-2,4-ditert-butylphenyl)-4-oxo-1H-quinoline-3-carboxamide.

11. The tablet as claimed in claim 2,

wherein the surfactant is sodium lauryl sulfate and is present in an amount of 0.6 wt% to 2 wt% by weight of the tablet.

12. The tablet as claimed in claim 2,

wherein the tablet further comprises an additional therapeutic agent which is N-(5-hydroxy-2,4-ditert-butylphenyl)-4-oxo-1H-quinoline-3-carboxamide.

13. The tablet as claimed in claim 5 or 7,

wherein Compound 1 Form I is present in an amount of 30 to 70 wt% by weight of the tablet.

14. The tablet as claimed in claim 4, 7, 10, or 12,

wherein the surfactant is sodium lauryl sulfate and is present in an amount of 0.6 wt% to 2 wt% by weight of the tablet.

15. The tablet as claimed in claim 6, 7, 9, or 10,

wherein the disintegrant is croscarmellose sodium.

16. The tablet as claimed in claim 11 or 12,

wherein the binder is polyvinylpyrrolidone; and

wherein Compound 1 Form I is present in an amount of 30 to 70 wt% by weight of the tablet.

17. The tablet as claimed in claim 4, 5, or 8,

wherein the surfactant is sodium lauryl sulfate and is present in an amount of 0.6 wt% to 2 wt% by weight of the tablet; and

wherein the tablet further comprises an additional therapeutic agent which is N-(5-hydroxy-2,4-ditert-butylphenyl)-4-oxo-1H-quinoline-3-carboxamide.

18. The tablet as claimed in claim 10,

wherein the binder is polyvinylpyrrolidone;

wherein the disintegrant is croscarmellose sodium; and

wherein the surfactant is sodium lauryl sulfate and is present in an amount of 0.6 wt% to 2 wt% by weight of the tablet.

19. The tablet as claimed in any one of claims 1-18, wherein the Compound 1 Form I is present in the tablet in an amount of 200 mg.

20. The tablet as claimed in any one of claims 1-19, wherein the filler is selected from cellulose, modified cellulose, sodium carboxymethyl cellulose, ethyl cellulose hydroxymethyl cellulose, hydroxypropylcellulose, cellulose acetate, microcrystalline cellulose, dibasic calcium phosphate, sucrose, lactose, corn starch, potato starch, and any combination thereof.

21. The tablet as claimed in any one of claims 1-20, wherein the filler is microcrystalline cellulose (MCC) and is present in the tablet in an amount ranging from 20 wt% to 55 wt% by weight of the tablet.

22. The tablet as claimed in any one of claims 1-21, wherein the disintegrant is croscarmellose sodium and is present in the tablet at a concentration of 2.5 to 6 wt% by weight of the tablet.

23. The tablet as claimed in any one of claims 1-22, wherein the binder is polyvinylpyrrolidone and has a concentration of 1 to 8 wt% by weight of the tablet.

24. The tablet as claimed in any one of claims 1-23, wherein the lubricant is selected from magnesium stearate, calcium stearate, zinc stearate, sodium stearate, stearic acid, aluminum stearate, leucine, glyceryl behenate, hydrogenated vegetable oil and any combination thereof.

25. The tablet as claimed in claim 24, wherein the lubricant is magnesium stearate and is present at a concentration of 0.15 to 4.5 wt% by weight of the tablet.

26. The tablet as claimed in claim 1-3, 5-7, 11, or 12, wherein Compound 1 Form I is present in the tablet in an amount of 30 to 70 wt% by weight of the tablet.

27. The tablet as claimed in any one of claims 1-26, wherein Compound 1 Form I is present in the tablet in an amount of 30 to 60 wt% by weight of the tablet.

28. The tablet as claimed in any one of claims 1-27, wherein the tablet further comprises a colorant.

29. The tablet as claimed in any one of claims 1-28, wherein the filler is microcrystalline cellulose (MCC) and is present in the tablet in an amount of 25 to 50 wt% by weight of the tablet;

wherein the disintegrant is croscarmellose sodium and is present in the tablet at a concentration of 2.5 to 6 wt% by weight of the tablet;

wherein the surfactant is sodium lauryl sulfate at a concentration of 0.6 to 2 wt% by weight of the tablet;

wherein the lubricant is magnesium stearate at a concentration of 0.15 to 4.5 wt% by weight of the tablet; and

wherein the binder is polyvinylpyrrolidone at a concentration of 2 to 5 wt% by weight of the tablet.

30. The tablet as claimed in claim 29, wherein the filler is microcrystalline cellulose (MCC) and is present in the tablet in an amount of 25 wt% by weight of the tablet;

wherein the disintegrant is croscarmellose sodium and is present in the tablet at a concentration of 6 wt% by weight of the tablet;

wherein the surfactant is sodium lauryl sulfate at a concentration of 0.8 wt% by weight of the tablet;

wherein the lubricant is magnesium stearate at a concentration of 1 wt% by weight of the tablet; and

wherein the binder is polyvinylpyrrolidone at a concentration of 2 wt% by weight of the tablet.

31. A method of producing a pharmaceutical composition comprising the steps of:

a) combining a therapeutically effective amount of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Compound 1) Form I in an amount ranging from 25 mg to 250 mg, polyvinylpyrrolidone, and a granulation excipient selected from the group consisting of: a glidant; a surfactant; a lubricant; a disintegrant; a filler, a diluent and combinations thereof to form an admixture;

b) mixing the admixture; and

c) compacting the admixture to form the pharmaceutical composition;

wherein the Form I is characterized by one or more peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation; and

wherein Compound 1 Form I is present in an amount of 30 to 70 wt% in the pharmaceutical composition.

32. The method as claimed in claim 31, wherein the pharmaceutical composition comprises a plurality of granules.

33. The method as claimed in claim 31, wherein compacting the admixture comprises compacting the admixture in a roller compactor forming compressed sheets of admixture; and milling the sheets of admixture to form a plurality of granules.

34. The method as claimed in claim 32, further comprising compressing the plurality of granules with a pharmaceutically acceptable excipient to form a tablet.

35. The method as claimed in claim 34, wherein the pharmaceutically acceptable excipient is selected from the group consisting of magnesium stearate, croscarmellose sodium and combinations thereof.

36. The method as claimed in claim 34, wherein the plurality of granules are compressed to produce a tablet having a hardness of 5-21 kP ± 20 percent.

37. The method as claimed in claim 31, wherein the step of compacting the admixture to form the pharmaceutical composition further comprises drying the admixture.

38. The method as claimed in claim 31, wherein mixing the admixture comprises mixing the admixture until the admixture is substantially homogenous.

39. The method as claimed in any one of claims 32-36, wherein the plurality of granules are formed by combining Compound 1 Form I with a granulation fluid comprising a surfactant and polyvinylpyrrolidone.

40. The method as claimed in claim 39, wherein the surfactant is sodium lauryl sulfate.

4. **Impugned Patent Application:** The present pre-grant opposition is against Indian Patent Application 3158/KOLNP/2012, entitled "PHARMACEUTICAL COMPOSITIONS OF 3-(6-(1-(2, 2-DIFLUOROBENZO[D][1, 3]DIOXOL-5-YL)CYCLOPROPANECARBOXAMIDO)-3-METHYLPYRIODIN-2-YL) BENZOIC ACID AND ADMINISTRATION THEREOF" and is drawn towards a pharmaceutical compositions comprising 3-(6-(1-(2,2-difluorobcnzo[d] [I ,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid(Compound I), methods for manufacturing such compositions and methods for administeringpharmaceutical compositions comprising the same.

5. **Disclosure in the impugned patent application:** As per the Applicant, the present invention relatesa pharmaceutical composition comprising compound 1, filler, disintegrant, surfactant, diluent, lubricant and at least one of a glidant and a binder.

6. **PRIOR ARTS:** The opponent wishes to rely on the following prior arts as evidence in support of the grounds of opposition.

i. WO 2009/073757 published on 11 June 2009 (annexed herewith as **Annexure 2)**
ii. WO 2010/019239 published on 18 February 2010(annexed herewith as **Annexure 3)**
iii. WO 1993/009763 published on 27 May 1993 (annexed herewith as **Annexure 4)**
iv. Development of Fast Dispersible Aceclofenac Tablets: Effect of Functionality of Superdisintegrants. C. MallikarjunaSetty et al. Indian J Pharm Sci. 2008 Mar-Apr; 70(2): 180–185. (annexed herewith as **Annexure 5)**
v. Development and Invitro Evaluation of Fast Dissolving Tablets Of Glipizide. Biraju Patel et al., International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 1, Suppl 1, Nov.-Dec. 2009.(annexed herewith as **Annexure 6)**
vi. Development of a rapidly dispersing tablet of a poorly wettable compound—formulation DOE and mechanistic study of effect of formulation excipients on wetting of celecoxib. Xiaorong He et al., International Journal of Pharmaceutics 353 (2008) 176–186.(annexed herewith as **Annexure 7)**
vii. Effect of the Mode of Super Disintegrant Incorporation on Dissolution in Wet Granulated Tablets. Marc S. Gordon et al., Journal of Pharmaceutical Sciences, Vol. 82, No. 2, February 1993.(annexed herewith as **Annexure 8)**
viii. The Effect of Different Superdisintegrants and their Concentrations on the Dissolution of Topiramate Immediate Release Tablets. V A.VamshiPriya et al., International Journal of Pharmaceutical

Sciences and Nanotechnology Volume 2 • Issue 2 • July – September 2009.(annexed herewith as **Annexure 9)**

7. It is submitted that all claims of the impugned patent application are liable to be refused on following grounds which are without prejudice to each other:
   (a) Section 25(1)(b): Lack of novelty
   (b) Section 25(1)(e): Lack of inventive step
   (c) Section 25(1)(f): Invention is not patentable under section 3(d)
   (d) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
   (e) Section 25(1)(h): Failed to disclose to the Controller the information required by section 8.

GROUND 1: LACK OF NOVELTY

8. Claims 1 to 40 are not Novel, and therefore have to be rejected under Section 25(1)(b) of The Patents Act.

9. The impugned patent application lacks novelty in view of WO 2009/073757 (WO'757). This document was published on 11 June 2009 which is prior to priority date of impugned patent application i.e. 07/04/2010.

10. WO'757 patent discloses tablet and the method of their preparation of the active ingredient 3-(6-(l-(2,2-Difluorobenzo[d][l,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin- 2-yl)benzoic acid (compound I).

11. WO'757 discloses tablet formulation of active ingredient 3-(6-(l-(2,2-Difluorobenzo[d][l,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin- 2-yl)benzoic acid (compound I) characterized as Form I characterized by X-ray diffraction peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees.

12. It is stated in WO'757 that the pharmaceutically acceptable compositions recited therein *"comprise pharmaceutically acceptable carrier, adjuvant, or vehicle, which as used herein, includes any and all …….dispersion aids, surface active agents, solid binders, lubricants and the like, as suited to a particular dosage form desired"*.

13. WO757 discloses polyvinylpyrrolidone as a pharmaceutical carrier; cellulose and its derivatives as sodium carboxymethylcellulose (which is also known as croscarmellose sodium); and lubricants such as sodium lauryl sulphate and magnesium stearate.

14. It is submitted that it is common general knowledge in the art that pharmaceutical carrier, also known as pharmaceutical excipient, is an umbrella category which encompasses binders, diluents/fillers, disintegrants.

15. Further, WO757 discloses that in tableting polyvinylpyrrolidone is used as a binder; lubricants used are sodium lauryl sulphate, magnesium stearate, and mixtures thereof; microcrystalline cellulose is present in the tablet as well as apart from croscarmellose sodium and other excipients.

16. WO757 discloses that an additional active agent N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide can be added to the composition of 3-(6-(l-(2,2-Difluorobenzo[d][l,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoicacid (compound I) Form I.

17. WO757 discloses that the amount of the active component may be 0.1mg/kg to 50mg/kg of subject body weight per day, one or more times a day. Therefore, the dosage amount per dose ranges from 0.7mg to 350mg considering the average body weight of an adult human i.e. 70kg.

18. Further, it is common general knowledge that sodium lauryl sulphate is used in the range of 0.5 to 2%; polyvinylpyrrolidone is used between 0.5 to 5%, and croscarmellose sodium is used between 0.5 to 5%. [For common general knowledge refer Handbook of Pharmaceutical Excipients]. It is well established in law that a prior art content is to be interpreted in the manner in which it would have been understood by the skilled person at the time it was made available. Therefore, a person skilled in the art reading the disclosure of WO757 would have inevitably interpreted the content of sodium lauryl sulphate,polyvinylpyrrolidone, and croscarmellose sodium to be the same as was generally known and used at the time of the invention.

19. Thus, in view of the disclosure of the prior art document WO757, the impugned patent application lacks novelty. Therefore, the impugned application ought to be rejected on this ground alone.

(b) GROUND 2: LACK OF INVENTIVE STEP

20. It is submitted that the invention as claimed is obvious and does not involve any inventive step in view of whatever was known and published in India or elsewhere prior to the priority date of impugned patent application i.e. prior to 07/04/2010, the earliest claimed priority.

21. It is submitted that all the claims of the impugned patent application are not inventive and are obvious in view of common general knowledge in art and combined with teachings of above-mentioned prior arts.

22. WO'757 patent discloses tablet and the method of their preparation of the active ingredient 3-(6-(l-(2,2-Difluorobenzo[d][l,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin- 2-yl)benzoic acid (compound I).

23. WO'757 discloses tablet formulation of active ingredient 3-(6-(l-(2,2-Difluorobenzo[d][l,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin- 2-yl)benzoic acid (compound I) characterized as Form I characterized by X-ray diffraction peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees.

24. It is stated in WO'757 that the pharmaceutically acceptable compositions recited therein *"comprise pharmaceutically acceptable carrier, adjuvant, or vehicle, which as used herein, includes any and all …….dispersion aids, surface active agents, solid binders, lubricants and the like, as suited to a particular dosage form desired"*.

25. WO757 discloses polyvinylpyrrolidone as a pharmaceutical carrier; cellulose and its derivatives as sodium carboxymethylcellulose (which is also known as croscarmellose sodium); and lubricants such as sodium lauryl sulphate and magnesium stearate.

26. It is submitted that it is common general knowledge in the art that pharmaceutical carrier, also known as pharmaceutical excipient, is an umbrella category which encompasses binders, diluents/fillers, disintegrants.

27. Further, WO757 discloses that in tableting polyvinylpyrrolidone is used as a binder; lubricants used are sodium lauryl sulphate, magnesium stearate, and mixtures thereof; microcrystalline cellulose is present in the tablet as well as apart from croscarmellose sodium and other excipients.

28. WO757 discloses that an additional active agent N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide can be added to the composition of 3-(6-(l-(2,2-Difluorobenzo[d][l,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoicacid (compound I) Form I.

29. WO757 discloses that the amount of the active component may be 0.1mg/kg to 50mg/kg of subject body weight per day, one or more times a day. Therefore, the dosage amount per dose ranges from 0.7mg to 350mg considering the average body weight of an adult human i.e. 70kg.

30. Further, it is common general knowledge that sodium lauryl sulphate is used in the range of 0.5 to 2%; polyvinylpyrrolidone is used between 0.5 to 5%, and croscarmellose sodium is used between 0.5 to 5%. [For common general knowledge refer Handbook of Pharmaceutical Excipients]. It is well established in law that a prior art content is to be interpreted in the manner in which it would have been understood by the skilled person at the time it was made available. Therefore, a person skilled in the art reading the disclosure of WO757 would have inevitably interpreted the content of sodium lauryl sulphate, polyvinylpyrrolidone, and croscarmellose sodium to be the same as was generally known and used at the time of the invention.

31. WO 2010/019239 (WO' 239) further discloses tablet composition ofN-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide.

32. WO' 239 further teaches that the tablet contains the active constituent and other excipients like filler, disintegrant, surfactant, binder and lubricant.

33. WO'239 discloses solid form of Compound 1 in the tablet is a solid dispersion comprising substantially amorphous or amorphous Compound 1 and apolymer, polyvinylpyrrolidone.

34. WO239 further discloses that the tablet composition comprises celluloses in concentrations of at least about 10 wt% by weight of the composition, sodium croscarmellosein concentrations of about 10 wt% or less by weight ofthe composition, sodium lauryl sulfate in concentrations of about 10 wt% or less by weight of the composition,

microcrystalline cellulosein concentrations of at least about 1wt% by weight of the composition, magnesium stearateconcentrations of about 2 wt% or less by weight of the composition.

35. WO 239 discloses that:

- Fillers suitable for the present invention are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary fillers include celluloses.
- the disintegrant should be such that Disintegrants suitable for the present invention enhance the dispersal of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. Exemplary disintegrants include sodium croscarmellose.
- Surfactants suitable for the present invention enhance the solubility of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physicalstability, the hardness, or the biological activity of the pharmaceutical composition. Exemplary surfactants include sodium lauryl sulfate (SLS).
- Binders suitable for the present invention enhance the tablet strength of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary binders include microcrystalline cellulose.

- Lubricants suitable for the present invention improve the compression and ejection of compressed pharmaceutical compositions from a die press and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, or the biological activity of the pharmaceutical composition. Exemplary lubricants include magnesium stearate.

36. WO757 discloses tablet composition of the active compound disclosed therein can have an additional CFTR modulator compound which has been disclosed therein as N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide.

37. Therefore, a person skilled in art when working with the objective of either producing a single tablet composition containing both the active compounds as mentioned in above paragraph or two different tablet compositions for each of the drug which are to be co-administered, is bound to employ excipients in the composition which are compatible with both the active compounds.

38. Hence, from the disclosure of WO757 and WO239 a person skilled in the art gets the teaching of the excipients which were common to tablet compositions of both the active compounds. It is observed that polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulphate, microcrystalline cellulose, and magnesium stearate are excipients which were common to the tablet compositions of both the active compounds.

39. WO1993/009763(WO'763) relates to pharmaceutical tablet compositions containing 10-98% of poorly water-soluble drug, 2-10% of polyvinylpyrrolidone as binder, disintegrant, lubricant, and diluent. The tablet compositions disclosed are such that they are particularly characterized by a rapid dissolution rate even after prolonged shelf-

life. The disclosed tablet compositions are further characterized by lower friability and superior compressibility.

40. Further, WO763 discloses that the tablet compositions disclosed therein may be prepared by direct compression or wet granulation followed by direct compression.

41. C. Mallikarjuna Setty et al. disclose a comparative evaluation of effect on dissolution profile of croscarmellose sodium, sodium starch glycolate, crospovidone on tablets of a practically insoluble drug.

42. The document states that of all the orally administered dosage forms, tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing.

43. The tablets disclosed therein are prepared by direct compression method, in general, are based on the action established by superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate.

44. In the dissolution study it was observed by the authors that the t_{50} and t_{80} (time for 50% and 80% of release) values decreased ($P<0.05$) with increase in the level of croscarmellose sodium. However, t_{50} and t_{80} values increased ($P<0.05$) with increase in the level of sodium starch glycolate. While t_{50} and t_{80}values did not change ($P>0.05$) with increase in the level of crospovidone. These results indicated that dissolutionparameter values of tablets containing croscarmellose sodium is much better than tablets containing sodium starch glycolate or crospovidone.

45. The authors have postulated that the rapid increase in dissolution of the insoluble drug with the increase in croscarmellose sodium may be attributed to rapid swelling and disintegration of tablet into apparently primary particles.

46. The authors of the paper also determined the effect of humidity on prepared tablets and concluded that at higher relative humidity, tablets containing high concentration of superdisintegrants get softened and hence, must be protected from atmospheric moisture.

47. Patel et al. disclose that tablets of a poorly soluble drug were prepared. Two superdisintegrantsviz, crospovidone and croscarmellose sodium (4%, 5%, 6%)with different binders vizPVPK-30 and pregelatinized starch (3%) were used to prepare the tablets.

48. The paper discloses that from the various formulations which were prepared, a formulation prepared by using 5% croscarmellose sodium with 3% PVP K30 was selected as optimized formulation based on the tablet characteristics such as hardness, friability, disintegration time, dissolution profile.

49. Stability studies were carried out at 25°C/60% RH and 40°C/75% RH foroptimized formulation. Stability studies on the optimized formulation indicated that there was nosignificant change found in physical appearance, disintegration time and wetting time of the tablets.

50. The tablets of were prepared by direct compression method using Croscarmellose sodium and in vitro drug release from the tablets shows significantly improved drug dissolution.

51. It was concluded that indirect compression method, croscarmellosesodium was best superdisintegrant with PVP K-30 as binding agent.

52. He et al designed various formulations for a drug which has extremely poor aqueous wettability and dispersibility. Results from a screening formulation statistical design of experiments (DOE) by applying drug dispersibility as criteria which directly corelates with drug dissolution. This study demonstrated that sodium lauryl sulfate (SLS), an anionic

surfactant, gives higher drug dispersibility than polysorbate 80, a neutral surfactant. The binder Kollidon 30 (also known as PVP K30) leads to better dispersibility, but slower disintegration than Kollidon 12 (PVP 12), HPMC, and HPC.

53. It is found that ionic surfactant resulted in better dispersibility than a neutral surfactant, probably due to charge dispersion.It was also found that Kollidon 30 (polyvinylpyrrolidone) gives better drug dispersionthanhydroxypropylmethyl cellulose and hydroxypropyl cellulose. This may be explained through a surface energy calculation, where the spreading coefficients between Kollidon 30 and the drug indicate formation of open porous granules in which pores can facilitate water uptake.

54. Within the range that was studied, the dispersibility of micronized drug increases as the amount of SLS and Kollidon 30 increases.

55. In the direct compression process disclosed therein, formulation components were mixed well and then compressed. In the dry granulation process, intra-granular components were mixed well, then processed on a roller compactor to form ribbons. The ribbons were screened through a mesh screen and mixed with extra-granular excipients and compressed.

56. In the wet granulation process, intra-granular excipients were mixed well, and placed into a mortar. A surfactant was added to the mixture of intragranular excipients. The resulting wet granules were screened through a mesh screen then dried and compressed after addition of extra-granular excipients.

57. Further formulations were made by the authors of the paper to study the effect of surfactants and binders on the wettability of the drug using the wet granulation procedure. In the surfactant study, three formulations were made containing SLS, polysorbate 80 or cetrimide.

In the binder study, three formulations were made containing Kollidon 30 (polyvinylpyrrolidone), HPMC or HPC.

58. In formulations of micronized drug tablets SLS (surfactant) was varied from 3.60 to 25.20 mg and Kollidon 30 (binder) was varied from 3.60 to 32.40 mg.

59. The authors concluded that tablets containing 0.8% SLS (total) produced significantly higher turbidity values i.e. were more dispersible and had higher dissolution than those containing 50/50 mixture of SLS and polysorbate 80(Table 9). In addition, tablets containing 0.8% SLS were also significantly harder than those containing polysorbate 80–SLScombination. As shown in Table 10, turbidity followed the rank order of SLS >cetrimidepolysorbate 80, indicating that ionic surfactantsdispersedrug more efficiently than neutral surfactants.

60. Table 11 of the document discloses that turbidity results demonstrate that the dispersibility of drug follows the rank order of Kollidon30 > HPC > HPMC. The formulation containing Kollidon 30as a binder has the best wettability because the contact angle in water is the lowest among the three formulations. In addition, the contact angle of the Kollidon 30 formulation reach esequilibrium more quickly than those of the HPMC and HPC formulations, indicating a quick and uniform wetting of the Kollidon30 formulation. The authors state that above discussed data suggests that one could use contactangle analysis as a quick way to screen formulations for which wetting is a concern.

61. Gordon et al disclosed that the effect of three different disintegrants on the dissolution of poorly soluble a drug using disintegrants – croscarmellose sodium, sodium starch glycolate, and crosposvidone. The tablets were evaluated for dissolution profile which resulted with increasing moisture content of the tablets. It was found that among the three disintegrants tested the disintegrant which resulted in best

dissolution profile despite increase in moisture content of the tablet was croscarmellose sodium.

62. Vamshi et al. prepared tablets of another poorly soluble drug using three different disintegrantscroscarmellose sodium, sodium starch glycolate, and crospovidone. The tablets comprise one of the said disintegrants and polyvinylpyrrolidone as well as magnesium stearate.

63. It was observed that due to croscarmellose sodium the dissolution was even faster than sodium starch glycolate, because it is one of the disintegrant, which disintegrate and dissolves faster than that of sodium starch glycolate and crospovidone due to its fine particle size than that of other disintegrants. All the drug was released within 30 minutes with croscarmellose sodium.

64. It is submitted that the claimed subject matter is obvious in view of the disclosure of the prior art documents discussed in preceding paragraphs.

65. Further, the applicant has failed to submit any comparative data in the specification establishing technical advancement of the claimed subject matter over similar compositions already known in art at the time of the invention for instance as compared to compositions of WO757 or WO2010037066 which was published on 01 April 2010 and which discloses solid composition of Lumacaftor.

66. Thus, the Applicant failed to provide any data in the specification as filed establishing technical advancement of the claimed invention.

67. In light of above, the impugned patent application lacks technical advancement and is obvious. Therefore, the claimed subject matter is devoid of Inventive merit and the impugned application should be rejected on this ground alone.

GROUND 3: Claims not patentable under Section 25(1)(f)

1) **The claims of impugned application are not patentable under Section 3(d) of the Act.**

68. It is submitted that the impugned patent application should not be allowed under Section 3(d) which states that "*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 or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

Explanation -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy."

69. The Opponent states that as discussed in preceding paragraphs the claimed subject matter of impugned patent application is neither novel nor inventive. The Opponent submits that the applicant has failed to submit any comparative data in the specification as filed establishing enhanced therapeutic efficacy of the claimed subject matter over similar compositions already known in art at the time of the invention for instance as compared to compositions of WO757 or WO2010037066 which was published on 01 April 2010 and which discloses solid composition of Lumacaftor.

70. Thus, the Opponent has not demonstrated any enhancement in the therapeutic efficacy of the claimed composition with respect to compositions of Lumacaftor already the known in the art at the time of the invention.

71. The method claimed in impugned application is nothing but mere use of a known process as established by the disclosure of prior art documents discussed in detail under the heading of Inventive Step.

72. Thus, the subject matter of impugned patent application squarely falls within the purview of Section 3(d) of the Act. Hence the impugned patent application should be rejected under Section 3(d) of the Act.

2) **The claims of impugned application are not patentable under Section 3(e) of the Act.**

73. The Opponent states that as discussed in preceding paragraphs the claimed subject matter of the impugned patent application are compositions which are mere admixture without any synergy and the method of preparation of these admixtures.

74. The Opponent submits that the applicant has failed to submit any comparative data in the specification as filed establishing any unexpected effect of the claimed subject matter over similar compositions already known in art at the time of the invention for instance as compared to compositions of WO757 or WO2010037066.

75. Thus, the Opponent has not demonstrated any synergy of the claimed composition with respect to compositions of Lumacaftor already the known in the art at the time of the invention.

76. Thus, the subject matter of impugned patent application squarely falls within the purview of Section 3(e) of the Act. Hence the impugned patent application should be rejected under Section 3(e) of the Act.

(d) GROUND 4: INSUFFICIENCY OF DISCLOSURE

77. The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

78. It is submitted that the component polyvinylpyrrolidone is available in many grades and variants which differ in their properties each of which have different properties depending on the molecular weight of the PVP as well as the broad method of synthesis of the PVP. The applicant has not specified grade or molecular weight of PVP to be used. Thus, claim 1 is too broad and the specification does not reveal best mode & manner of carrying out the invention and in absence this information a person of ordinary skill in the art has to carry out undue experimentation to arrive at the invention.

79. The impugned application claims different methods of preparation of the claimed compositions. However, the specification does not disclose which method of preparation is best suited for which of the claimed formulations. A person of ordinary skill in the art has to experiment with each of the methods to ascertain which method works best for preparation of which of the claimed formulations.

80. The impugned patent application does not provide adequate teaching to a person skilled in the art to practice the invention. In light of above, it is clear that impugned patent application does not sufficiently and clearly describe the invention. Therefore, the impugned patent application should be refused on this ground alone.

(e) <u>GROUND 5 -Section 25(1)(h)</u>

81. The patentee has failed to disclose to the Controller the information required under Section 8.The applicant is required to provide all the information regarding the prosecution of the equivalent applications till the grant of the Indian application to the Controller in writing from time to time and also within the prescribed time.

82. It is observed that applicant has not submitted all the information pertinent to adjudication of patentability of impugned application to the Patent Office.

83. The applicant has not filed the details of the prosecution of corresponding applications at the Patent Office and has, thus, failed to comply with the requirements of the provisions of Section 8 of the Act.

84. The Applicant has not informed the Patent Office that the corresponding Japanese applications JP2013523833, JP2016128454, JP2018058886 and the corresponding Chinese application CN102917692 have been refused in correspond in jurisdictions. However, the Applicant neither informed the same to the Patent Office nor submitted all the information relating to prosecution of these applications to the Patent Office. It is submitted that the Applicant has withheld important information from the Ld Controller with malafide intent.

85. The opponents crave leave to file further submissions and evidence with respect to this ground.

86. Therefore, the impugned application should be rejected on this basis alone.

P R A Y E R

In the fact and circumstances of the case, the Opponent prays as follows:

i. that the Indian Patent application number 3158/KOLNP/2012 dated17/10/2012 in the name of VERTEX PHARMACEUTICALS INCORPORATED, be refused under Section 25(1) of the Patents (Amendment) Act, 2005;

ii. the Opponent may be allowed to file further documents as evidence if necessary to support its averments;

iii. the Opponent may be allowed to make further submissions in case the applicant makes any amendments in the claims;

Dated this 09th ay of July, 2021

RAJESHWARI H. IN/PA - 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

To,
The Controller of Patents
The Patent Office, Kolkata

Clean claims

23.02.2021

We Claim:

1. A tablet for oral administration comprising:

a. 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Compound 1) Form I wherein the Form I is characterized by one or more peaks within one or more 2θ value ranges selected from 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation, and wherein the Compound 1 Form I is present in an amount ranging from 25 mg to 250 mg;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a lubricant; and

f. a binder;

wherein the binder is polyvinylpyrrolidone.

2. The tablet for oral administration as claimed in claim 1,

wherein the disintegrant is croscarmellose sodium and is present in an amount of 6 wt% to 10 wt% by weight of the tablet.

3. The tablet as claimed in claims 1 or 2,

wherein the surfactant is sodium lauryl sulfate and is present in an amount of 0.6 wt% to 2 wt% by weight of the tablet.

4. The tablet as claimed in any one of claims 1-3,

wherein Compound 1 Form I is present in an amount of 30 wt% to 70 wt% by weight of the tablet.

5. The tablet as claimed in any one of claims 1-4,

wherein the binder is polyvinylpyrrolidone;

wherein the disintegrant is croscarmellose sodium and is present in an amount of 6 wt% to 10 wt% by weight of the tablet; and

wherein the surfactant is sodium lauryl sulfate and is present in an amount of 0.6 wt% to 2 wt% by weight of the tablet.

6. The tablet as claimed in any one of claims 1-5, wherein the Compound 1 Form I is present in the tablet in an amount of 200 mg or 100 mg.

7. The tablet as claimed in any one of claims 1-6, wherein the filler is selected from cellulose, modified cellulose, sodium carboxymethyl cellulose, ethyl cellulose hydroxymethyl cellulose, hydroxypropylcellulose, cellulose acetate, microcrystalline cellulose, dibasic calcium phosphate, sucrose, lactose, corn starch, potato starch, and any combination thereof.

8. The tablet as claimed in any one of claims 1-7, wherein the filler is microcrystalline cellulose (MCC) and is present in the tablet in an amount ranging from 20 wt% to 55 wt% by weight of the tablet.

9. The tablet as claimed in any one of claims 1-8, wherein the binder is polyvinylpyrrolidone and is present in the tablet at a concentration of 1 wt% to 8 wt% by weight of the tablet.

10. The tablet as claimed in any one of claims 1-9, wherein the lubricant is selected from magnesium stearate, calcium stearate, zinc stearate, sodium stearate, stearic acid, aluminum stearate, leucine, glyceryl behenate, hydrogenated vegetable oil and any combination thereof.

11. The tablet as claimed in claim 10, wherein the lubricant is magnesium stearate and is present in the tablet at a concentration of 0.15 wt% to 4.5 wt% by weight of the tablet.

12. The tablet as claimed in any one of claims 1-11, wherein Compound 1 Form I is present in the tablet in an amount of 30 wt% to 60 wt% by weight of the tablet.

13. The tablet as claimed in any one of claims 1-12, wherein the tablet further comprises a colorant.

14. The tablet as claimed in any one of claims 1-13,

wherein the filler is microcrystalline cellulose (MCC) and is present in the tablet at a concentration of 25 wt% to 50 wt% by weight of the tablet;

wherein the disintegrant is croscarmellose sodium and is present in the tablet at a concentration of 6 wt% to 10 wt % by weight of the tablet;

wherein the surfactant is sodium lauryl sulfate and is present in the tablet at a concentration of 0.6 wt% to 2 wt% by weight of the tablet;

wherein the lubricant is magnesium stearate and is present in the tablet at a concentration of 0.15 wt% to 4.5 wt% by weight of the tablet; and

wherein the binder is polyvinylpyrrolidone and is present in the tablet at a concentration of 2 wt% to 5 wt% by weight of the tablet.

15. The tablet as claimed in claim 14,

wherein the filler is microcrystalline cellulose (MCC) and is present in the tablet at a concentration of 25 wt% by weight of the tablet;

wherein the disintegrant is croscarmellose sodium and is present in the tablet at a concentration of 6 wt% by weight of the tablet;

wherein the surfactant is sodium lauryl sulfate and is present in the tablet at a concentration of 0.8 wt% by weight of the tablet;

wherein the lubricant is magnesium stearate, and is present in the tablet at a concentration of 1 wt% by weight of the tablet; and

wherein the binder is polyvinylpyrrolidone and is present in the tablet at a concentration of 3 wt% by weight of the tablet.

16. A method of producing a pharmaceutical composition comprising the steps of:

a) combining 3-(6-(1-(2,2-difluorobenzo[d] [1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Compound 1) Form I, polyvinylpyrrolidone, and one or more granulation excipients selected from the group consisting of: a glidant; a surfactant; a lubricant; a disintegrant; a filler, a diluent and combinations thereof to form an admixture;

b) mixing the admixture; and

c) compacting the admixture to form the pharmaceutical composition;

wherein the Form I is characterized by one or more peaks within one or more 2θ value ranges selected from 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation; and

wherein Compound 1 Form I is present in an amount of 30 wt% to 70 wt% in the pharmaceutical composition.

17. The method as claimed in claim 16, wherein the pharmaceutical composition comprises a plurality of granules.

18. The method as claimed in claim 16, wherein compacting the admixture comprises compacting the admixture in a roller compactor to form compressed sheets of admixture; and milling the sheets of admixture to form a plurality of granules.

19. The method as claimed in claim 17, further comprising compressing the plurality of granules with a pharmaceutically acceptable excipient to form a tablet.

20. The method as claimed in claim 19, wherein the pharmaceutically acceptable excipient is selected from the group consisting of magnesium stearate, croscarmellose sodium and combinations thereof.

21. The method as claimed in claim 19, wherein the plurality of granules are compressed to produce a tablet having a hardness of 5-21 kP ± 20 percent.

22. The method as claimed in claim 16, wherein the step of compacting the admixture to form the pharmaceutical composition further comprises drying the admixture.

23. The method as claimed in claim 16, wherein mixing the admixture comprises mixing the admixture until the admixture is substantially homogenous.

24. The method as claimed in any one of claims 17 or 19-21, wherein the plurality of granules are formed by combining Compound 1 Form I with a granulation fluid comprising a surfactant and polyvinylpyrrolidone.

25. The method as claimed in claim 24, wherein the surfactant is sodium lauryl sulfate.

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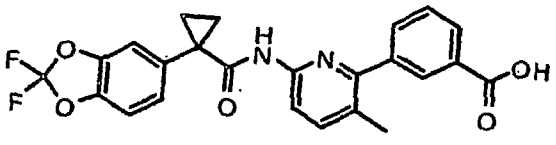
(54) Title: SOLID FORMS OF 3-(6-(1-(2,2-DIFLUOROBENZO[D][1,3] DIOXOL-5-YL) CYCLOPROPANECARBOXAMIDO)-3-METHYLPYRIDIN-2-YL) BENZOIC ACID

(I)



(57) Abstract: The present invention relates to a substantially crystalline and free solid state form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3- methylPyridin-2-yl)benzoic acid (Form I) of following formula: (I), pharmaceutical compositions thereof, and methods of treatment therewith.

VPI/07-145 WO

SOLID FORMS OF 3-(6-(1-(2,2-DIFLUOROBENZO[D][1,3]DIOXOL-5-YL) CYCLOPROPANECARBOXAMIDO)-3-METHYLPYRIDIN-2-YL)BENZOIC ACID

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit under 35 U.S.C. § 119 to United States provisional patent application serial number 61/012,162, filed December 7, 2007, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

[002] The present invention relates to solid state forms, for example, crystalline forms, of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid, pharmaceutical compositions thereof, and methods therewith.

BACKGROUND OF THE INVENTION

[003] CFTR is a cAMP/ATP-mediated anion channel that is expressed in a variety of cells types, including absorptive and secretory epithelia cells, where it regulates anion flux across the membrane, as well as the activity of other ion channels and proteins. In epithelia cells, normal functioning of CFTR is critical for the maintenance of electrolyte transport throughout the body, including respiratory and digestive tissue. CFTR is composed of approximately 1480 amino acids that encode a protein made up of a tandem repeat of transmembrane domains, each containing six transmembrane helices and a nucleotide binding domain. The two transmembrane domains are linked by a large, polar, regulatory (R)-domain with multiple phosphorylation sites that regulate channel activity and cellular trafficking.

[004] The gene encoding CFTR has been identified and sequenced (See Gregory, R. J. et al. (1990) Nature 347:382-386; Rich, D. P. et al. (1990) Nature 347:358-362), (Riordan, J. R. et al. (1989) Science 245:1066-1073). A defect in this gene causes mutations in CFTR resulting in cystic fibrosis ("CF"), the most common fatal genetic disease in humans. Cystic fibrosis affects approximately one in every 2,500 infants in the United States. Within the general United States population, up to 10 million people carry a single copy of the defective gene without apparent ill effects. In contrast, individuals with two copies of the CF associated gene suffer from the debilitating and fatal effects of CF, including chronic lung disease.

[005] In patients with cystic fibrosis, mutations in CFTR endogenously expressed in respiratory epithelia leads to reduced apical anion secretion causing an imbalance in ion and fluid transport. The resulting decrease in anion transport contributes to enhanced mucus accumulation

in the lung and the accompanying microbial infections that ultimately cause death in CF patients. In addition to respiratory disease, CF patients typically suffer from gastrointestinal problems and pancreatic insufficiency that, if left untreated, results in death. In addition, the majority of males with cystic fibrosis are infertile and fertility is decreased among females with cystic fibrosis. In contrast to the severe effects of two copies of the CF associated gene, individuals with a single copy of the CF associated gene exhibit increased resistance to cholera and to dehydration resulting from diarrhea – perhaps explaining the relatively high frequency of the CF gene within the population.

[006] Sequence analysis of the CFTR gene of CF chromosomes has revealed a variety of disease causing mutations (Cutting, G. R. et al. (1990) Nature 346:366-369; Dean, M. et al. (1990) Cell 61:863:870; and Kerem, B-S. et al. (1989) Science 245:1073-1080; Kerem, B-S et al. (1990) Proc. Natl. Acad. Sci. USA 87:8447-8451). To date, > 1000 disease causing mutations in the CF gene have been identified (http://www.genet.sickkids.on.ca/cftr/). The most prevalent mutation is a deletion of phenylalanine at position 508 of the CFTR amino acid sequence, and is commonly referred to as ΔF508-CFTR. This mutation occurs in approximately 70% of the cases of cystic fibrosis and is associated with a severe disease.

[007] The deletion of residue 508 in ΔF508-CFTR prevents the nascent protein from folding correctly. This results in the inability of the mutant protein to exit the ER, and traffic to the plasma membrane. As a result, the number of channels present in the membrane is far less than observed in cells expressing wild-type CFTR. In addition to impaired trafficking, the mutation results in defective channel gating. Together, the reduced number of channels in the membrane and the defective gating lead to reduced anion transport across epithelia leading to defective ion and fluid transport. (Quinton, P. M. (1990), FASEB J. 4: 2709-2727). Studies have shown, however, that the reduced numbers of ΔF508-CFTR in the membrane are functional, albeit less than wild-type CFTR. (Dalemans et al. (1991), Nature Lond. 354: 526-528; Denning et al., supra; Pasyk and Foskett (1995), J. Cell. Biochem. 270: 12347-50). In addition to ΔF508-CFTR, other disease causing mutations in CFTR that result in defective trafficking, synthesis, and/or channel gating could be up- or down-regulated to alter anion secretion and modify disease progression and/or severity.

[008] Although CFTR transports a variety of molecules in addition to anions, it is clear that this role (the transport of anions) represents one element in an important mechanism of transporting ions and water across the epithelium. The other elements include the epithelial Na^+ channel, ENaC, $Na^+/2Cl^-/K^+$ co-transporter, Na^+-K^+-ATPase pump and the basolateral membrane K^+ channels, that are responsible for the uptake of chloride into the cell.

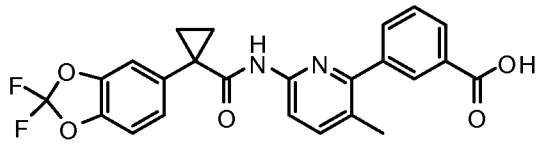
[009] These elements work together to achieve directional transport across the epithelium via their selective expression and localization within the cell. Chloride absorption takes place by the coordinated activity of ENaC and CFTR present on the apical membrane and the Na^+-K^+-ATPase pump and Cl- channels expressed on the basolateral surface of the cell. Secondary active transport of chloride from the luminal side leads to the accumulation of intracellular chloride, which can then passively leave the cell via Cl^- channels, resulting in a vectorial transport. Arrangement of $Na^+/2Cl^-/K^+$ co-transporter, Na^+-K^+-ATPase pump and the basolateral membrane K^+ channels on the basolateral surface and CFTR on the luminal side coordinate the secretion of chloride via CFTR on the luminal side. Because water is probably never actively transported itself, its flow across epithelia depends on tiny transepithelial osmotic gradients generated by the bulk flow of sodium and chloride.

[0010] As discussed above, it is believed that the deletion of residue 508 in ΔF508-CFTR prevents the nascent protein from folding correctly, resulting in the inability of this mutant protein to exit the ER, and traffic to the plasma membrane. As a result, insufficient amounts of the mature protein are present at the plasma membrane and chloride transport within epithelial tissues is significantly reduced. Infact, this cellular phenomenon of defective ER processing of ABC transporters by the ER machinery, has been shown to be the underlying basis not only for CF disease, but for a wide range of other isolated and inherited diseases. The two ways that the ER machinery can malfunction is either by loss of coupling to ER export of the proteins leading to degradation, or by the ER accumulation of these defective/misfolded proteins [Aridor M, *et al.*, Nature Med., 5(7), pp 745- 751 (1999); Shastry, B.S., *et al.*, Neurochem. International, 43, pp 1-7 (2003); Rutishauser, J., *et al.*, Swiss Med Wkly, 132, pp 211-222 (2002); Morello, JP *et al.*, TIPS, 21, pp. 466- 469 (2000); Bross P., *et al.*, Human Mut., 14, pp. 186-198 (1999)].

[0011] 3-(6-(1-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid in salt form is disclosed in International PCT Publication WO 2007056341 (said publication being incorporated herein by reference in its entirety) as a modulator of CFTR activity and thus useful in treating CFTR-mediated diseases such as cystic fibrosis. However, there is a need for stable solid forms of said compound that can be used readily in pharmaceutical compositions suitable for use as therapeutics.

SUMMARY OF THE INVENTION

[0012] The present invention relates to solid forms of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (hereinafter "Compound 1") which has the structure below:



Compound 1.

[0013] Compound 1 and pharmaceutically acceptable compositions thereof are useful for treating or lessening the severity of cystic fibrosis. In one aspect, Compound 1 is in a substantially crystalline and salt free form referred to as Form I as described and characterized herein.

[0014] Processes described herein can be used to prepare the compositions of this invention comprising Form I. The amounts and the features of the components used in the processes would be as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 is an X-ray diffraction pattern calculated from a single crystal structure of Compound 1 in Form I.

[0016] Figure 2 is an actual X-ray powder diffraction pattern of Compound 1 in Form I.

[0017] Figure 3 is an overlay of an X-ray diffraction pattern calculated from a single crystal of Compound 1 in Form I, and an actual X-ray powder diffraction pattern of Compound 1 in Form I.

[0018] Figure 4 is a differential scanning calorimetry (DSC) trace of Compound 1 in Form I.

[0019] Figure 5 is a conformational picture of Compound 1 in Form I based on single crystal X-ray analysis.

[0020] Figure 6 is a conformational picture of Compound 1 in Form I based on single crystal X-ray analysis as a dimer formed through the carboxylic acid groups.

[0021] Figure 7 is a conformational picture of Compound 1 in Form I based on single crystal X-ray analysis showing that the molecules are stacked upon each other.

[0022] Figure 8 is conformational picture of Compound 1 in Form I based on single crystal X-ray analysis showing a different view (down a).

[0023] Figure 9 is an ^{1}HNMR analysis of Compound 1 in Form I in a 50 mg/mL, 0.5 methyl cellulose-polysorbate 80 suspension at T(0).

[0024] **Figure 10** is an ^{1}HNMR analysis of Compound 1 in Form I in a 50 mg/mL, 0.5 methyl cellulose-polysorbate 80 suspension stored at room temperature for 24 hours.

[0025] **Figure 11** is an ^{1}HNMR analysis of Compound 1 • HCl standard.

DETAILED DESCRIPTION OF THE INVENTION

[0026] *Definitions*

[0027] As used herein, the following definitions shall apply unless otherwise indicated.

[0028] The term "CFTR" as used herein means cystic fibrosis transmembrane conductance regulator or a mutation thereof capable of regulator activity, including, but not limited to, ΔF508 CFTR and G551D CFTR (see, e.g., http://www.genet.sickkids.on.ca/cftr/, for CFTR mutations).

[0029] As used herein “crystalline” refers to compounds or compositions where the structural units are arranged in fixed geometric patterns or lattices, so that crystalline solids have rigid long range order. The structural units that constitute the crystal structure can be atoms, molecules, or ions. Crystalline solids show definite melting points.

[0030] The term "modulating" as used herein means increasing or decreasing, e.g. activity, by a measurable amount.

[0031] In one aspect, the invention features a form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid characterized as Form I.

[0032] In another embodiment, Form I is characterized by one or more peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation.

[0033] In another embodiment, Form I is characterized by one or more peaks at 15.4, 16.3, and 14.5 degrees.

[0034] In another embodiment, Form I is further characterized by a peak at 14.6 to 15.0 degrees.

[0035] In another embodiment, Form I is further characterized by a peak at 14.8 degrees.

[0036] In another embodiment, Form I is further characterized by a peak at 17.6 to 18.0 degrees.

[0037] In another embodiment, Form I is further characterized by a peak at 17.8 degrees.

[0038] In another embodiment, Form I is further characterized by a peak at 16.4 to 16.8 degrees.

[0039] In another embodiment, Form I is further characterized by a peak at 16.4 to 16.8 degrees.

[0040] In another embodiment, Form I is further characterized by a peak at 16.6 degrees.

[0041] In another embodiment, Form I is further characterized by a peak at 7.6 to 8.0 degrees.

[0042] In another embodiment, Form I is further characterized by a peak at 7.8 degrees.

[0043] In another embodiment, Form I is further characterized by a peak at 25.8 to 26.2 degrees.

[0044] In another embodiment, Form I is further characterized by a peak at 26.0 degrees.

[0045] In another embodiment, Form I is further characterized by a peak at 21.4 to 21.8 degrees.

[0046] In another embodiment, Form I is further characterized by a peak at 21.6 degrees.

[0047] In another embodiment, Form I is further characterized by a peak at 23.1 to 23.5 degrees.

[0048] In another embodiment, Form I is further characterized by a peak at 23.3 degrees.

[0049] In some embodiments, Form I is characterized by a diffraction pattern substantially similar to that of Figure 1.

[0050] In some embodiments, Form I is characterized by a diffraction pattern substantially similar to that of Figure 2.

[0051] In some embodiments, the particle size distribution of D90 is about 82 μm or less for Form I.

[0052] In some embodiments, the particle size distribution of D50 is about 30 μm or less for Form I.

[0053] In one aspect, the invention features a pharmaceutical composition comprising Form I and a pharmaceutically acceptable carrier.

[0054] In one aspect, the present invention features a method of treating a CFTR mediated disease in a human comprising administering to the human an effective amount of Form I.

[0055] In some embodiments, the method comprises administering an additional therapeutic agent.

[0056] In some embodiements, the disease is selected from cystic fibrosis, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, hereditary emphysema, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear plasy, Pick's disease, several polyglutamine neurological disorders asuch as Huntington, spinocerebullar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease, Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, and Sjogren's disease.

[0057] In one embodiment, the present invention provides a method of treating cystic fibrosis in a human, comprising administering to said human an effective amount of Form I.

[0058] In one aspect, the present invention features a kit comprising Form I and instructions for use thereof.

[0059] In one aspect, the present invention features a process of preparing Form I comprising dispersing or dissolving the HCl salt of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid in an appropriate solvent for an effective amount of time.

[0060] In one embodiment, the present invention features a process of preparing Form I comprising dispersing the HCl salt of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid in an appropriate solvent for an effective amount of time.

[0061] In some embodiments, the appropriate solvent is water or a alcohol/water mixture.

[0062] In some embodiments, the appropriate solvent is water or 50% methanol/water mixture.

[0063] In some embodiments, the appropriate solvent is water.

[0064] In some embodiments, the appropriate solvent is a mixture comprising 50% methanol and 50% water.

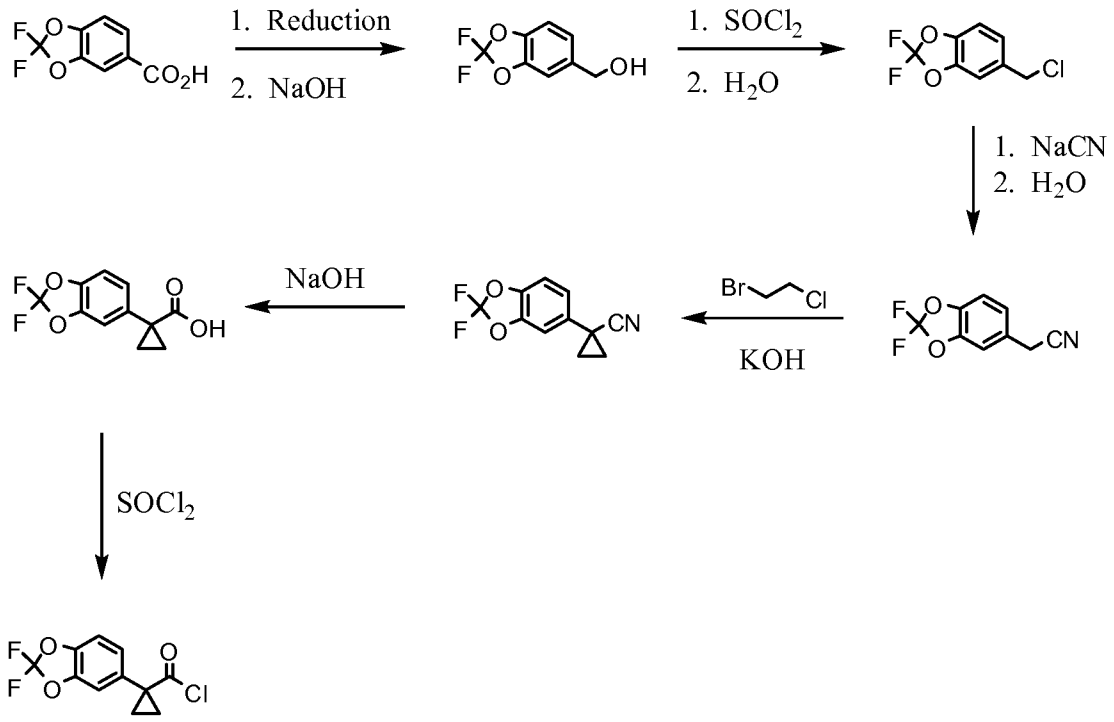
[0065] In some embodiments, the effective amount of time is about 2 to about a day. In some embodiments, the effective amount of time is about 2 to about 18 hours. In some embodiments, the effective amount of time is about 2 to about 12 hours. In some embodiments, the effective amount of time is about 2 to about 6 hours.

[0066] In one aspect, the invention features a crystal form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid having a monoclinic crystal system, a $P2_1/n$ space group, and the following unit cell dimensions: a = 4.9626 (7) Å , b = 12.2994 (18) Å, c = 33.075 (4) Å, $\alpha = 90°$, $\beta = 93.938$ (9)°, and $\gamma = 90°$.

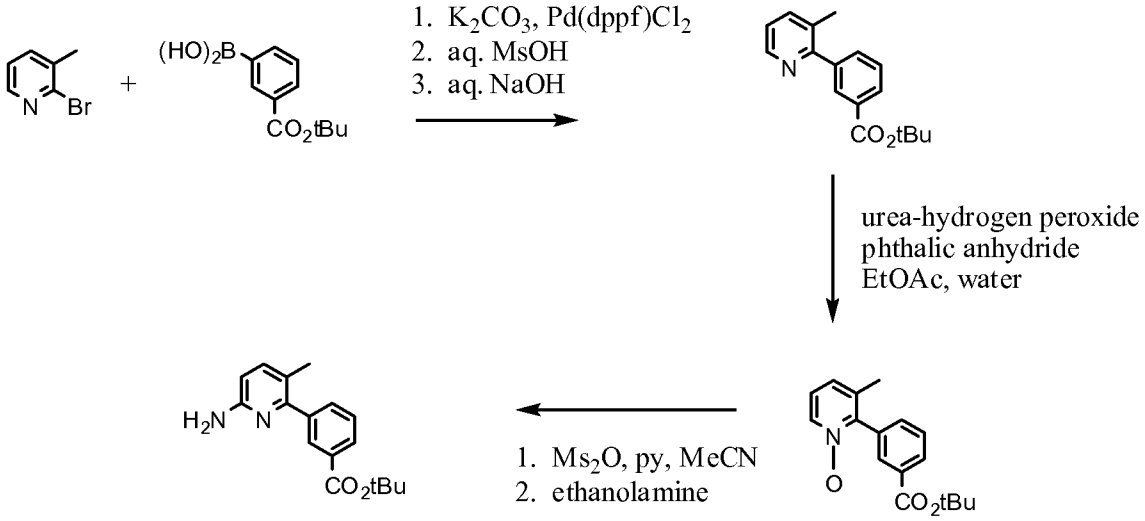
[0067] *Methods of Preparing Form I.*

[0068] In one embodiment, Form I is prepared from dispersing or dissolving a salt form, such as HCL, of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid in an appropriate solvent for an effective amount of time. In another embodiment, Form I is prepared from dispersing a salt form, such as HCL, of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid in an appropriate solvent for an effective amount of time. In another embodiment, Form I is formed directly from 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)-t-butylbenzoate and an appropriate acid, such as formic acid. In one embodiment, the HCl salt form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid is the starting point and in one embodiment can be prepared by coupling an acid chloride moiety with an amine moiety according to Schemes 1-3.

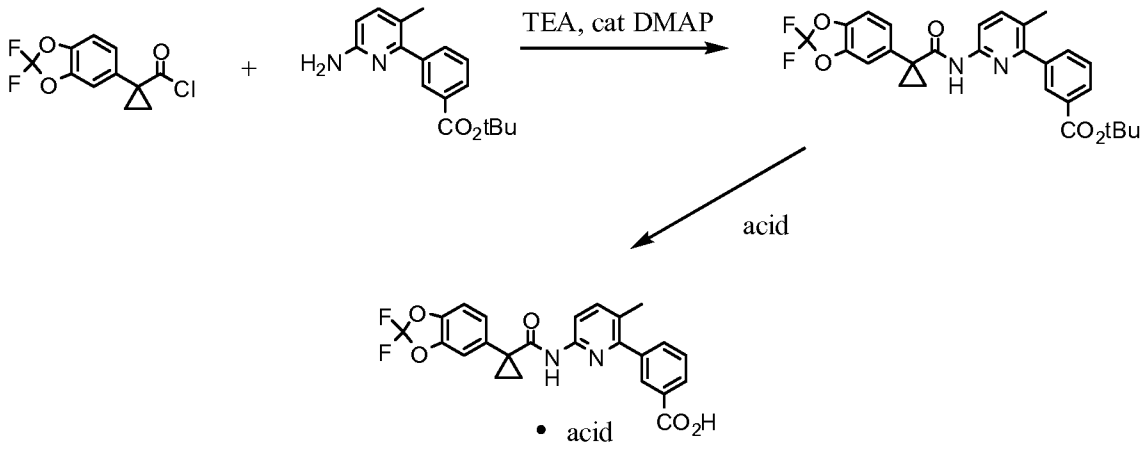
[0069] Scheme 1. Synthesis of the acid chloride moiety.



[0070] Scheme 2. Synthesis of the amine moiety.



[0071] Scheme 3. Formation of an acid salt of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid.



[0072] Using the HCl, for example, salt form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid as a starting point, Form I can be formed in high yields by dispersing or dissolving the HCl salt form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid in an appropriate solvent for an effective amount of time. Other salt forms of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid may be used such as, for example, other mineral or organic acid forms. The other salt forms result from hydrolysis of the t-butyl ester with the corresponding acid. Other acids/salt forms include nitric, sulfuric, phosphoric, boric, acetic, benzoic, malonic, and the like. The salt form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid may or may not be soluble depending upon the solvent used, but lack of solubility does not hinder formation of Form I. For example, in one embodiment, the appropriate solvent may be water or an alcohol/water mixture such as 50% methanol/water mixture, even though the HCl salt form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid is only sparingly soluble in water. In one embodiment, the appropriate solvent is water.

[0073] The effective amount of time for formation of Form I from the salt form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid can be any time between 2 to 24 hours or greater. Generally, greater than 24 hours is not needed to obtain high yields (~98%), but certain solvents may require greater amounts of time. It is also recognized that the amount of time needed is inversely proportional to the temperature. That is, the higher the temperature the less time needed to affect dissociation of acid to form Form I. When the solvent is water, stirring the dispersion for approximately 24

hours at room temperature gives Form I in an approximately 98% yield. If a solution of the salt form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid is desired for process purposes, an elevated temperature may be used. After stirring the solution for an effective amount of time at the elevated temperature, recrystallization upon cooling yields substantially pure forms of Form I. In one embodiment, substantially pure refers to greater than about 90% purity. In another embodiment, substantially pure refers to greater than about 95% purity. In another embodiment, substantially pure refers to greater than about 98% purity. In another embodiment, substantially pure refers to greater than about 99% purity. The temperature selected depends in part on the solvent used and is well within the capabilities of someone of ordinary skill in the art to determine. In one embodiment, the temperature is between room temperature and about 80 °C. In another embodiment, the temperature is between room temperature and about 40 °C. In another embodiment, the temperature is between about 40 °C and about 60 °C. In another embodiment, the temperature is between about 60 °C and about 80 °C.

[0074] In some embodiments, Form I may be further purified by recrystallization from an organic solvent. Examples of organic solvents include, but are not limited to, toluene, cumene, anisole, 1-butanol, isopropylacetate, butyl acetate, isobutyl acetate, methyl t-butyl ether, methyl isobutyl ketone, or 1-propanol/water (at various ratios). Temperature may be used as described above. For example, in one embodiment, Form I is dissolved in 1-butanol at 75 °C until it is completely dissolved. Cooling down the solution to 10 °C at a rate of 0.2 °C/min yields crystals of Form I which may be isolated by filtration.

[0075] *Uses, Formulation and Administration*

[0076] *Pharmaceutically acceptable compositions*

[0077] In another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise Form I as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[0078] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form

desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0079] *Uses of Compounds and Pharmaceutically Acceptable Compositions*

[0080] In yet another aspect, the present invention provides a method of treating a condition, disease, or disorder implicated by CFTR. In certain embodiments, the present invention provides a method of treating a condition, disease, or disorder implicated by a deficiency of CFTR activity, the method comprising administering a composition comprising a solid state form of Form I described herein to a subject, preferably a mammal, in need thereof.

[0081] A "CFTR-mediated disease" as used herein is a disease selected from cystic fibrosis, Hereditary emphysema, Hereditary hemochromatosis, Coagulation-Fibrinolysis deficiencies, such as Protein C deficiency, Type 1 hereditary angioedema, Lipid processing

deficiencies, such as Familial hypercholesterolemia, Type 1 chylomicronemia, Abetalipoproteinemia, Lysosomal storage diseases, such as I-cell disease/Pseudo-Hurler, Mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, Polyendocrinopathy/Hyperinsulemia, Diabetes mellitus, Laron dwarfism, Myleoperoxidase deficiency, Primary hypoparathyroidism, Melanoma, Glycanosis CDG type 1, Hereditary emphysema, Congenital hyperthyroidism, Osteogenesis imperfecta, Hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), Neurophyseal DI, Neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Progressive supranuclear plasy, Pick's disease, several polyglutamine neurological disorders asuch as Huntington, Spinocerebullar ataxia type I, Spinal and bulbar muscular atrophy, Dentatorubal pallidoluysian, and Myotonic dystrophy, as well as Spongiform encephalopathies, such as Hereditary Creutzfeldt-Jakob disease, Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, and Sjogren's disease.

[0082] In certain embodiments, the present invention provides a method of treating a CFTR-mediated disease in a human comprising the step of administering to said human an effective amount of a composition comprising Form I described herein.

[0083] According to an alternative preferred embodiment, the present invention provides a method of treating cystic fibrosis in a human comprising the step of administering to said human a composition comprising Form I described herein.

[0084] According to the invention an "effective amount" of Form I or a pharmaceutically acceptable composition thereof is that amount effective for treating or lessening the severity of any of the diseases recited above.

[0085] Form I or a pharmaceutically acceptable composition thereof may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of the diseases reicted above.

[0086] In certain embodiments, Form I described herein or a pharmaceutically acceptable composition thereof is useful for treating or lessening the severity of cystic fibrosis in patients who exhibit residual CFTR activity in the apical membrane of respiratory and non-respiratory epithelia. The presence of residual CFTR activity at the epithelial surface can be readily detected using methods known in the art, e.g., standard electrophysiological, biochemical, or histochemical techniques. Such methods identify CFTR activity using *in vivo* or *ex vivo* electrophysiological techniques, measurement of sweat or salivary Cl^- concentrations, or *ex vivo*

biochemical or histochemical techniques to monitor cell surface density. Using such methods, residual CFTR activity can be readily detected in patients heterozygous or homozygous for a variety of different mutations, including patients homozygous or heterozygous for the most common mutation, ΔF508.

[0087] In one embodiment, Form I described herein or a pharmaceutically acceptable composition thereof is useful for treating or lessening the severity of cystic fibrosis in patients within certain genotypes exhibiting residual CFTR activity, e.g., class III mutations (impaired regulation or gating), class IV mutations (altered conductance), or class V mutations (reduced synthesis) (Lee R. Choo-Kang, Pamela L., Zeitlin, *Type I, II, III, IV, and V cystic fibrosis Tansmembrane Conductance Regulator Defects and Opportunities of Therapy*; Current Opinion in Pulmonary Medicine 6:521 – 529, 2000). Other patient genotypes that exhibit residual CFTR activity include patients homozygous for one of these classes or heterozygous with any other class of mutations, including class I mutations, class II mutations, or a mutation that lacks classification.

[0088] In one embodiment, Form I described herein or a pharmaceutically acceptable composition thereof is useful for treating or lessening the severity of cystic fibrosis in patients within certain clinical phenotypes, e.g., a moderate to mild clinical phenotype that typically correlates with the amount of residual CFTR activity in the apical membrane of epithelia. Such phenotypes include patients exhibiting pancreatic insufficiency or patients diagnosed with idiopathic pancreatitis and congenital bilateral absence of the vas deferens, or mild lung disease.

[0089] The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the

specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0090] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0091] In certain embodiments, the dosage amount of Form I in the dosage unit form is from 100 mg to 1,000 mg. In another embodiment, the dosage amount of Form I is from 200 mg to 900 mg. In another embodiment, the dosage amount of Form I is from 300 mg to 800 mg. In another embodiment, the dosage amount of Form I is from 400 mg to 700 mg. In another embodiment, the dosage amount of Form I is from 500 mg to 600 mg.

[0092] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0093] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0094] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0095] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0096] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[0097] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or

preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0098] It will also be appreciated that Form I described herein or a pharmaceutically acceptable composition thereof can be employed in combination therapies, that is, Form I can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0099] In one embodiment, the additional agent is selected from a mucolytic agent, bronchodialator, an anti-biotic, an anti-infective agent, an anti-inflammatory agent, a CFTR modulator other than a compound of the present invention, or a nutritional agent.

[00100] In another embodiment, the additional agent is a compound selected from gentamicin, curcumin, cyclophosphamide, 4-phenylbutyrate, miglustat, felodipine, nimodipine, Philoxin B, geniestein, Apigenin, cAMP/cGMP modulators such as rolipram, sildenafil, milrinone, tadalafil, amrinone, isoproterenol, albuterol, and almeterol, deoxyspergualin, HSP 90 inhibitors, HSP 70 inhibitors, proteosome inhibitors such as epoxomicin, lactacystin, etc.

[00101] In another embodiment, the additional agent is a compound disclosed in WO 2004028480, WO 2004110352, WO 2005094374, WO 2005120497, or WO 2006101740.

[00102] In another embodiment, the additiona agent is a benzo(c)quinolizinium derivative that exhibits CFTR modulation activity or a benzopyran derivative that exhibits CFTR modulation activity.

[00103] In another embodiment, the addditional agent is a compound disclosed in US7202262, US6992096, US20060148864, US20060148863, US20060035943, US20050164973, WO2006110483, WO2006044456, WO2006044682, WO2006044505, WO2006044503, WO2006044502, or WO2004091502.

[00104] In another embodiment, the additional agent is a compound disclosed in WO2004080972, WO2004111014, WO2005035514, WO2005049018, WO2006002421, WO2006099256, WO2006127588, or WO2007044560.

[00105] In another embodiment, the an additional agent selected from compounds disclosed in U.S. Patent Application Serial No. 11/165,818, published as U.S. Published Patent Application No. 2006/0074075, filed June 24, 2005, and hereby incorporated by reference in its entirety. In another embodiment, the additional agent is N-(5-hydroxy-2,4-ditert-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide. These combinations are useful for treating the diseases described herein including cystic fibrosis. These combinations are also useful in the kits described herein.

[00106] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00107] Form I described herein or a pharmaceutically acceptable composition thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising Form I described herein or a pharmaceutically acceptable composition thereof, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising Form I described herein or a pharmaceutically acceptable composition thereof, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[00108] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLES

[00109] **Methods & Materials**

[00110] Differential Scanning Calorimetry (DSC)

[00111] The Differential scanning calorimetry (DSC) data of Form I were collected using a DSC Q100 V9.6 Build 290 (TA Instruments, New Castle, DE). Temperature was calibrated with indium and heat capacity was calibrated with sapphire. Samples of 3-6 mg were weighed into aluminum pans that were crimped using lids with 1 pin hole. The samples were scanned from 25°C to 350°C at a heating rate of 1.0°C/min and with a nitrogen gas purge of 50 ml/min. Data were collected by Thermal Advantage Q SeriesTM version 2.2.0.248 software and analyzed by Universal Analysis software version 4.1D (TA Instruments, New Castle, DE). The reported numbers represent single analyses.

[00112] XRPD (X-ray Powder Diffraction)

[00113] The X-Ray diffraction (XRD) data of Form 1 were collected on a Bruker D8 DISCOVER powder diffractometer with HI-STAR 2-dimensional detector and a flat graphite monochromator. Cu sealed tube with Kα radiation was used at 40 kV, 35mA. The samples were placed on zero-background silicon wafers at 25°C. For each sample, two data frames were collected at 120 seconds each at 2 different θ_2 angles: 8° and 26°. The data were integrated with GADDS software and merged with DIFFRACT^{plus}EVA software. Uncertainties for the reported peak positions are ± 0.2 degrees.

[00114] Vitride® (sodium bis(2-methoxyethoxy)aluminum hydride [or $NaAlH_2(OCH_2CH_2OCH_3)_2$], 65 wgt% solution in toluene) was purchased from Aldrich Chemicals.

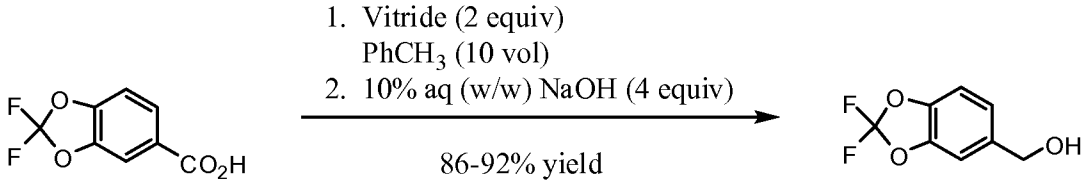
[00115] 2,2-Difluoro-1,3-benzodioxole-5-carboxylic acid was purchased from Saltigo (an affiliate of the Lanxess Corporation).

[00116] Anywhere in the present application where a name of a compound may not correctly describe the structure of the compound, the structure supersedes the name and governs.

[00117] **Synthesis of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid • HCl.**

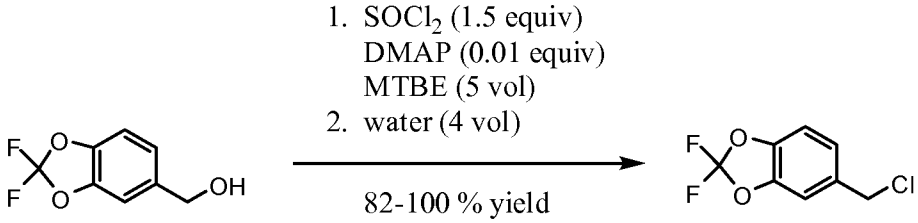
[00118] **Acid Chloride Moiety**

[00119] Synthesis of (2,2-difluoro-1,3-benzodioxol-5-yl)-methanol.



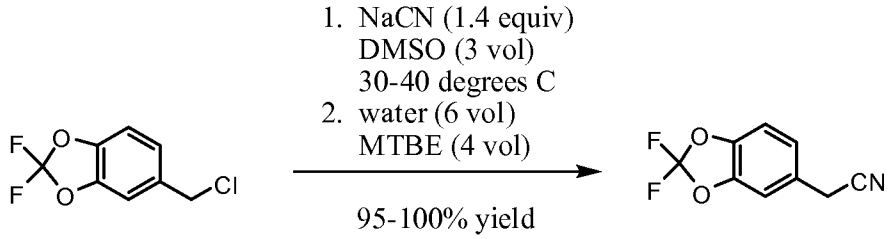
[00120] Commercially available 2,2-difluoro-1,3-benzodioxole-5-carboxylic acid (1.0 eq) is slurried in toluene (10 vol). Vitride® (2 eq) is added via addition funnel at a rate to maintain the temperature at 15-25 °C. At the end of addition the temperature is increased to 40 °C for 2 h then 10% (w/w) aq. NaOH (4.0 eq) is carefully added via addition funnel maintaining the temperature at 40-50 °C. After stirring for an additional 30 minutes, the layers are allowed to separate at 40 °C. The organic phase is cooled to 20 °C then washed with water (2 x 1.5 vol), dried (Na_2SO_4), filtered, and concentrated to afford crude (2,2-difluoro-1,3-benzodioxol-5-yl)-methanol that is used directly in the next step.

[00121] Synthesis of 5-chloromethyl-2,2-difluoro-1,3-benzodioxole.



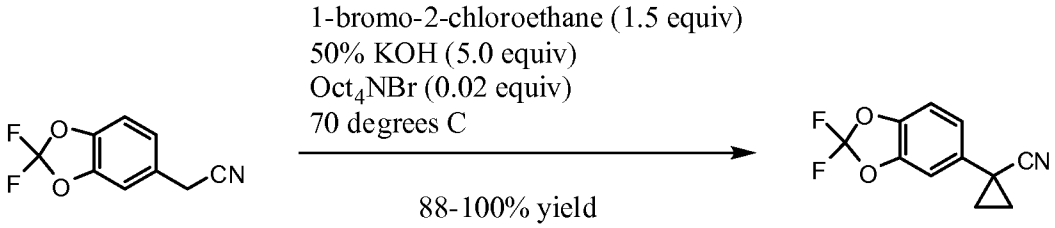
[00122] (2,2-difluoro-1,3-benzodioxol-5-yl)-methanol (1.0 eq) is dissolved in MTBE (5 vol). A catalytic amount of DMAP (1 mol %) is added and $SOCl_2$ (1.2 eq) is added via addition funnel. The $SOCl_2$ is added at a rate to maintain the temperature in the reactor at 15-25 °C. The temperature is increased to 30 °C for 1 hour then cooled to 20 °C then water (4 vol) is added via addition funnel maintaining the temperature at less than 30 °C. After stirring for an additional 30 minutes, the layers are allowed to separate. The organic layer is stirred and 10% (w/v) aq. NaOH (4.4 vol) is added. After stirring for 15 to 20 minutes, the layers are allowed to separate. The organic phase is then dried (Na_2SO_4), filtered, and concentrated to afford crude 5-chloromethyl-2,2-difluoro-1,3-benzodioxole that is used directly in the next step.

[00123] Synthesis of (2,2-difluoro-1,3-benzodioxol-5-yl)-acetonitrile.



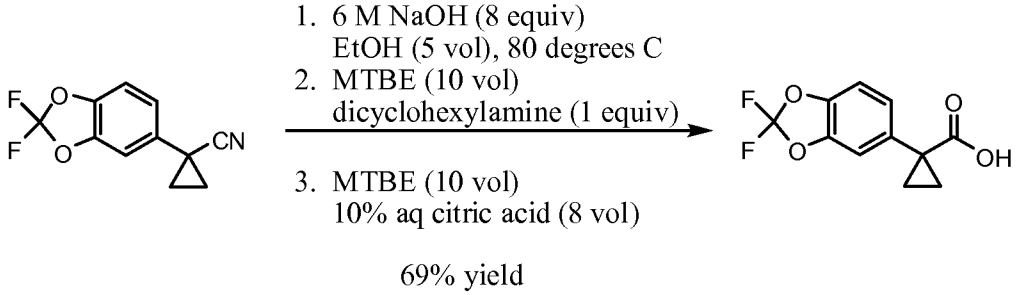
[00124] A solution of 5-chloromethyl-2,2-difluoro-1,3-benzodioxole (1 eq) in DMSO (1.25 vol) is added to a slurry of NaCN (1.4 eq) in DMSO (3 vol) maintaining the temperature between 30-40 °C. The mixture is stirred for 1 hour then water (6 vol) is added followed by MTBE (4 vol). After stirring for 30 min, the layers are separated. The aqueous layer is extracted with MTBE (1.8 vol). The combined organic layers are washed with water (1.8 vol), dried (Na_2SO_4), filtered, and concentrated to afford crude (2,2-difluoro-1,3-benzodioxol-5-yl)-acetonitrile (95%) that is used directly in the next step.

[00125] Synthesis of (2,2-difluoro-1,3-benzodioxol-5-yl)-cyclopropanecarbonitrile.



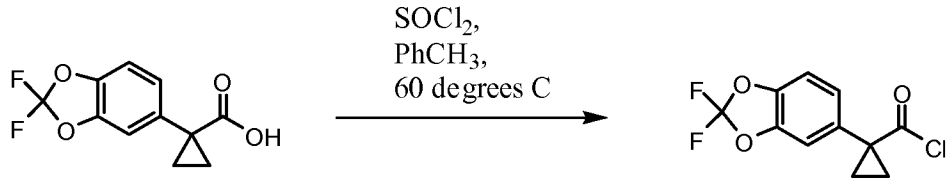
[00126] A mixture of (2,2-difluoro-1,3-benzodioxol-5-yl)-acetonitrile (1.0 eq), 50 wt % aqueous KOH (5.0 eq) 1-bromo-2-chloroethane (1.5 eq), and Oct_4NBr (0.02 eq) is heated at 70 °C for 1 h. The reaction mixture is cooled then worked up with MTBE and water. The organic phase is washed with water and brine then the solvent is removed to afford (2,2-difluoro-1,3-benzodioxol-5-yl)-cyclopropanecarbonitrile.

[00127] Synthesis of 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-cyclopropanecarboxylic acid.



[00128] (2,2-difluoro-1,3-benzodioxol-5-yl)-cyclopropanecarbonitrile is hydrolyzed using 6 M NaOH (8 equiv) in ethanol (5 vol) at 80 °C overnight. The mixture is cooled to room temperature and ethanol is evaporated under vacuum. The residue is taken into water and MTBE, 1 M HCl was added and the layers are separated. The MTBE layer was then treated with dicyclohexylamine (0.97 equiv). The slurry is cooled to 0 °C, filtered and washed with heptane to give the corresponding DCHA salt. The salt is taken into MTBE and 10% citric acid and stirred until all solids dissolve. The layers are separated and the MTBE layer was washed with water and brine. Solvent swap to heptane followed by filtration gives 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-cyclopropanecarboxylic acid after drying in a vacuum oven at 50 °C overnight.

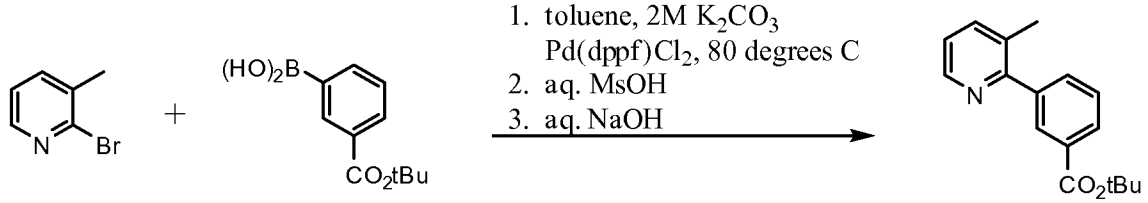
[00129] Synthesis of 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-cyclopropanecarbonyl chloride.



[00130] 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-cyclopropanecarboxylic acid (1.2 eq) is slurried in toluene (2.5 vol) and the mixture heated to 60 °C. $SOCl_2$ (1.4 eq) is added via addition funnel. The toluene and $SOCl_2$ are distilled from the reaction mixture after 30 minutes. Additional toluene (2.5 vol) is added and distilled again.

[00131] **<u>Amine Moiety</u>**

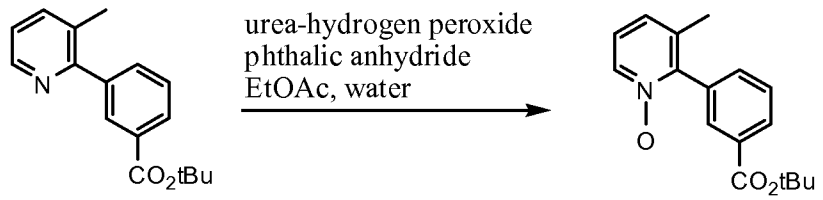
[00132] Synthesis of *tert*-butyl-3-(3-methylpyridin-2-yl)benzoate.



[00133] 2-Bromo-3-methylpyridine (1.0 eq) is dissolved in toluene (12 vol). K_2CO_3 (4.8 eq) is added followed by water (3.5 vol) and the mixture heated to 65 °C under a stream of N_2 for 1 hour. 3-(*t*-Butoxycarbonyl)phenylboronic acid (1.05 eq) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.015 eq) are then added and the mixture is heated to 80 °C. After 2 hours, the heat is turned off, water is added (3.5 vol) and the layers are allowed to separate. The organic phase is then washed with water (3.5 vol) and extracted with 10% aqueous methanesulfonic acid (2 eq MsOH, 7.7 vol). The aqueous phase is made basic with 50% aqueous NaOH (2 eq) and extracted with EtOAc (8 vol).

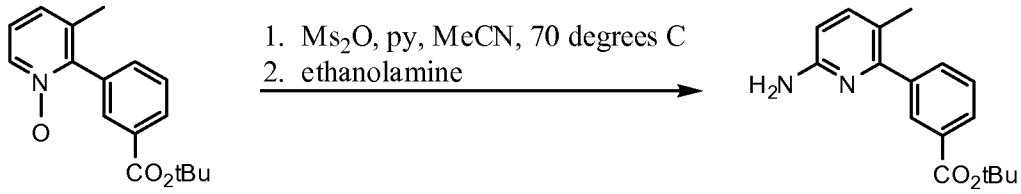
The organic layer is concentrated to afford crude *tert*-butyl-3-(3-methylpyridin-2-yl)benzoate (82%) that is used directly in the next step.

[00134] Synthesis of 2-(3-(*tert*-butoxycarbonyl)phenyl)-3-methylpyridine-1-oxide.



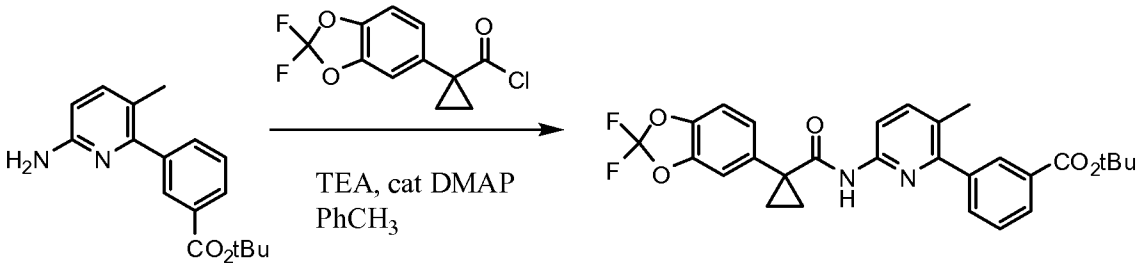
[00135] *tert*-Butyl-3-(3-methylpyridin-2-yl)benzoate (1.0 eq) is dissolved in EtOAc (6 vol). Water (0. 3 vol) is added followed by urea-hydrogen peroxide (3 eq). The phthalic anhydride (3 eq) is added portion-wise as a solid to maintain the temperature in the reactor below 45 °C. After completion of phthalic anhydride addition, the mixture is heated to 45 °C. After stirring for an additional 4 hours, the heat is turned off. 10% w/w aqueous Na_2SO_3 (1.5 eq) is added via addition funnel. After completion of Na_2SO_3 addition, the mixture is stirred for an additional 30 minutes and the layers separated. The organic layer is stirred and 10% w/w aq. Na_2CO_3 (2 eq) is added. After stirring for 30 minutes, the layers are allowed to separate. The organic phase is washed 13% w/v aq NaCl. The organic phase is then filtered and concentrated to afford crude 2-(3-(*tert*-butoxycarbonyl)phenyl)-3-methylpyridine-1-oxide (95%) that is used directly in the next step.

[00136] Synthesis of *tert*-butyl-3-(6-amino-3-methylpyridin-2-yl)benzoate.



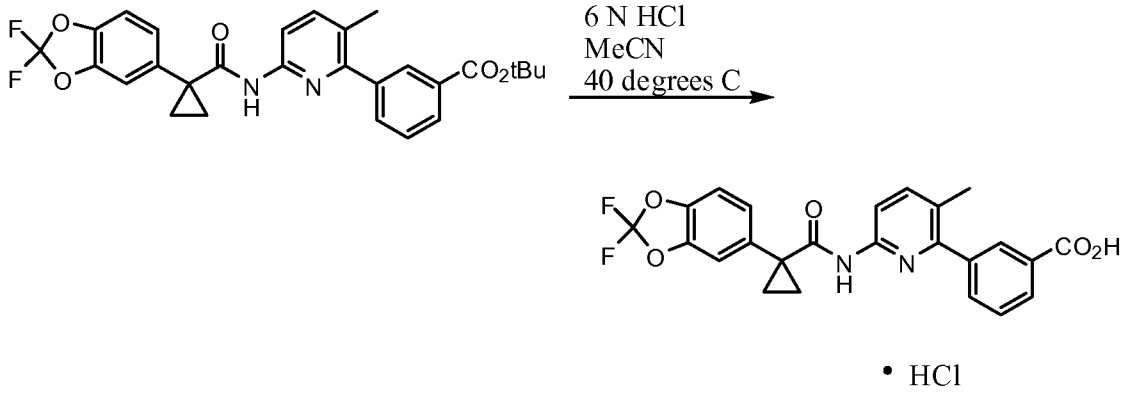
[00137] A solution of 2-(3-(*tert*-butoxycarbonyl)phenyl)-3-methylpyridine-1-oxide (1 eq) and pyridine (4 eq) in MeCN (8 vol) is heated to 70 °C. A solution of methanesulfonic anhydride (1.5 eq) in MeCN (2 vol) is added over 50 min via addition funnel maintaining the temperature at less than 75 °C. The mixture is stirred for an additional 0.5 hours after complete addition. The mixture is then allowed to cool to ambient. Ethanolamine (10 eq) is added via addition funnel. After stirring for 2 hours, water (6 vol) is added and the mixture is cooled to 10 °C. After stirring for NLT 3 hours, the solid is collected by filtration and washed with water (3 vol), 2:1 MeCN/water (3 vol), and MeCN (2 x 1.5 vol). The solid is dried to constant weight (<1% difference) in a vacuum oven at 50 °C with a slight N_2 bleed to afford *tert*-butyl-3-(6-amino-3-methylpyridin-2-yl)benzoate as a red-yellow solid (53% yield).

[00138] Synthesis of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)-t-butylbenzoate.



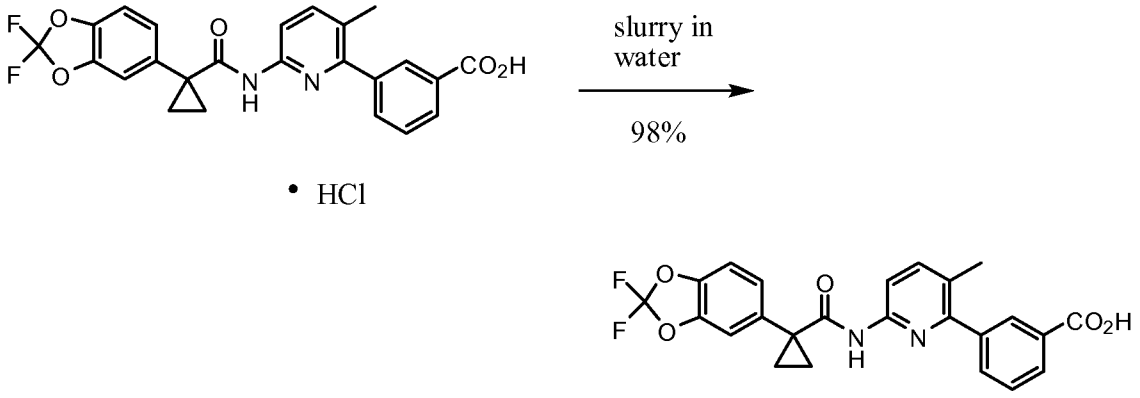
[00139] The crude acid chloride is dissolved in toluene (2.5 vol based on acid chloride) and added via addition funnel to a mixture of *tert*-butyl-3-(6-amino-3-methylpyridin-2-yl)benzoate (1 eq), dimethylaminopyridine (DMAP, 0.02 eq), and triethylamine (3.0 eq) in toluene (4 vol based on *tert*-butyl-3-(6-amino-3-methylpyridin-2-yl)benzoate). After 2 hours, water (4 vol based on *tert*-butyl-3-(6-amino-3-methylpyridin-2-yl)benzoate) is added to the reaction mixture. After stirring for 30 minutes, the layers are separated. The organic phase is then filtered and concentrated to afford a thick oil of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)-t-butylbenzoate (quantitative crude yield). MeCN (3 vol based on crude product) is added and distilled until crystallization occurs. Water (2 vol based on crude product) is added and the mixture stirred for 2 h. The solid is collected by filtration, washed with 1:1 (by volume) MeCN/water (2 x 1 vol based on crude product), and partially dried on the filter under vacuum. The solid is dried to constant weight (<1% difference) in a vacuum oven at 60 °C with a slight N_2 bleed to afford 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)-t-butylbenzoate as a brown solid.

[00140] Syntheisis of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid • HCL salt.



[00141] To a slurry of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)-t-butylbenzoate (1.0 eq) in MeCN (3.0 vol) is added water (0.83 vol) followed by concentrated aqueous HCl (0.83 vol). The mixture is heated to 45 ± 5 °C. After stirring for 24 to 48 hours the reaction is complete and the mixture is allowed to cool to ambient. Water (1.33 vol) is added and the mixture stirred. The solid is collected by filtration, washed with water (2 x 0.3 vol), and partially dried on the filter under vacuum. The solid is dried to constant weight (<1% difference) in a vacuum oven at 60 °C with a slight N_2 bleed to afford 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid • HCl as an off-white solid.

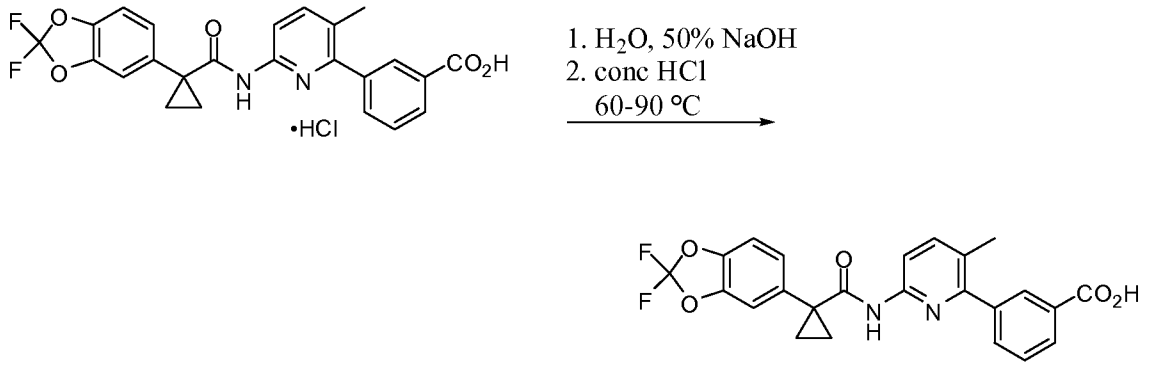
[00142] Synthesis of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Form I).



Form I

[00143] A slurry of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid • HCl (1 eq) in water (10 vol) is stirred at ambient temperature. A sample is taken after stirring for 24 hours. The sample is filtered and the solid washed with water (2 x). The solid sample is submitted for DSC analysis. When DSC analysis indicates complete conversion to Form I, the solid is collected by filtration, washed with water (2 x 1.0 vol), and partially dried on the filter under vacuum. The solid is dried to constant weight (<1% difference) in a vacuum oven at 60 °C with a slight N_2 bleed to afford Form I as an off-white solid (98% yield). ^{1}H NMR (400 MHz, DMSO-d6) 9.14 (s, 1H), 7.99-7.93 (m, 3H), 7.80-7.78 (m, 1H), 7.74-7.72 (m, 1H), 7.60-7.55 (m, 2H), 7.41-7.33 (m, 2H), 2.24 (s, 3H), 1.53-1.51 (m, 2H), 1.19-1.17 (m, 2H).

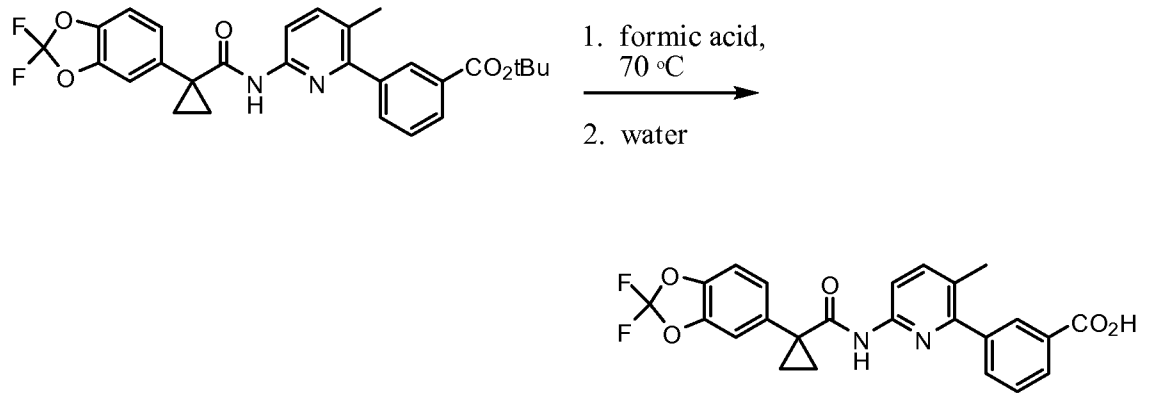
[00144] Synthesis of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Form I) using water and base.



Form I

[00145] To a slurry of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid • HCl (1 eq) in water (10 vol) stirred at ambient temperature is added 50% w/w aq. NaOH (2.5 eq). The mixture is stirred for NLT 15 min or until a homogeneous solution. Concentrated HCl (4 eq) is added to crystallize Form I. The mixture is heated to 60 °C or 90 °C if needed to reduce the level of the t-butylbenzoate ester. The mixture is heated until HPLC analysis indicates NMT 0.8% (AUC) t-butylbenzoate ester. The mixture is then cooled to ambient and the solid is collected by filtration, washed with water (3 x 3.4 vol), and partially dried on the filter under vacuum. The solid is dried to constant weight (<1% difference) in a vacuum oven at 60 °C with a slight N_2 bleed to afford Form I as an off-white solid (97% yield).

[00146] Synthesis of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Form I) directly from benzoate.



Form I

[00147] A solution of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)-t-butylbenzoate (1.0 eq) in formic acid (3.0 vol) is heated to 70 ± 10 °C. The reaction is continued until the reaction is complete (NMT 1.0% AUC 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)-t-butylbenzoate) or heating for NMT 8 h. The mixture is allowed to cool to ambient. The solution is added to water (6 vol) heated at 50 °C and the mixture stirred. The mixture is then heated to 70 ± 10 °C until the level of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)-t-butylbenzoate is NMT 0.8% (AUC). The solid is collected by filtration, washed with water (2 x 3 vol), and partially dried on the filter under vacuum. The solid is dried to constant weight (<1% difference) in a vacuum oven at 60 °C with a slight N_2 bleed to afford Compound 1 in Form I as an off-white solid.

[00148] An X-ray diffraction pattern calculated from a single crystal structure of Compound 1 in Form I is shown in Figure 1. Table 1 lists the calculated peaks for Figure 1.

[00149] Table 1.

Peak Rank	2θ Angle [degrees]	Relative Intensity [%]
11	14.41	48.2
8	14.64	58.8
1	15.23	100.0
2	16.11	94.7
3	17.67	81.9
7	19.32	61.3
4	21.67	76.5
5	23.40	68.7
9	23.99	50.8
6	26.10	67.4
10	28.54	50.1

[00150] An actual X-ray powder diffraction pattern of Compound 1 in Form I is shown in Figure 2. Table 2 lists the actual peaks for Figure 2.

[00151] Table 2.

Peak Rank	2θ Angle [degrees]	Relative Intensity [%]
7	7.83	37.7
3	14.51	74.9
4	14.78	73.5
1	15.39	100.0
2	16.26	75.6
6	16.62	42.6
5	17.81	70.9

Peak Rank	2θ Angle [degrees]	Relative Intensity [%]
9	21.59	36.6
10	23.32	34.8
11	24.93	26.4
8	25.99	36.9

[00152] An overlay of an X-ray diffraction pattern calculated from a single crystal structure of Compound 1 in Form I, and an actual X-ray powder diffraction pattern of Compound 1 in Form I is shown in Figure 3. The overlay shows good agreement between the calculated and actual peak positions, the difference being only about 0.15 degrees.

[00153] The DSC trace of Compound 1 in Form I is shown in Figure 4. Melting for Compound 1 in Form I occurs at about 204 °C.

[00154] Conformational pictures of Compound 1 in Form I based on single crystal X-ray analysis are shown in Figures 5-8. Figures 6-8 show hydrogen bonding between carboxylic acid groups of a dimer and the resulting stacking that occurs in the crystal. The crystal structure reveals a dense packing of the molecules. Compound 1 in Form I is monoclinic, $P2_1/n$, with the following unit cell dimensions: a = 4.9626(7) Å, b = 12.299(2) Å, c = 33.075 (4) Å, β = 93.938(9)°, V = 2014.0 $Å^3$, Z = 4. Density of Compound 1 in Form I calculated from structural data is 1.492 g/cm^3 at 100 K.

[00155] ^{1}HNMR spectra of Compound 1 are shown in Figures 9-11 (Figures 9 and 10 depict Compound 1 in Form I in a 50 mg/mL, 0.5 methyl cellulose-polysorbate 80 suspension, and Figure 11 depicts Compound 1 as an HCl salt).

[00156] Table 3 below recites additional analytical data for Compound 1.

[00157] Table 3.

Cmpd No.	LC/MS M+1	LC/RT min	NMR
1	453.3	1.93	H NMR (400 MHz, DMSO-d6) 9.14 (s, 1H), 7.99-7.93 (m, 3H), 7.80-7.78 (m, 1H), 7.74-7.72 (m, 1H), 7.60-7.55 (m, 2H), 7.41-7.33 (m, 2H), 2.24 (s, 3H), 1.53-1.51 (m, 2H), 1.19-1.17 (m, 2H)

[00158] *ASSAYS*

[00159] **Assays for Detecting and Measuring ΔF508-CFTR Correction Properties of Compounds**

[00160] Membrane potential optical methods for assaying ΔF508-CFTR modulation properties of compounds

[00161] The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today 4(9): 431-439).

[00162] These voltage sensitive assays are based on the change in fluorescence resonant energy transfer (FRET) between the membrane-soluble, voltage-sensitive dye, $DiSBAC_2(3)$, and a fluorescent phospholipid, CC2-DMPE, which is attached to the outer leaflet of the plasma membrane and acts as a FRET donor. Changes in membrane potential (V_m) cause the negatively charged $DiSBAC_2(3)$ to redistribute across the plasma membrane and the amount of energy transfer from CC2-DMPE changes accordingly. The changes in fluorescence emission were monitored using VIPR™ II, which is an integrated liquid handler and fluorescent detector designed to conduct cell-based screens in 96- or 384-well microtiter plates.

[00163] *1. Identification of Correction Compounds*

[00164] To identify small molecules that correct the trafficking defect associated with ΔF508-CFTR; a single-addition HTS assay format was developed. The cells were incubated in serum-free medium for 16 hrs at 37 °C in the presence or absence (negative control) of test compound. As a positive control, cells plated in 384-well plates were incubated for 16 hrs at 27 °C to "temperature-correct" ΔF508-CFTR. The cells were subsequently rinsed 3X with Krebs Ringers solution and loaded with the voltage-sensitive dyes. To activate ΔF508-CFTR, 10 μM forskolin and the CFTR potentiator, genistein (20 μM), were added along with Cl^--free medium to each well. The addition of Cl^--free medium promoted Cl^- efflux in response to ΔF508-CFTR activation and the resulting membrane depolarization was optically monitored using the FRET-based voltage-sensor dyes.

[00165] *2. Identification of Potentiator Compounds*

[00166] To identify potentiators of ΔF508-CFTR, a double-addition HTS assay format was developed. During the first addition, a Cl^--free medium with or without test compound was added to each well. After 22 sec, a second addition of Cl^--free medium containing 2 - 10 μM forskolin was added to activate ΔF508-CFTR. The extracellular Cl^- concentration following both additions was 28 mM, which promoted Cl^- efflux in response to ΔF508-CFTR activation and the resulting membrane depolarization was optically monitored using the FRET-based voltage-sensor dyes.

[00167] *3. Solutions*

Bath Solution #1: (in mM)	NaCl 160, KCl 4.5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7.4 with NaOH.
Chloride-free bath solution:	Chloride salts in Bath Solution #1 are substituted with gluconate salts.
CC2-DMPE:	Prepared as a 10 mM stock solution in DMSO and stored at -20°C.
$DiSBAC_2(3)$:	Prepared as a 10 mM stock in DMSO and stored at -20°C.

[00168] *4. Cell Culture*

[00169] NIH3T3 mouse fibroblasts stably expressing ΔF508-CFTR are used for optical measurements of membrane potential. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal bovine serum, 1 X NEAA, β-ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For all optical assays, the cells were seeded at 30,000/well in 384-well matrigel-coated plates and cultured for 2 hrs at 37 °C before culturing at 27 °C for 24 hrs for the potentiator assay. For the correction assays, the cells are cultured at 27 °C or 37 °C with and without compounds for 16 - 24 hours.

[00170] *Electrophysiological Assays for assaying ΔF508-CFTR modulation properties of compounds*

[00171] *1. Using Chamber Assay*

[00172] Using chamber experiments were performed on polarized epithelial cells

expressing ΔF508-CFTR to further characterize the ΔF508-CFTR modulators identified in the optical assays. $FRT^{\Delta F508\text{-}CFTR}$ epithelial cells grown on Costar Snapwell cell culture inserts were mounted in an Ussing chamber (Physiologic Instruments, Inc., San Diego, CA), and the monolayers were continuously short-circuited using a Voltage-clamp System (Department of Bioengineering, University of Iowa, IA, and, Physiologic Instruments, Inc., San Diego, CA). Transepithelial resistance was measured by applying a 2-mV pulse. Under these conditions, the FRT epithelia demonstrated resistances of 4 KΩ/ cm^2 or more. The solutions were maintained at 27 ºC and bubbled with air. The electrode offset potential and fluid resistance were corrected using a cell-free insert. Under these conditions, the current reflects the flow of Cl^- through ΔF508-CFTR expressed in the apical membrane. The I_{SC} was digitally acquired using an MP100A-CE interface and AcqKnowledge software (*v*3.2.6; BIOPAC Systems, Santa Barbara, CA).

[00173] *2. Identification of Correction Compounds*

[00174] Typical protocol utilized a basolateral to apical membrane Cl^- concentration gradient. To set up this gradient, normal ringer was used on the basolateral membrane, whereas apical NaCl was replaced by equimolar sodium gluconate (titrated to pH 7.4 with NaOH) to give a large Cl^- concentration gradient across the epithelium. All experiments were performed with intact monolayers. To fully activate ΔF508-CFTR, forskolin (10 μM) and the PDE inhibitor, IBMX (100 μM), were applied followed by the addition of the CFTR potentiator, genistein (50 μM).

[00175] As observed in other cell types, incubation at low temperatures of FRT cells stably expressing ΔF508-CFTR increases the functional density of CFTR in the plasma membrane. To determine the activity of correction compounds, the cells were incubated with 10 μM of the test compound for 24 hours at 37°C and were subsequently washed 3X prior to recording. The cAMP- and genistein-mediated I_{SC} in compound-treated cells was normalized to the 27°C and 37°C controls and expressed as percentage activity. Preincubation of the cells with the correction compound significantly increased the cAMP- and genistein-mediated I_{SC} compared to the 37°C controls.

[00176] *3. Identification of Potentiator Compounds*

[00177] Typical protocol utilized a basolateral to apical membrane Cl^- concentration gradient. To set up this gradient, normal ringers was used on the basolateral membrane and was permeabilized with nystatin (360 μg/ml), whereas apical NaCl was replaced by equimolar sodium gluconate (titrated to pH 7.4 with NaOH) to give a large Cl^- concentration gradient across the

epithelium. All experiments were performed 30 min after nystatin permeabilization. Forskolin (10 μM) and all test compounds were added to both sides of the cell culture inserts. The efficacy of the putative ΔF508-CFTR potentiators was compared to that of the known potentiator, genistein.

[00178] *4. Solutions*

Basolateral solution (in mM):	NaCl (135), $CaCl_2$ (1.2), $MgCl_2$ (1.2), K_2HPO_4 (2.4), $KHPO_4$ (0.6), N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (10), and dextrose (10). The solution was titrated to pH 7.4 with NaOH.
Apical solution (in mM):	Same as basolateral solution with NaCl replaced with Na Gluconate (135).

[00179] *5. Cell Culture*

[00180] Fisher rat epithelial (FRT) cells expressing ΔF508-CFTR ($FRT^{\Delta F508\text{-}CFTR}$) were used for Ussing chamber experiments for the putative ΔF508-CFTR modulators identified from our optical assays. The cells were cultured on Costar Snapwell cell culture inserts and cultured for five days at 37 °C and 5% CO_2 in Coon's modified Ham's F-12 medium supplemented with 5% fetal calf serum, 100 U/ml penicillin, and 100 μg/ml streptomycin. Prior to use for characterizing the potentiator activity of compounds, the cells were incubated at 27 °C for 16 - 48 hrs to correct for the ΔF508-CFTR. To determine the activity of corrections compounds, the cells were incubated at 27 °C or 37 °C with and without the compounds for 24 hours.

[00181] *6. Whole-cell recordings*

The macroscopic ΔF508-CFTR current ($I_{\Delta F508}$) in temperature- and test compound-corrected NIH3T3 cells stably expressing ΔF508-CFTR were monitored using the perforated-patch, whole-cell recording. Briefly, voltage-clamp recordings of $I_{\Delta F508}$ were performed at room temperature using an Axopatch 200B patch-clamp amplifier (Axon Instruments Inc., Foster City, CA). All recordings were acquired at a sampling frequency of 10 kHz and low-pass filtered at 1 kHz. Pipettes had a resistance of 5 – 6 MΩ when filled with the intracellular solution. Under these recording conditions, the calculated reversal potential for Cl^- (E_{Cl}) at room temperature was -28 mV. All recordings had a seal resistance > 20 GΩ and a series resistance < 15 MΩ. Pulse generation, data acquisition, and analysis were performed using a PC equipped with a Digidata 1320 A/D interface in conjunction with Clampex 8 (Axon Instruments

Inc.). The bath contained < 250 µl of saline and was continuously perifused at a rate of 2 ml/min using a gravity-driven perfusion system.

[00182] *7. Identification of Correction Compounds*

[00183] To determine the activity of correction compounds for increasing the density of functional ΔF508-CFTR in the plasma membrane, we used the above-described perforated-patch-recording techniques to measure the current density following 24-hr treatment with the correction compounds. To fully activate ΔF508-CFTR, 10 µM forskolin and 20 µM genistein were added to the cells. Under our recording conditions, the current density following 24-hr incubation at 27°C was higher than that observed following 24-hr incubation at 37 °C. These results are consistent with the known effects of low-temperature incubation on the density of ΔF508-CFTR in the plasma membrane. To determine the effects of correction compounds on CFTR current density, the cells were incubated with 10 µM of the test compound for 24 hours at 37°C and the current density was compared to the 27°C and 37°C controls (% activity). Prior to recording, the cells were washed 3X with extracellular recording medium to remove any remaining test compound. Preincubation with 10 µM of correction compounds significantly increased the cAMP- and genistein-dependent current compared to the 37°C controls.

[00184] *8. Identification of Potentiator Compounds*

[00185] The ability of ΔF508-CFTR potentiators to increase the macroscopic ΔF508-CFTR Cl^- current ($I_{\Delta F508}$) in NIH3T3 cells stably expressing ΔF508-CFTR was also investigated using perforated-patch-recording techniques. The potentiators identified from the optical assays evoked a dose-dependent increase in $I_{\Delta F508}$ with similar potency and efficacy observed in the optical assays. In all cells examined, the reversal potential before and during potentiator application was around -30 mV, which is the calculated E_{Cl} (-28 mV).

[00186] *9. Solutions*

Intracellular solution (in mM):	Cs-aspartate (90), CsCl (50), $MgCl_2$ (1), HEPES (10), and 240 µg/ml amphotericin-B (pH adjusted to 7.35 with CsOH).
Extracellular solution (in mM):	*N*-methyl-D-glucamine (NMDG)-Cl (150), $MgCl_2$ (2), $CaCl_2$ (2), HEPES (10) (pH adjusted to 7.35 with HCl).

[00187] *10. Cell Culture*

[00188] NIH3T3 mouse fibroblasts stably expressing ΔF508-CFTR are used for whole-cell recordings. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal bovine serum, 1 X NEAA, β-ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For whole-cell recordings, 2,500 - 5,000 cells were seeded on poly-L-lysine-coated glass coverslips and cultured for 24 - 48 hrs at 27 °C before use to test the activity of potentiators; and incubated with or without the correction compound at 37 °C for measuring the activity of correctors.

[00189] *11. Single-channel recordings*

[00190] The single-channel actdivities of temperature-corrected ΔF508-CFTR stably expressed in NIH3T3 cells and activities of potentiator compounds were observed using excised inside-out membrane patch. Briefly, voltage-clamp recordings of single-channel activity were performed at room temperature with an Axopatch 200B patch-clamp amplifier (Axon Instruments Inc.). All recordings were acquired at a sampling frequency of 10 kHz and low-pass filtered at 400 Hz. Patch pipettes were fabricated from Corning Kovar Sealing #7052 glass (World Precision Instruments, Inc., Sarasota, FL) and had a resistance of 5 - 8 MΩ when filled with the extracellular solution. The ΔF508-CFTR was activated after excision, by adding 1 mM Mg-ATP, and 75 nM of the cAMP-dependent protein kinase, catalytic subunit (PKA; Promega Corp. Madison, WI). After channel activity stabilized, the patch was perifused using a gravity-driven microperfusion system. The inflow was placed adjacent to the patch, resulting in complete solution exchange within 1 - 2 sec. To maintain ΔF508-CFTR activity during the rapid perifusion, the nonspecific phosphatase inhibitor F^- (10 mM NaF) was added to the bath solution. Under these recording conditions, channel activity remained constant throughout the duration of the patch recording (up to 60 min). Currents produced by positive charge moving from the intra- to extracellular solutions (anions moving in the opposite direction) are shown as positive currents. The pipette potential (V_p) was maintained at 80 mV.

[00191] Channel activity was analyzed from membrane patches containing ≤ 2 active channels. The maximum number of simultaneous openings determined the number of active channels during the course of an experiment. To determine the single-channel current amplitude, the data recorded from 120 sec of ΔF508-CFTR activity was filtered "off-line" at 100 Hz and then used to construct all-point amplitude histograms that were fitted with multigaussian functions using Bio-Patch Analysis software (Bio-Logic Comp. France). The total microscopic current and open probability (P_o) were determined from 120 sec of channel activity. The P_o was determined using the Bio-Patch software or from the relationship $P_o = I/i(N)$, where I = mean

current, i = single-channel current amplitude, and N = number of active channels in patch.

[00192] *12. Solutions*

Extracellular solution (in mM): NMDG (150), aspartic acid (150), $CaCl_2$ (5), $MgCl_2$ (2), and HEPES (10) (pH adjusted to 7.35 with Tris base).

Intracellular solution (in mM): NMDG-Cl (150), $MgCl_2$ (2), EGTA (5), TES (10), and Tris base (14) (pH adjusted to 7.35 with HCl).

[00193] *13. Cell Culture*

[00194] NIH3T3 mouse fibroblasts stably expressing ΔF508-CFTR are used for excised-membrane patch-clamp recordings. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal bovine serum, 1 X NEAA, β-ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For single channel recordings, 2,500 - 5,000 cells were seeded on poly-L-lysine-coated glass coverslips and cultured for 24 - 48 hrs at 27 °C before use.

[00195] Using the procedures described above, the activity, i.e., EC50s, of Compound 1 has been measured and is shown in Table 4.

[00196] Table 4.

IC50/EC50 Bins: +++ <= 2.0 < ++ <= 5.0 < +		
PercentActivity Bins: + <= 25.0 < ++ <= 100.0 < +++		
Cmpd. No.	BinnedEC50	BinnedMaxEfficacy
1	+++	+++

We claim:

1. 3-(6-(1-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid characterized as Form I.

2. Form I of claim 1, wherein the Form I is characterized by one or more peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation.

3. Form I of claim 2, wherein the Form I is characterized by one or more peaks at 15.4, 16.3, and 14.5 degrees.

4. Form I of claim 2, wherein the Form I is further characterized by a peak at 14.6 to 15.0 degrees.

5. Form I of claim 4, wherein the Form I is further characterized by a peak at 14.8 degrees.

6. Form I of claim 4, wherein the Form I is further characterized by a peak at 17.6 to 18.0 degrees.

7. Form I of claim 6, wherein the Form I is further characterized by a peak at 17.8 degrees.

8. Form I of claim 6, wherein the Form I is further characterized by a peak at 16.4 to 16.8 degrees.

9. Form I of claim 8, wherein the Form I is further characterized by a peak at 16.4 to 16.8 degrees.

10. Form I of claim 9, wherein the Form I is further characterized by a peak at 16.6 degrees.

11. Form I of claim 9, wherein the Form I is further characterized by a peak at 7.6 to 8.0 degrees.

12. Form I of claim 11, wherein the Form I is further characterized by a peak at 7.8 degrees.

13. Form I of claim 11, wherein the Form I is further characterized by a peak at 25.8 to 26.2 degrees.

14. Form I of claim 13, wherein the Form I is further characterized by a peak at 26.0 degrees.

15. Form I of claim 13, wherein the Form I is further characterized by a peak at 21.4 to 21.8 degrees.

16. Form I of claim 15, wherein the Form I is further characterized by a peak at 21.6 degrees.

17. Form I of claim 15, wherein the Form I is further characterized by a peak at 23.1 to 23.5 degrees.

18. Form I of claim 17, wherein the Form I is further characterized by a peak at 23.3 degrees.

19. Form I of claim 1, wherein the Form I is characterized by a diffraction pattern substantially similar to that of Figure 1.

20. Form I of claim 1, wherein the Form I is characterized by a diffraction pattern substantially similar to that of Figure 2.

21. Form I of claim 1, wherein the particle size distribution of D90 is about 82 μm or less.

22. Form I of claim 1, wherein the particle size distribution of D50 is about 30 μm or less.

23. A pharmaceutical composition comprising Form I of claim 1, and a pharmaceutically acceptable carrier.

24. A method of treating cystic fibrosis in a mammal comprising administering to the mammal an effective amount of Form I of claim 1.

25. The method of claim 24, wherein the method comprises administering an additional therapeutic agent.

26. A kit comprising Form I of claim 1 and instuctions for use thereof.

27. A process for preparing the Form I of claim 1 comprising suspending or dissolving the HCl salt of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid in an appropriate solvent for an effective amount of time.

28. The process of claim 27, wherein the appropriate solvent is water or 50% methanol/water mixture.

29. The process of claim 27, wherein the appropriate solvent is water.

30. The process of claim 27, wherein the effective amount of time is 2 to 24 hours.

31. The process of claim 27, wherein the effective amount of time is 2 to 6 hours.

32. A crystal form of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid having a monoclinic crystal system, a $P2_1/n$ space group, and the following unit cell dimensions:

a = 4.9626 (7) Å $\alpha = 90°$

b = 12.2994 (18) Å $\beta = 93.938\ (9)°$

c = 33.075 (4) Å $\gamma = 90°$.

Figure 1

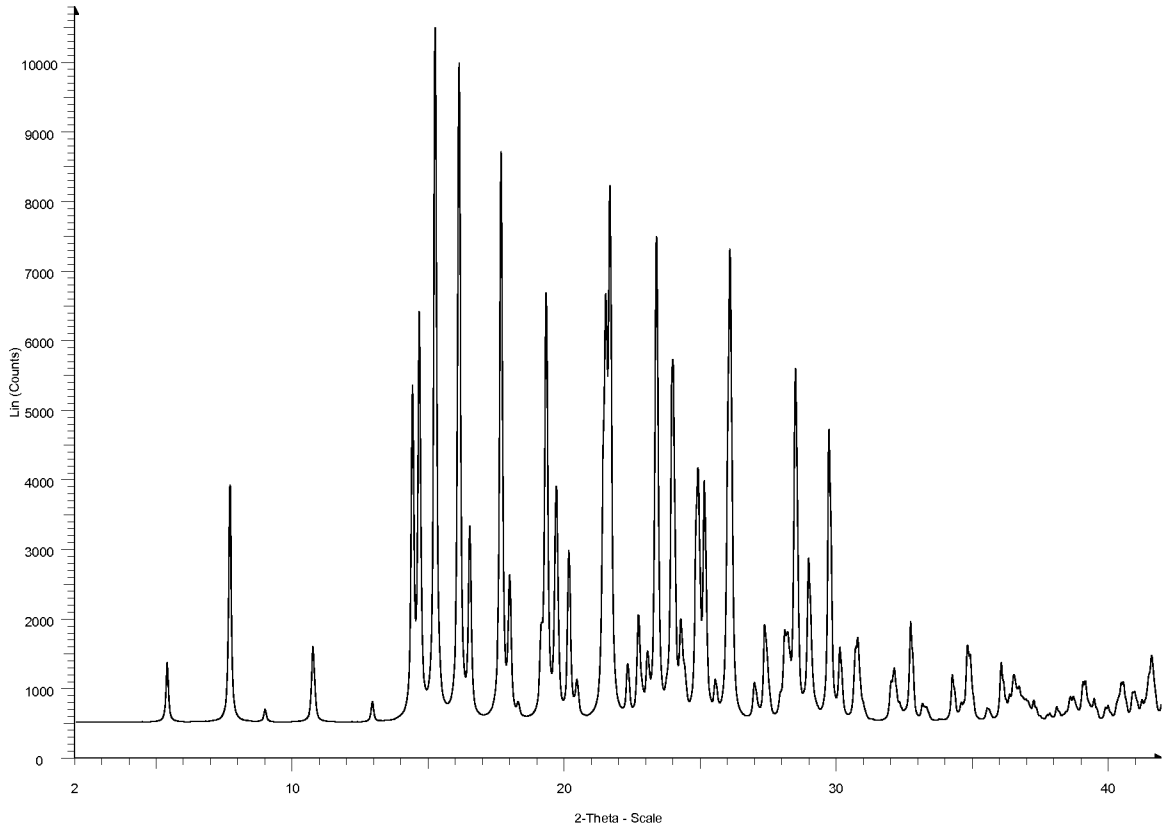

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Figure 2

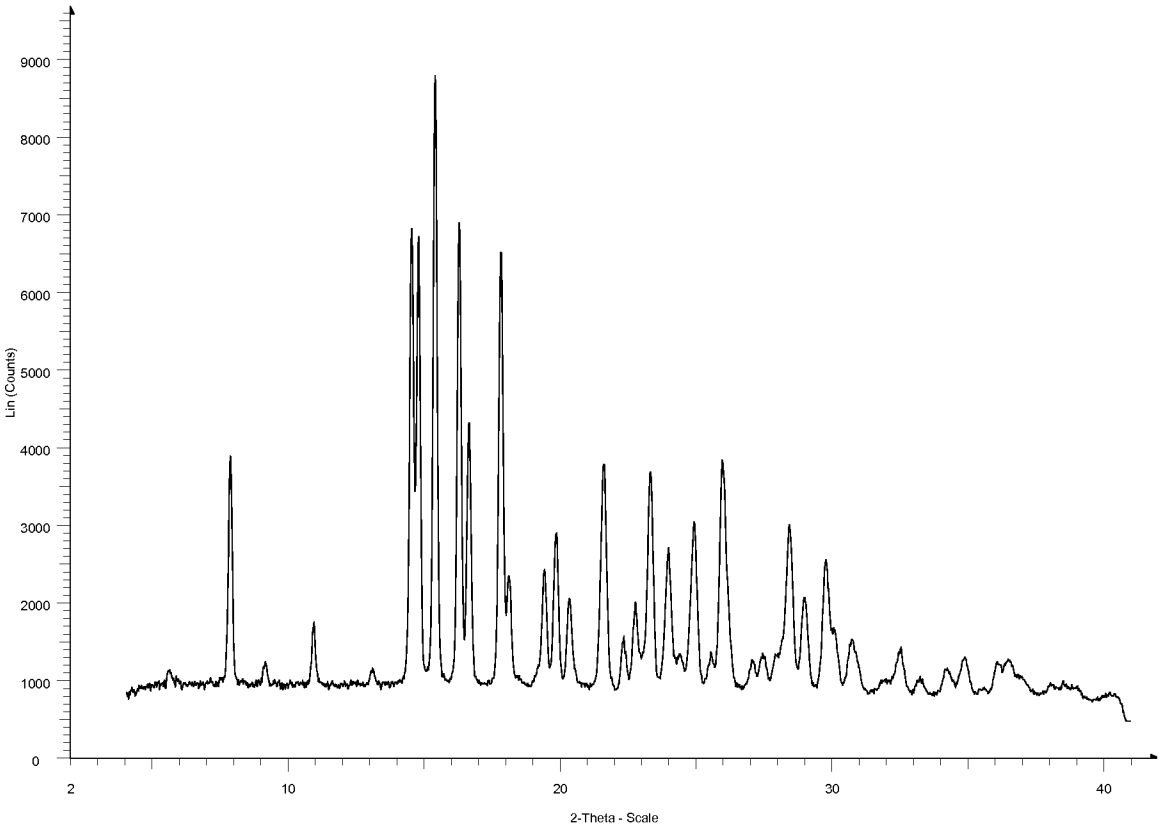
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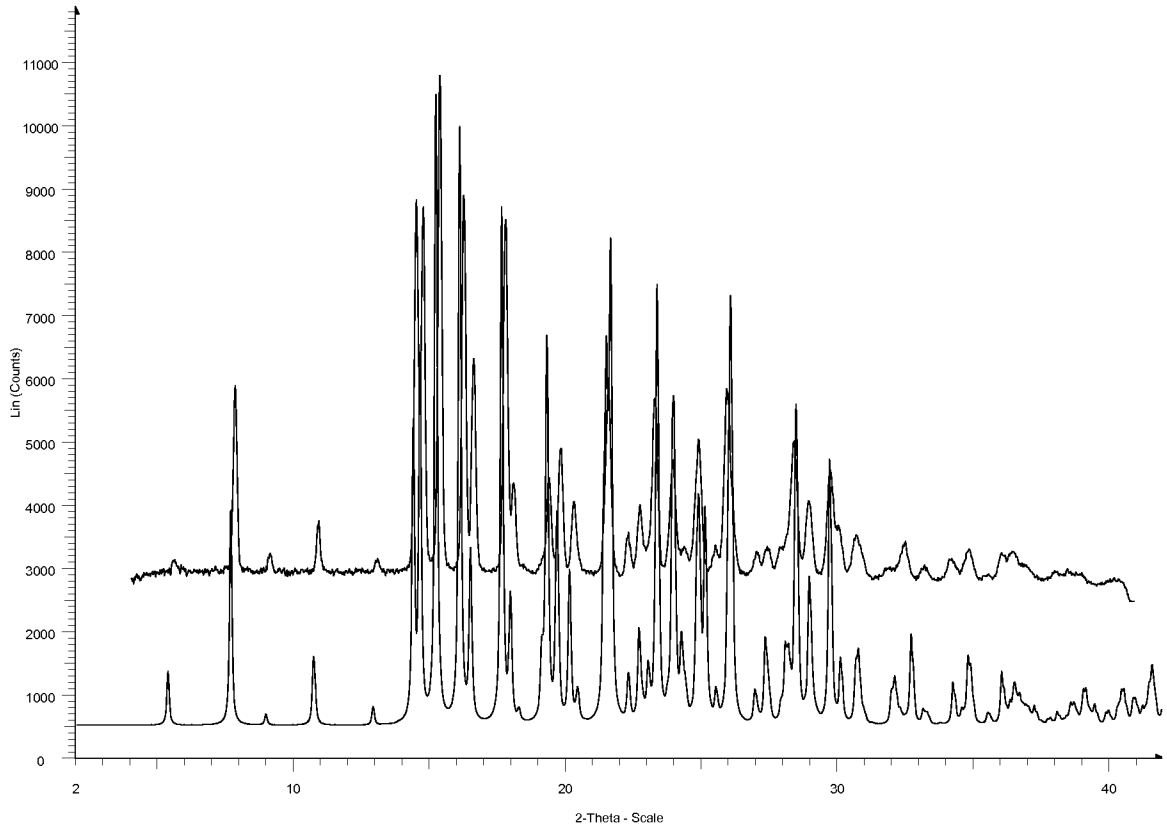
Figure 3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2
10
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30
40
2-Theta - Scale

Figure 4

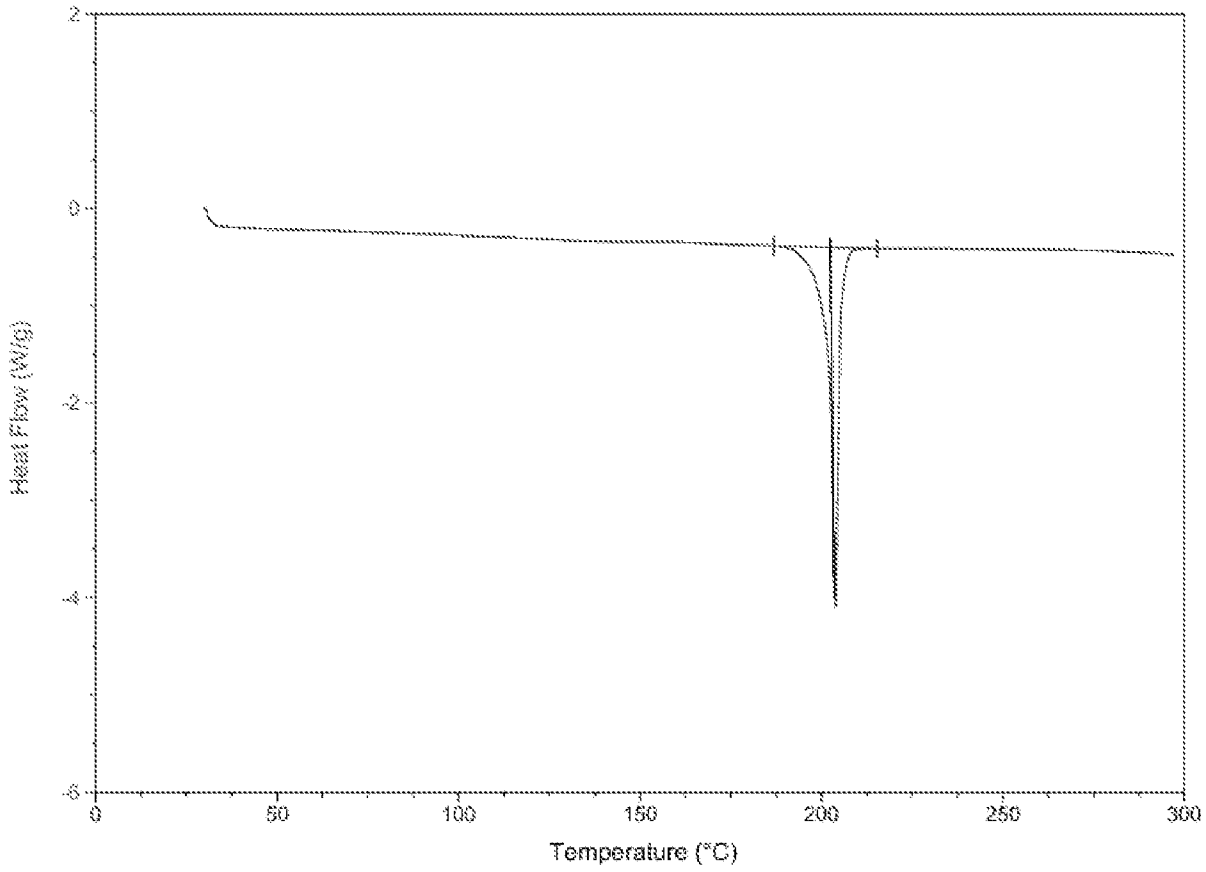


Figure 5

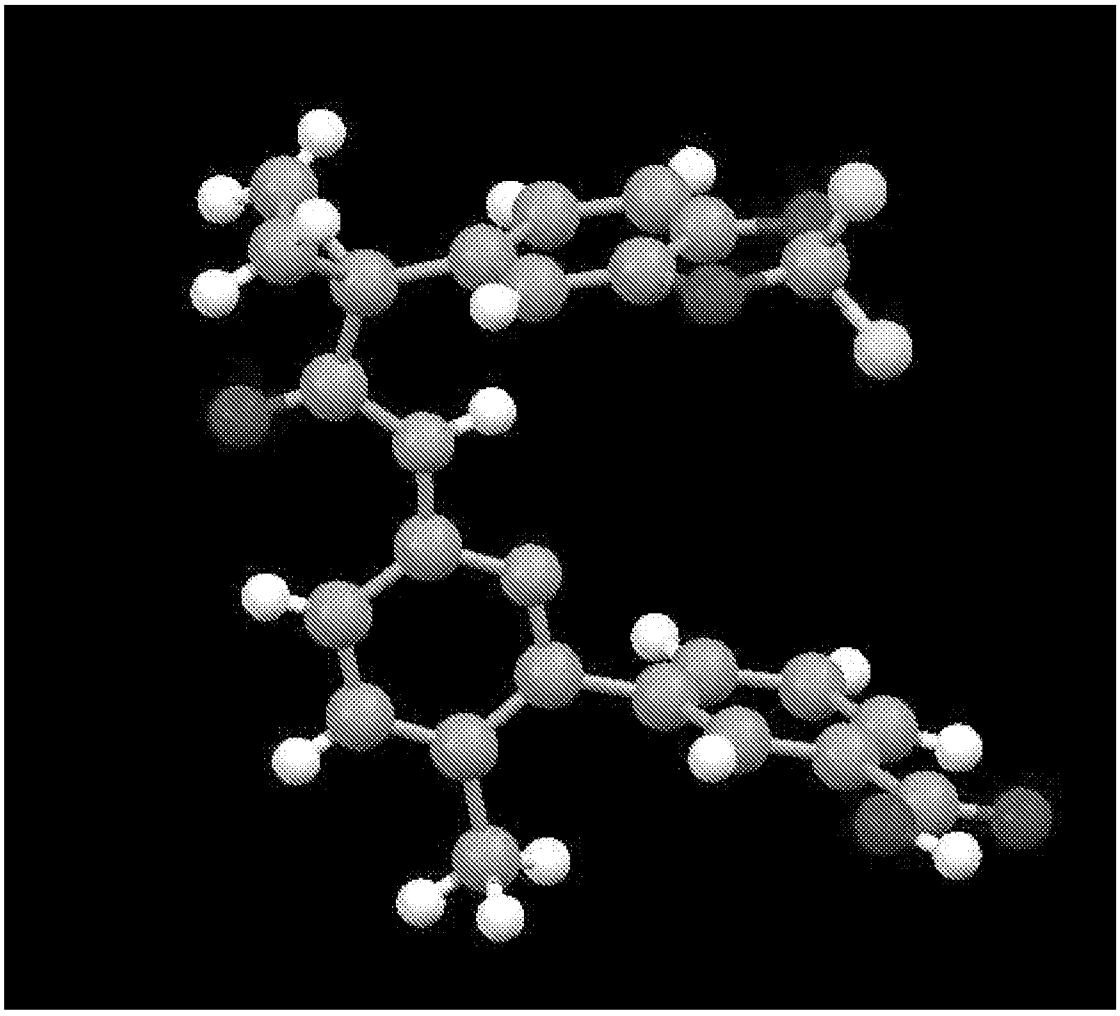


Figure 6

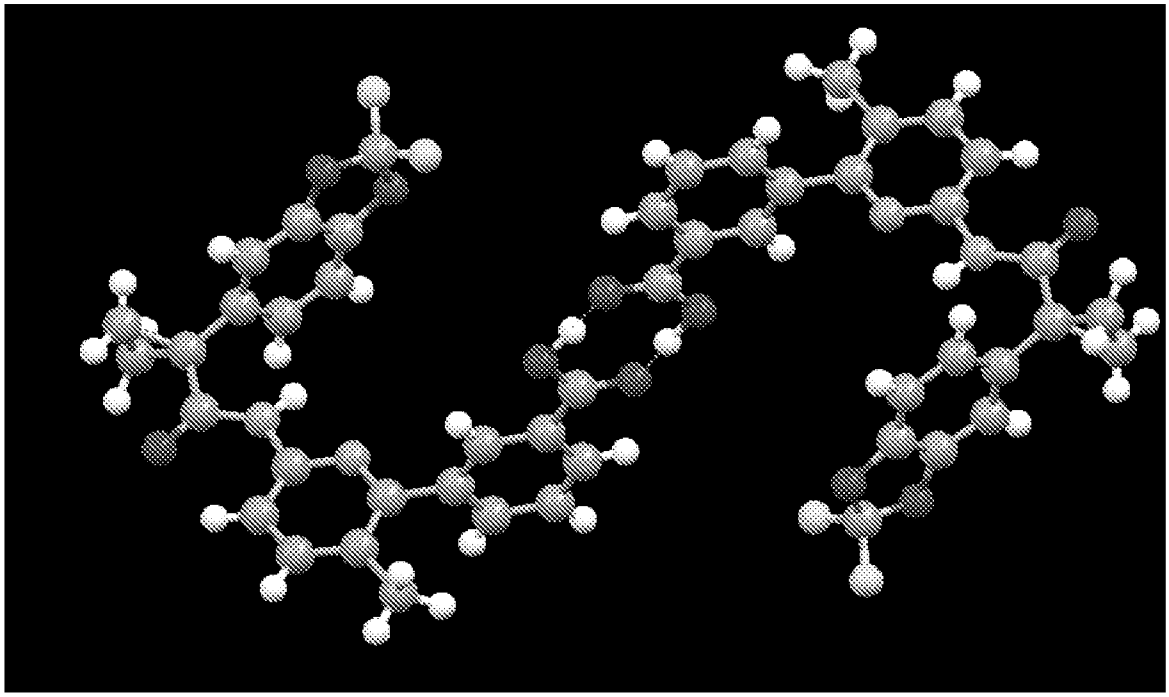


Figure 7

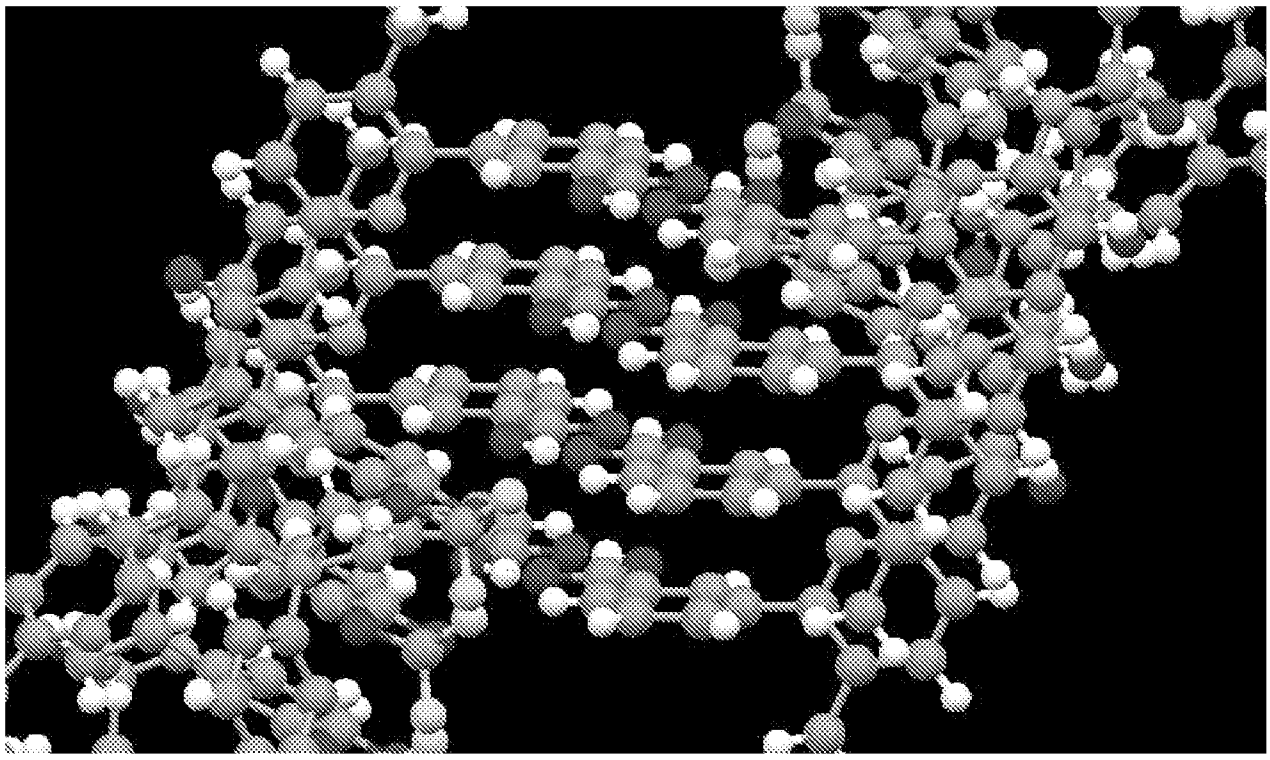


Figure 8

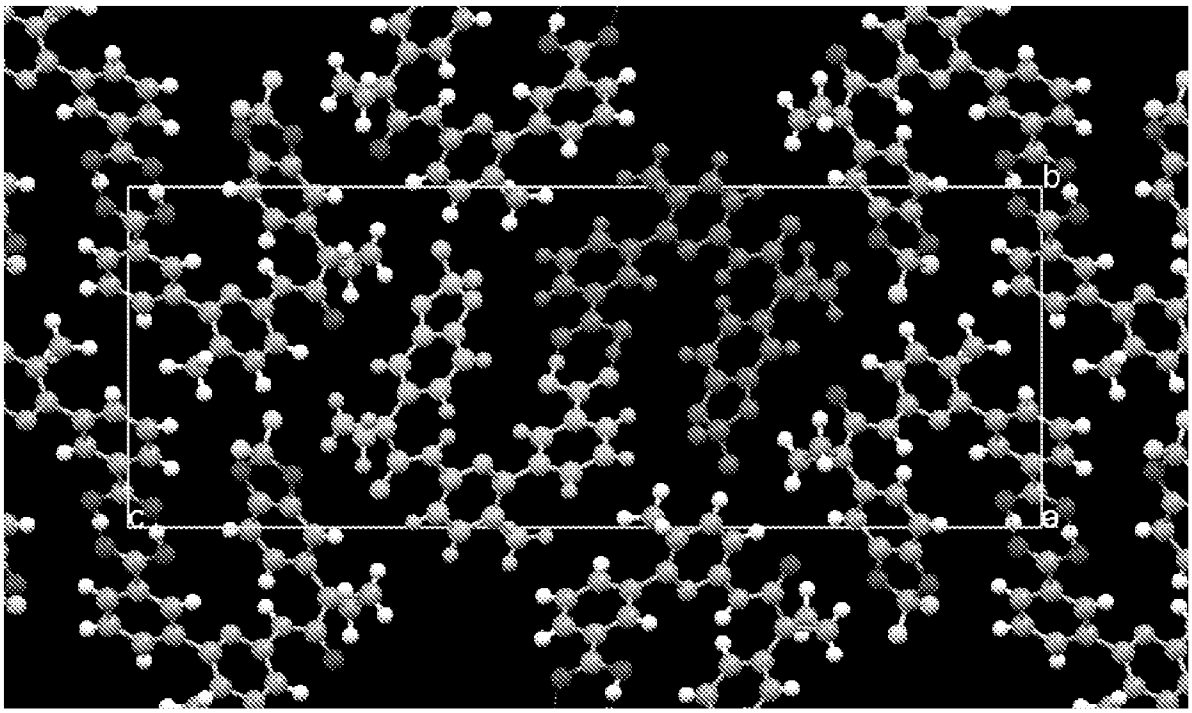


Figure 9

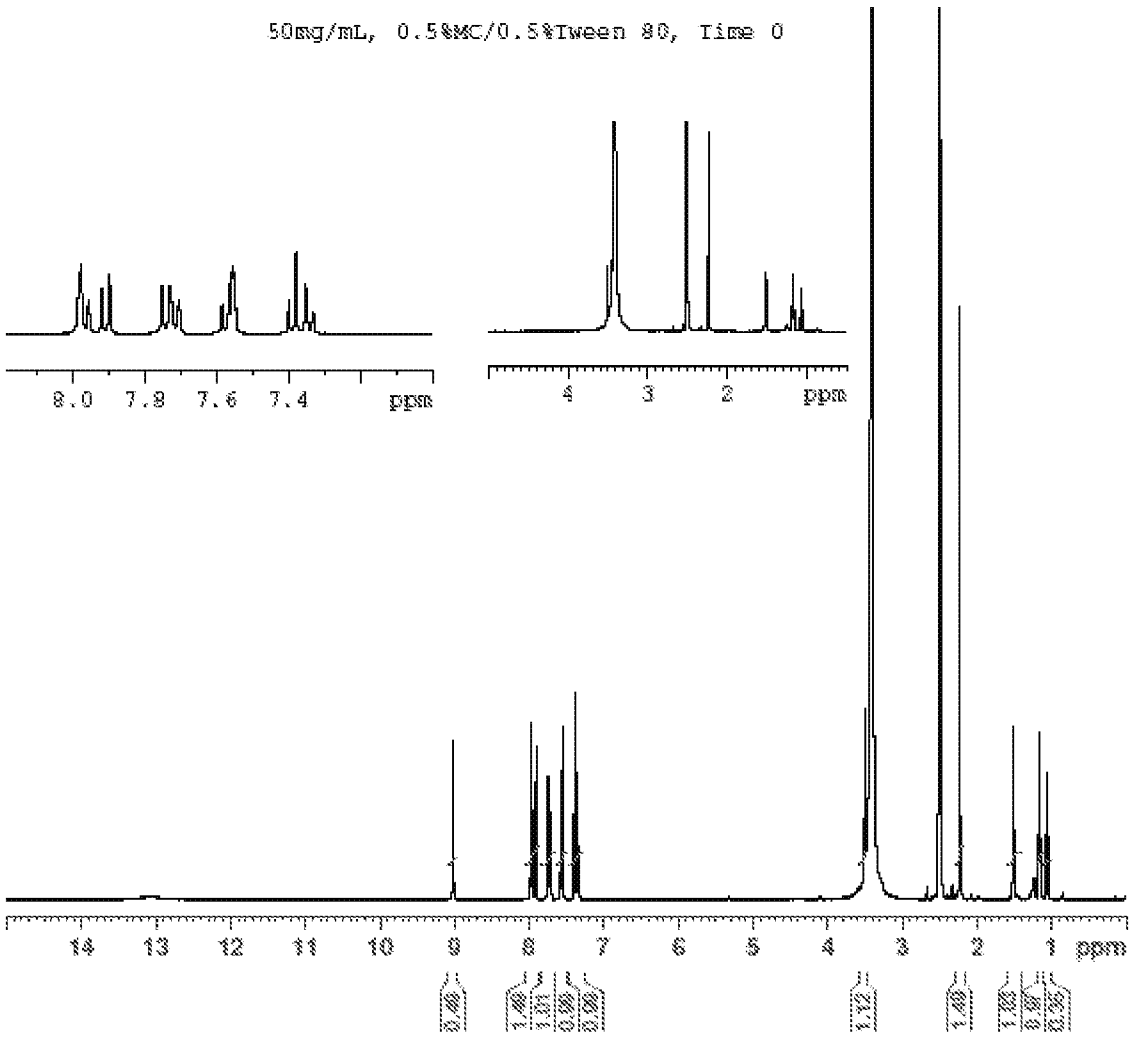

50mg/mL, 0.5%MC/0.5%Tween 80, Time 0
8.0
7.8
7.6
7.4
ppm
4
3
2
ppm
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

Figure 10

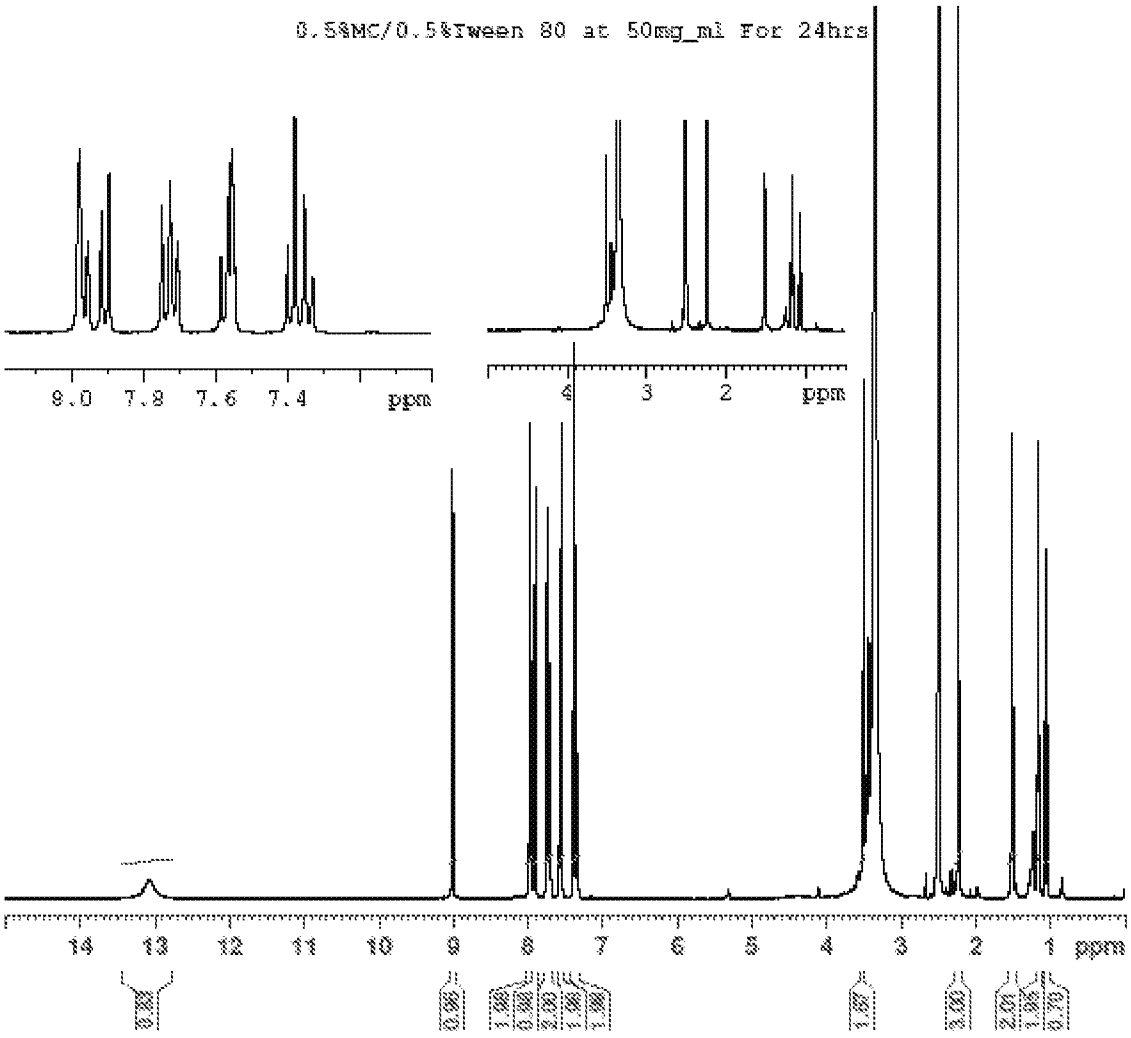
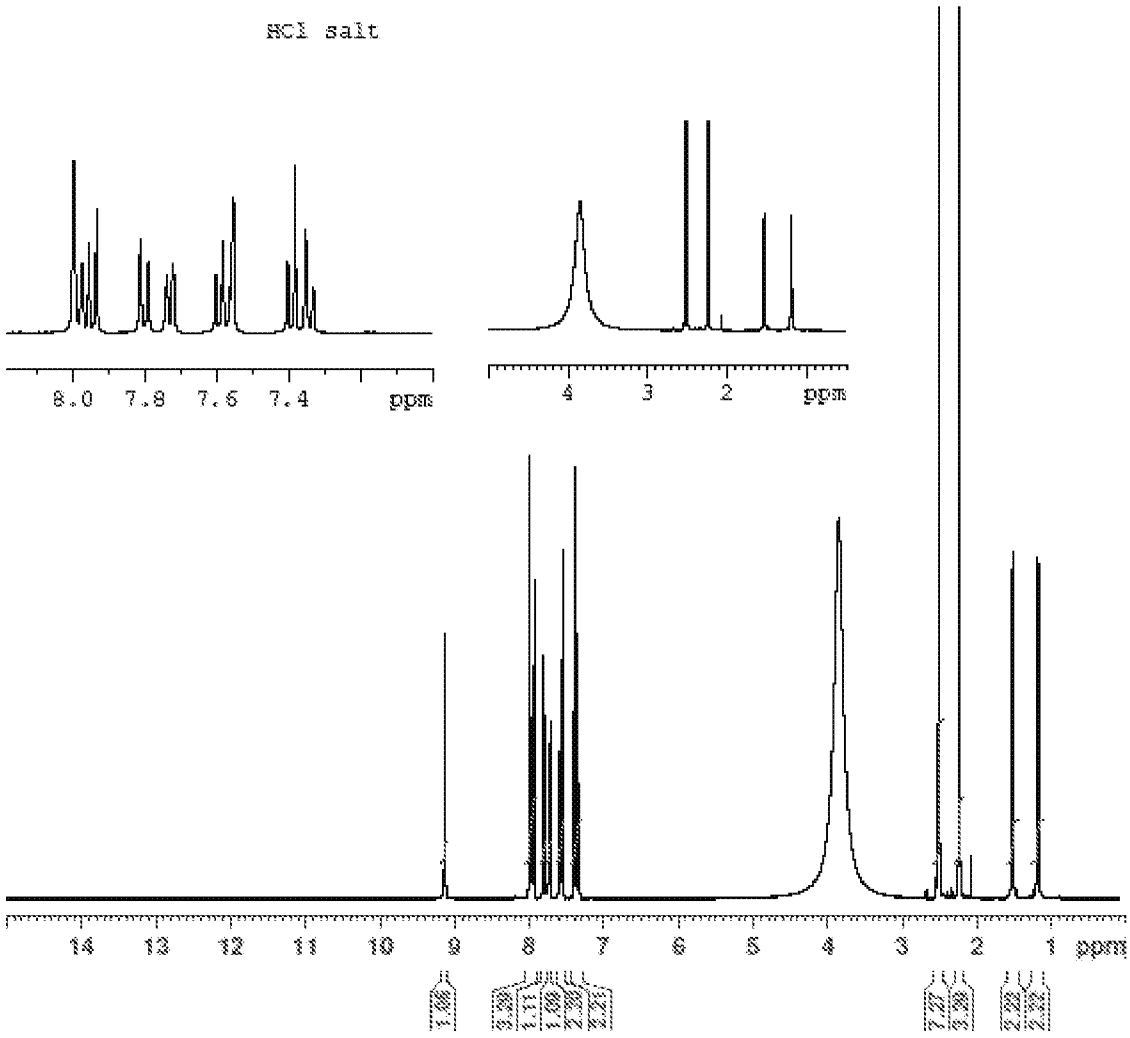

0.5%MC/0.5%Tween 80 at 50mg_ml For 24hrs
8.0 7.8 7.6 7.4 ppm
4 3 2 ppm
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm

Figure 11



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/085456

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/12 A61K31/443 A61P11/00

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)
C07D 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 practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN 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 2007/056341 A (VERTEX PHARMA [US]; HADIDA RUAH SARA [US]; HAMILTON MATTHEW [US]; MILL) 18 May 2007 (2007-05-18) cited in the application page 94; compound 396 claim 6 page 105, paragraph 330	1-32

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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	Date of mailing of the international search report
18 February 2009	26/02/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Seitner, Irmgard

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007056341 A	18-05-2007	AU 2006311650 A1	18-05-2007
		CA 2627358 A1	18-05-2007
		EP 1945632 A1	23-07-2008
		KR 20080066086 A	15-07-2008
		NO 20082674 B	07-08-2008
		US 2008306062 A1	11-12-2008
		US 2008113985 A1	15-05-2008
		US 2008019915 A1	24-01-2008

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61/181,527	27 May 2009 (27.05.2009)	us
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WO 2010/019239 A2

(54) Title: PHARMACEUTICAL COMPOSITION AND ADMINISTRATIONS THEREOF

(57) Abstract: The present invention relates to pharmaceutical compositions comprising a solid dispersion of N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline- 3-carboxamide, methods of manufacturing pharmaceutical compositions of the present invention, and methods of administering pharmaceutical compositions of the present invention.

PHARMACEUTICAL COMPOSITION AND ADMINISTRATIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This Application claims priority to USSN 61/088,704 filed on August 13, 2008, USSN 61/088,801, filed on August 14, 2008, USSN 61/090,096, filed on August 19, 2008, USSN 61/146,163, filed on January 21, 2009, USSN 61/181,527, filed on May 27, 2009, and USSN 61/183,345, filed on June 2, 2009, each of which is incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to pharmaceutical compositions comprising a solid dispersion of N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide, and methods of manufacturing and administering pharmaceutical compositions comprising N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide.

BACKGROUND

[0003] Cystic fibrosis (CF) is a recessive genetic disease that affects approximately 30,000 children and adults in the United States and approximately 30,000 children and adults in Europe. Despite progress in the treatment of CF, there is no cure.

[0004] CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes an epithelial chloride ion channel responsible for aiding in the regulation of salt and water absorption and secretion in various tissues. Small molecule drugs, known as potentiators that increase the probability of CFTR channel opening represent one potential therapeutic strategy to treat CF.

[0005] Specifically, CFTR is a cAMP/ATP-mediated anion channel that is expressed in a variety of cells types, including absorptive and secretory epithelia cells, where it regulates anion flux across the membrane, as well as the activity of other ion channels and proteins. In epithelia cells, normal functioning of CFTR is critical for the maintenance of electrolyte transport throughout the body, including respiratory and digestive tissue. CFTR is composed of approximately 1480 amino acids that encode a protein made up of a tandem repeat of transmembrane domains, each containing six transmembrane helices and a nucleotide binding domain. The two transmembrane domains are linked by a large, polar, regulatory (R)-domain with multiple phosphorylation sites that regulate channel activity and cellular trafficking.

[0006] The gene encoding CFTR has been identified and sequenced (See Gregory, **R. J.** et al. (1990) Nature 347:382-386; Rich, **D. P.** et al. (1990) Nature 347:358-362), (Riordan, **J. R.**

et al. (1989) Science 245:1066-1073). A defect in this gene causes mutations in CFTR resulting in cystic fibrosis ("CF"), the most common fatal genetic disease in humans. Cystic fibrosis affects approximately one in every 2,500 infants in the United States. Within the general United States population, up to 10 million people carry a single copy of the defective gene without apparent ill effects. In contrast, individuals with two copies of the CF associated gene suffer from the debilitating and fatal effects of CF, including chronic lung disease.

[0007] In patients with CF, mutations in CFTR endogenously expressed in respiratory epithelia leads to reduced apical anion secretion causing an imbalance in ion and fluid transport. The resulting decrease in anion transport contributes to enhanced mucus accumulation in the lung and the accompanying microbial infections that ultimately cause death in CF patients. In addition to respiratory disease, CF patients typically suffer from gastrointestinal problems and pancreatic insufficiency that, if left untreated, results in death. In addition, the majority of males with cystic fibrosis are infertile and fertility is decreased among females with cystic fibrosis. In contrast to the severe effects of two copies of the CF associated gene, individuals with a single copy of the CF associated gene exhibit increased resistance to cholera and to dehydration resulting from diarrhea - perhaps explaining the relatively high frequency of the CF gene within the population.

[0008] Sequence analysis of the CFTR gene of CF chromosomes has revealed a variety of disease causing mutations (Cutting, G. R. et al. (1990) Nature 346:366-369; Dean, M. et al. (1990) Cell 61:863:870; and Kerem, B-S. et al. (1989) Science 245:1073-1080; Kerem, B-S et al. (1990) Proc. Natl. Acad. Sci. USA 87:8447-8451). To date, > 1000 disease causing mutations in the CF gene have been identified (http://www.genet.sickkids.on.ca/cftr/). The most prevalent mutation is a deletion of phenylalanine at position 508 of the CFTR amino acid sequence, and is commonly referred to as ΔF508-CFTR. This mutation occurs in approximately 70% of the cases of cystic fibrosis and is associated with a severe disease.

[0009] The deletion of residue 508 in ΔF508-CFTR prevents the nascent protein from folding correctly. This results in the inability of the mutant protein to exit the ER, and traffic to the plasma membrane. As a result, the number of channels present in the membrane is far less than observed in cells expressing wild-type CFTR. In addition to impaired trafficking, the mutation results in defective channel gating. Together, the reduced number of channels in the membrane and the defective gating lead to reduced anion transport across epithelia leading to defective ion and fluid transport. (Quinton, P. M. (1990), FASEB J. 4: 2709-2727). Studies have shown, however, that the reduced numbers of ΔF508-CFTR in the

membrane are functional, albeit less than wild-type CFTR. (Dalemans et al. (1991), Nature Lond. 354: 526-528; Denning et al., supra; Pasyk and Foskett (1995), J. Cell. Biochem. 270: 12347-50). In addition to ΔF508-CFTR, other disease causing mutations in CFTR that result in defective trafficking, synthesis, and/or channel gating could be up- or down-regulated to alter anion secretion and modify disease progression and/or severity.

[0010] Although CFTR transports a variety of molecules in addition to anions, it is clear that this role (the transport of anions) represents one element in an important mechanism of transporting ions and water across the epithelium. The other elements include the epithelial Na+ channel, ENaC, Na+/2C1-/K+ co-transporter, Na+-K+-ATPase pump and the basolateral membrane K+ channels, that are responsible for the uptake of chloride into the cell.

[0011] These elements work together to achieve directional transport across the epithelium via their selective expression and localization within the cell. Chloride absorption takes place by the coordinated activity of ENaC and CFTR present on the apical membrane and the Na+-K+-ATPase pump and Cl ion channels expressed on the basolateral surface of the cell. Secondary active transport of chloride from the luminal side leads to the accumulation of intracellular chloride, which can then passively leave the cell via Cl- channels, resulting in a vectorial transport. Arrangement of Na+/2C1-/K+ co-transporter, Na+-K+-ATPase pump and the basolateral membrane K+ channels on the basolateral surface and CFTR on the luminal side coordinate the secretion of chloride via CFTR on the luminal side. Because water is probably never actively transported itself, its flow across epithelia depends on tiny transepithelial osmotic gradients generated by the bulk flow of sodium and chloride.

[0012] As discussed above, it is believed that the deletion of residue 508 in ΔF508-CFTR prevents the nascent protein from folding correctly, resulting in the inability of this mutant protein to exit the ER, and traffic to the plasma membrane. As a result, insufficient amounts of the mature protein are present at the plasma membrane and chloride transport within epithelial tissues is significantly reduced. In fact, this cellular phenomenon of defective ER processing of ABC transporters by the ER machinery has been shown to be the underlying basis not only for CF disease, but for a wide range of other isolated and inherited diseases.

[0013] N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide is a potent and selective CFTR potentiator of wild-type and mutant (including e.g., ΔF508, Rl 17H, and G551D) forms of human CFTR. N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide is useful for treatment of adult patients with cystic fibrosis and at least one G55 ID-CFTR allele.

[0014] Accordingly, there is a need for stable bioavailable pharmaceutical compositions of N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]- 1,4-dihydro-4-oxoquinoline-3-carboxamide useful for treating patients suffering from CF and methods of administering the same.

SUMMARY OF THE INVENTION

[0015] In general, the invention relates to pharmaceutical compositions comprising a solid dispersion of N-[2,4-bis(l, l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide ("Compound **1").** The pharmaceutical compositions may also include one or more of the following excipients: a filler, a disintegrant, a glidant, a lubricant, a binder, and a surfactant.

[0016] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound **1,** wherein the solid dispersion comprises about **25 mg** of amorphous Compound **1.** In certain embodiments, the solid dispersion comprises about **25 mg** of substantially amorphous Compound **1.**

[0017] **hi** one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about **50 mg** of amorphous Compound **1.** In certain embodiments, the solid dispersion comprises about **50 mg** of substantially amorphous Compound **1.**

[0018] hi one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about **75 mg** of amorphous Compound **1.** In certain embodiments, the solid dispersion comprises about **75 mg** of substantially amorphous Compound **1.**

[0019] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 100 **mg** of amorphous Compound **1.** In certain embodiments, the solid dispersion comprises about 100 **mg** of substantially amorphous Compound **1.**

[0020] hi one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 150 **mg** of amorphous Compound 1. hi certain embodiments, the solid dispersion comprises about 150 **mg** of substantially amorphous Compound 1.

[0021] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 250 **mg** of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 250 **mg** of substantially amorphous Compound 1.

[0022] In one aspect, the solid form of Compound 1 in the pharmaceutical composition is a solid dispersion comprising substantially amorphous or amorphous Compound 1 and a polymer, such as hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose acetate succinate (HPMCAS), vinylpyrrolidone/vinyl acetate copolymer (PVP/VA), polyvinylpyrrolidone (PVP), methacrylic acid/methacrylate copolymers, hydroxypropyl cellulose (HPC), or any combination thereof. Embodiments of this aspect include one or more of the following: The solid dispersion is a powder having mean particle diameter of greater than about 5 μm or the solid dispersion has a bulk density of about 0.10 g/cc or greater.

[0023] In some instances, the solid dispersion has a concentration of at least 20 wt% of Compound 1, by weight of the solid dispersion. In other instances, the solid dispersion comprises 80 wt% or less of HPMCAS or PVPAVA. Some solid dispersions comprise from about 40 wt% to about 60 wt% of substantially amorphous or amorphous Compound 1 by weight of the solid dispersion and from about 60 wt% to about 40 wt% of polymer by weight of the solid dispersion. Other solid dispersions comprise from about 65 wt% to about 95 wt% of substantially amorphous or amorphous Compound 1 by weight of the solid dispersion and from about 45 wt% to about 5 wt% of polymer by weight of the solid dispersion.

[0024] Solid dispersions can also optionally comprise additives such as a surfactant (e.g., sodium lauryl sulfate (SLS)), which can be present in a concentration of less than 10 wt% of surfactant by weight of solid dispersion.

[0025] Still other solid dispersions comprise from about 45 wt% to about 85 wt% of substantially amorphous or amorphous Compound 1, from about 0.45 wt% to about 0.55 wt% of SLS, and from about 14.45 wt% to about 55.55 wt% of HPMCAS or PVP/VA by weight of the solid dispersion.

[0026] In still further embodiments, the pharmaceutical compositions also comprise a filler (e.g., lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like) or any combination thereof) in concentrations of at least about 10 wt% by weight of the composition; a disintegrant (e.g., sodium croscarmellose, sodium starch glycolate, or a combination thereof) in concentrations of about 10 wt% or less by weight of the composition; a surfactant (e.g., sodium lauryl sulfate, sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate, or any combination thereof) in concentrations of about 10 wt% or less by weight of the composition; a binder (e.g., microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn (maize) starch, modified cellulose (e.g., hydroxymethyl cellulose), or any combination thereof) in concentrations of at least about 1

wt% by weight of the composition; a glidant (e.g., colloidal silicon dioxide, talc, or a combination thereof) in concentrations of about 2 wt% or less by weight of the composition; and a lubricant (e.g., magnesium stearate, stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof) in concentrations of about 2 wt% or less by weight of the composition.

[0027] Such pharmaceutical compositions can optionally comprise one or more colorants, fragrances, and/or flavors to enhance its visual appeal, taste, and scent.

[0028] Another aspect of the present invention provides a pharmaceutical composition consisting of a tablet that comprises a solid dispersion, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a dissolution of at least about 50% in about 30 minutes, and the solid dispersion comprises substantially amorphous Compound 1. As noted below, dissolution is measured with a standard USP Type II apparatus that employs a dissolution media of 0.6% sodium lauryl sulfate dissolved in 900 mL of DI water (or a volume of media having the same ratio of SLS to DI water) at a temperature of about 37 ^{0}C. A single experimental tablet is tested in each test vessel of the apparatus. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.7% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8) at a temperature of about 37 ^{0}C. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.5% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8) at a temperature of about 37 ^{0}C. A single experimental tablet is tested in each test vessel of the apparatus.

[0029] Another aspect of the present invention provides a pharmaceutical composition consisting of a tablet that comprises a solid dispersion comprising amorphous or substantially amorphous Compound 1 and HPMCAS or PVP/VA; and, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a hardness of at least about 5 Kp.

[0030] In yet another aspect, the tablets described herein are coated.

[0031] In another aspect, the coated tablets described herein are colored.

[0032] In still another aspect, the colored, coated tablets include text or images. For instance, the text or images can be printed on the colored, coated tablet.

In still other aspects, the colored, coated tablets include about 3 wt% of a film coating comprising a blue colorant, such as OPADRY® II. In some embodiments, the colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a black ink, such as Opacode® WB or Opacode® S-1-17823. In still further embodiments, the colored, coated tablets are coated with a colorant, waxed, and then labeled

with a logo, other image, and/or text using a suitable ink. In some embodiments, the tablets are coated with about 3 wt% of colorant, and waxed with Carnauba wax powder weighed out in the amount of about 0.01% w/w of the starting tablet core weight. The waxed tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink.

[0033] Another aspect of the present invention provides a method of producing a pharmaceutical composition comprising the steps of providing an admixture of a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, and compressing the admixture into a tablet having a dissolution of at least about 50% in about 30 minutes. In one example, the admixture is compressed to a hardness of at least about 5 Kp.

[0034] Another aspect of the present invention provides a method of producing a pharmaceutical composition comprising the steps of providing an admixture of a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, and compressing the admixture into a tablet having a dissolution of at least about 70% in about 30 minutes.

[0035] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1. In some embodiments, the tablet is orally administered to the patient once per day. Other tablets useful in this method comprise a solid dispersion containing at least about 50 mg of substantially amorphous or amorphous Compound 1. Some tablets useful in this method comprise a solid dispersion containing at least about 75 mg of substantially amorphous or amorphous Compound 1. Other tablets useful in this method comprise a solid dispersion containing at least about 100 mg of substantially amorphous or amorphous Compound 1. Yet other tablets useful in this method comprise a solid dispersion containing at least about 150 mg of substantially amorphous or amorphous Compound 1. In another method, the administration comprises orally administering to a patient at least once per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 250 mg of substantially amorphous or amorphous Compound 1.

In some embodiments, the present invention provides for a method of orally administering the pharmaceutical compositions described herein at least once a day. In other embodiments, the present invention provides for a method of orally administering the pharmaceutical composition described herein once a day. hi some embodiments, the present invention provides for a method of orally administering the pharmaceutical composition described herein twice a day.

[0036] In one aspect, the invention also provides a method of treating or lessening the severity of a disease in a patient comprising administering to said patient one of the compositions as defined herein, and said disease is selected from cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear plasy, Pick's disease, several polyglutamine neurological disorders such as Huntington's, spinocerebullar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, Sjogren's disease, Osteoporosis, Osteopenia, Gorham's Syndrome, chloride channelopathies such as myotonia congenita (Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, and Primary Ciliary Dyskinesia (PCD), a term for inherited disorders of the structure and/or function of cilia, including PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary aplasia.

BRIEF DESCRIPTION OF THE FIGURES

[0037] Figure 1 presents a graphical illustration of the dissolution profiles of exemplary tablets according to the present invention.

[0038] This figure is presented by way of example and is not intended to be limiting.

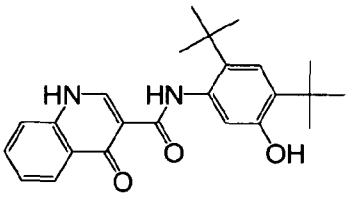
DETAILED DESCRIPTION

[0039] The present invention provides a pharmaceutical composition comprising a solid dispersion of N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide, a method of manufacturing a pharmaceutical composition comprising N-[2,4-bisClJ-dimethylethyO-S-hydroxypheny^-l^-dihydro^-oxoquinoline-S-carboxamide, and a method of administering a pharmaceutical composition comprising a solid form of N-[2,4-bis(1,**1**-dimethylethyl)-5-hydroxyphenyl]- **1**,4-dihydro-4-oxoquinoline-3 -carboxamide.

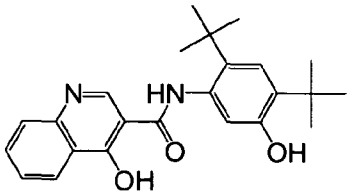
[0040] I. DEFINITIONS

[0041] As used herein, the term "active pharmaceutical ingredient" or "API" refers to a biologically active compound. Exemplary APIs include a CF potentiator (e.g., N-[2,4-bis(l,l-dimemylemyl)-5-hydroxyphenyl]-l,4-dmydro-4-oxoquinoline-3-carboxamide).

[0042] As used herein, the term "Compound 1" is used interchangeably with "N-[2,4-bisCU-dimethylethy^-S-hydroxyphenylJ-l^-dihydro^-oxoquinoline-S-carboxamide", which has the following structure:



[0043] "Compound 1" also means tautomeric forms such as:



[0044] As used herein, the term "amorphous" refers to a solid material having no long range order in the position of its molecules. Amorphous solids are generally supercooled liquids in which the molecules are arranged in a random manner so that there is no well-defined arrangement, e.g., molecular packing, and no long range order. Amorphous solids are generally isotropic, i.e. exhibit similar properties in all directions and do not have definite melting points. For example, an amorphous material is a solid material having no sharp characteristic crystalline peak(s) in its X-ray power diffraction (XRPD) pattern (i.e., is not

crystalline as determined by XRPD). Instead, one or several broad peaks (e.g., halos) appear in its XRPD pattern. Broad peaks are characteristic of an amorphous solid. See, US 2004/0006237 for a comparison of XRPDs of an amorphous material and crystalline material.

[0045] As used herein, the term "substantially amorphous" refers to a solid material having little or no long range order in the position of its molecules. For example, substantially amorphous materials have less than about 15% crystallinity (e.g., less than about 10% crystallinity or less than about 5% crystallinity). It is also noted that the term 'substantially amorphous' includes the descriptor, 'amorphous', which refers to materials having no (0%) crystallinity.

[0046] As used herein, the term "dispersion" refers to a disperse system in which one substance, the dispersed phase, is distributed, in discrete units, throughout a second substance (the continuous phase or vehicle). The size of the dispersed phase can vary considerably (e.g. single molecules, colloidal particles of nanometer dimension, to multiple microns in size). In general, the dispersed phases can be solids, liquids, or gases. In the case of a solid dispersion, the dispersed and continuous phases are both solids. In pharmaceutical applications, a solid dispersion can include: an amorphous drug in an amorphous polymer; an amorphous drug in crystalline polymer; a crystalline drug in an amorphous polymer; or a crystalline drug in crystalline polymer. In this invention, a solid dispersion can include an amorphous drug in an amorphous polymer or an amorphous drug in crystalline polymer. In some embodiments, a solid dispersion includes the polymer constituting the dispersed phase, and the drug constitutes the continuous phase. Or, a solid dispersion includes the drug constituting the dispersed phase, and the polymer constitutes the continuous phase.

[0047] As used herein, the term "solid dispersion" generally refers to a solid dispersion of two or more components, usually one or more drugs (e.g., one drug (e.g., Compound I)) and polymer, but possibly containing other components such as surfactants or other pharmaceutical excipients, where the drug(s) (e.g., Compound 1) is substantially amorphous (e.g., having about 15% or less (e.g., about 10% or less, or about 5% or less)) of crystalline drug (e.g., N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide) or amorphous (i.e., having no crystalline drug), and the physical stability and/or dissolution and/or solubility of the substantially amorphous or amorphous drug is enhanced by the other components. Solid dispersions typically include a compound dispersed in an appropriate carrier medium, such as a solid state carrier. For example, a carrier comprises a polymer (e.g., a water-soluble polymer or a partially water-soluble polymer) and can include optional excipients such as functional excipients (e.g., one or more

surfactants) or nonfunctional excipients (e.g., one or more fillers). Another exemplary solid dispersion is a co-precipitate or a co-melt of N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide with at least one polymer.

[0048] A "Co-precipitate" is a product after dissolving a drug and a polymer in a solvent or solvent mixture followed by the removal of the solvent or solvent mixture. Sometimes the polymer can be suspended in the solvent or solvent mixture. The solvent or solvent mixture includes organic solvents and supercritical fluids. A "co-melt" is a product after heating a drug and a polymer to melt, optionally in the presence of a solvent or solvent mixture, followed by mixing, removal of at least a portion of the solvent if applicable, and cooling to room temperature at a selected rate.

[0049] As used herein, "crystallinity" refers to the degree of structural order in a solid. For example, Compound 1, which is substantially amorphous, has less than about 15% crystallinity, or its solid state structure is less than about 15% crystalline. In another example, Compound 1, which is amorphous, has zero (0%) crystallinity.

[0050] As used herein, a "CF potentiator" refers to a compound that exhibits biological activity characterized by increasing gating functionality of the mutant CFTR protein present in the cell surface to approximately wild type levels.

[0051] As used herein, an "excipient" is an inactive ingredient in a pharmaceutical composition. Examples of excipients include fillers or diluents, surfactants, binders, glidants, lubricants, disintegrants, and the like.

[0052] As used herein, a "disintegrant" is an excipient that hydrates a pharmaceutical composition and aids in tablet dispersion. Examples of disintegrants include sodium croscarmellose and/or sodium starch glycolate.

[0053] As used herein, a "diluent" or "filler" is an excipient that adds bulkiness to a pharmaceutical composition. Examples of fillers include lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like) or any combination thereof.

[0054] As used herein, a "surfactant" is an excipient that imparts pharmaceutical compositions with enhanced solubility and/or wetability. Examples of surfactants include sodium lauryl sulfate (SLS), sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate (e.g., Tween™), or any combination thereof.

[0055] As used herein, a "binder" is an excipient that imparts a pharmaceutical composition with enhanced cohesion or tensile strength (e.g., hardness). Examples of binders include dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose, and modified cellulose (e.g., hydroxymethyl cellulose).

[0056] As used herein, a "glidant" is an excipient that imparts a pharmaceutical compositions with enhanced flow properties. Examples of glidants include colloidal silica and/or talc.

[0057] As used herein, a "colorant" is an excipient that imparts a pharmaceutical composition with a desired color. Examples of colorants include commercially available pigments such as FD&C Blue # 1 Aluminum Lake, FD&C Blue #2, other FD&C Blue colors, titanium dioxide, iron oxide, and/or combinations thereof.

[0058] As used herein, a "lubricant" is an excipient that is added to pharmaceutical compositions that are pressed into tablets. The lubricant aids in compaction of granules into tablets and ejection of a tablet of a pharmaceutical composition from a die press. Examples of lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[0059] As used herein, "friability" refers to the property of a tablet to remain intact and withhold its form despite an external force of pressure. Friability can be quantified using the mathematical expression presented in equation 1:

$$\%friabiliy = 100 \times \frac{(W_0 - W_f)}{W_0} \qquad (1)$$

wherein W_0 is the original weight of the tablet and W_f is the final weight of the tablet after it is put through the friabilator.

[0060] Friability is measured using a standard USP testing apparatus that tumbles experimental tablets for 100 revolutions. Some tablets of the present invention have a friability of less than about 1% (e.g., less than about 0.75%, less than about 0.50%, or less than about 0.30%)

[0061] As used herein, "mean particle diameter" is the average particle diameter as measured using techniques such as laser light scattering, image analysis, or sieve analysis.

[0062] . As used herein, "bulk density" is the mass of particles of material divided by the total volume the particles occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume. Bulk density is not an intrinsic property of a material; it can change depending on how the material is processed.

[0063] II. PHARMACEUTICAL COMPOSITION

[0064] In one aspect, the present invention provides a pharmaceutical composition comprising a CF potentiator **API** (e.g., a solid dispersion of Compound **1).**

[0065] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of substantially amorphous Compound **1,** wherein the solid dispersion comprises about 25 mg of substantially amorphous Compound 1.

[0066] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound **1,** wherein the solid dispersion comprises about **50 mg** of substantially amorphous Compound 1.

[0067] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1**,** wherein the solid dispersion comprises about **75 mg** of substantially amorphous Compound **1.**

[0068] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises about 100 **mg** of substantially amorphous Compound **1.**

[0069] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound **1,** wherein the solid dispersion comprises about 150 **mg** of substantially amorphous Compound 1.

[0070] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1**,** wherein the solid dispersion comprises about 250 **mg** of substantially amorphous Compound 1.

[0071] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound **1,** wherein the solid dispersion comprises about **25 mg** of amorphous Compound **1.**

[0072] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound **1,** wherein the solid dispersion comprises about **50 mg** of amorphous Compound **1.**

[0073] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound **1,** wherein the solid dispersion comprises about **75 mg** of amorphous Compound **1.**

[0074] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about **100 mg** of amorphous Compound **1.**

[0075] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound **1,** wherein the solid dispersion comprises about 150 **mg** of amorphous Compound **1.**

[0076] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 250 **mg** of amorphous Compound 1**.**

[0077] Another aspect of the present invention provides a pharmaceutical composition comprising a solid dispersion of Compound 1 in which the solid dispersion comprises a polymer.

[0078] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about **25 mg** of substantially amorphous Compound **1.**

[0079] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound **1** and HPMCAS, wherein the solid dispersion comprises about **50 mg** of substantially amorphous Compound 1.

[0080] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about **75 mg** of substantially amorphous Compound **1.**

[0081] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 100 **mg** of substantially amorphous Compound 1.

[0082] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 150 **mg** of substantially amorphous Compound **1.**

[0083] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 250 **mg** of substantially amorphous Compound **1.**

[0084] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about **25 mg** of amorphous Compound **1.**

[0085] hi one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 50 mg of amorphous Compound 1.

[0086] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound **1** and HPMCAS, wherein the solid dispersion comprises about **75 mg** of amorphous Compound 1.

[0087] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 100 **mg** of amorphous Compound 1.

[0088] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 150 **mg** of amorphous Compound 1.

[0089] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 250 **mg** of amorphous Compound 1.

[0090] **hi** one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about **25 mg** of substantially amorphous Compound 1.

[0091] hi one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of substantially amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about 50 mg of substantially amorphous Compound 1.

[0092] In one embodiment, the present invention provides **a** pharmaceutical composition comprising **a** solid dispersion of substantially amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about **75 mg** of substantially amorphous Compound **1.**

[0093] hi one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of substantially amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about 100 mg of substantially amorphous Compound **1.**

[0094] hi one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of substantially amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about 150 mg of substantially amorphous Compound 1.

[0095] hi one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of substantially amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about 250 mg of substantially amorphous Compound **1.**

[0096] hi one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about 25 mg of amorphous Compound 1.

[0097] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about 50 mg of amorphous Compound 1.

[0098] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about 75 mg of amorphous Compound 1.

[0099] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound **1** and PVP/VA, wherein the solid dispersion comprises about 100 mg of amorphous Compound **1.**

[00100] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about 150 mg of amorphous Compound 1.

[00101] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1 and PVP/VA, wherein the solid dispersion comprises about 250 mg of amorphous Compound 1.

[00102] One aspect of the present invention provides a pharmaceutical composition comprising a CF potentiator API (e.g., a solid dispersion of Compound 1) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof).

[00103] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and a polymer;
b. a filler;
c. a disintegrant;
d. a surfactant;
e. a binder;
f. a glidant; and
g. a lubricant,

wherein the solid dispersion comprises about 25 mg of substantially amorphous Compound 1.

[00104] In one embodiment, the present invention provides **a** pharmaceutical composition comprising:

a. **a** solid dispersion of substantially amorphous Compound 1 and **a** polymer;
b. **a** filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 50 mg of substantially amorphous Compound 1.

[00105] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 75 mg of substantially amorphous Compound 1.

[00106] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 100 mg of substantially amorphous Compound 1.

[00107] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 150 mg of substantially amorphous Compound 1.

[00108] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 250 mg of substantially amorphous Compound 1.

[00109] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 25 mg of amorphous Compound 1.

[00110] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 50 mg of amorphous Compound 1.

[00111] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 75 mg of amorphous Compound 1.

[00112] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 100 mg of amorphous Compound 1.

[00113] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 150 mg of amorphous Compound 1.

[00114] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 250 mg of amorphous Compound 1.

[00115] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 25 mg of substantially amorphous Compound 1.

[00116] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 50 mg of substantially amorphous Compound 1.

[00117] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 75 mg of substantially amorphous Compound 1.

[00118] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 100 mg of substantially amorphous Compound 1.

[00119] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 150 mg of substantially amorphous Compound 1.

[00120] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 250 mg of substantially amorphous Compound 1.

[00121] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 25 mg of amorphous Compound 1.

[00122] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 50 mg of amorphous Compound 1.

[00123] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about **75 mg** of amorphous Compound 1.

[00124] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and PVPAVA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 100 mg of amorphous Compound 1.

[00125] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 150 mg of amorphous Compound 1.

[00126] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 250 mg of amorphous Compound 1.

[00127] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
b. a filler;
c. a disintegrant;
d. a surfactant;
e. a binder;
f. a glidant; and
g. a lubricant,

wherein the solid dispersion comprises about 25 mg of substantially amorphous Compound 1.

[00128] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
b. a filler;
c. a disintegrant;
d. a surfactant;
e. a binder;
f. a glidant; and
g. a lubricant,

wherein the solid dispersion comprises about 50 mg of substantially amorphous Compound 1.

[00129] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
b. a filler;
c. a disintegrant;
d. a surfactant;
e. a binder;
f. a glidant; and
g. a lubricant,

wherein the solid dispersion comprises about 75 mg of substantially amorphous Compound 1.

[00130] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 100 mg of substantially amorphous Compound 1.

[00131] In one embodiment, the present invention provides **a** pharmaceutical composition comprising:

a. **a** solid dispersion of substantially amorphous Compound 1 and HPMCAS;

b. **a** filler;

c. **a** disintegrant;

d. **a** surfactant;

e. **a** binder;

f. **a** glidant; and

g. **a** lubricant,

wherein the solid dispersion comprises about 150 **mg** of substantially amorphous Compound 1.

[00132] In another embodiment, **the** present invention provides **a** pharmaceutical composition comprising:

a. **a** solid dispersion of substantially amorphous Compound 1 and HPMCAS;

b. **a** filler;

c. **a** disintegrant;

d. **a** surfactant;

e. **a** binder;

f. **a** glidant; and

g. **a** lubricant,

wherein the solid dispersion comprises about **250 mg** of substantially amorphous Compound 1.

[00133] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and HPMCAS;
b. a filler;
c. a disintegrant;
d. a surfactant;
e. a binder;
f. a glidant; and
g. a lubricant,

wherein the solid dispersion comprises about 25 mg of amorphous Compound 1.

[00134] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and HPMCAS;
b. a filler;
c. a disintegrant;
d. a surfactant;
e. a binder;
f. a glidant; and
g. a lubricant,

wherein the solid dispersion comprises about 50 mg of amorphous Compound 1.

[00135] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and HPMCAS;
b. a filler;
c. a disintegrant;
d. a surfactant;
e. a binder;
f. a glidant; and
g. a lubricant,

wherein the solid dispersion comprises about 75 mg of amorphous Compound 1.

[00136] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and HPMCAS;
b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 100 mg of amorphous Compound 1.

[00137] In one embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and HPMCAS;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 150 mg of amorphous Compound 1.

[00138] In another embodiment, the present invention provides a pharmaceutical composition comprising:

a. a solid dispersion of amorphous Compound 1 and HPMCAS;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant,

wherein the solid dispersion comprises about 250 mg of amorphous Compound 1.

[00139] In one embodiment, the pharmaceutical composition comprises a solid dispersion, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the solid dispersion comprises Compound 1 and a polymer.

[00140] In other embodiments, the pharmaceutical composition comprises a solid dispersion a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the solid dispersion comprises from about 45 wt% to about 65 wt% (e.g., about 50 wt%) of Compound 1 by weight of the dispersion and a polymer.

[00141] In some embodiments, the pharmaceutical composition comprises a solid dispersion a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the solid dispersion comprises from about 75 wt% to about 95 wt% (e.g., about 80 wt%) of Compound 1 by weight of the dispersion and a polymer.

[00142] Suitable solid dispersions of Compound 1, i.e., N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide, include, without limitation, those dispersions described in PCT publication no. WO 2007/079139, which is hereby incorporated by reference in its entirety.

[00143] In one embodiment, the pharmaceutical composition of the present invention comprises a solid dispersion of Compound 1. For example, the solid dispersion comprises substantially amorphous Compound 1, where Compound 1 is less than about 15% (e.g., less than about 10% or less than about 5%) crystalline, and at least one polymer. In another example, the solid dispersion comprises amorphous Compound 1, i.e., Compound 1 has about 0% crystallinity. The concentration of Compound 1 in the solid dispersion depends on several factors such as the amount of pharmaceutical composition needed to provide a desired amount of Compound 1 and the desired dissolution profile of the pharmaceutical composition.

[00144] Polymers useful in these solid dispersions are inert, pharmaceutically acceptable polymers that are at least partially soluble in water or biological fluids. Polymers can include homopolymers (e.g., polysaccharides) or copolymers (e.g., block copolymers). In one example, the solid dispersion comprises substantially amorphous or amorphous N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide and at least one polymer independently selected from hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose acetate succinate (HPMCAS), vinylpyrrolidone/vinyl acetate copolymer (PVP/VA), polyvinylpyrrolidone (PVP), methacrylic acid/methacrylate copolymers, hydroxypropyl cellulose (HPC), or any combination thereof. In another example, the solid dispersion comprises substantially amorphous or amorphous N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide and HPMCAS or PVP/VA.

[00145] In another embodiment, the pharmaceutical composition comprises a solid dispersion that contains substantially amorphous Compound 1 and HPMCAS or PVP/VA, in which the solid dispersion has a mean particle diameter, measured by light scattering (e.g., using a Malvern Mastersizer available from Malvern Instruments in England) of greater than about 5 μm (e.g., greater than about 6 μm, greater than about 7 μm, greater than about 8 μm,

or greater than about 10 μm). For example, the pharmaceutical composition comprises a solid dispersion that contains amorphous Compound 1 and HPMCAS or PVP/VA, in which the solid dispersion has a mean particle diameter, measured by light scattering, of greater than about 5 μm (e.g., greater than about 6 μm, greater than about 7 μm, greater than about 8 μm, or greater than about 10 μm). In another example, the pharmaceutical composition comprises a solid dispersion comprising substantially amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering, of from about 7 μm to about 25 μm. For instance, the pharmaceutical composition comprises a solid dispersion comprising amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering, of from about 7 μm to about 25 μm. In yet another example, the pharmaceutical composition comprises a solid dispersion comprising substantially amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering, of from about 10 μm to about 35 μm. For instance, the pharmaceutical composition comprises a solid dispersion comprising amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering, of from about 10 μm to about 35 μm. In another example, the pharmaceutical composition comprises a solid dispersion comprising substantially amorphous Compound 1 and HPMCAS or PVP/VA, in which the solid dispersion has a bulk density of about 0.10 g/cc or greater (e.g., 0.15 g/cc or greater, 0.17 g/cc or greater). For instance, the pharmaceutical composition comprising a solid dispersion comprising amorphous Compound 1 and HPMCAS or PVP/VA, in which the solid dispersion has a bulk density of about 0.10 g/cc or greater (e.g., 0.15 g/cc or greater, 0.17 g/cc or greater). In another instance, the pharmaceutical composition comprises a solid dispersion that comprises substantially amorphous Compound 1 and HPMCAS or PVP/VA, in which the solid dispersion has a bulk density of from about 0.10 g/cc to about 0.45 g/cc (e.g., from about 0.15 g/cc to about 0.42 g/cc, or from about 0.17 g/cc to about 0.40 g/cc). In still another instance, the pharmaceutical composition comprises a solid dispersion that includes amorphous Compound 1 and HPMCAS or PVP/VA, in which the solid dispersion has a bulk density of from about 0.10 g/cc to about 0.45 g/cc (e.g., from about 0.15 g/cc to about 0.42 g/cc, or from about 0.17 g/cc to about 0.40 g/cc). In another example, the pharmaceutical composition comprises a solid dispersion that comprises substantially amorphous Compound 1 and HPMCAS, in which the solid dispersion has a bulk density of from about 0.10 g/cc to about 0.45 g/cc (e.g., from about 0.15 g/cc to about 0.42 g/cc, or from about 0.17 g/cc to about 0.40 g/cc). For instance, the pharmaceutical composition includes a solid dispersion

that comprises amorphous Compound 1 and HPMCAS, in which the solid dispersion has a bulk density of from about 0.10 g/cc to about 0.45 g/cc (e.g., from about 0.15 g/cc to about 0.42 g/cc, or from about 0.17 g/cc to about 0.40 g/cc).

[00146] Alternative solid dispersions comprise substantially amorphous or amorphous Compound **1** and HPMCAS or PVP/VA, wherein substantially amorphous Compound 1 or amorphous Compound **1** is present in an amount of at least 20 wt% (e.g., at least 40 wt%, at least 45 wt%, at least 49 wt%, or at least 50 wt%) by weight of the solid dispersion. In some embodiments, the solid dispersion comprises HPMCAS or PVP/VA and from about 20 wt% to about 99 wt% (e.g., from about 40 wt% to about 90 wt%, from about 42 wt% to about 88 wt%, from about 45 wt% to about 85 wt%, or from about 50 wt% to about 80 wt%) of substantially amorphous or amorphous Compound 1 by weight of the solid dispersion. For example, the solid dispersion comprises HPMCAS or PVP/VA and from about 40 wt% to about 60 wt% (e.g., from about 42 wt% to about 57 wt%, from about 45 wt% to about 55 wt%, or from about 47 wt% to about 53 wt%) of substantially amorphous or amorphous Compound 1 by weight of the solid dispersion. In another example, the solid dispersion comprises HPMCAS or PVP/VA and from about 65 wt% to about 95 wt% (e.g., from about 67 wt% to about 92 wt%, from about 70 wt% to about 90 wt%, or from about 72 wt% to about 88 wt%) of substantially amorphous Compound 1 or amorphous Compound 1 by weight of the solid dispersion.

[00147] In other embodiments, the solid dispersion comprises 80 wt% or less (e.g., 60 wt% or less, 55 wt% or less, or 50 wt% or less) of polymer (e.g., HPMCAS, PVP/VA, PVP, methacrylic acid/methacrylate copolymer, HPC, or any combination thereof) by weight of solid dispersion. hi some instances, the solid dispersion comprises from about 1 wt% to about 80 wt% (e.g., from about 10 wt% to about 60 wt%) of polymer (e.g., HPMCAS, PVP/VA, PVP, methacrylic acid/methacrylate copolymer, HPC, or any combination thereof).

[00148] Some solid dispersions comprise from about 40 wt% to about 60 wt% (e.g., from about 42 wt% to about 57 wt%, from about 45 wt% to about 55 wt%, or from about 47 wt% to about 53 wt%) of substantially amorphous Compound 1 by weight of the solid dispersion and from about 60 wt% to about 40 wt% of polymer (e.g., HPMCAS, PVP/VA, PVP, methacrylic acid/methacrylate copolymer, HPC, or any combination thereof)- Alternative solid dispersions comprise from about 40 wt% to about 60 wt% (e.g., from about 42 wt% to about 57 wt%, from about 45 wt% to about 55 wt%, or from about 47 wt% to about 53 wt%) of amorphous Compound 1 by weight of the solid dispersion and from about

60 wt% to about 40 wt% of polymer (e.g., HPMCAS, PVP/VA, PVP, methacrylic acid/methacrylate copolymer, HPC, or any combination thereof).

[00149] Other solid dispersions comprise from about 65 wt% to about 95 wt% (e.g., from about 67 wt% to about 92 wt%, from about 70 wt% to about 90 wt%, or from about 72 wt% to about 88 wt%) of substantially amorphous Compound 1 by weight of the solid dispersion and from about 45 wt% to about 5 wt% of polymer (e.g., HPMCAS, PVP/VA, PVP, methacrylic acid/methacrylate copolymer, HPC, or any combination thereof). For instance, the solid dispersion comprises from about 65 wt% to about 95 wt% (e.g., from about 67 wt% to about 92 wt%, from about 70 wt% to about 90 wt%, or from about 72 wt% to about 88 wt%) of amorphous Compound 1 by weight of the solid dispersion and from about 45 wt% to about 5 wt% of polymer (e.g., HPMCAS, PVP/VA, PVP, methacrylic acid/methacrylate copolymer, HPC, or any combination thereof).

[00150] Solid dispersions useful in embodiments of the present invention can optionally comprise a surfactant. Suitable surfactants include sodium lauryl sulfate (SLS), sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate (e.g., Tween™), any combination thereof, or the like. In one example, the solid dispersion comprises less than 5 wt% (less than 3.0 wt%, less than 1.5 wt%, or less than 1.0 wt%) of surfactant by weight of solid dispersion. In another example, the solid dispersion comprises from about 0.30 wt% to about 0.80 wt% (e.g., from about 0.35 wt% to about 0.70 wt%, from about 0.40 wt% to about 0.60 wt%, or from about 0.45 wt% to about 0.55 wt%) of surfactant by weight of solid dispersion.

[00151] In alternative embodiments, the solid dispersion comprises from about 45 wt% to about 85 wt% of substantially amorphous or amorphous Compound 1, from about 0.45 wt% to about 0.55 wt% of SLS, and from about 14.45 wt% to about 55.55 wt% of HPMCAS or PVP/VA by weight of the solid dispersion. One exemplary solid dispersion contains about 50 wt% of substantially amorphous or amorphous Compound 1, about 49.5 wt% of HPMCAS or PVP/VA, and about 0.5 wt% of SLS, by weight of the solid dispersion. Another exemplary solid dispersion contains about 80 wt% of substantially amorphous or amorphous Compound 1, about 19.5 wt% of HPMCAS or PVP/VA, and about 0.5 wt% of SLS.

[00152] hi alternative embodiments, the solid dispersion comprises from about 45 wt% to about 85 wt% of substantially amorphous or amorphous Compound 1, from about 0.45 wt% to about 0.55 wt% of SLS, and from about 14.45 wt% to about 55.55 wt% of HPMCAS by weight of the solid dispersion. One exemplary solid dispersion contains about 50 wt% of

substantially amorphous or amorphous Compound 1, about 49.5 wt% of HPMCAS, and about 0.5 wt% of SLS, by weight of the solid dispersion Another exemplary solid dispersion contains about 80 wt% of substantially amorphous or amorphous Compound 1, about 19 5 wt% of HPMCAS or PVP/VA, and about 0.5 wt% of SLS.

[00153] In addition to the solid dispersion of Compound 1, pharmaceutical compositions of the present invention also comprise one or more excipients such as fillers, disintegrants, surfactants, binders, glidants, lubricants, colorants, or fragrances.

[00154] Fillers suitable for the present invention are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary fillers include lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e g., mannitol, sucrose, or the like), or any combination thereof. In one embodiment, the pharmaceutical composition comprises at least one filler in an amount of at least about 10 wt% (e.g., at least about 20 wt%, at least about 25 wt%, or at least about 27 wt%) by weight of the composition. For example, the pharmaceutical composition comprises from about 10 wt% to about 60 wt% (e.g., from about 20 wt% to about 55 wt%, from about 25 wt% to about 50 wt%, or from about 27 wt% to about 45 wt%) of filler, by weight of the composition. In another example, the pharmaceutical composition comprises at least about 20 wt% (e.g., at least 25 wt% or at least 27 wt%) of lactose, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 20 wt% to about 60 wt% (e.g., from about 25 wt% to about 55 wt% or from about 27 wt% to about 45 wt%) of lactose, by weight of the composition.

[00155] Disintegrants suitable for the present invention enhance the dispersal of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. Exemplary disintegrants include sodium croscarmellose, sodium starch glycolate, or a combination thereof. In one embodiment, the pharmaceutical composition comprises disintegrant in an amount of about 10 wt% or less (e.g., about 7 wt% or less, about 6 wt% or less, or about 5 wt% or less) by weight of the composition For example, the pharmaceutical composition comprises from about 1 wt% to about 10 wt% (e.g., from about 1.5 wt% to about 7.5 wt% or from about 2.5 wt% to about 6 wt%) of disintegrant, by weight of the composition. In another example, the pharmaceutical composition comprises about 10 wt% or less (e g., 7 wt% or less, 6 wt% or less, or 5 wt% or less) of sodium croscarmellose, by

weight of the composition. In yet another example, the pharmaceutical composition comprises from about 1 wt% to about 10 wt% (e.g., from about 1.5 wt% to about 7.5 wt% or from about 2.5 wt% to about 6 wt%) of sodium croscarmellose, by weight of the composition. In some examples, the pharmaceutical composition comprises from about 0.1% to about 10 wt% (e.g., from about 0.5 wt% to about 7.5 wt% or from about 1.5 wt% to about 6 wt%) of disintegrant, by weight of the composition. In still other examples, the pharmaceutical composition comprises from about 0.5% to about 10 wt% (e.g., from about 1.5 wt% to about 7.5 wt% or from about 2.5 wt% to about 6 wt%) of disintegrant, by weight of the composition.

[00156] Surfactants suitable for the present invention enhance the solubility of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. Exemplary surfactants include sodium lauryl sulfate (SLS), sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate (e.g., Tween™), any combination thereof, or the like. In one embodiment, the pharmaceutical composition comprises a surfactant in an amount of about 10 wt% or less (e.g., about 5 wt% or less, about 2 wt% or less, about 1 wt% or less, about 0.8 wt% or less, or about 0.6 wt% or less) by weight of the composition. For example, the pharmaceutical composition includes from about 10 wt% to about 0.1 wt% (e.g., from about 5 wt% to about 0.2 wt% or from about 2 wt% to about 0.3 wt%) of surfactant, by weight of the composition. In another example, the pharmaceutical composition comprises 10 wt% or less (e.g., about 5 wt% or less, about 2 wt% or less, about 1 wt% or less, about 0.8 wt% or less, or about 0.6 wt% or less) of sodium lauryl sulfate, by weight of the composition. hi yet another example, the pharmaceutical composition comprises from about 10 wt% to about 0.1 wt% (e.g., from about 5 wt% to about 0.2 wt% or from about 2 wt% to about 0.3 wt%) of sodium lauryl sulfate, by weight of the composition.

[00157] Binders suitable for the present invention enhance the tablet strength of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary binders include microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn (maize) starch, modified cellulose (e.g., hydroxymethyl cellulose), or any combination thereof. In one embodiment, the pharmaceutical composition comprises a binder in an amount of at least about 1 wt% (e.g., at least about 10 wt%, at least about 15 wt%, at least about 20 wt%, or at

least about 22 wt%) by weight of the composition. For example, the pharmaceutical composition comprises from about 5 wt% to about 50 wt% (e.g., from about 10 wt% to about 45 wt% or from about 20 wt% to about 45 wt%) of binder, by weight of the composition. In another example, the pharmaceutical composition comprises at least about 1 wt% (e.g., at least about 10 wt%, at least about 15 wt%, at least about 20 wt%, or at least about 22 wt%) of microcrystalline cellulose, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 5 wt% to about 50 wt% (e.g., from about 10 wt% to about 45 wt% or from about 20 wt% to about 45 wt%) of microcrystalline cellulose, by weight of the composition.

[00158] Glidants suitable for the present invention enhance the flow properties of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary glidants include colloidal silicon dioxide, talc, or a combination thereof. In one embodiment, the pharmaceutical composition comprises a glidant in an amount of 2 wt% or less (e.g., 1.75 wt%, 1.25 wt% or less, or 1.00 wt% or less) by weight of the composition. For example, the pharmaceutical composition comprises from about 2 wt% to about 0.05 wt% (e.g., from about 1.5 wt% to about 0.07 wt% or from about 1.0 wt% to about 0.09 wt%) of glidant, by weight of the composition. In another example, the pharmaceutical composition comprises 2 wt% or less (e.g., 1.75 wt%, 1.25 wt% or less, or 1.00 wt% or less) of colloidal silicon dioxide, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 2 wt% to about 0.05 wt% (e.g., from about 1.5 wt% to about 0.07 wt% or from about 1.0 wt% to about 0.09 wt%) of colloidal silicon dioxide, by weight of the composition.

[00159] Lubricants suitable for the present invention improve the compression and ejection of compressed pharmaceutical compositions from a die press and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, or the biological activity of the pharmaceutical composition. Exemplary lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, sodium stearyl fumarate, or any combination thereof. In one embodiment, the pharmaceutical composition comprises a lubricant in an amount of 2 wt% or less (e.g., 1.75 wt%, 1.25 wt% or less, or 1.00 wt% or less) by weight of the composition. For example, the pharmaceutical composition comprises from about 2 wt% to about 0.10 wt% (e.g., from about 1.5 wt% to about 0.15 wt% or from about 1.3 wt% to about 0.30 wt%) of lubricant, by

weight of the composition. In another example, the pharmaceutical composition comprises 2 wt% or less (e.g., 1.75 wt%, 1.25 wt% or less, or 1.00 wt% or less) of magnesium stearate, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 2 wt% to about 0.10 wt% (e.g., from about 1.5 wt% to about 0.15 wt% or from about 1.3 wt% to about 0.30 wt%) of magnesium stearate, by weight of the composition.

[00160] Pharmaceutical compositions of the present invention can optionally comprise one or more colorants, flavors, and/or fragrances to enhance the visual appeal, taste, and/or scent of the composition. Suitable colorants, flavors, or fragrances are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. In one embodiment, the pharmaceutical composition comprises a colorant, a flavor, and/or a fragrance. For example, the pharmaceutical composition comprises less than about 1 wt% (e.g., less than about 0.75 wt% or less than about 0.5 wt%) of each optionally ingredient, i.e., colorant, flavor and/or fragrance, by weight of the composition. In another example, the pharmaceutical composition comprises less than about 1 wt% (e.g., less than about 0.75 wt% or less than about 0.5 wt%) of a colorant. In still another example, the pharmaceutical composition comprises less than about 1 wt% (e.g., less than about 0.75 wt% or less than about 0.5 wt%) of a blue colorant (e.g., FD&C Blue # 1 and/or FD&C Blue #2 Aluminum Lake, commercially available from Colorcon, Inc. of West Point, PA.)

[00161] In some embodiments, the pharmaceutical composition can be made into tablets and the tablets can be coated with a colorant and optionally labeled with a logo, other image and/or text using a suitable ink. In still other embodiments, the pharmaceutical composition can be made into tablets and the tablets can be coated with a colorant, waxed, and optionally labeled with a logo, other image and/or text using a suitable ink. Suitable colorants and inks are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. The suitable colorants and inks can be any color and are water based or solvent based. In one embodiment, tablets made from the pharmaceutical composition are coated with a colorant and then labeled with a logo, other image, and/or text using a suitable ink. For example, tablets comprising pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of film coating comprising a

colorant. The colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink. In another example, tablets comprising pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of a film coating comprising a blue colorant (e.g., OPADRY® II, commercially available from Colorcon, Inc. of West Point, PA.). The colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a black ink (e.g., Opacode® WB, commercially available from Colorcon, Inc. of West Point, PA.). In another embodiment, tablets made from the pharmaceutical composition are coated with a colorant, waxed, and then labeled with a logo, other image, and/or text using a suitable ink. For example, tablets comprising pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of film coating comprising a colorant. The colored tablets can be waxed with Carnauba wax powder weighed out in the amount of about 0.01% w/w of the starting tablet core weight. The waxed tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink. In another example, tablets comprising pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of a film coating comprising a blue colorant (e.g., OPADRY® II, commercially available from Colorcon, Inc. of West Point, PA.). The colored tablets can be waxed with Carnauba wax powder weighed out in the amount of about 0.01% w/w of the starting tablet core weight. The waxed tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a black ink (e.g., Opacode® S-l-17823 - a solvent based ink, commercially available from Colorcon, Inc. of West Point, PA.).

[00162] One exemplary pharmaceutical composition comprises from about 5 wt% to about 50 wt% (e.g., from about 5 wt% to about 25 wt%, from about 15 wt% to about 40 wt%, or from about 30 wt% to about 50 wt%) of a solid dispersion, by weight of the composition, comprising from about 40 wt% to about 60 wt% of substantially amorphous Compound 1, by weight of the dispersion, and from about 60 wt% to about 40 wt% of a polymer, by weight of the dispersion; from about 25 wt% to about 50 wt% of a filler; from about 1 wt% to about 10 wt% of a disintegrant; from about 2 wt% to about 0.3 wt% of a surfactant; from about 5 wt% to about 50 wt% of a binder; from about 2 wt% to about 0.05 wt% of a glidant; and from about 2 wt% to about 0.1 wt% of a lubricant. Or, the pharmaceutical composition comprises from about 5 wt% to about 50 wt% (e.g., from about 5 wt% to about 25 wt%, from about 15 wt% to about 40 wt%, or from about 30 wt% to about 50 wt%) of a solid dispersion, by

weight of the composition, comprising from about 40 wt% to about 60 wt% of amorphous Compound 1, by weight of the dispersion, and from about 60 wt% to about 40 wt% of a polymer, by weight of the dispersion; from about 25 wt% to about 50 wt% of a filler; from about 1 wt% to about 10 wt% of a disintegrant; from about 2 wt% to about 0.3 wt% of a surfactant; from about 5 wt% to about 50 wt% of a binder; from about 2 wt% to about 0.05 wt% of a glidant; and from about 2 wt% to about 0.1 wt% of a lubricant.

[00163] Another exemplary pharmaceutical composition comprises from about 5 wt% to about 50 wt% (e.g., from about 5 wt% to about 25 wt%, from about 15 wt% to about 40 wt%, or from about 30 wt% to about 50 wt%) of a solid dispersion, by weight of the composition, comprising from about 70 wt% to about 90 wt% of substantially amorphous Compound 1, by weight of the dispersion, and from about 30 wt% to about 10 wt% of a polymer, by weight of the dispersion; from about 25 wt% to about 50 wt% of a filler; from about 1 wt% to about 10 wt% of a disintegrant; from about 2 wt% to about 0.3 wt% of a surfactant; from about 5 wt% to about 50 wt% of a binder; from about 2 wt% to about 0.05 wt% of a glidant; and from about 2 wt% to about 0.1 wt% of a lubricant. Or, the pharmaceutical composition comprises from about 5 wt% to about 50 wt% (e.g., from about 5 wt% to about 25 wt%, from about 15 wt% to about 40 wt%, or from about 30 wt% to about 50 wt%) of a solid dispersion, by weight of the composition, comprising from about 70 wt% to about 90 wt% of amorphous Compound 1, by weight of the dispersion, and from about 30 wt% to about 10 wt% of a polymer, by weight of the dispersion; from about 25 wt% to about 50 wt% of a filler; from about 1 wt% to about 10 wt% of a disintegrant; from about 2 wt% to about 0.3 wt% of a surfactant; from about 5 wt% to about 50 wt% of a binder; from about 2 wt% to about 0.05 wt% of a glidant; and from about 2 wt% to about 0.1 wt% of a lubricant.

[00164] One pharmaceutical composition of the present invention comprises about 15 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 50 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 49.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 35 wt% of microcrystalline cellulose by weight of the composition; about 43 wt% of lactose by weight of the composition; about 5 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.125 wt% of colloidal silicon dioxide by weight of the composition; and about 0.5 wt% of magnesium stearate by weight of the composition. Or, the pharmaceutical composition of the present invention comprises about 15 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 50 wt% of amorphous Compound 1 by weight of the

dispersion, about 49.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 35 wt% of microcrystalline cellulose by weight of the composition; about 43 wt% of lactose by weight of the composition; about 5 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.125 wt% of colloidal silicon dioxide by weight of the composition; and about 0.5 wt% of magnesium stearate by weight of the composition.

[00165] Another pharmaceutical composition of the present invention comprises about 31 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 50 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 49.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 25 wt% of microcrystalline cellulose by weight of the composition; about 38 wt% of lactose by weight of the composition; about 5 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.125 wt% of colloidal silicon dioxide by weight of the composition; and about 0.5 wt% of magnesium stearate by weight of the composition. Or, the pharmaceutical composition of the present invention comprises about 31 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 50 wt% of amorphous Compound 1 by weight of the dispersion, about 49.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 25 wt% of microcrystalline cellulose by weight of the composition; about 38 wt% of lactose by weight of the composition; about 5 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.125 wt% of colloidal silicon dioxide by weight of the composition; and about 0.5 wt% of magnesium stearate by weight of the composition.

[00166] Another pharmaceutical composition of the present invention comprises about 40 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of PVP/VA by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 27 wt% of microcrystalline cellulose by weight of the composition; about 27 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; about 1 wt% of magnesium stearate by weight of the composition, and about 0.4 wt% of colorant by weight of the composition. Or, the pharmaceutical composition of the present invention comprises about 40 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80

wt% of amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of PVP/VA by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 27 wt% of microcrystalline cellulose by weight of the composition; about 27 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; about 1 wt% of magnesium stearate by weight of the composition, and about 0.4 wt% of colorant by weight of the composition.

[00167] Another pharmaceutical composition of the present invention comprises about 40 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 27 wt% of microcrystalline cellulose by weight of the composition; about 27 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; about 1 wt% of magnesium stearate by weight of the composition, and about 0.4 wt% of colorant by weight of the composition. Or, the pharmaceutical composition of the present invention comprises about 40 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 27 wt% of microcrystalline cellulose by weight of the composition; about 27 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; about 1 wt% of magnesium stearate by weight of the composition, and about 0.4 wt% of colorant by weight of the composition.

[00168] In still another pharmaceutical composition of the present invention comprises about 34.5 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; about 1 wt% of magnesium stearate by weight of the composition.

[00169] In yet a further pharmaceutical composition of the present invention, a caplet shaped pharmaceutical tablet composition having a hardness of 9.5 Kp ± 15 percent comprises about 34 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30 wt% of lactose by weight of the composition; about 3 wt% of sodium croscaπnellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of decomposition; and about 1 wt% of magnesium stearate by weight of the composition. In certain embodiments, the caplet shaped pharmaceutical tablet contains 150 mg of Compound 1. In certain embodiments, the caplet shaped pharmaceutical tablet contains 100 mg of Compound 1.

[00170] In still another pharmaceutical composition of the present invention, a caplet shaped pharmaceutical tablet composition having an initial hardness of 11 Kp ± 20 percent comprises about 40 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In certain embodiments, the caplet shaped pharmaceutical tablet contains 150 mg of Compound 1.

[00171] In still another pharmaceutical composition of the present invention, a caplet shaped pharmaceutical tablet composition having an initial hardness of 11 Kp ± 20 percent comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscaπnellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the caplet shaped pharmaceutical tablet composition contains 100 mg of Compound 1. In other

aspects, the caplet shaped pharmaceutical tablet composition includes a colorant coating and a printed logo or text. In some embodiments of this aspect, the caplet shaped pharmaceutical tablet composition includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In certain embodiments, the caplet shaped pharmaceutical tablet contains 150 mg of Compound 1.

[00172] In another pharmaceutical composition of the present invention, a caplet shaped pharmaceutical tablet composition having an initial hardness of between about 6 and 16 Kp comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the caplet shaped pharmaceutical tablet composition contains 100 mg of Compound 1. In some further aspects, the caplet shaped pharmaceutical tablet composition comprises a colorant coated, a wax coating, and a printed logo or text. In some embodiments of this aspect, the caplet shaped pharmaceutical tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In some instances, the colorant coating is blue OPADRY® II. In some instances, the wax coating comprises Carnauba wax. In certain aspects, the ink for the printed logo or text is a solvent based ink. In some aspects, the caplet shaped pharmaceutical tablet composition contains 150 mg of Compound **1.**

[00173] In still another pharmaceutical composition of the present invention, a pharmaceutical tablet composition having an initial hardness of between about 9 and 21 Kp comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some embodiments, the caplet shaped pharmaceutical tablet composition contains 150 mg of Compound 1. hi some

aspects, the caplet shaped pharmaceutical tablet composition further comprises a colorant coated, a wax coating, and a printed logo or text. hi some instances, the tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In still other instances, the wax coating comprises Carnauba wax. In some embodiments, the ink for the printed logo or text is a solvent based ink. hi some aspects, the caplet shaped pharmaceutical tablet composition contains 100 mg of Compound **1.**

[00174] In yet a further pharmaceutical composition of the present invention, a pharmaceutical composition comprises about 34 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In certain embodiments, the pharmaceutical composition contains 150 mg of Compound 1. In other embodiments, the pharmaceutical composition contains 100 mg of Compound **1.**

[00175] In still another pharmaceutical composition of the present invention, a pharmaceutical composition comprises about 40 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In certain embodiments, the pharmaceutical composition contains 150 mg of Compound 1. hi other embodiments, the pharmaceutical composition contains 100 mg of Compound 1.

[00176] In still another pharmaceutical composition of the present invention, a pharmaceutical composition comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the

dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the pharmaceutical composition contains 100 mg of Compound 1. In other embodiments, the pharmaceutical composition contains 150 mg of Compound 1. In other aspects, the pharmaceutical composition is formed as a tablet composition that includes a colorant coating and a printed logo or text. In some embodiments of this aspect, the pharmaceutical tablet composition includes a blue OPADRY® II coating and a water or solvent based ink logo or text.

[00177] In another pharmaceutical composition of the present invention, a pharmaceutical composition comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the pharmaceutical tablet contains 100 mg of Compound 1. In other embodiments, the pharmaceutical composition contains 150 mg of Compound 1. In some further aspects, the pharmaceutical composition is formed as a tablet and comprises a colorant coated, a wax coating, and a printed logo or text. In some embodiments of this aspect, the pharmaceutical tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In some instances, the colorant coating is blue OPADRY® II. hi some instances, the wax coating comprises Carnauba wax. In certain aspects, the ink for the printed logo or text is a solvent based ink.

[00177] It is also noted that pharmaceutical compositions of the present invention can be processed into a tablet form, capsule form, or suspension that is suited for oral administration or can be reconstituted in an aqueous solvent (e.g., DI water or saline) for oral, IV, or inhalation (e.g., nebulizer) administration.

[00178] Another aspect of the present invention provides a pharmaceutical composition consisting of a tablet that includes a CF potentiator API (e.g., a solid dispersion of N-[2,4-

bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a dissolution of at least about 50% (e.g., at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 99%) in about 30 minutes. In one example, the pharmaceutical composition consists of a tablet that includes a CF potentiator API (e.g., a solid dispersion of Compound 1) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a dissolution of from about 50% to about 100% (e.g., from about 55% to about 95% or from about 60% to about 90%) in about 30 minutes. In another example, the pharmaceutical composition consists of a tablet that comprises a solid dispersion comprising substantially amorphous or amorphous Compound 1 and HPMCAS or PVP/VA; and, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a dissolution of at least about 50% (e.g., at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 99%) in about 30 minutes. In still another example, the pharmaceutical composition consists of a tablet that comprises a solid dispersion comprising substantially amorphous or amorphous Compound 1 and HPMCAS or PVP/VA; and, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a dissolution of from about 50% to about 100% (e.g., from about 55% to about 95% or from about 60% to about 90%) in about 30 minutes.

[00179] In one embodiment, the tablet comprises a solid dispersion comprising at least about 25 mg (e.g., at least about 30 mg, at least about 40 mg, or at least about 50 mg) of substantially amorphous or amorphous Compound 1; and PVP/VA and SLS. In another embodiment, the tablet comprises a solid dispersion comprising at least about 25 mg (e.g., at least about 30 mg, at least about 40 mg, at least about 50 mg, at least about 100 mg, or at least 150 mg) of substantially amorphous or amorphous Compound 1; and HPMCAS and SLS.

[00180] Dissolution can be measured with a standard USP Type II apparatus that employs a dissolution media of 0.6% sodium lauryl sulfate dissolved in 900 mL of DI water, stirring at about 50-75 rpm at a temperature of about 37 ^{0}C. A single experimental tablet is tested in each test vessel of the apparatus. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.7% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8), stirring at about 65 rpm at a

temperature of about 37 ^{0}C. A single experimental tablet is tested in each test vessel of the apparatus. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.5% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8), stirring at about 65 rpm at a temperature of about 37 ^{0}C. A single experimental tablet is tested in each test vessel of the apparatus.

[00181] Another aspect of the present invention provides a pharmaceutical composition consisting of a tablet that comprises a CF potentiator API (e.g., a solid dispersion of Compound 1) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a hardness of at least about 5 Kp. In one example, the pharmaceutical composition consists of a tablet that comprises a CF potentiator API (e.g., a solid dispersion of Compound 1) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a hardness of at least about 5 Kp (e.g., at least about 5.5, at least about 6 Kp, or at least about 7 Kp).

[00182] III. METHOD OF PRODUCING A PHARMACEUTICAL COMPOSITION

[00183] Another aspect of the present invention provides a method of producing a pharmaceutical composition comprising providing an admixture of a solid dispersion of substantially amorphous or amorphous N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, and compressing the admixture into a tablet having a dissolution of at least about 50% in about 30 minutes.

[00184] Each of the ingredients of this admixture is described above and in the Examples below. Furthermore, the admixture can comprise optional additives such as one or more colorants, one or more flavors, and/or one or more fragrances as described above and in the Examples below. And, the relative concentrations (e.g., wt%) of each of these ingredients (and any optional additives) in the admixture is also presented above and in the Examples below. The ingredients constituting the admixture can be provided sequentially or in any combination of additions; and, the ingredients or combination of ingredients can be provided in any order. hi one embodiment the lubricant is the last component added to the admixture.

[00185] hi one embodiment, the admixture comprises a solid dispersion of substantially amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a

filler, wherein each of these ingredients is provided in a powder form (e.g., provided as particles having a mean diameter, measured by light scattering, of 250 μm or less (e.g., 150 μm or less, 100 μm or less, 50 μm or less, 45 μm or less, 40 μm or less, or 35 μm or less)). For instance, the admixture comprises a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, wherein each of these ingredients is provided in a powder form (e.g , provided as particles having a mean diameter, measured by light scattering, of 250 μm or less (e.g., 150 μm or less, 100 μm or less, 50 μm or less, 45 μm or less, 40 μm or less, or 35 μm or less)).

[00186] In another embodiment, the admixture comprises a solid dispersion of substantially amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, wherein each of these ingredients is substantially free of water. Each of the ingredients comprises less than 5 wt% (e.g , less than 2 wt%, less than 1 wt%, less than 0.75 wt%, less than 0.5 wt%, or less than 0.25 wt%) of water by weight of the ingredient. For instance, the admixture comprises a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, wherein each of these ingredients is substantially free of water. To wit, each of the ingredients comprises less than 5 wt% (e.g., less than 2 wt%, less than 1 wt%, less than 0.75 wt%, less than 0.5 wt%, or less than 0.25 wt%) of water by weight of the ingredient.

[00187] In another embodiment, compressing the admixture into a tablet is accomplished by filling a form (e g., a mold) with the admixture and applying pressure to admixture This can be accomplished using a die press or other similar apparatus. It is also noted that the application of pressure to the admixture in the form can be repeated using the same pressure during each compression or using different pressures during the compressions. In another example, the admixture is compressed using a die press that applies sufficient pressure to form a tablet having a dissolution of about 50% or more at about 30 minutes (e.g., about 55% or more at about 30 minutes or about 60% or more at about 30 minutes). For instance, the admixture is compressed using a die press to produce a tablet hardness of at least about 5 Kp (at least about 5.5 Kp, at least about 6 Kp, at least about 7 Kp, at least about 11 Kp, or at least 21Kp). In some instances, the admixture is compressed to produce a tablet hardness of between about 6 and 21 Kp.

[00188] In some embodiments, tablets comprising a pharmaceutical composition as described herein can be coated with about 3.0 wt% of a film coating comprising a colorant by weight of the tablet. In certain instances, the colorant suspension or solution used to coat the

tablets comprises about 20%w/w of solids by weight of the colorant suspension or solution. In still further instances, the coated tablets can be labeled with a logo, other image or text.

[00189] In another embodiment, the method of producing a pharmaceutical composition comprises providing an admixture of a solid dispersion of substantially amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler; mixing the admixture until the admixture is substantially homogenous, and compressing the admixture into a tablet as described above or in the Examples below. Or, the method of producing a pharmaceutical composition comprises providing an admixture of a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler; mixing the admixture until the admixture is substantially homogenous, and compressing the admixture into a tablet as described above or in the Examples below. For example, the admixture is mixed by stirring, blending, shaking, or the like using hand mixing, a mixer, a blender, any combination thereof, or the like. When ingredients or combinations of ingredients are added sequentially, mixing can occur between successive additions, continuously throughout the ingredient addition, after the addition of all of the ingredients or combinations of ingredients, or any combination thereof. The admixture is mixed until it has a substantially homogenous composition.

[00190] IV. ADMINISTRATION OF A PHARMACEUTICAL FORMULATION

[00191] In another aspect, the invention also provides a method of treating or lessening the severity of a disease in a patient comprising administering to said patient one of the compositions as defined herein, and said disease is selected from cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease,

Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear plasy, Pick's disease, several polyglutamine neurological disorders such as Huntington's, spinocerebullar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt- Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, or Sjogren's disease, Osteoporosis, Osteopenia, Gorham's Syndrome, chloride channelopathies such as myotonia congenita (Thomson and Becker forms), Banter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, and Primary Ciliary Dyskinesia (PCD), a term for inherited disorders of the structure and/or function of cilia, including PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary aplasia.

[00192] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1.

[00193] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 50 mg of substantially amorphous or amorphous Compound 1.

[00194] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 75 mg of substantially amorphous or amorphous Compound 1.

[00195] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about lOOmg of substantially amorphous or amorphous Compound 1.

[00196] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day the

composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 150 mg of substantially amorphous or amorphous Compound 1.

[00197] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 250 mg of substantially amorphous or amorphous Compound 1.

[00198] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1.

[00199] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 50 mg of substantially amorphous or amorphous Compound 1.

[00200] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 75 mg of substantially amorphous or amorphous Compound 1.

[00201] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 100 mg of substantially amorphous or amorphous Compound 1.

[00202] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 150 mg of substantially amorphous or amorphous Compound 1.

[00203] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient twice per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 250 mg of substantially amorphous or amorphous Compound **1.**

[00204] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once every 12 hours. The composition comprises a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1.

[00205] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once every 12 hours. The composition comprises a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 50 mg of substantially amorphous or amorphous Compound 1.

[00206] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once every 12 hours. The composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 75 mg of substantially amorphous or amorphous Compound 1.

[00207] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once every 12 hours day. The composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 100 mg of substantially amorphous or amorphous Compound 1.

[00208] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once every 12 hours. The composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 150 mg of substantially amorphous or amorphous Compound 1.

[00209] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once every 12 hours. The composition comprising a solid dispersion of substantially amorphous or amorphous

Compound 1, in which the solid dispersion comprises at least about 250 mg of substantially amorphous or amorphous Compound 1.

[00210] In still other aspects of the present invention, a pharmaceutical composition as described herein is orally administered to a patient once every 24 hours.

[00211] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1.

[00212] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 50 mg of substantially amorphous or amorphous Compound **1.**

[00213] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 75 mg of substantially amorphous or amorphous Compound 1.

[00214] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 100 mg of substantially amorphous or amorphous Compound 1.

[00215] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 150 mg of substantially amorphous or amorphous Compound 1.

[00216] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 250 mg of substantially amorphous or amorphous Compound 1.

[00217] Another aspect of the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition containing a solid dispersion of substantially amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, each of which is described above and in the Examples below, wherein the solid dispersion comprises at least 25 mg (e.g., at least 35 mg, at least 40 mg, or at least 45 mg) of substantially amorphous Compound 1.

[00218] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 25 mg of substantially amorphous or amorphous Compound 1;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00219] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 50 mg of substantially amorphous or amorphous Compound 1;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00220] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 75 mg of substantially amorphous or amorphous Compound 1;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00221] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 100 mg of substantially amorphous or amorphous Compound 1;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00222] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 150 mg of substantially amorphous or amorphous Compound 1;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00223] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 250 mg of substantially amorphous or amorphous Compound 1;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00224] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 25 mg of substantially amorphous or amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00225] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 50 mg of substantially amorphous or amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00226] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 75 mg of substantially amorphous or amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00227] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 100 mg of substantially amorphous or amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00228] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 150 mg of substantially amorphous or amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00229] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 250 mg of substantially amorphous or amorphous Compound 1 and PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00230] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 25 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00231] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 50 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00232] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 75 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. **a** glidant; and

g. **a** lubricant.

[00233] In some embodiments, the present invention provides a method of administering a pharmaceutical composition comprising orally administering to a patient at least one tablet comprising:

a. a solid dispersion comprising about 100 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

[00234] In some embodiments, **the** present invention provides **a** method of administering **a** pharmaceutical composition comprising orally administering to **a** patient **at** least one tablet comprising:

a. **a** solid dispersion comprising about 150 **mg** of substantially amorphous or amorphous Compound 1 and HPMCAS;

b. **a** filler;

c. **a** disintegrant;

d. **a** surfactant;

e. **a** binder;

f. **a** glidant; and

g. **a** lubricant.

[00235] In some embodiments, **the** present invention provides **a** method of administering **a** pharmaceutical composition comprising orally administering to **a** patient **at** least one tablet comprising:

a. **a** solid dispersion comprising about **250 mg** of substantially amorphous or amorphous Compound 1 and HPMCAS;

b. **a** filler;

c. **a** disintegrant;

d. **a** surfactant;

e. **a** binder;

f. **a** glidant; and

g. a lubricant.

[00236] In some embodiments, the present invention provides for a method of orally administering the pharmaceutical composition described herein once a day. In other embodiments, the present invention provides for a method of orally administering the pharmaceutical composition described herein twice a day.

[00237] Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1. In some embodiments, the tablet is orally administered to the patient once per day. In another method, the administration comprises orally administering to a patient twice per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 25 mg of substantially amorphous or amorphous Compound 1. Some tablets useful in this method comprise a solid dispersion containing at least about 50 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient twice per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 50 mg of substantially amorphous or amorphous Compound 1. Some tablets useful in this method comprise a solid dispersion containing at least about 75 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient twice per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler-, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 75 mg of substantially amorphous or amorphous Compound 1. Another aspect of the present invention provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion comprises at least about 100 mg of substantially amorphous or amorphous Compound 1. In some embodiments, the tablet is orally administered to the patient once per day. In another method,

the administration comprises orally administering to a patient twice per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 100 mg of substantially amorphous or amorphous Compound 1. Other tablets useful in this method comprise a solid dispersion containing at least about 150 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient twice per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 150 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient at least once per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 250 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient once per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 250 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient twice per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 250 mg of substantially amorphous or amorphous Compound 1.

[00238] In one embodiment, the method of administering a pharmaceutical composition including orally administering to a patient at least once per day at least one tablet including a pharmaceutical composition containing a solid dispersion of amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, each of which is described above and in the Examples below, wherein the solid dispersion comprises at least 25 mg (e.g., at least 35 mg, at least 40 mg, or at least 45 mg) of substantially amorphous Compound 1.

[00239] In one embodiment, the method of administering a pharmaceutical composition includes orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition containing a solid dispersion of substantially amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, wherein

the solid dispersion comprises from about **30 mg** to about 300 **mg** (e.g., from about **40 mg** to about 280 **mg** or from about **45 mg** to about 260 **mg,** or from about **50 mg** to about 200 **mg)** of substantially amorphous Compound 1 **Or,** the method of administering **a** pharmaceutical composition includes orally administering to a patient at least once per **day** at least one tablet comprising a pharmaceutical composition containing a solid dispersion of amorphous Compound **1,** a filler, a binder, **a** glidant, a disintegrant, a surfactant, and **a** lubricant, wherein the solid dispersion comprises from about **30 mg** to about 300 **mg (e.g.,** from about **40 mg** to about 280 **mg** or from about **45 mg** to about 260 **mg,** or from about **50 mg** to about 200 **mg)** of amorphous Compound **1.**

[00240] In another embodiment, the method of administering a pharmaceutical composition includes orally administering to a patient once per day at least one tablet comprising a pharmaceutical composition containing a solid dispersion of Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, each of which is described above and in the Examples below, wherein the solid dispersion comprises at least 25 mg (e g , at least 35 mg, at least 40 mg, at least 45 mg, at least 75 mg, at least about 100 mg, at least about 150 mg, or at least 250 mg,) of substantially amorphous Compound 1 or amorphous Compound 1. For example, the method of administering a pharmaceutical composition includes orally administering to a patient once per day one tablet comprising a pharmaceutical composition containing a solid dispersion of Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, wherein the solid dispersion comprises at least 75 mg (e.g., at least 100 mg, at least 125 mg, at least 140 mg, at least 150 mg, or at least 250 mg) of substantially amorphous Compound 1 or amorphous Compound 1. In another example, the method of administering a pharmaceutical composition includes orally administering to a patient once per day a plurality of tablets (e g , two tablets, three tablets, four or five tablets), wherein each tablet comprises a pharmaceutical composition compπsmg a solid dispersion of substantially amorphous Compound 1 or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, wherein the solid dispersion comprises at least 25 mg (e g., at least 35 mg, at least 40 mg, at least 45 mg, at least 75 mg, at least about 150 mg, or at least 250 mg,) of substantially amorphous Compound 1 or amorphous Compound 1.

[00241] In another embodiment, the method of administering a pharmaceutical composition includes orally administering to a patient twice per day at least one tablet comprising a pharmaceutical composition containing a solid dispersion of Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, each of which is described above and in the Examples below, wherein the solid dispersion comprises at least 25 mg (e.g., at least 35

mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 75 mg, at least about 150 mg, or at least 250 mg,) of substantially amorphous Compound 1 or amorphous Compound 1. For example, the method of administering a pharmaceutical composition includes orally administering to a patient twice per day one tablet comprising a pharmaceutical composition containing a solid dispersion of Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, wherein the solid dispersion comprises at least 75 mg (e.g., at least 100 mg, at least 125 mg, at least 140 mg, at least 150 mg, or at least 250 mg) of substantially amorphous Compound 1 or amorphous Compound 1. In another example, the method of administering a pharmaceutical composition includes orally administering to a patient twice per day a plurality of tablets (e.g., two tablets, three tablets, four or five tablets), wherein each tablet comprises a pharmaceutical composition comprising a solid dispersion of substantially amorphous Compound 1 or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, wherein the solid dispersion comprises at least 25 mg (e.g., at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 75 mg, at least about 150 mg, or at least 250 mg,) of substantially amorphous Compound 1 or amorphous Compound 1.

[00242] It is noted that the methods of administration of the present invention can optionally include orally administering a beverage (water, milk, or the like), food, and/or additional pharmaceutical compositions including additional APIs. When the method of administration includes orally administering a beverage (water, milk, or the like), food (including a standard high fat high calorie CF meal or snack), and/or additional pharmaceutical compositions including additional APIs, the oral administration of the beverage, food, and/or additional API can occur concurrently with the oral administration of the tablet, prior to the oral administration of the tablet, and/or after the administration of the tablet. For instance, in one example, the method of administering a pharmaceutical composition includes orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition containing a solid dispersion of substantially amorphous Compound 1 or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, a lubricant, and a second API. In another example, the method of administering a pharmaceutical composition includes orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition comprising a solid dispersion of substantially amorphous Compound 1 or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, wherein the solid dispersion comprises at least 25 mg (e.g., at least 35 mg, at least 45 mg, or at least 50 mg) of substantially amorphous

Compound 1 or amorphous Compound 1, and orally administering to a patient at least once per day a second pharmaceutical composition comprising a second API. In still other examples, the method of administering a pharmaceutical composition includes orally administering to a patient every 12 hours at least one tablet comprising a pharmaceutical composition as described herein, in which the tablet is administered about 30 minutes after consuming a high fat, high calorie CF meal or snack.

[00243] It will also be appreciated that the compound and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compound and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00244] In one embodiment, the additional agent is selected from a mucolytic agent, bronchodialator, an anti-biotic, an anti-infective agent, an anti-inflammatory agent, a CFTR modulator other than Compound 1 of the present invention, or a nutritional agent.

[00245] In one embodiment, the additional agent is an antibiotic. Exemplary antibiotics useful herein include tobramycin, including tobramycin inhaled powder (TIP), azithromycin, aztreonam, including the aerosolized form of aztreonam, amikacin, including liposomal formulations thereof, ciprofloxacin, including formulations thereof suitable for administration by inhalation, levoflaxacin, including aerosolized formulations thereof, and combinations of two antibiotics, e.g., fosfomycin and tobramycin.

[00246] In another embodiment, the additional agent is a mucolyte. Exemplary mucolytes useful herein includes Pulmozyme®.

[00247] In another embodiment, the additional agent is a bronchodialator. Exemplary bronchodialtors include albuterol, metaprotenerol sulfate, pirbuterol acetate, salmeterol, or tetrabuline sulfate.

[00248] In another embodiment, the additional agent is effective in restoring lung airway surface liquid. Such agents improve the movement of salt in and out of cells, allowing mucus in the lung airway to be more hydrated and, therefore, cleared more easily. Exemplary such agents include hypertonic saline, denufosol tetrasodium ([[(3S, 5R)-5-(4-amino-2-oxopyrimidin-l-yl)-3-hydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl] [[[(2R,3S,4R,5R)-5-(2,4-dioxopyrimidin-l-yl)-3, 4-dihydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl]oxy-hydroxyphosphoryl] hydrogen phosphate), or bronchitol (inhaled formulation of mannitol).

[00249] In another embodiment, the additional agent is an anti-inflammatory agent, i.e., an agent that can reduce the inflammation in the lungs. Exemplary such agents useful herein include ibuprofen, docosahexanoic acid (DHA), sildenafil, inhaled glutathione, pioglitazone, hydroxychloroquine, or simavastatin.

[00250] In another embodiment, the additional agent is a CFTR modulator other than compound 1, i.e., an agent that has the effect of modulating CFTR activity. Exemplary such agents include ataluren ("PTC124®"; 3-[5-(2-fluorophenyl)-l,2,4-oxadiazol-3-yl]benzoic acid), sinapultide, lancovutide, depelestat (a human recombinant neutrophil elastase inhibitor), cobiprostone (7-{(2R, 4aR, 5R, 7aR)-2-[(3S)-l,l-difluoro-3-methylpentyl]-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl}heptanoic acid), or (3-(6-(l-(2,2-difluorobenzo[d][l,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid. hi another embodiment, the additional agent is (3-(6-(l-(2,2-difluorobenzo[d][l,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid.

[00251] In another embodiment, the additional agent is a nutritional agent. Exemplary such agents include pancrelipase (pancreating enzyme replacement), including Pancrease®, Pancreacarb®, Ultrase®, or Creon®, Liprotomase® (formerly Trizytek®), Aquadeks®, or glutathione inhalation. In one embodiment, the additional nutritional agent is pancrelipase.

[00252] VI. EXAMPLES

[00253] hi order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[00254] A. Manufacture of Tablets

[00255] Intermediate **A**

[00256] A solvent system of methylethyl ketone (MEK) and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was added to a reactor equipped with a

magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HG grade, commercially available from Biddle Sawyer Corporation in New York, New York or Shin-Etsu Chemical Co. in Tokyo, Japan), sodium lauryl sulfate (SLS), and N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 49.5 wt% hypromellose acetate succinate / 0.5 wt% sodium lauryl sulfate (SLS) / 50 wt% N-[2,4-bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 20 wt% dissolved solids. The actual amounts of ingredients and amounts of solvents used to generate this mixture are recited in Table Al, below:

Table Al: Solid Spray Dispersion Ingredients for Intermediate A

	Units	Batch
N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]- 1,4-dihydro-4-oxoquinoline-3-carboxamide	**Kg**	9.00
hypromellose acetate succinate	**Kg**	8.91
SLS	**Kg**	0.09
Total Solids	**Kg**	**18.00**
MEK	**Kg**	64.80
Water	**Kg**	7.20
Total Solvents	**Kg**	**72.00**
Total Spray Solution **Weight**	**Kg**	**90.00**

[00257] The mixture was mixed at room temperature until it was substantially homogenous and all components were substantially dissolved.

[00258] A spray drier, Niro Mobile Minor Spray Dryer with extended chamber, fitted with a 1.3 mm two-fluid atomizer situated approximately 5 cm from the top of the spray drying vessel was used in accordance with the spray dry parameters in Table A2.

Table A2: Dry spray process parameters used to generate Intermediate A.

Parameter	Value
Atomization Flow Rate	10.5 kg/hr
Feed Flow Rate	7 kg/hr
Inlet Temperature	~105 °C
Outlet Temperature	40 °C ± 5 °C
Vacuum Dryer Temperature	55 °C
Vacuum Drying Time	24 hours

[00259] An inertial cyclone separated the product from the process gas and solvent vapors, and a filter bag collected the fine particles not separated by the cyclone. The resultant product was transferred to a vacuum tray dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate A.

[00260] Intermediate **B**

[00261] A solvent system of MEK, DI water, and acetone, formulated according to the ratio 65 wt% MEK / 9 wt% DI water / 26 wt% acetone, was heated to a temperature of 20 - 30 ^{0}C in a reactor equipped with a magnetic stirrer and thermal circuit. Into this solvent system, a copolymer of vinylpyrrolidone and vinylacetatepolyvinylpyrrolidone (PVP VA-64 commercially available from Shanghai Lite Chemical Technology Co., Ltd. Shanghai, China), SLS, and N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% PVPVA-64 / 0.5 wt% sodium lauryl sulfate / 80 wt% N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 11.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table Bl, below:

Table Bl: Solid Spray Dispersion Ingredients for Intermediate B

	Units	Batch 1
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	24.00
PVPVA-64	Kg	5.850
SLS	Kg	0.1500
Total Solids	**Kg**	**30.00**
MEK	Kg	150.1
Water	Kg	20.78
Acetone	Kg	60.03
Total Solvents	**Kg**	**230.9**
Total Spray Solution Weight	**Kg**	**260.9**

[00262] The mixture was maintained at a temperature of 20 - 30 ^{0}C and mixed until it was substantially homogenous and all components were substantially dissolved.

[00263] A spray drier, Niro Production Minor Spray Dryer, fitted with pressure nozzles (Spray Systems Maximum Passage series SK-MFP having orifice size 72), was used under normal spray drying mode, following the dry spray process parameters recited in Table B2, below. The spray nozzle was situated approximately 5 cm from the top of the spray drying vessel.

Table B2: Dry spray process parameters used to generate Intermediate **B.**

Parameter	**Value**
Feed Pressure	30 – 100 bar
Feed Flow Rate	15 – 25 Kg/hr
Inlet Temperature	85 – 125 °C
Outlet Temperature	45 – 75 °C
Vacuum Dryer Temperature	55 °C ± 5 °C

I Vacuum Drying Time	I 24 hours

[00264] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product was transferred to a tray vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate **B.**

[00265] Intermediate **C:**

[00266] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 ^{0}C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% hypromellose acetate succinate / 0.5 wt% SLS / 80 wt% N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]- 1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 12.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table Cl, below:

Table Cl: Solid Spray Dispersion Ingredients for Intermediate C.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	24.00
HPMCAS	Kg	5.850
SLS	Kg	0.1500
Total Solids	**Kg**	**30.00**
MEK	Kg	189.0
Water	Kg	21.00
Total Solvents	**Kg**	**210.0**
Total Spray Solution Weight	**Kg**	**260.9**

[00267] The mixture was maintained at a temperature of 20 - 30 °C and mixed until it was substantially homogenous and all components were substantially dissolved.

[00268] A spray drier, Niro Production Minor Spray Dryer, fitted with pressure nozzles (Spray Systems Maximum Passage series SK-MFP having orifice size 72), was used under normal spray drying mode, following the dry spray process parameters recited in Table C2, below. The spray nozzle was situated approximately 5 cm from the top of the spray drying vessel.

Table C2: Dry spray process parameters used to generate Intermediate C.

Parameter	Target Value
Feed Pressure	30 – 100 bar
Feed Flow Rate	15 – 25 Kg/hr
Inlet Temperature	85 – 125 °C

Outlet Temperature	45 – 75 °C
Vacuum Dryer Temperature	55 °C (+/-5 °C)
Vacuum Drying Time	24 hours

[00269] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product was transferred to a tray vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate C.

[00270] Intermediate **D:**

[00271] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 ^{0}C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% hypromellose acetate succinate /0.5 wt% SLS / 80 wt% N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 12.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table Dl, below:

Table Dl: Solid Spray Dispersion Ingredients for Intermediate D.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	1.60
HPMCAS	Kg	0.390
SLS	Kg	0.010
Total Solids	Kg	**2.00**
MEK	Kg	12.6
Water	Kg	1.40
Total Solvents	Kg	**14.0**
Total Spray Solution Weight	Kg	**16.0**

[00272] The mixture was maintained at a temperature of 20 - 30 ^{0}C and mixed until it was substantially homogenous and all components were substantially dissolved.

[00273] A spray drier, Niro Mobil Minor Spray Dryer fitted with a 1.0mm two fluid nozzle, was used in normal spray drying mode, following the dry spray process parameters recited in Table D2, below.

Table D2: Dry spray process parameters used to generate Intermediate **D.**

Parameter	**Value**
Atomization Ratio	1.5
Feed Flow Rate	4.5 – 5.0 Kg/hr
Outlet Temperature	60°C
Vacuum Dryer Temperature	55 °C (+/-5 °C)

I Vacuum Drying Time	I 192 hours

[00274] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product contained 6.3% MEK and 0.7% Water and had a mean particle size of 7um and a bulk density of O.23g/cc. The wet product was transferred to a tray vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate D. The dry Intermediate D contained <0.5% MEK and 0.3% Water.

[00275] Intermediate E:

[00276] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 °C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% hypromellose acetate succinate / 0.5 wt% SLS / 80 wt% N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]- 1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 10.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table El, below:

Table El: Solid Spray Dispersion Ingredients for Intermediate E.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	43.93
HPMCAS	Kg	10.72
SLS	Kg	0.2750
Total Solids	**Kg**	**54.93**
MEK	Kg	421.8
Water	Kg	46.90
Total Solvents	**Kg**	**468.7**
Total Spray Solution Weight	**Kg**	**523.6**

[00277] The mixture temperature was adjusted to a range of 30 - 45 ^{0}C and mixed until it was substantially homogenous and all components were substantially dissolved.

[00278] A spray drier, Niro PSD4 Commercial Spray Dryer, fitted with pressure nozzles (Spray Systems Maximum Passage series SK-MFP having orifice/core size 54/21, 53/21 or 52/21) equipped with anti-bearding cap, was used under normal spray drying mode, following the dry spray process parameters recited in Table E2, below.

Table E2: Dry spray process parameters used to generate Intermediate E.

IParameter	**IValue**	**I**

Feed Pressure	20 – 40 bar
Feed Flow Rate	90 – 160 Kg/hr
Inlet Temperature	75 – 125 °C
Outlet Temperature	35 – 55 °C
Vacuum Dryer Temperature	80 °C (+/-5 °C)
Vacuum Drying Time	156 hours

[00279] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product contained 8.8 - 12.5%wt. MEK/Water a mean particle size of 16 - 24um and a bulk density of 0.28 - 0.36g/cc. The wet product was transferred to a 350L stainless steel double cone vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate E. The dry Intermediate E contained <0.3% MEK and 0.8% Water.

[00280] Intermediate F:

[00281] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 ^{0}C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% hypromellose acetate succinate / 0.5 wt% SLS / 80 wt% N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]- 1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 10.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table Fl, below:

Table Fl: Solid Spray Dispersion Ingredients for Intermediate F.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	70.0
HPMCAS	Kg	17.1
SLS	Kg	0.438
Total Solids	**Kg**	**87.5**
MEK	Kg	671
Water	Kg	74.6
Total Solvents	**Kg**	**746**
Total Spray Solution Weight	**Kg**	**833**

[00282] The mixture temperature was adjusted to a range of 20 - 45 ^{0}C and mixed until it was substantially homogenous and all components were substantially dissolved.

[00283] A spray drier, Niro PSD4 Commercial Spray Dryer, fitted with pressure nozzle (Spray Systems Maximum Passage series SK-MFP having orifice/core size 54/21) equipped

with anti-bearding cap, was used under normal spray drying mode, following the dry spray process parameters recited in Table F2, below.

Table F2: Dry spray process parameters used to generate Intermediate F.

Parameter	Value
Feed Pressure	20 bar
Feed Flow Rate	92 – 100 Kg/hr
Inlet Temperature	93 – 99 °C
Outlet Temperature	53 – 57 °C
Vacuum Dryer Temperature	80 °C for 2 hours then 110 °C (+/-5 °C)
Vacuum Drying Time	20 – 24 hours

[00284] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product contained 8.5 - 9.7% MEK and 0.56 - 0.83% Water and had a mean particle size of 17 - 19um and a bulk density of 0.27 - 0.33g/cc. The wet product was transferred to a 4000L stainless steel double cone vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate F. The dry Intermediate F contained <0.03% MEK and 0.3% Water.

[00285] Intermediate G:

[00286] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 ^{0}C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt % hypromellose acetate succinate / 0.5 wt % SLS / 80 wt% N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxy ρhenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 10.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table Gl, below:

Table Gl: Solid Spray Dispersion Ingredients for Intermediate G.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	24.0
HPMCAS	Kg	5.85
SLS	Kg	0.15
Total Solids	**Kg**	**30.0**
MEK	Kg	230.1
Water	Kg	25.6
Total Solvents	**Kg**	**255.7**
Total Spray Solution Weight	**Kg**	**285.7**

[00287] The mixture temperature was adjusted to a range of 20 - 45 ^{0}C and mixed until it was substantially homogenous and all components were substantially dissolved.

[00288] A spray drier, Niro Production Minor Spray Dryer, fitted with pressure nozzle (Spray Systems Maximum Passage series SK-MFP having orifice size 72) was used under normal spray drying mode, following the dry spray process parameters recited in Table G2, below.

Table G2: Dry spray process parameters used to generate Intermediate G.

Parameter	Value
Feed Pressure	33 bar
Feed Flow Rate	18 – 24 Kg/hr
Inlet Temperature	82 – 84 °C
Outlet Temperature	44 – 46 °C
Vacuum Dryer Temperature	80 °C for 2 hours then 110 °C (+/-5 °C)
Vacuum Drying Time	48 hours

[00289] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product contained 10.8% MEK and 0.7% Water and had a mean particle size of 19um and a bulk density of 0.32g/cc. The wet product was transferred to a 4000L stainless steel double cone vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate. The dry Intermediate G contained <0.05% MEK and 0.7% Water.

[00290] Example 1: Exemplary Tablet 1 (Formulated to have 25 mg of Compound 1)

[00291] A batch of round core 3/8" tablets was formulated to have approximately 25 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 1, below.

Table 1: Ingredients for Exemplary Tablet 1.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate A	15.29%	51.23	512.5
Microcrystalline cellulose	35.00%	117.25	1172
Lactose	43.85%	146.00	1460
Sodium croscarmellose	5.000%	16.75	167.5
SLS	0.500%	1.675	16.75
Colloidal silicon dioxide	0.125%	0.4188	4.188
Magnesium stearate	0.50%	1.675	16.75
Total	**100%**	**335**	**3350**

[00292] Intermediate A, microcrystalline cellulose (FMC MCC Avicel® PH102, commercially available from FMC BioPolymer Corporation of Philadelphia, PA), lactose (Foremost FastFlo® Lactose #316 commercially available from Foremost Farms USA of

Baraboo, WI), sodium croscarmellose (FMC Ac-Di-Sol®, commercially available from FMC BioPolymer Corporation of Philadelphia, PA), SLS, and colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide, commercially available from Cabot Corporation of Alpharetta, GA) were sieved through a 20 mesh screen to remove lumps.

[00293] Each of the sieved ingredients was added to a 16 quart V-blender in the following order:

[00294] **1)** lactose;

[00295] **2)** SLS;

[00296] **3)** sodium croscarmellose;

[00297] **4)** colloidal silicon dioxide;

[00298] **5)** Intermediate **A;** and

[00299] **6)** microcrystalline cellulose PHlOl

[00300] The mixture was blended for 25 minutes in a V-blender at 20-24 rpm. Magnesium stearate was sieved through a 30 mesh screen to remove lumps, and added to the mixture, which was blended for another 3 minutes.

[00301] Once the final blend has been completed, the mixture was transferred to a Piccola B-Tooling, 10 Station rotary tablet press (half tooled) for compression. Pressing the mixture into tablets generated 3/8" round tablets having approximately 25 mg of N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide.

[00302] Example 2: Exemplary Tablet 2 (Formulated to have 50 mg of Compound **1)**

[00303] A batch of round core 3/8" tablets was formulated to have about 50 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 2, below.

Table 2: Ingredients for Exemplary Tablet 2.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate A	30.60%	102.50	1025.0
Microcrystalline cellulose	25.00%	83.75	837.5
Lactose	38.28%	128.23	1282.3
Sodium croscarmellose	5.000%	16.75	167.5
SLS	0.500%	1.675	16.75
Colloidal silicon dioxide	0.125%	0.4188	4.188
Magnesium stearate	0.50%	1.675	16.75
Total	**100%**	**335**	**3350**

[00304] Intermediate A, microcrystalline cellulose, lactose, sodium croscarmellose, SLS, and colloidal silicon dioxide were sieved through a 20 mesh screen to remove lumps, and each of the sieved ingredients was added to a 16 quart V-blender in the following order:

[00305] **1)** lactose;

[00306] **2) SLS;**

[00307] **3)** sodium croscarmellose;

[00308] **4)** colloidal silicon dioxide;

[00309] **5)** Intermediate **A;** and

[00310] **6)** microcrystalline cellulose PHlOl

[00311] The mixture was blended for 25 minutes in a V-blender at 20-24 rpm. Magnesium stearate was sieved through a 30 mesh screen to remove lumps, and added to the mixture, which was blended for another 3 minutes.

[00312] Once the final blend has been completed, the mixture was transferred to a Piccola B-Tooling, 10 Station rotary tablet press (half tooled) for compression. Pressing the mixture into tablets generated 3/8" round tablets having approximately 50 mg of N-[2,4-Bis(l,l-dimethylethyl)-5-hydroxyphenyl]-l,4-dihydro-4-oxoquinoline-3-carboxamide.

[00313] Example 3: Exemplary Tablet 3 (Formulated with PVP/VA Polymer to have 150 mg of Compound 1)

[00314] A batch of caplet-shaped tablets was formulated to have about 150 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 3, below.

Table 3: Ingredients for Exemplary Tablet 3.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate B	40.000%	187.50	240.00
Microcrystalline cellulose	27.063%	126.86	162.38
Lactose	27.063%	126.86	162.38
Sodium croscarmellose	3.000%	14.06	18.00
SLS	0.500%	2.34	3.00
Colloidal silicon dioxide	1.000%	4.69	6.00
Coloring	0.375%	1.76	2.25
Magnesium stearate	1.000%	4.69	6.00
Total	**100%**	**469**	**600**

[00315] A glidant blend of colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide) and SLS was produced by hand mixing these two ingredients, in the amounts given in Table 3, and filtering the resulting mix through a 70 mesh screen sieve. A color blend of coloring (Colorcon Blue # 1 Aluminum Lake #5516) and sodium croscarmellose (FMC Ac-Di-Sol®) was produced by hand mixing these two ingredients, in the amounts given in Table 3, and filtering the resulting mix through a 70 mesh screen sieve. The glidant blend and the color blend were hand mixed and added to a 2 L blending container. Intermediate B was added to this mixture in the 2 L blending container, and the contents 2 L blending container

were hand mixed and filtered through a 30 mesh screen sieve. The resulting mixture was mixed on a Turbula mixer for 20 minutes at a rate of 22 rpm.

[00316] The microcrystalline cellulose (FMC MCC Avicel® PH102) and lactose (Foremost FastFlo® Lactose #316) were each filtered through a 30 mesh screen sieve and added to the blending container. The resulting mixture was mixed on a Turbula mixer for 20 minutes at a rate of 22 rpm.

[00317] Magnesium Stearate was filtered through a 70 mesh screen sieve and added to the mixture in the blending container, and the resulting mixture was mixed for 5 minutes at a rate of 22 rpm.

[00318] The resulting mixture was compressed into tablets using a gravity fed boot tooled with 0.64" x 0.32" caplet type **B** tooling set to produce a tablet having an initial hardness of about 8 Kp ± 15%.

[00319] Example 4: Exemplary Tablet 4 (Formulated with HPMCAS Polymer to have 150 mg of Compound **1)**

[00320] A batch of caplet-shaped tablets was formulated to have about 150 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 4, below.

Table 4: Ingredients for Exemplary Tablet 4.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate C	34.091%	187.50	204.55
Microcrystalline cellulose	30.017%	165.09	180.10
Lactose	30.017%	165.09	180.10
Sodium croscarmellose	3.000%	16.50	18.00
SLS	0.500%	2.75	3.00
Colloidal silicon dioxide	1.000%	5.50	6.00
Coloring	0.375%	2.06	2.25
Magnesium stearate	1.000%	5.50	6.00
Total	100%	550	600

[00321] A glidant blend of colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide) and SLS was produced by hand mixing these two ingredients, in the amounts given in Table 4, and filtering the resulting mix through a 70 mesh screen sieve. A color blend including coloring (Colorcon Blue #1 Aluminum Lake #5516) and sodium croscarmellose (FMC Ac-Di-Sol®) was produced by hand mixing these two ingredients, in the amounts given in Table 4, and filtering the resulting mix through a 70 mesh screen sieve. The glidant blend and the color blend were hand mixed and added to a 2 L blending container.

Intermediate C was added to this mixture in the 2 L blending container, and the contents 2 L blending container were hand mixed and filtered through a 30 mesh screen sieve. The resulting mixture was mixed on a Turbula mixer for 20 minutes at a rate of 22 rpm.

[00322] The microcrystalline cellulose (FMC MCC Avicel® PH 102) and lactose (Foremost FastFlo® Lactose #316) were each filtered through a 30 mesh screen sieve and added to the blending container. The resulting mixture was mixed on a Turbula mixer for 20 minutes at a rate of 22 rpm.

[00323] Magnesium stearate was filtered through a 70 mesh screen sieve and added to the mixture in the blending container, and the resulting mixture was mixed for 5 minutes at a rate of 22 rpm.

[00324] The resulting mixture was compressed into tablets using a tablet press tooled with 0.64" x 0.32" caplet type B tooling set to produce a tablet having an initial hardness of about 9.5 Kp ± 15%.

[00325] Example 5: Exemplary Tablet 5 (Formulated with HPMCAS Polymer to have 150 mg of Compound 1)

[00326] A batch of caplet-shaped tablets was formulated to have about 150 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 5, below.

Table 5: Ingredients for Exemplary Tablet 5.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate G	34.564%	190.10	21000.00
Microcrystalline cellulose	29.968%	164.82	18207.62
Lactose	29.968%	164.82	18207.62
Sodium croscarmellose	3.000%	16.50	1822.71
SLS	0.500%	2.75	303.78
Colloidal silicon dioxide	1.000%	5.50	607.57
Magnesium stearate	1.000%	5.50	607.57
Total	**100%**	**550**	**607560**

[00327] A blend of colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide), SLS, sodium croscarmellose (FMC Ac-Di-Sol®), and approximately 10% of the lactose (Foremost FastFlo® Lactose #316) given in Table 5 was produced by mixing these ingredients in a V-blender to provide about 125 inversions. This mixture, Preblend 1, was cone-milled through a 40 mesh screen sieve, collected and stored for subsequent use.

[00328] Approximately 20% of the lactose (Foremost FastFlo® Lactose #316) given in Table 5 was cone-milled through a 30 mesh screen sieve, collected and stored for subsequent use as Preblend 2. Intermediate G was filtered through a 30 mesh screen, collected and stored for subsequent use as Preblend 3. The microcrystalline cellulose (FMC MCC Avicel®

PH102) was filtered through a 30 mesh screen, collected and stored for subsequent use as Preblend 4.

[00329] A V-blender was charged with Preblend 2, the remaining 70% of the lactose (Foremost FastFlo® Lactose #316) given in Table 3, Preblend 3, Preblend 1, and Preblend 4, in that order, and blended for about 500 inversions. The blended mixture was tested for uniformity.

[00330] Magnesium Stearate was filtered through a 70 mesh screen sieve and added to the mixture in the blending container, and the resulting mixture was mixed to provide about 125 inversions.

[00331] The resulting mixture was compressed into tablets using a Killian TlOO press tooled with 0.64" x 0.32" caplet type B tooling set to produce a tablet having an initial hardness of about 11 Kp ± 20%.

[00332] Example 6: Exemplary Tablet 6 (Formulated with HPMCAS Polymer to have 100 me of Compound 1)

[00333] A batch of caplet-shaped tablets was formulated to have about 150 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 6, below.

Table 6: Ingredients for Exemplary Tablet 6.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate G	34.564%	126.73	9000.06
Microcrystalline cellulose	29.968%	109.88	7803.32
Lactose	29.968%	109.88	7803.32
Sodium croscarmellose	3.000%	11.00	781.17
SLS	0.500%	1.83	130.19
Colloidal silicon dioxide	1.000%	3.67	260.39
Magnesium stearate	1.000%	3.67	260.39
Total	**100%**	**367**	**26040**

[00334] A blend of colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide), SLS, sodium croscarmellose (FMC Ac-Di-Sol®), and approximately 10% of the lactose (Foremost FastFlo® Lactose #316) given in Table 6 was produced by mixing these ingredients in a V-blender to provide about 125 inversions. This mixture, Preblend 1, was cone-milled through a 40 mesh screen sieve, collected and stored for subsequent use.

[00335] Approximately 20% of the lactose (Foremost FastFlo® Lactose #316) given in Table 6 was cone-milled through a 30 mesh screen sieve, collected and stored for subsequent use as Preblend 2. Intermediate G was filtered through a 30 mesh screen, collected and stored for subsequent use as Preblend 3. The microcrystalline cellulose (FMC MCC Avicel®

PH102) was filtered through a 30 mesh screen, collected and stored for subsequent use as Preblend 4.

[00336] A V-blender was charged with Preblend 2, the remaining 70% of the lactose (Foremost FastFlo® Lactose #316) given in Table 3, Preblend 3, Preblend 1, and Preblend 4, in that order, and blended for about 500 inversions. The blended mixture was tested for uniformity.

[00337] Magnesium Stearate was filtered through a 70 mesh screen sieve and added to the mixture in the blending container, and the resulting mixture was mixed to provide about 125 inversions.

[00338] The resulting mixture was compressed into tablets using a Killian TlOO press tooled with 0.64" x 0.32" caplet type **B** tooling set to produce a tablet having an initial hardness of about 11 Kp ± 20%.

[00339] Example 7: Exemplary Tablets 7 and 8 (Tablet 5 and 6 with Sprav-Coatine

[00340] A batch of caplet-shaped tablets from Example 5 and 6 was spray-coated with OPADRY® II (Blue, Colorcon) to a weight gain of about 3.0% using a 24" coating pan configured with the parameters in Table 7 followed by logo printing using Opacode® WB (Black, Colorcon).

[00341] Table 7: Spray-Coating Process Parameters

Coating Parameters 24" Pan	Target
Pan Load (kg)	15
Inlet Temperature (°C)*	*
Pan Speed (rpm)	14
Jog Time	TBD
# of Spray Guns	2
Solids Content (%w/w)	20
Gun to Bed Distance (inches)	6
Inlet Air Flow (cfm)	250, 300**
Spray Rate (g/min)	70
Exhaust Temperature (°C)	50
Atomization Pressure (psi)	25
Pattern Pressure (psi)	25

* Inlet temperature is monitored to achieve target exhaust temperature. Initial inlet temperature should be set at about 75°C to achieve target exhaust temp.

** The target Inlet Air Flow was 250, 300 for Tablet 7 and Tablet 8, respectively.

[00342] The OPADRY® II suspension was prepared by measuring an amount of de-ionized water which when combined with OPADRY® II would produce a total solids content of 20 %w/w. The water is mixed to a vortex followed by addition of OPADRY® II over a period

of approximately 5 minutes. Once the OPADRY® II powder was wetted, mixing was continued to ensure that all solid material is well-dispersed. The suspension is then charged into a Thomas 24" pan coating instrument using coating conditions outlined in Table 7.

[00343] Core tablets are placed into the coating pan and pre-warmed. The inlet temperature was increased from room temperature to about 55^0C and then increased as necessary to provide the exhaust temperature in Table 7. The coating process was performed with 20% w/w OPADRY® II (85 Series Blue) coating dispersion to obtain a target weight gain of about 3%. The coated tablets were then allowed to tumble for about 2 minutes without spraying. The bed temperature was then allowed to cool to about 35^0C.

[00344] Once coated with OPADRY® II, the tablets are then labeled using a Hartnett Delta tablet printer charged with Opacode® WB.

[00345] Example 8: Exemplary Tablet 9 (Formulated with HPMCAS Polymer to have 100 mg of Compound 1)

[00346] A batch of caplet-shaped tablets was formulated to have about 100 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 8, below.

Table 8: Ingredients for Exemplary Tablet 9.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate F	34.09%	125.1	23.86
Microcrystalline cellulose	30.51%	112.0	21.36
Lactose	30.40%	111.6	21.28
Sodium croscarmellose	3.000%	11.01	2.100
SLS	0.500%	1.835	0.3500
Colloidal silicon dioxide	0.500%	1.835	0.3500
Magnesium stearate	1.000%	3.670	0.7000
Total	**100%**	**367**	**70**

[00347] The colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide) and the microcrystalline cellulose (FMC MCC Avicel® PH102) were passed through a 30 mesh screen.

[00348] The sodium croscarmellose (FMC Ac-Di-Sol®), SLS, Intermediate F, and lactose (Foremost FastFlo® Lactose #316) were also passed, individually in the preceding order, through the same 30 mesh screen. A nitrogen purge was used when screening Intermediate F. The screened components were loaded into a 10 cubic feet V-blender, which was purged with nitrogen, and blended for about 180 (+/- 10) inversions.

[00349] The Magnesium Stearate was filtered through a 40 mesh screen sieve into the blending container and mixed to provide about 54 inversions.

[00350] The resulting mixture was compressed into tablets using a fully tooled 36 Fette 2090 press with 0.568" x 0.2885" caplet type B tooling set to produce a tablet having an initial target hardness of about 10 Kp ± 20%.

[00351] Example 9: Exemplary Tablet 10 (Tablet 9 with Spray-Coating')

[00352] A batch of caplet-shaped tablets from Example 8 was spray-coated with OPADRY® II (Blue, Colorcon) to a weight gain of about 3.0% using a 24" coating pan configured with the parameters in Table 9 followed by wax coating and then printing using Opacode® S-I-17823 (Solvent based Black, Colorcon).

[00353] Table 9: Spray-Coating Process Parameters

Coating Parameters 24" Pan	Target
Pan Load (kg)	14
Inlet Temperature (°C)*	*
Pan Speed (rpm)	10
Jog Time (sec)	
# of Spray Guns	2
Solids Content (%w/w)	20
Gun to Bed Distance (inches)	6
Inlet Air Flow (cfm)	300
Spray Rate (g/min)	35
Exhaust Temperature (°C)	50
Atomization Pressure (psi)	42

* Inlet temperature is monitored to achieve target exhaust temperature. Initial inlet temperature should be set at about 75°C to achieve target exhaust temp.

[00354] The OPADRY® II suspension was prepared by measuring an amount of de-ionized water which when combined with OPADRY® II would produce a total solids content of 20 %w/w. The water is mixed to a vortex followed by addition of OPADRY® II over a period of approximately 5 minutes. Once the OPADRY® II powder was wetted, mixing was continued to ensure that all solid material is well-dispersed. The suspension is then charged into a Thomas 24" pan coating instrument using coating conditions outlined in Table 9.

[00355] Uncoated tablets are placed into the coating pan and pre-warmed. The inlet was increased from room temperature to about 55^0C and then increased as necessary to provide the exhaust temperature in Table 9. The coating process was performed with 20% w/w OPADRY® II (85 Series Blue) coating dispersion to obtain a target weight gain of about 3%. The coated tablets were then allowed to tumble for about 2 minutes without spraying. The bed temperature was then allowed to cool to about 35^0C.

[00356] Upon cooling, the Camauba wax powder was weighed out in the amount of about 0.01% w/w of the starting tablet core weight. With the air flow off, the carnauba wax powder was sprinkled evenly on the tablet bed. The pan bed was turned on to the speed indicated in

Table 9. After 5 minutes, the air flow was turned on (without heating) to the setting indicated in Table 9. After about one minute the air flow and pan were turned off.

[00357] Once coated with OPADRY® II, the tablets are then labeled using a Hartnett Delta tablet printer charged with Opacode® S-l-17823.

[00358] Example 10: Exemplary Tablet 11 (Formulated with HPMCAS Polymer to have 150 mg of Compound 1)

[00359] A batch of caplet-shaped tablets was formulated to have about 100 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 11, below.

Table 10: Ingredients for Exemplary Tablet 11.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate F	34.09%	187.5	23.86
Microcrystalline cellulose	30.51%	167.8	21.36
Lactose	30.40%	167.2	21.28
Sodium croscarmellose	3.000%	16.50	2.100
SLS	0.500%	2.750	0.3500
Colloidal silicon dioxide	0.500%	2.750	0.3500
Magnesium stearate	1.000%	5.500	0.7000
Total	**100%**	**550**	**70**

[00360] The colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide) and the microcrystalline cellulose (FMC MCC Avicel® PH102) were passed through a 30 mesh screen.

[00361] The sodium croscarmellose (FMC Ac-Di-Sol®), SLS, Intermediate F, and lactose (Foremost FastFlo® Lactose #316) were also passed, individually in the preceding order, through the same 30 mesh screen. A nitrogen purge was used when screening Intermediate F. The screened components were loaded into a 10 cubic feet V-blender, which was purged with nitrogen, and blended for about 180 (+/- 10) inversions.

[00362] The Magnesium Stearate was filtered through a 40 mesh screen sieve into the blending container and mixed to provide about 54 inversions.

[00363] The resulting mixture was compressed into tablets using a fully tooled 36 Fette 2090 press with 0.568" x 0.2885" caplet type B tooling set to produce a tablet having an initial target hardness of about 10 Kp ± 20%.

[00364] Example 11: Exemplary Tablet 12 (Tablet U with Sprav-Coating)

[00365] A batch of caplet-shaped tablets from Example 10 was spray-coated with OPADRY® II (Blue, Colorcon) to a weight gain of about 3.0% using a 24" coating pan configured with the parameters in Table 11 followed by wax coating and then printing using Opacode® S-l-17823 (Solvent based Black, Colorcon).

[00366] Table 11: Spray-Coating Process Parameters

Coating Parameters 24" Pan	Target
Pan Load (kg)	14
Inlet Temperature (°C)*	*
Pan Speed (rpm)	10
Jog Time (sec)	2-5 sec every 60 sec
# of Spray Guns	2
Solids Content (%w/w)	20
Gun to Bed Distance (inches)	6
Inlet Air Flow (cfm)	300
Spray Rate (g/min)	35
Exhaust Temperature (°C)	50
Atomization Pressure (psi)	42

* Inlet temperature is monitored to achieve target exhaust temperature. Initial inlet temperature should be set at about 75°C to achieve target exhaust temp.

[00367] The **OP**ADRY® **II** suspension was prepared by measuring an amount of de-ionized water which when combined with OPADRY® II would produce a total solids content of 20 %w/w. The water is mixed to a vortex followed by addition of OPADRY® II over a period of approximately 5 minutes. Once the OPADRY® II powder was wetted, mixing was continued to ensure that all solid material is well-dispersed. The suspension is then charged into a Thomas 24" pan coating instrument using coating conditions outlined in Table 11.

[00368] Uncoated tablets are placed into the coating pan and pre-warmed. The inlet was increased from room temperature to about 55^0C and then increased as necessary to provide the exhaust temperature in Table 9. The coating process was performed with 20% w/w OPADRY® II (85 Series Blue) coating dispersion to obtain a target weight gain of about 3%. The coated tablets were then allowed to tumble for about 2 minutes without spraying. The bed temperature was then allowed to cool to about 35°C.

[00369] Upon cooling, the Carnauba wax powder was weighed out in the amount of about 0.01% w/w of the starting tablet core weight. With the air flow off, the carnauba wax powder was sprinkled evenly on the tablet bed. The pan bed was turned on to the speed indicated in Table 11. After 5 minutes, the air flow was turned on (without heating) to the setting indicated in Table 11. After about one minute the air flow and pan were turned off.

[00370] Once coated with OPADRY® II, the tablets are then labeled using a Hartnett Delta tablet printer charged with Opacode® S-l-17823.

[00371] B. Administration of Pharmaceutical Formulations

[00372] Example 12: Exemplary Administration A

[00373] Human patients are orally administered a pharmaceutical formulation according to Table 12:

Table 12: Exemplary administration **A** of pharmaceutical formulations of the present invention.

Frequency of dosing (per day)	Tablet Description	Conditions
One administration	3×50 mg Tablets of Example 2	Administered with 240 mL of water under fasting conditions
One administration	150 mg Tablet of Example 3	Administered with 240 mL of water under fasting conditions
One administration	150 mg Tablet of Example 3	Administered with 240 mL of water, 30 minutes after start of a high fat breakfast
One administration	150 mg Tablet of Example 4	Administered with 240 mL of water under fasting conditions
One administration	150 mg Tablet of Example 4	Administered with 240 mL of water, 30 minutes after start of a high fat breakfast

[00374] The pharmaceutical formulations are administered to subjects between 7:00 AM and 9:00 AM, and the pharmaceutical formulation is given at approximately the same time (within a 1-hour window) on each dosing occasion. For administrations that occur under patient fasting, food is allowed 4 hours after the pharmaceutical formulation is administered. For administrations that permit feeding, breakfast is given about 30 minutes prior to the dosing time and is consumed in about 25 minutes. In each of these administrations, the patient is instructed not to lie down for 4 hours after taking the study drug.

[00375] Example 13: Exemplary Administration **B**

[00376] Human patients are orally administered a pharmaceutical formulation according to Table 13:

Table 13: Exemplary administration **B** of pharmaceutical formulations of the present invention.

Frequency of dosing	Dosage
12 hr. intervals	25 mg Tablet of Example 1
12 hr. intervals	1×25 mg Tablet of Example 1, and 1×50 mg Tablet of Example 2
12 hr. intervals	3×50 mg Tablet of

	Example 2
12 hr. intervals	5×50 mg Tablet of Example 2
12 hr. intervals	150 mg Tablet of Example 5
12 hr. intervals	100 mg Tablet of Example 6

[00377] The pharmaceutical formulations are administered to patients approximately every 12 hours.

[00378] Example 14: Dissolution Profile of Several Exemplary Tablets

[00379] Referring to Figure 1, the dissolution profiles of several exemplary tablets are graphically illustrated. It is noted that each of the exemplary tablets illustrated in Figure 1 are at least 50% dissolved at about 30 minutes.

OTHER EMBODIMENTS

[00380] All publications and patents referred to in this disclosure are incorporated herein by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Should the meaning of the terms in any of the patents or publications incorporated by reference conflict with the meaning of the terms used in this disclosure, the meaning of the terms in this disclosure are intended to be controlling. Furthermore, the foregoing discussion discloses and describes merely exemplary embodiments of the present invention. One skilled in the art will readily recognize from such discussion and from the accompanying drawings and claims, that various changes, modifications and variations can be made therein without departing from the spirit and scope of the invention as defined in the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

a. a solid dispersion comprising substantially amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

2. The pharmaceutical composition of claim 1, wherein the solid dispersion comprises substantially amorphous Compound 1 and a polymer, and the polymer comprises HPMC, HPMCAS, PVP/VA, PVP, methacrylic acid/methacrylate copolymer, HPC, or any combination thereof.

3. The pharmaceutical composition of claim 2, wherein the solid dispersion has a mean particle diameter of greater than about 5 μm.

4. The pharmaceutical composition of claim 2, wherein the solid dispersion has a bulk density of about 0.10 g/cc or greater.

5. The pharmaceutical composition of claim 2, wherein the solid dispersion comprises substantially amorphous Compound 1, and Compound 1 is present in a concentration of at least 20 wt% by weight of the solid dispersion.

6. The pharmaceutical composition of claim 5, wherein the solid dispersion comprises 80 wt% or less of HPMCAS or PVP/VA.

7. The pharmaceutical composition of claim 5, wherein the solid dispersion comprises a surfactant.

8. The pharmaceutical composition of claim 7, wherein the solid dispersion comprises less than 10 wt% of surfactant by weight of solid dispersion.

9. The pharmaceutical composition of claim 8, wherein the solid dispersion comprises a surfactant, and the surfactant is SLS.

10. The pharmaceutical composition of claim 9, wherein the solid dispersion comprises amorphous Compound 1.

11. The pharmaceutical composition of claim 1, wherein the solid dispersion comprises from about 45 wt% to about 85 wt% of substantially amorphous Compound 1, from about 0.45 wt% to about 0.55 wt% of SLS, and from about 14.45 wt% to about 55.55 wt% of HPMCAS or PVP/VA by weight of the solid dispersion.

12. The pharmaceutical composition of claim 1, wherein the solid dispersion comprises from about 40 wt% to about 60 wt% of substantially amorphous Compound 1 by weight of the solid dispersion and from about 60 wt% to about 40 wt% of polymer by weight of the solid dispersion.

13. The pharmaceutical composition of claim 1, wherein the solid dispersion comprises from about 65 wt% to about 95 wt% of substantially amorphous Compound 1 by weight of the solid dispersion and from about 45 wt% to about 5 wt% of polymer by weight of the solid dispersion.

14. The pharmaceutical composition of any of claims 1-13, wherein the filler is lactose, sorbitol, cellulose, calcium phosphate, starch, sugar, or any combination thereof.

15. The pharmaceutical composition of any of claims 1-14, wherein the filler is lactose and has a concentration of at least about 10 wt% by weight of the composition.

16. The pharmaceutical composition of any of claims 1-15, wherein the disintegrant is sodium croscarmellose, sodium starch glycolate, or a combination thereof.

17. The pharmaceutical composition of any of claims 1-16, wherein the disintegrant is sodium croscarmellose and has a concentration of about 10 wt% or less by weight of the composition.

18. The pharmaceutical composition of any of claims 1-17, wherein the surfactant is sodium lauryl sulfate, sodium stearyl fumarate, polyoxyethylene 20 sorbitan mono-oleate, or any combination thereof.

19. The pharmaceutical composition of any of claims 1-18, wherein the surfactant is sodium lauryl sulfate and has a concentration of about 10 wt% or less by weight of the composition.

20. The pharmaceutical composition of any of claims 1-19, wherein the binder is microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, modified cellulose, or any combination thereof.

21. The pharmaceutical composition of any of claims 1-20, wherein the binder is microcrystalline cellulose and has a concentration of at least about 1 wt% by weight of the composition.

22. The pharmaceutical composition of any of claims 1-21, wherein the glidant is colloidal silicon dioxide, talc, or a combination thereof.

23. The pharmaceutical composition of any of claims 1-22, wherein the glidant is colloidal silicon dioxide and has a concentration of 2 wt% or less by weight of the composition.

24. The pharmaceutical composition of any of claims 1-23, wherein the lubricant is magnesium stearate, stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

25. The pharmaceutical composition of any of claims 1-24, wherein the lubricant is magnesium stearate and has a concentration of about 2 wt% by weight of the composition.

26. The pharmaceutical composition of any of claims 1-25, further comprising a colorant.

27. The pharmaceutical composition of any of claims 1-26, wherein the colorant is a blue pigment having a concentration of less than 1 wt% by weight of the composition.

28. A pharmaceutical composition comprising

a. from about 5 wt% to about 50 wt% of a solid dispersion, by weight of the composition, comprising from about 40 wt% to about 60 wt% of substantially amorphous Compound 1, by weight of the dispersion, and from about 60 wt% to about 40 wt% of a polymer, by weight of the dispersion;

b. from about 25 wt% to about 50 wt% of a filler;

c. from about 1 wt% to about 10 wt% of a disintegrant;

d. from about 2 wt% to about 0.3 wt% of a surfactant;

e. from about 5 wt% to about 50 wt% of a binder;

f. from about 2 wt% to about 0.05 wt% of a glidant; and

h. from about 2 wt% to about 0.1 wt% of a lubricant.

29. A pharmaceutical composition comprising

a. from about 5 wt% to about 50 wt% of a solid dispersion, by weight of the composition, comprising from about 70 wt% to about 90 wt% of substantially amorphous Compound 1, by weight of the dispersion, and from about 30 wt% to about 10 wt% of a polymer, by weight of the dispersion;

b. from about 25 wt% to about 50 wt% of a filler;

c. from about 1 wt% to about 10 wt% of a disintegrant;

d. from about 2 wt% to about 0.3 wt% of a surfactant;

e. from about 5 wt% to about 50 wt% of a binder;

f. from about 2 wt% to about 0.05 wt% of a glidant; and

h. from about 2 wt% to about 0.1 wt% of a lubricant.

30. The pharmaceutical composition of any of claims 1-29, further comprising a tablet, a capsule, or a suspension.

31. The pharmaceutical composition of claim 30, further comprising a tablet, and the tablet has a hardness of at least 5 Kp.

32. A pharmaceutical composition consisting of a tablet that comprises a solid dispersion, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a dissolution of at least about 50% in about 30 minutes, and the solid dispersion comprises substantially amorphous Compound 1.

33. The pharmaceutical composition of claim 32, wherein the solid dispersion comprises substantially amorphous Compound 1 and HPMCAS or PVP/VA.

34. The pharmaceutical composition of claim 33, wherein the solid dispersion comprises at least about 25 mg of substantially amorphous Compound 1, and PVP/VA and SLS.

35. The pharmaceutical composition of claim 33, wherein the solid dispersion comprises at least about 25 mg of substantially amorphous Compound 1, and HPMCAS and SLS.

36. A pharmaceutical composition consisting of a tablet that comprises

a. a solid dispersion comprising substantially amorphous Compound 1, and HPMCAS or PVP/VA;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

37. The pharmaceutical composition of claim 36, wherein the solid dispersion further comprises SLS.

38. A method of producing a pharmaceutical composition comprising

providing an admixture comprising

a. a solid dispersion comprising substantially amorphous Compound 1;

b. a binder;

c. a glidant;

d. a surfactant;

e. a lubricant;

f. a disintegrant; and

g. a filler, and

compressing the admixture into a tablet having a dissolution of at least about 50% in about 30 minutes.

39. The method of claim 38, wherein the admixture is compressed to produce a tablet having a hardness of at least 5 Kp.

40. The method of claim 38, further comprising mixing the admixture until the admixture is substantially homogenous.

41. A method of administering a pharmaceutical composition comprising orally administering to a patient at least once per day at least one tablet comprising

a pharmaceutical composition comprising

a. a solid dispersion comprising at least about 25 mg of substantially amorphous Compound 1;

b. a filler;

c. a binder;

d. a glidant;

e. a disintegrant;

f. a surfactant; and

g. a lubricant.

42. The method of claim 41, wherein the tablet comprising the pharmaceutical composition comprising the solid dispersion comprising substantially amorphous Compound 1, the filler, the binder, the glidant, the disintegrant, the surfactant, and the lubricant is orally administered to the patient once per day or about every 12 hours.

43. The method of claim 42, wherein the solid dispersion further comprises at least 75 mg of substantially amorphous Compound 1.

44. A method of administering a pharmaceutical composition comprising orally administering to a patient at least once per day at least one tablet comprising

a pharmaceutical composition comprising

a. a solid dispersion comprising at least about 25 mg of substantially amorphous Compound 1;
b. a filler;
c. a binder;
d. a glidant;
e. a disintegrant;
f. a surfactant, and
g. a lubricant.

45. A pharmaceutical composition consisting of a tablet comprising

a. a solid dispersion comprising from about 20 wt% to about 99 wt% of substantially amorphous Compound 1 by weight of the dispersion and a polymer selected from HPMCAS or PVP/VA;
b. from about 27 wt% to about 45 wt% of a filler comprising lactose;
c. from about 2.5 wt% to about 6.0 wt% of a disintegrant comprising sodium croscarmellose;
d. from about 2.0 wt% to about 0.3 wt% of a surfactant comprising sodium lauryl sulfate;
e. from about 20 wt% to about 45 wt% of a binder comprising microcrystalline cellulose;
f. from about 1.0 wt% to about 0.09 wt% of a glidant comprising colloidal silicon dioxide; and
g. from about 1.3 wt% to about 0.3 wt% of a lubricant comprising magnesium stearate.

46. A pharmaceutical composition comprising

a. about 15 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 50 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 49.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion;

b. about 35 wt% of microcrystalline cellulose by weight of the composition;

c. about 43 wt% of lactose by weight of the composition; about 5 wt% of sodium croscarmellose by weight of the composition;

d. about 0.5 wt% of SLS by weight of the composition;

e. about 0.125 wt% of colloidal silicon dioxide by weight of the composition; and

f. about 0.5 wt% of magnesium stearate by weight of the composition.

47. A pharmaceutical composition comprising

a. about 31 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 50 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 49.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion;

b. about 25 wt% of microcrystalline cellulose by weight of the composition;

c. about 38 wt% of lactose by weight of the composition;

d. about 5 wt% of sodium croscarmellose by weight of the composition;

e. about 0.5 wt% of SLS by weight of the composition;

f. about 0.125 wt% of colloidal silicon dioxide by weight of the composition; and

g. about 0.5 wt% of magnesium stearate by weight of the composition.

48. A pharmaceutical composition comprising

a. about 40 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt%

of PVP/VA by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion;

b. about 27 wt% of microcrystalline cellulose by weight of the composition;

c. about 27 wt% of lactose by weight of the composition;

d. about 3 wt% of sodium croscarmellose by weight of the composition;

e. about 0.5 wt% of SLS by weight of the composition;

f. about 1 wt% of colloidal silicon dioxide by weight of the composition;

g. about 1 wt% of magnesium stearate by weight of the composition; and

h. about 0.4 wt% of colorant by weight of the composition.

49. A pharmaceutical composition comprising

a. about 40 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion;

b. about 27 wt% of microcrystalline cellulose by weight of the composition;

c. about 27 wt% of lactose by weight of the composition;

d. about 3 wt% of sodium croscarmellose by weight of the composition;

e. about 0.5 wt% of SLS by weight of the composition;

f. about 1 wt% of colloidal silicon dioxide by weight of the composition;

g. about 1 wt% of magnesium stearate by weight of the composition; and

h. about 0.4 wt% of colorant by weight of the composition.

50. A pharmaceutical composition comprising:

a. a solid dispersion comprising amorphous Compound 1 and a polymer;

b. a filler;

c. a disintegrant;

d. a surfactant;

e. a binder;

f. a glidant; and

g. a lubricant.

51. The pharmaceutical composition of claim 50, wherein the solid dispersion comprises substantially amorphous Compound 1 and a polymer, and the polymer comprises HPMC, HPMCAS, PVP/VA, PVP, methacrylic acid/methacrylate copolymer, HPC, or any combination thereof.

52. The pharmaceutical composition of claim 51, wherein the solid dispersion has a mean particle diameter of greater than about 5 μm.

53. The pharmaceutical composition of claim 51, wherein the solid dispersion has a bull-density of about 0.10 g/cc or greater.

54. The pharmaceutical composition of claim 51, wherein the solid dispersion comprises amorphous Compound 1, and Compound 1 is present in a concentration of at least 20 wt% by weight of the solid dispersion.

55. The pharmaceutical composition of claim 54, wherein the solid dispersion comprises 80 wt% or less of HPMCAS or PVP/VA.

56. The pharmaceutical composition of claim 55, wherein the solid dispersion comprises a surfactant.

57. The pharmaceutical composition of claim 56, wherein the solid dispersion comprises less than 10 wt% of surfactant by weight of solid dispersion.

58. The pharmaceutical composition of claim 57, wherein the solid dispersion comprises a surfactant, and the surfactant is SLS.

59. The pharmaceutical composition of claim 50, wherein the solid dispersion comprises from about 45 wt% to about 85 wt% of amorphous Compound 1, from about 0.45 wt% to about 0.55 wt% of SLS, and from about 14.45 wt% to about 55.55 wt% of HPMCAS or PVP/VA by weight of the solid dispersion.

60. The pharmaceutical composition of claim 50, wherein the solid dispersion comprises from about 40 wt% to about 60 wt% of amorphous Compound 1 by weight of the solid dispersion and from about 60 wt% to about 40 wt% of polymer by weight of the solid dispersion.

61. The pharmaceutical composition of claim 50, wherein the solid dispersion comprises from about 65 wt% to about 95 wt% of amorphous Compound 1 by weight of the solid dispersion and from about 45 wt% to about 5 wt% of polymer by weight of the solid dispersion.

62. The pharmaceutical composition of any of claims 50-61, wherein the filler is lactose, sorbitol, cellulose, calcium phosphate, starch, sugar, or any combination thereof.

63. The pharmaceutical composition of any of claims 50-62, wherein the filler is lactose and has a concentration of at least about 10 wt% by weight of the composition.

64. The pharmaceutical composition of any of claims 50-63, wherein the disintegrant is sodium croscarmellose, sodium starch glycolate, or a combination thereof.

65. The pharmaceutical composition of any of claims 50-64, wherein the disintegrant is sodium croscarmellose and has a concentration of about 10 wt% or less by weight of the composition.

66. The pharmaceutical composition of any of claims 50-65, wherein the surfactant is sodium lauryl sulfate, sodium stearyl fumarate, polyoxyethylene 20 sorbitan mono-oleate, or any combination thereof.

67. The pharmaceutical composition of any of claims 50-66, wherein the surfactant is sodium lauryl sulfate and has a concentration of about 10 wt% or less by weight of the composition.

68. The pharmaceutical composition of any of claims 50-67, wherein the binder is microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, modified cellulose, or any combination thereof.

69. The pharmaceutical composition of any of claims 50-68, wherein the binder is microcrystalline cellulose and has a concentration of at least about 1 wt% by weight of the composition.

70. The pharmaceutical composition of any of claims 50-69, wherein the glidant is colloidal silicon dioxide, talc, or a combination thereof.

71. The pharmaceutical composition of any of claims 50-70, wherein the glidant is colloidal silicon dioxide and has a concentration of 2 wt% or less by weight of the composition.

72. The pharmaceutical composition of any of claims 50-71, wherein the lubricant is magnesium stearate, stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

73. The pharmaceutical composition of any of claims 50-72, wherein the lubricant is magnesium stearate and has a concentration of about 2 wt% by weight of the composition.

74. The pharmaceutical composition of any of claims 50-73, further comprising a colorant.

75. The pharmaceutical composition of any of claims 50-74, wherein the colorant is a blue pigment having a concentration of less than 1 wt% by weight of the composition.

76. The pharmaceutical composition of any of claims 31-37 and 45, wherein the tablet further comprises a coating.

77. The pharmaceutical composition of claim 76, wherein the coating comprises a colorant.

78. The pharmaceutical composition of claim 77, wherein the colorant comprises OPADRY® II.

79. The pharmaceutical composition of claims 76-78, wherein the coating further comprises a wax coating.

80. The pharmaceutical composition of claim 79, wherein the wax coating comprises a Carnauba wax powder.

81. The pharmaceutical composition of claims 76-80, wherein the tablet further comprises ink images or ink text printed on the coating.

82. A caplet shaped pharmaceutical tablet composition having a hardness of 9.5 Kp ± 15 percent, comprising

a. about 34 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially

amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion;

b. about 30 wt% of microcrystalline cellulose by weight of the composition;

c. about 30 wt% of lactose by weight of the composition;

d. about 3 wt% of sodium croscarmellose by weight of the composition;

e. about 0.5 wt% of SLS by weight of the composition;

f. about 1 wt% of colloidal silicon dioxide by weight of the composition; and

g. about 1 wt% of magnesium stearate by weight of the composition.

83. The caplet shaped pharmaceutical tablet composition of claim 82, wherein the tablet contains 150 mg of Compound 1.

84. The caplet shaped pharmaceutical tablet composition of claim 82, wherein the tablet contains 100 mg of Compound 1.

85. A caplet shaped pharmaceutical tablet composition having an initial hardness of 11 Kp ± 20 percent, comprising

a. about 40 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion;

b. about 30 wt% of microcrystalline cellulose by weight of the composition;

c. about 30 wt% of lactose by weight of the composition;

d. about 3 wt% of sodium croscarmellose by weight of the composition;

e. about 0.5 wt% of SLS by weight of the composition;

f. about 1 wt% of colloidal silicon dioxide by weight of the composition; and

g. about 1 wt% of magnesium stearate by weight of the composition.

86. The caplet shaped pharmaceutical tablet composition of claim 85, wherein the tablet contains 150 mg of Compound 1.

87. The caplet shaped pharmaceutical tablet composition of claim 85, wherein the tablet contains 100 mg of Compound 1.

88. A caplet shaped pharmaceutical tablet composition having an initial hardness of 11 Kp ± 20 percent, comprising

a. about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion;
b. about 30 wt% of microcrystalline cellulose by weight of the composition;
c. about 30.4 wt% of lactose by weight of the composition;
d. about 3 wt% of sodium croscarmellose by weight of the composition;
e. about 0.5 wt% of SLS by weight of the composition;
f. about 1 wt% of colloidal silicon dioxide by weight of the composition; and
g. about 1 wt% of magnesium stearate by weight of the composition.

89. The caplet shaped pharmaceutical tablet composition of claim 88, wherein the tablet contains 100 mg of Compound 1.

90. The caplet shaped pharmaceutical tablet composition of claim 88, wherein the tablet contains 150 mg of Compound 1.

91. The caplet shaped pharmaceutical tablet composition of claim 88, wherein the tablet includes a colorant coating and a printed logo or text.

92. The caplet shaped pharmaceutical tablet composition of claim 91, wherein the tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text.

93. A caplet shaped pharmaceutical tablet composition having an initial hardness of between about 6 and 16 Kp, comprising

a. about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion;
b. about 30.5 wt% of microcrystalline cellulose by weight of the composition;
c. about 30.4 wt% of lactose by weight of the composition;
d. about 3 wt% of sodium croscarmellose by weight of the composition;
e. about 0.5 wt% of SLS by weight of the composition;
f. about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and
g. about 1 wt% of magnesium stearate by weight of the composition.

94. The caplet shaped pharmaceutical tablet composition of claim 93, wherein the composition contains 100 mg of Compound 1.

95. The caplet shaped pharmaceutical tablet composition of claim 93, wherein the composition contains 150 mg of Compound 1.

96. The caplet shaped pharmaceutical tablet composition of claim 93, wherein the tablet further comprises a colorant coated, a wax coating, and a printed logo or text.

97. The caplet shaped pharmaceutical tablet composition of claim 96, wherein the tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text.

98. The caplet of claim 96, wherein the wax coating comprises Carnauba wax.

99. The caplet of claim 96, wherein the ink for the printed logo or text is a solvent based ink.

100. A caplet shaped pharmaceutical tablet composition having an initial hardness of between about 9 and 21 Kp, comprising

a. about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion;
b. about 30.5 wt% of microcrystalline cellulose by weight of the composition;
c. about 30.4 wt% of lactose by weight of the composition;
d. about 3 wt% of sodium croscarmellose by weight of the composition;
e. about 0.5 wt% of SLS by weight of the composition;
f. about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and
g. about 1 wt% of magnesium stearate by weight of the composition.

101. The caplet shaped pharmaceutical tablet composition of claim 100, wherein the tablet contains 150 mg of Compound 1.

102. The caplet shaped pharmaceutical tablet composition of claim 100, wherein the composition contains 100 mg of Compound 1.

103. The caplet shaped pharmaceutical tablet composition of claim 100, wherein the tablet further comprises a colorant coated, a wax coating, and a printed logo or text.

104. The caplet shaped pharmaceutical tablet composition of claim 103, wherein the tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text.

105. The caplet of claim 103, wherein the wax coating comprises Carnauba wax.

106. The caplet of claim 103, wherein the ink for the printed logo or text is a solvent based ink.

107. A method of treating or lessening the severity of a disease in a patient comprising administering to said patient a pharmaceutical composition according to claims 1- 37 and 45-101, wherein said disease is selected from cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild

pulmonary disease, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear plasy, Pick's disease, several polyglutamine neurological disorders such as Huntington's, spinocerebullar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, or Sjogren's disease, Osteoporosis, Osteopenia, Gorham's Syndrome, chloride channelopathies such as myotonia congenita (Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, and Primary Ciliary Dyskinesia (PCD), a term for inherited disorders of the structure and/or function of cilia, including PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary aplasia.

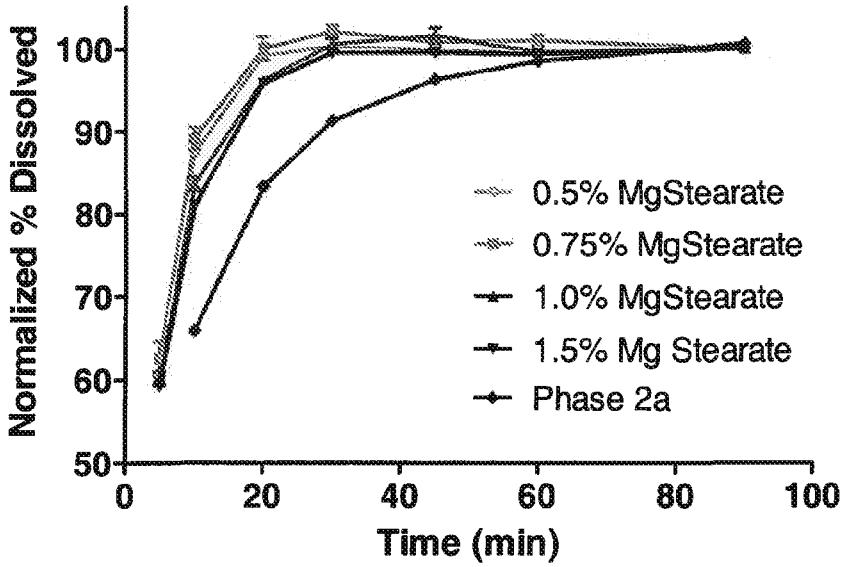
108. The method of claim 107, wherein said disease is cystic fibrosis.

109. The method of claim 108, wherein said patient has cystic fibrosis transmembrane receptor (CFTR) with a ΔF508 mutation.

110. The method of claim 109, wherein said patient has cystic fibrosis transmembrane receptor (CFTR) with a R117H mutation.

111. The method of claim 109, wherein said patient has cystic fibrosis transmembrane receptor (CFTR) with a G551D mutation.

FIGURE 1


Normalized % Dissolved
100
90
80
70
60
50
0
20
40
60
80
100
Time (min)
0.5% MgStearate
0.75% MgStearate
1.0% MgStearate
1.5% Mg Stearate
Phase 2a

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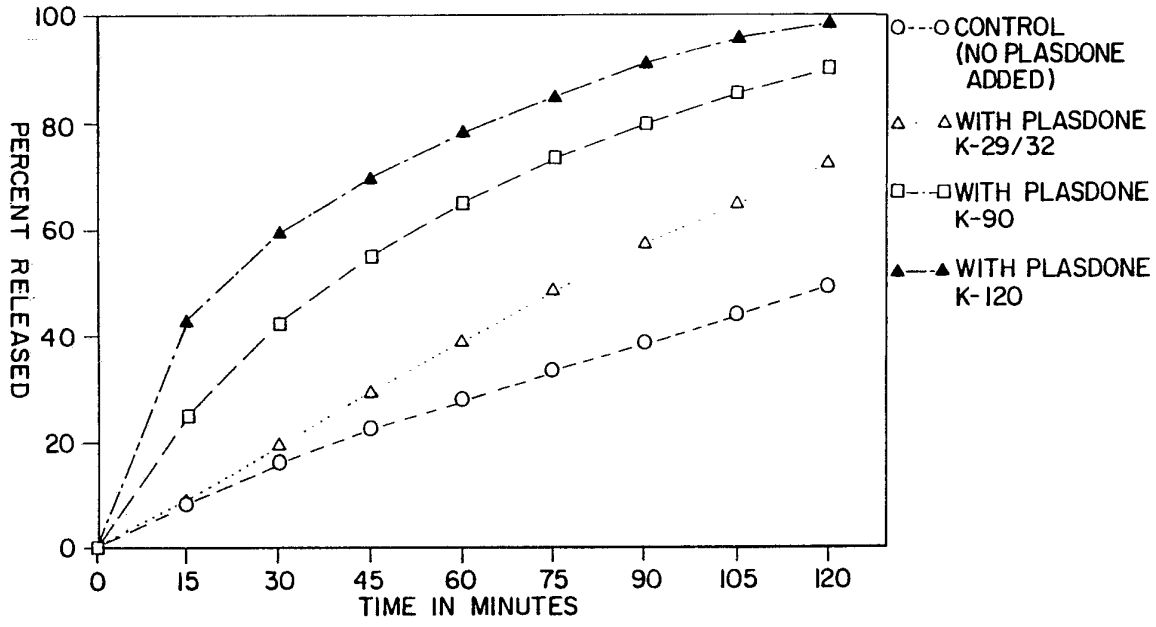

(57) Abstract

A pharmaceutical tablet is provided herein having an effective dissolution rate. The tablet contains a pharmaceutically-active ingredient and a substantially linear, i.e. non-crosslinked K-30 to K-120 PVP, preferably above 116, as a binding agent. The PVP used herein preferably is made by a polymerization process in which the vinyl pyrrolidone monomer is polymerized in the presence of an initiator which produces a linear PVP polymerization, and a residual initiator level of less than 500 ppm.

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PHARMACEUTICAL TABLET WITH PVP HAVING AN ENHANCED DRUG DISSOLUTION RATE

This invention relates to a pharmaceutical tablet containing polyvinylpyrrolidone (PVP) as a binder for a pharmaceutically-active ingredient therein, and more particularly, to such tablets which dissolve readily in water to release their active material even after the product has experienced a considerable period of shelf-time.

PVP is used widely as a binding agent for pharmaceutical tablets. However, it is essential that the PVP binder itself not interfere with the normal dissolution rate of the tablet in water. Suitable PVP polymers presently used as a binder agent in pharmaceutical tablets are prepared by free radical polymerization in the presence of a free radical initiator, as described in Polymer Journal 17, No. 1, p 143-152 (1985). These free radical polymerization initiators are used in amounts of about 0.05 to 10% by weight of the monomer, and, preferably about 0.1 to 5% by weight of an initiator is required. Hydrogen peroxide, di-t-butyl peroxide, dicumyl peroxide, t-butylperoxy pivalate (TBPP) and t-butylperoxy benzoate (TBPB) are widely used free radical polymerization initiators for the preparation of PVP polymers. TBPP, for example, undergoes thermal homolysis to produce t-butoxy and t-butyl free radicals.

The methyl and t-butoxy free radicals, respectively, have high bond dissociation energies (BDE) of 104 and 105 kcal/mole, respectively. Therefore, these radicals can readily abstract a labile hydrogen atom from the PVP polymer to transfer the site of initiation and hence convert an otherwise linear polymer into a branched polymer. If this process is carried too far, the PVP

polymer produced will have poor water solubility and/or become gels. In addition, the half-life of such TBPP initiator, i.e. the time at a given temperature to effect a loss of one-half of the perester's active oxygen content, is a lengthy 24.6 hours at 50°C. Accordingly, TBPP requires a high reaction temperature, e.g. 60°-80°C., to carry out the polymerization within a reasonable period of time. Accordingly, the choice of initiator is critical to preclude the formation of branched rather than linear PVP polymers both during polymerization and afterwards during ageing of pharmaceutical tablets containing such PVP as a binding agent.

A pharmaceutical tablet is provided herein containing a pharmaceutically-active ingredient and a K-30 to K-120, preferably above 116, PVP as a binding agent, suitably about 0.5-10% by weight, preferably about 5%. Preferably, the PVP is made by a free radical initiated polymerization process in which vinylpyrrolidone monomer is polymerized in the presence of a low energy peroxy radical initiators, such as t-amylperoxy pivalate (TAPP), an azo initiator, or a redox initiator, and at the lowest possible reaction temperatures. These named initiator materials are effective polymerization initiators for PVP polymerization, but, because of their structure, i.e. they are relatively poor hydrogen abstractors in the backbone of the PVP polymer and/or the low polymerization temperature.

Azo initiators are preferred because they generate free radicals that are of low energy. A similar effect is obtained using a low temperature free radical initiator that has an acceptable half-life at lower temperatures because the rate expression for transfer to polymer is dependent on temperature.

Such polymerization processes of the invention are carried out at a lower temperature than similar polymerizations using conventional free radical initiators,

which themselves are active hydrogen abstractors. Because of the structure of the initiator, or because lower temperatures can be used, linear PVP polymers of high molecular weight which exhibit more rapid water solubility in use in pharmaceutical tablets are provided herein. Furthermore, the low transfer to polymer property of these initiators enable the residual initiator to be decomposed at elevated temperatures without causing crosslinking. For example, a PVP K-90 polymer mixture prepared in water can be post-heated at 60-80°C. to reduce the residual initiator level to less than 500 ppm.

Preferably the PVP obtained has a K-value in excess of 116, e.g. 119-140, and a viscosity average molecular weight* of at least one million, a weight average molecular weight** of at least two million, and a relative viscosity*** of at least 1.2, most preferably about 1.2-1.5. Preferably, also, the tablet contains a suitable

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* determined using viscosity measurments method according to Scholtan, W.; Makromol. Chem., 7, 209 (1951).

** determined by gel permeation chromatography using formula : log Mw = 2.82 · log K value + 0.594

*** A single solution of the PVP sample is prepared in water at 1% w/v. The relative viscosity, η rel' is computed by diving the flow time in seconds of the aforementioned solution (as determined in an Ostwald-Fenske capillary viscometer) by the flow time of water. The K-value is then obtained from Fikentsher's equation.

filler and/or lubricant. In the most preferred form of the invention, the pharmaceutical tablet consists essentially of, by weight, about 10-98% of poorly water-soluble drug, about 2-10% of PVP K-116-140, about 0.5-2% of a lubricant, 0-3% disintegrant and about 0-85% of a filler, and is prepared either by direct compression or by using wet granulation.

The pharmaceutical tablets provided herein are particularly characterized by a rapid dissolution rate even after a prolonged shelf-life; accordingly, the PVP polymer prepared and used herein performs its binding function without an accompanying adverse side effect of a reduced dissolution rate for the active material in the tablet.

In accordance with one embodiment of the invention, a free radical polymerization process for polymerizing vinylpyrrolidone to form PVP is provided herein. Preferably the free radical polymerization initiator is, (1) a peroxy ester which radicals are weak hydrogen abstractors, e.g. t-amylperoxy pivalate (TAPP); (2) an azo initiator, or (3) a redox catalyst. These initiators and catalysts provide low energy pathways during polymerization of VP monomer. The order of energy of polymerization, and hence the degree of crosslinking of PVP, is:

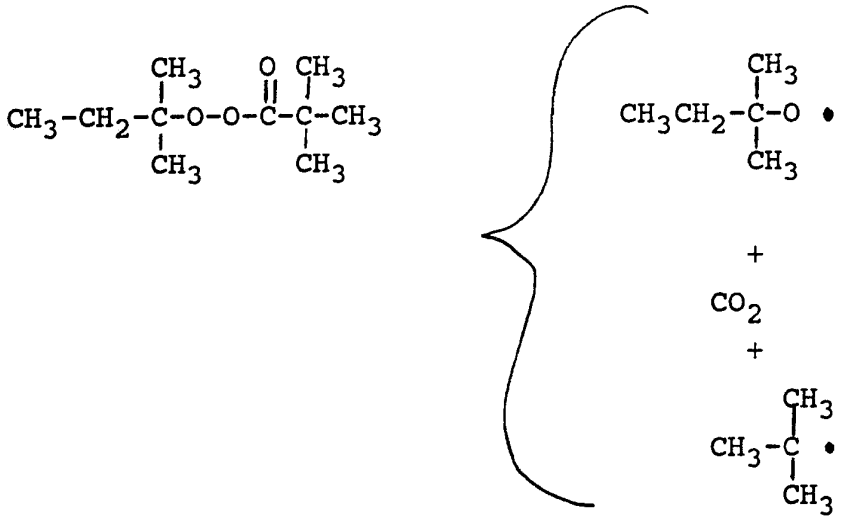
Redox Catalyst	<	Azo Initiator	<	Peroxide; Initiator

and for peroxides

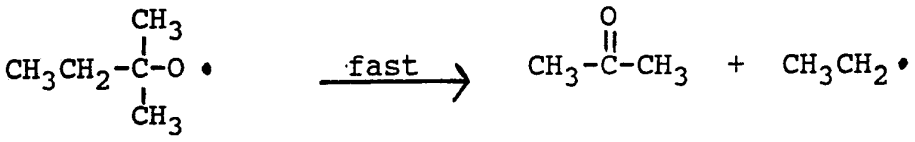
TAPP	<	TAPP	<	peroxy benzoates.

TAPP, for example, undergoes thermal homolysis as follows:

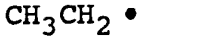
Thermal Homolysis of TAPP

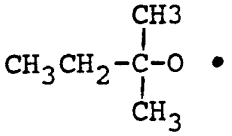


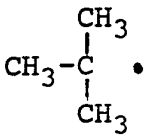
followed by β-scission of the t-amyloxy radical:



Accordingly the active free radical species of TAPP are:

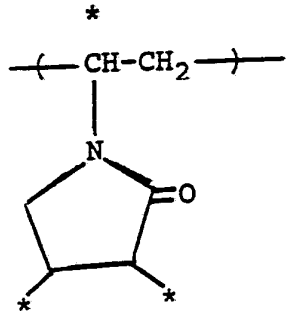
 ethyl radical

 t-amyloxy radical

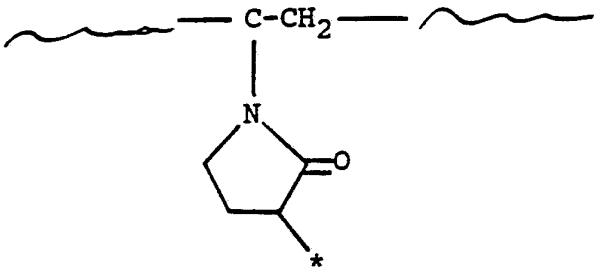
 t-butyl radical

The ethyl and t-amyloxy free radicals thus produced have a BDE of only 98 kcal/mole; therefore TAPP is a relatively weak hydrogen abstractor. Thus, substantially linear PVP polymers of high molecular weight and excellent water solubility are provided using the TAPP initiator of the invention.

More particularly, as shown below, polyvinylpyrrolidone formed by free radical polymerization of vinylpyrrolidone has several active hydrogen sites, indicated by the asterisks, for hydrogen abstraction by the active free radical species of TBPP.



which could produce the branched and crosslinked PVP polymers shown below:



TAPP, and other low energy or poor transfer to polymer initiators, on the other hand, have only weak hydrogen abstractors or are effective for polymerization at low temperatures, and produce substantially linear PVP polymers which exhibit excellent water dissolution, even after ageing.

Furthermore, it is known that lower molecular weight polymers are produced when high polymerization temperatures or long reaction periods are required. TAPP, and azo and redox catalysts, can effect PVP polymerizations at lower temperatures, than these more active higher temperature initiators; therefore, it is possible to produce herein high molecular weight, linear PVP polymers using these defined initiators. TAPP, for example, can afford initiation and low residual peroxide residue after polymerization; furthermore it is a low energy producing radical generator with reduced capacity to extract a proton from the PVP polymer. This fact enhances the stability of the PVP polymer. Even if it contains some initiator residue, it will pass the tests used to determine tablet stability, e.g. accelerated ageing-dissolution testing. However, further heating of the formed polymer solution before drying to powder guarantees the reduction of the amount of active initiator to very low levels (< 500 ppm). This post polymerization step occurs without branching or crosslinking because of the poor ability of the initiator to abstract protons from the PVP chain.

The t-amylperoxy pivalate initiator, for example, can be employed in the polymerization of vinylpyrrolidone in an amount of about 0.01 to 10% by wt. of the monomers, preferably about 0.1 to 5%.

The PVP polymers thus-produced are characterized by substantially water soluble (more linear, less branched), of stable molecular weight than PVP polymers made with more aggressive free radical initiators.

The t-amylperoxy pivalate may be obtained from the Pennwalt Corp. under their trade name of Lupersol 554M75, which is sold as a 75% by weight active solution in odorless mineral spirits.

Suitable azo-type initiators for use herein include 2,2'-azobis(isobutyronitrile), often referred to as AIBN, which is sold by Dupont under the tradename Vazo 64; 2,2'-azobis(2-methylbutanenitrile), which is Vazo 67; 2,2'-azobis(2,4-dimethylpentanenitrile, often referred to as ABVN, which is Vazo 52; 1,1'-azobis(cyclohexanecarbonitrile, Vazo 88; 2,2'-azobis(2-methylpropanimidamide) dihydrochloride; 2,2'-azobis(2-acetoxypropane; 2-tert-butylazo) isobutyronitrile; 2(tert-butylazo)-2-methylbutanenitrile; and 1-(tert-butylazo) cyclohexane-carbonitrile, sold by Pennwalt as Luazo 79, Luazo 82 and Luazo 96, respectively.

These azo-type initiators generate highly selective tertiary alkyl radicals which have a reduced propensity to attack the backbone of the polymer. This effect reduces chain branching and crosslinking and should free radicals be generated in subsequent polymer storage (even after the post polymerization heating step designed to assure very low levels of residual initiator) prevents the possibility of further reactions such as crosslinking.

A lower energy is required to generate radicals by a redox mechanism; hence the reaction is carried out at lower temperatures which does not favor transfer to polymer. If a slight excess of reducing agent is employed, no residual peroxide is available at the end.

Addition of small quantitites of reducing agents to peroxides greatly accelerates radical generation. Such Redox initiators, i.e., systems based on mixtures of oxidizing and reducing agents, initiate through the occurrence of one-electron transfer steps that form free-radical intermediates. Free-radical polymerizastion is used in redox mechanisms, as for example, in the system ferrous ion plus hydrogen peroxide (Fenton's reagent), since it provides an intervention of free radicals and allows their rate of formation to be measured. Many redox initiators are known and numerous "recipes" are current in polymerization technology.

Redox initiators for use herein are classified according to their solubilities (in water or organic liquids) or their mode of radical generation.

The powerfully oxidizing properties of mixtures of hydrogen peroxide and ferrous salts, discovered by Fenton in 1894, are attributed to the participation of OH and HO_2 radicals.

Organic peroxides or persalts such as potassium persulfate enter into similar reactions, which are essentially one-electron transfers with concomitant cleavage of the -O-O- bond.

Other transition metal ions such as Ti^{3+} can enter into similar reactions.

With potassium persulfate as oxidizing agent, the analogous reactions occur. Other metal ions react with persulfates generating free radicals. Reducing agents such as those containing sulfite salts convert ferric for ferrous ion and hence propagate the decomposition of the persufate salts or organic peroxides to free radicals. The advantage is that this method of polymer initiation can occur at much lower temperatures as compared to homolytic peroxide cleavage.

For example, hydroperoxides are well-known components of redox systems and their reduction by ferrous salts has been investigated in detail. The primary step is the one-electron transfer and bond cleavage process. The product is an alkyloxy rather than a hydroxyl radical. Among the hydroperoxides are cumene, p-menthane, and p-isopropylcumene. It is common practice to add a second reducing agent such as glucose, fructose, dihydroxyacetone, or sodium formaldehyde sulfoxylate to reduce the ferric ion formed to ferrous and so keep up the rate of initiation.

Strongly reducing metal ions may enter into redox processes with compounds other than peroxide; for example, Ti^{3+} can reduce hydroxylamine in acid solution to NH_2 radicals. Other metal ions (Cr^{2+}, V^{2+}, Fe^{2+}) behave

similarly. These combinations are capable of initiating VP polymerization.

In the redox systems so far discussed, themetal ion is the reducing component; however, many strongly oxidizing metal ions participate in single-electron transfer reactions, with free radical generation.

Systems in which two relatively stable salts form a redox pair may be used in the polymerizations herein. Typical oxidizing agents are potassium persulfate, potassium ferricyanide, ceric sulfate, potassium permanganate, t-butyl hydroperoxide, cumene hydroperoxide, pinane hydroperoxide, and diisopropylbenzene hydroperoxide. Reducing agents include sodium hyposulfite, sodium metabisulfite, sodium sulfide, sodium thiosulfate, and hydrazine hydrate. No transition metal derivatives are included in these examples. Both oxidizing and reducing components form free radicals, which, in principle, may initiate polymerization, although the behavior in any given system depends on the radical and monomer reactivities.

Organic peroxides may react in nonaqueous solution by redox processes. It has long been known that benzoyl peroxide can enter into relatively rapid reactions with primary, secondary, and tertiary amines.

The most familiar systems include diacyl peroxides and tertiary amines, of which benzoyl peroxide and dimethylaniline are typical. The reactants form a complex which cleaves into radicals.

In each of the above cases a reducing agent must be present to regenerate the ferrous ion. Examples would be sodium hyposulfite, sodium metabisulfite, sodium sulfide and sodium thiosulfate. Numerous recipes are avilable and are known to those skilled in the art.

Redox systems capable of free radical initiation can also be generated by the reaction of dibenzoyl peroxides and dimethylaniline, and other dialkyl peroxides

and organic reducing agents such as those containing sulfinic acids, alpha-ketols, formic acid, thiols and hydrazines.

Obviously the literature of redox systems is quite extensive and has recently been reviewed by for example C.H. Bamford, page 123, V. 3 of "Comprehensive Polymer Science", (1989), G.C. Eastmond et al. editors.

Redox reactions have been applied to the polymerization of PVP. Apparently the low temperature polymerization of VP and potassium persulfate reported by S.N. Trubitsyna et al. (Izv. Vuzov SSSR, Khimiya i khim. Tekhnolgiya, Vol. 22, 720 (1979) is such an example.

To achieve linearity, a source of radicals at the lowest possible temperature that efficiently promotes polymerization is theoretically the fest approach to linear polymer synthesis. Hence water soluble redox reactions such as indicated below are possible.

$$R\text{-}O\text{-}O\text{-}R \xrightarrow{Fe^{+2}} R\text{-}O\cdot + {}^{-}O\text{-}R$$

or

$$Fe^{2+} + {}^{-}O_3S\text{-}O\text{-}O\text{-}SO_3{}^{-} \longrightarrow Fe^{3+} + {}^{-}O_3S\text{-}O\cdot + SO_4{}^{2-}$$

$$Fe^{2+} + {}^{-}O_3S\text{-}O\cdot \longrightarrow Fe^{3+} + SO_4{}^{2-}$$

or

$$Fe^{2+} + ROOH \longrightarrow Fe^{3+} + {}^{-}OH + \cdot OR$$

or

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {}^{-}OH + \cdot OH$$

(Fenton's Reagent)

IN THE DRAWINGS

FIGS. 1 and 2 are graphs representing dissolution rates, in percent drug released vs. time, from a pharmaceutical tablet containing PVP of differing K-values.

FIG. 3 is a graph representing compressibility, expressed in hardness (kp) vs. force (kg), for a pharmaceutical tablet containing PVP of differing K-values.

FIG. 4 is a graph representing friability, in percent vs. force (kg) for a pharmaceutical tablet containing PVP of differing K-values.

In accordance with another aspect of the invention, a pharmaceutical tablet is provided herein which has an enhanced drug dissolution rate and consists essentially of an active pharmaceutical ingredient and polyvinylpyrrolidone having a K-value in excess of 116, preferably 119-140. This PVP binder is present in an amount of about 0.5-10% by weight of the tablet. The product is further characterized by lower friability and superior compressibility, as compared to similar tablets using PVP of lower K-values. Preferably, the PVP of the present invention has a viscosity average molecular weight of at least one million, a weight average molecular weight of at least two million, and a relative viscosity of at least 1.2, most preferably about 1.2-1.5. Preferably, also, the tablet contains a suitable filler and/or lubricant. In the most preferred form of the invention, the pharmaceutical tablet consists essentially of, by weight, about 10-25% of poorly water-soluble drug, about 2-10% of PVP K-116-140, about 0.5-2% of a lubricant and about 65-85% of a filler, and is made by compression using wet granulation.

Pharmaceutical tablets were prepared by direct compression (A) or using wet granulation followed by compression (B).

A. Tablets by Direct Compression

All ingredients, except magnesium stearate, were blended in a twin-shell blender for 12 minutes. Magnesium stearate then was added and blended for an additional three minutes. The mixture was then compressed on a Stokes B-2 rotary press to produce tablets of uniform weight (450 mg) and hardness of 8-10 KP.

B. Tablets by Wet Granulation

1. Granulating Solution - In each formulation the binder consisted of PVP K-140 or PVP K-120 or PVP K-90 (50 g.) or Plasdone K-29/32 (100 g.) dissolved in purified water (450 g. for PVP K-90 or Plasdone K-120 and 300 g. for PVP K-29/32). The mixing time was 30 minutes for all binder solutions.

2. Granulation - Acetaminophen (1500 g.) was transferred in a planetary mixer and 300 g. of the granulating solution was added slowly and mixed for 5 minutes at a speed number 1. To ensure even and complete granulation, the mixing blades and the bowl were scraped well with a spatula before allowing the granulation to mix for another 10 minutes at speed #2 (total mixing time - 15 minutes). The granulation end point was reached when the moistened powder mass had a "snowball" consistency and no dry powder was detected in the bowl. The sides of the mixer bowl could be easily cleaned by the movement of the formed granules.

The wet milling step was accomplished by passing the granulation through a Newark #30 screen by hand. The milled batch was placed on paper-lined trays and introduced into an over set at 40°C. for about 4 hours. The dried granules were passed through a 12-mesh screen using an oscillator (Erweka AR 400). Lubrication was performed by mixing magnesium stearate (0.5% of the weight of the milled batch to be tableted) for 3 minutes in a twin-shell v. blender.

3. Tableting - The tablets were compressed on a rotary tablet-press (Stokes B-2) to a targeted mass of 200 mg. The compressed force was also monitored during the tableting operation utilizing an oscillascope.

A. TABLET BY DIRECT COMPRESSION

EXAMPLE 1

CONTROL (NO PVP)

INGREDIENTS	PERCENT
Sulfathiazole	22.2
Fast-Flo Lactose/Ditab (1:1)	76.8
Magnesium Stearate	1.0
	100.0

WITH PVP

Sulfathiazole	22.2
Fast-Flo Lactose/Ditab (1:1)	71.8
PVP K-29/32, PVP K-90, PVP K-120 or PVP K-140	5.0
Magnesium Stearate	1.0
	100.0

EXAMPLE 2

CONTROL (NO PVP)

INGREDIENTS	PERCENT
Hydrochlorothiazide	10.0
Fast-Flo Lactose/Ditab (1:1)	89.0
Magnesium Stearate	1.0
	100.0

WITH PVP

Hydrochlorothiazide	10.0
Fast-Flo Lactose/Ditab (1:1)	84.0
PVP K-29/32, PVP K-90, PVP K-120 or PVP K-140	5.0
Magnesium Stearate	1.0
	100.0

B. TABLET BY WET GRANULATION

EXAMPLE 3A

WET GRANULATION	PERCENT
Acetaminophen	83.0
PVP K-29/32	4.2
Water	12.8
	100.0

EXAMPLE 3B

WET GRANULATION	PERCENT
Acetaminophen	83.3
PVP K-90, K-120 or K-140	1.7
Water	15.0
	100.0

TABLET	PERCENT
Acetaminophen Granule	99.5
Magnesium Stearate	0.5
	100.0

PERFORMANCE TESTS

1. Dissolution - This test was performed on tablets stored for more than 12 hours after compression, using USP dissolution apparatus 2 (Vanderkamp 6000) with a paddle rotational speed of 100 rpm. Aqueous 0.1 N-HCl was utilized as the dissolution medium (900 ml). The amount of sulfathiazole or hydrochlorothiazide released in the medium as a function of time was determined using a UV spectrometer which measured the peaks at 280 nm (sulfathiazole) and 272 nm (hydrochlorothiazide).

2. Hardness - The tablet hardness was determined 24 hours after compression using a Model HT-300 (Key International Inc.) hardness tester. 10 Tablets were tested for each batch and the mean value was calculated. Hardness is measured in kilopounds (KP) (1 KP = 9.8 Newtons).

3. Friability - 10 tablets were weighed and placed in a friabilation apparatus and rotated on a wheel for 4 minutes at 25 rpm. Then the tablets were placed on a screen to allow any powder to pass through. The 10 tablets were reweighed. The results are expressed as follows:

$$\text{Friability} = \frac{\text{(Initial weight) - (Final Weight) X 100}}{\text{Initial Weight}}$$

RESULTS

DISSOLUTION RATE PROFILE

FIGURE 1 AND 2. The T-60 (time to release 60% of the drug - See Table 1) for sulfathiazole and hydrochlorothiazide with Plasdone® K-120 is faster than with no Plasdone® (sulfathiazole - > 3.75 times; hydrochlorothiazide - 2.25 times); Plasdone® K-29/32 (sulfathiazole - > 1.14 times; hydrochlorothiazide - 1.55 times) and Plasdone® K-90 (sulfathiazole - > 2.18 times; hydrochlorothiazide - 1.73 times).

COMPRESSION FORCE PROFILE

FIGURE 3. Plasdone® K-120 when compressed at 1500 kg. yielded tablets with 8-10 kp whereas Plasdone® K-29/32 and K-90 each required at least 2000 kg to yield tablets with the same hardness.

FRIABILITY

FIGURE 4. Friability results for tablets containing Plasdone® K-120 at 1500 kg force were 0.9% (sulfathiazole), 0.5% (hydrochlorothiazide) whereas tablets made with Plasdone® K-29/32 and Plasdone® K-90 at the same compression force were 1.4% (sulfathiazole), 0.8% (hydrochlorothiazide) and 1.7% (sulfathiazole), 0.9% (hydrochlorothiazide) respectively.

TABLE 1

DISSOLUTION RATE OF TABLETS (T-60)

	PHARMACEUTICALLY ACTIVE INGREDIENT		
TABLETS PREPARED BY USING	SULFATHIAZOLE (EX. 1)	HYDROCHLOROTHIAZIDE (EX. 2)	ACETAMINOPHEN (EXS. 3A and 3B)
No Plasdone® (Control)	> 120 min	90 min	-
Plasdone® K-29/32	105 min	58 min	222 min
Plasdone® K-90	55 min	52 min	128 min
Plasdone® K-120	32 min	40 min	95 min
Plasdone® K-140	19 min	30 min	81 min

TYPICAL PHARMACEUTICALLY - ACTIVE INGREDIENTS

Sulfathiazole	Sulfadiazine
Acetaminophen	Probenicid
Acetazolamide	Hydrochlorothiazide
Amoxicillin	Hydrocortisone
Aspirin	Hydroflumethiazide
Acetohexamide	Ibuprofen
Chloroambucil	Iodogninol
Chlorothiazide	Levodopa
Chloramphenicol	Mebendazole
Codeine	Mephobarbital
Diazepam	Meprobamate
Diethylstibesterol	Methazolamide
Dipyramidole	Methotrexate
Frgocalciferol	Metronidazole
Frythromycin	Naproxen
Fluoxymesterone	Norfloxacin
Furazolidone	Oxymetholone
Glutethiamide	Oxyphenbutazone
Griseofulvin	Oxytetracycline
Polythiazide	Pindolol
Sulfamerazine	Sulfamethizole
Sulfamethoxazole	Trichlormethiazide

Preparation of Polyvinylpyrrolidone
(TAPP Initiator)

EXAMPLE 4

A 2-liter reactor provided with agitation, gas inlet, condenser, and thermocouple was charged with 270 g. (2.3 moles) of non-stabilized vinylpyrrolidone monomer, which was buffered with a solution of 0.27 g. of tetrasodium pyrophosphate in 1,080 g. of deionized water. The reactor was swept clean of oxygen by admitting nitrogen gas through the inlet tube. Then the reactor was heated to 55°C. and 0.25 g. of t-amylperoxy pivalate (TAPP) was added (< 0.1% by wt. of vinylpyrrolidone). The mixture was heated at 56°-59°C. for 5 hours, whereupon an additional 0.25 g. of TAPP was added and the reaction continued for 2 hours. At the end of the reaction period, the mixture was heated to 85°C. and held at this temperature until the residual peroxide level was less than 500 ppm. The product included 21% solids; the residual monomer content was 0.04%. The PVP polymer product in water thus-obtained was characterized by being substantially linear, a K-value of 90, low residual initiator level, and excellent water dissolution.

EXAMPLE 5 (t-BPP)

A 5-liter reactor equipped with a turbine agitator, N_2 gas subsurface sparge, condenser and thermocople was charged with 3,326 g. of deionized water, 1.6 g. of NH_4OH (38% NH_3) and 2-5 ppm EDTA. Then was added 1,000 g. of unstabilized vinyl pyrrolidone, the mixture sparged with N_2 and heated to 55°C. t-Butylperoxy pivalate (0.23 g.) was added and the polymerization begun as evidenced by a modest exotherm.

The temperature was maintained at 70-80°C. for 2 hours and residual VP measured. Small charges of t-BPP (0.05 grams) were added as requird to bring the residual VP to below 0.1%. Thereafter the temperature was raised to 85°C. until residual peroxide was less than 500 ppm; the solids level was 17-18%. The aqueous solution then was dried and milled to provide the polymer in powder form.

EXAMPLE 6 (t-BPP)

A 12-liter four-necked flask equipped with mecahnical stirrer, reflux condenser, thermometer, and glass stopper was purged with nitrogen for 15 minutes. 1150 g. of vinylpyrrolidone and 3850 g. of distilled water were then charged and a poitive nitrogen pressure was maintained throughout the reaction. The reactants were heated to 55°C., in 20 minutes and 3 ml of t-butylperoxy pivalate was then added to the vinylpyrrolidone/water mixture through one of the necks of the flask. The temperature of the reactor was then maintained at 55°C. for 3 hours after which the system was heated to 80°C. in one-half hour and maintained at 80°C. for another 15 minutes. The reactor was then cooled to room temperature and the product discharged. The product had the following properties.

Density	0.8493 gm/ml
K value	91.1
APHA color	5/10
vinylpyrrolidone	0.054 wt %

EXAMPLE 7

The procedure of Example 4 was followed using 2,2'-azobis(isobutyronitrile) as the initiator with similar results.

EXAMPLE 8

The procedure of Example 4 is followed using hydrogen peroxide-potassium persulfate redox catalyst with similar results.

EXAMPLE 9

The procedure of Example 4 was followed using t-butylperoxy benzoate. The PVP polymer obtained (K-90) had a relatively poorer water dissolution than the PVP polymer of Example 4.

EXAMPLE 10

A. Pharmaceutical tablets were prepared using acetaminophen as the active ingredient and 1% and 2% by weight of the PVP powder prepared as in Example 4. The tablet was immersed in water and the amount of tablet dissolved with time was determined.

B. A similar pharmaceutical tablet was prepared using PVP prepared using the t-butylperoxy benzoate initiator of Example 9.

The tablets thus prepared were compared with respect to water dissolution at various periods of shelf-life. The results are shown in Tables 2 and 3 below.

TABLE 2*

Ex. No.	Shelf-Life (months)	Total % of Tablet Dissolved Immersion Time (min) 60	120	180	240	300
10-A	0	36.4	52.8	63.0	70.4	77.0
10-B	0	33.6	50.4	61.1	68.9	75.4
10-A	1 at 45°C.	33.0	49.7	60.8	68.8	75.1
10-B	1 at 45°C.	30.4	46.3	56.3	63.8	69.6

* 1% PVP level

TABLE 3*

Ex. No.	Shelf-Life (months)	Total % of Tablet Dissolved Immersion Time (min) 60	120	180	240	300
10-A	0	43.9	63.8	74.7	80.7	84.9
10-B	0	33.8	55.4	65.3	71.1	75.5
10-A	1 at 45°C.	42.5	59.3	69.1	76.1	81.1
10-B	1 at 45°C.	38.9	56.0	65.3	71.1	75.5

* 2% PVP level

The results shown in Tables 2 and 3 demonstrate that pharmaceutical tablets made with PVP prepared using t-amylperoxy pivalate as initiator dissolved in water at a significantly greater rate, e.g., after 1 month at 45°C., than similar tablets prepared using PVP binders made from t-butylperoxy benzoate initiated polymerizations.

EXAMPLE 11

The comparative experiments of Example 10 were repeated using hydrochlorothiazide as the active pharmaceutical ingredient in the tablet. Similar results were obtained with respect to dissolution rate of the tablet in water.

EXAMPLE 12

Comparative experiments also were carried out using acetylsalicylic acid, chloramphenicol, chloropromazine, methyl paraben, sulfothiazole, trimethoprine, and various non-sterioidal anti-inflammatory drugs as the active pharmaceutical ingredients at 1 and 2% levels in place of acetaminophen in Examples 10A and 10B. Similar differences in dissolution rates were obtained.

WHAT IS CLAIMED IS:

1. A pharmaceutical tablet having an enhanced dissolution rate even after an extended shelf-life consisting essentially of an active pharmaceutical ingredient and 0.5-10% by weight of PVP as a binder therefor, said PVP being prepared by polymerizing vinyl pyrrolidone in the presence of a polymerization initiator selected from a peroxyester free radical initiator whose thermal homolysis reaction provides free radicals which are weak hydrogen abstractors, an azo initiator, or a redox initiator, and said PVP is characterized by being a substantially linear; non-crosslinked polymer having a high degree of water solubility.

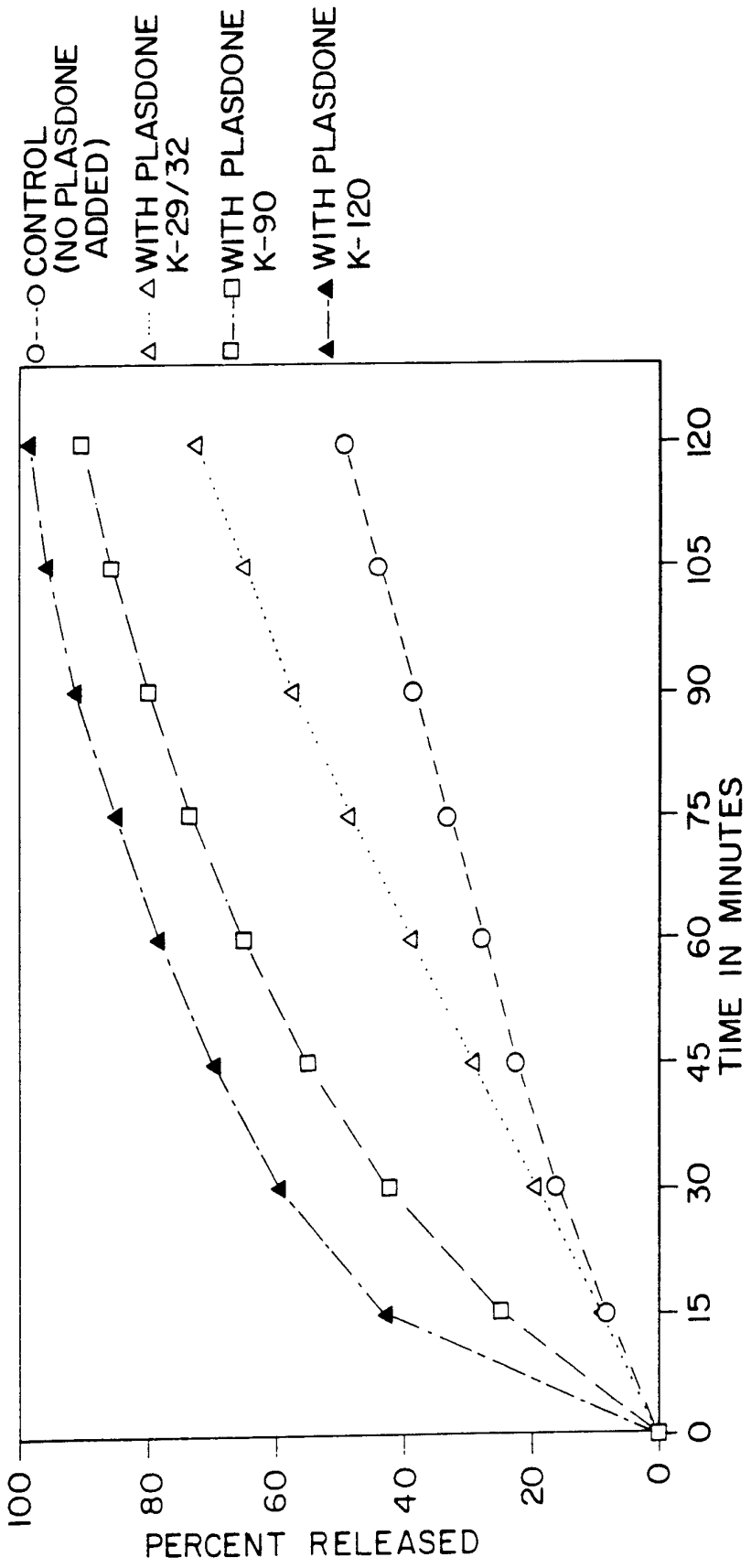
2. A pharmaceutical tablet according to claim 1 wherein said PVP has a residual initiator level of less than 500 ppm.

3. A pharmaceutical tablet according to claim 2 wherein said PVP product is subjected to a post-heat treatment to reduce the initiator level to less than 500 ppm.

4. A pharmaceutical tablet which is characterized by an enhanced drug dissolution rate, low tablet friability and superior tablet compressibility consisting essentially of a pharmaceutically active ingredient and PVP having a K-value in excess of 116, preferably 119-140, as a binder, optionally with a filler or a lubricant, or both, prepared by wet granulation or direct compression, having a PVP viscosity average molecular weight of at least one million, a weight average molecular weight of at least two million and a relative viscosity of at least 1.20.

5. A pharmaceutical tablet according to claim 4 characterized by about 10-98% of a poorly water-soluble drug, about 2-10% of PVP K-116-140, about 0.5-2% of a lubricant, 0-3% disintegrant, and about 0-85% of a filler.

FIG. 1


CONTROL (NO PLASDONE ADDED)
WITH PLASDONE K-29/32
WITH PLASDONE K-90
WITH PLASDONE K-120
PERCENT RELEASED
100
80
60
40
20
0
0
15
30
45
60
75
90
105
120
TIME IN MINUTES

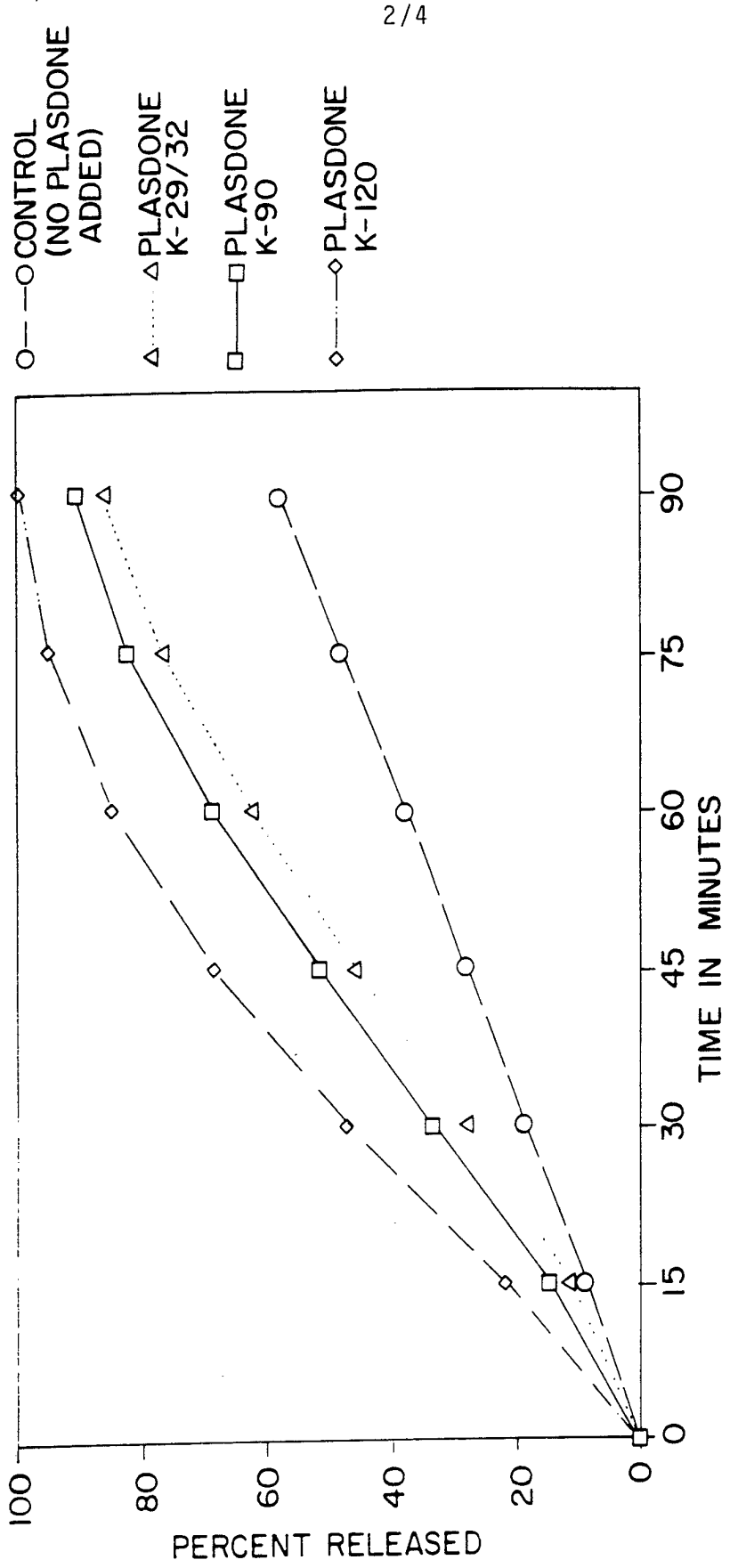
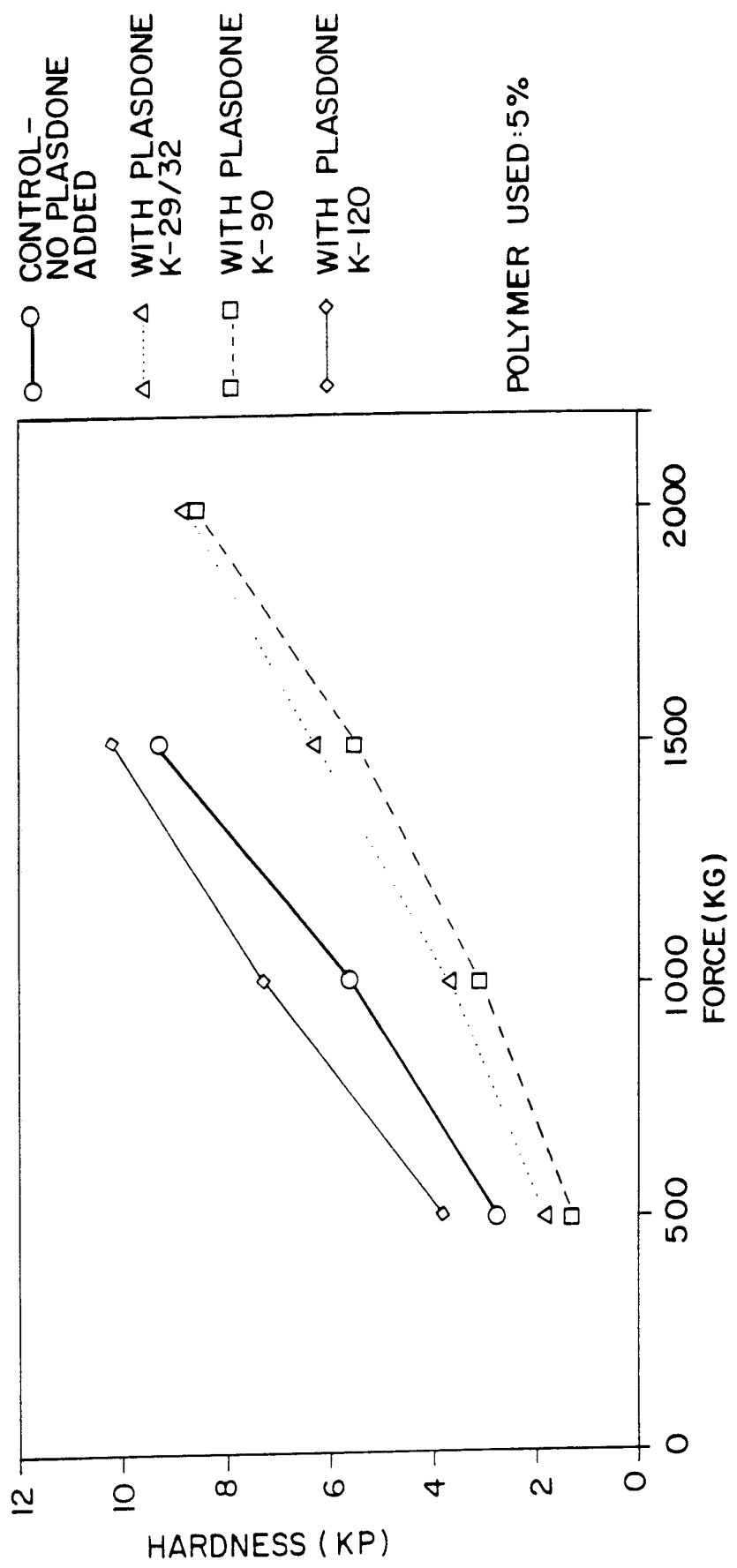

CONTROL (NO PLASDONE ADDED)
PLASDONE K-29/32
PLASDONE K-90
PLASDONE K-120
PERCENT RELEASED
100
80
60
40
20
0
TIME IN MINUTES
0
15
30
45
60
75
90

FIG.2

FIG.3


CONTROL-
NO PLASDONE
ADDED
WITH PLASDONE
K-29/32
WITH PLASDONE
K-90
WITH PLASDONE
K-120
POLYMER USED:5%
HARDNESS (KP)
FORCE (KG)
0
2
4
6
8
10
12
0
500
1000
1500
2000

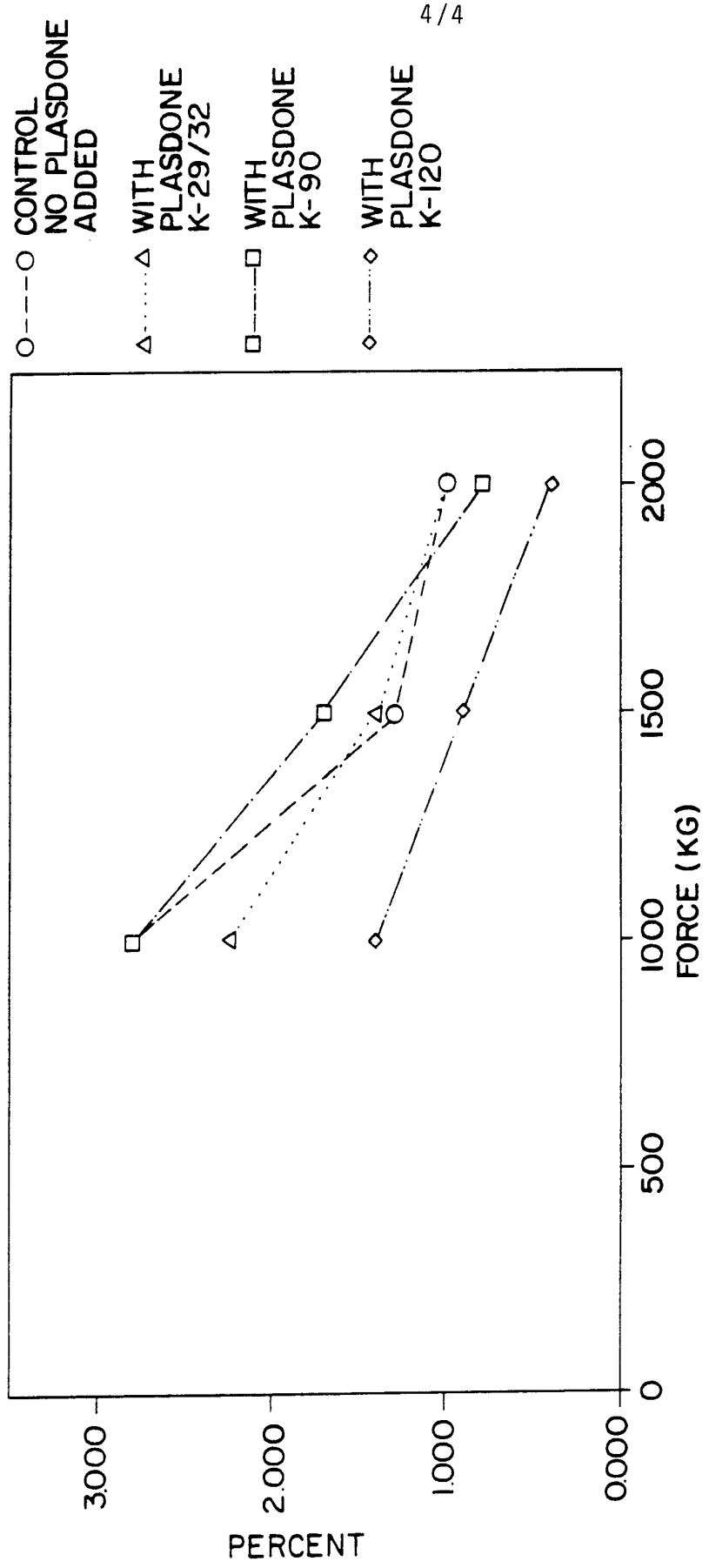

CONTROL NO PLASDONE ADDED
WITH PLASDONE K-29/32
WITH PLASDONE K-90
WITH PLASDONE K-120
0
500
1000
1500
2000
FORCE (KG)
0.000
1.000
2.000
3.000
PERCENT

FIG.4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/09821

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/14
US CL :424/484

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)

U.S. : 424/484, 467, 469, 473, 499

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,344,934 (MARTIN ET AL) 17 AUGUST 1982; See entire document.	1-5
Y	US, A, 5,009,897 (BRINKER ET AL) 23 APRIL 1991; See entire document.	1-5
Y	US, A, 5,035,897 (AYER ET AL) 30 JULY 1991 See entire document.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 29 DECEMBER 1992	Date of mailing of the international search report 24 MAR 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer WILLIAM E. BENSTON, JR. Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

Development of Fast Dispersible Aceclofenac Tablets: Effect of Functionality of Superdisintegrants

C. Mallikarjuna Setty, D. V. K. Prasad, [...], and B. Sa

Abstract

Aceclofenac, a non-steroidal antiinflammatory drug, is used for posttraumatic pain and rheumatoid arthritis. Aceclofenac fast-dispersible tablets have been prepared by direct compression method. Effect of superdisintegrants (such as, croscarmellose sodium, sodium starch glycolate and crospovidone) on wetting time, disintegration time, drug content, *in vitro* release and stability parameters has been studied. Disintegration time and dissolution parameters ($t_{50\%}$ and $t_{80\%}$) decreased with increase in the level of croscarmellose sodium. Where as, disintegration time and dissolution parameters increased with increase in the level of sodium starch glycolate in tablets. However, the disintegration time values did not reflect in the dissolution parameter values of crospovidone tablets and release was dependent on the aggregate size in the dissolution medium. Stability studies indicated that tablets containing superdisintegrants were sensitive to high humidity conditions. It is concluded that fast-dispersible aceclofenac tablets could be prepared by direct compression using superdisintegrants.

Keywords: Fast dispersible tablets, aceclofenac, croscarmellose sodium, sodium starch glycolate, crospovidone, disintegration time, dissolution

Aceclofenac, (2-[2-[2-(2,6-dichlorophenyl)aminophenyl]acetyl]oxyacetic acid), a nonsteroidal antiinflammatory drug (NSAID) has been indicated for various painful indications[1] and proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse effects and thus, resulted in a greater compliance with treatment[2]. Aceclofenac is practically insoluble. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. Clear aceclofenac-loaded soft capsules have been prepared to accelerate the absorption[3]. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion)[4]. The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.

Of all the orally administered dosage forms, tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing. Because of changes in various physiological functions associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy. The paediatric and geriatrics patients are of particular concern. To overcome this, dispersible tablets[5] and fast-disintegrating tablets[6] have been developed. Most commonly used methods to prepare these tablets are; freeze-drying/Lyophilization[7], tablet molding[8] and direct-compression methods[9]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in oral cavity[7,10]. The main disadvantages of tablets produced are, in addition to the cost intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug[5]. Moulded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern[8,11]. Main advantages of direct compression are, low manufacturing cost and high mechanical integrity of the tablets[9,12]. Therefore, direct-compression appears to be a better option for manufacturing of tablets. The fast disintegrating tablets prepared by direct compression method, in general, are based on the action established by superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate. The effect of functionality differences of the superdisintegrants on tablet disintegration has been studied[13]. The objective of the present work was to develop fast dispersible aceclofenac tablets and to study the effect of functionality differences of superdisintegrants on the tablet properties and to provide information on the storage conditions of these tablets.

MATERIALS AND METHODS

Aceclofenac (Aristo Pharmaceuticals Ltd, Mumbai, India), croscarmellose sodium, sodium starch glycolate, and microcrystalline cellulose (Maple Biotech Pvt Ltd., Pune, India), aspartame (Ranbaxy, New Delhi, India). Crospovidone (Concertina Pharma Pvt., Ltd, Hyderabad, India). Talc and magnesium stearate were purchased from S. D. Fine Chem Ltd., Mumbai India.

Blending and tableting:

Tablets containing 100mg of aceclofenac were prepared by direct compression method and the various formulae used in the study are shown in Table 1. The drug, diluents, superdisintegrant and sweetener were passed through sieve # 40. All the above ingredients were properly mixed together (in a poly-bag). Talc and magnesium stearate were passed through

sieve # 80, mixed, and blended with initial mixture in a poly-bag. The powder blend was compressed into tablets on a ten-station rotary punch-tableting machine (Rimek Mini Press-1) using 7 mm concave punch set.

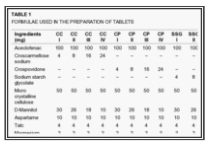


TABLE 1

FORMULAE USED IN THE PREPARATION OF TABLETS

Evaluation of dispersible tablets:

Tablets were evaluated for weight variation, hardness, friability, thickness and disintegration time[14], wetting time[15] and stability[16]. In weight variation test, twenty tablets were selected at random and average weight was determined using an electronic balance (Shimadzu, AX200, Japan). Tablets were weighed individually and compared with average weight. The Pfizer hardness tester and the Roche friabilator were used to test hardness and friability loss respectively. Disintegration time was determined using USP tablet disintegration test apparatus (ED2L, Electrolab, India) using 900 ml of distilled water without disk at room temperature (30°)[13]. Thickness of tablet was determined by using dial caliper (Mitutoya, Model CD-6 CS, Japan). To measure wetting time of tablet, a piece of tissue paper was folded twice and placed in a small Petri dish containing sufficient water. A tablet was kept on the paper and the time for complete wetting of tablet was measured.

Stability studies:

The stability of selected formulations was tested according to International Conference on Harmonization guidelines for zone III and IV. The formulations were stored at accelerated (40± 2°/75±5% RH) and long-term (30±2°/65±5% RH) test conditions in stability chambers (Lab-Care, India) for six months following open dish method[17]. At the end of three months, tablets were tested for disintegration time, hardness friability, thickness, drug content and moisture uptake.

Dissolution Study:

In vitro release of aceclofenac from tablets was monitored by using 900 ml of SIF (USP phosphate buffer solution, pH 7.4) at 37±0.5° and 75 rpm using programmable dissolution tester [Paddle type, model TDT-08L, Electrolab, (USP), India]. Aliquots were withdrawn at one minute time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions, were assayed spectrophotometrically (UV-1700, Shimadzu, Japan) at 274 nm.

Statistical analysis:

Each tablet formulation was prepared in duplicate, and each analysis was duplicated. Effect of formulation variables on disintegration time and release parameters ($t_{50\%}$ and $t_{80\%}$) were tested for significance by using analysis of variance (ANOVA: single factor) with the aid of Microsoft® Excel 2002. Difference was considered significant when $P < 0.05$.

RESULTS AND DISCUSSION

Since, the flow properties of the powder mixture are important for the uniformity of mass of the tablets, the flow of the powder mixture was analyzed before compression to tablets. Low Hasner`s ratio (≤1.32), compressibility index (≤24.68) and angle of repose (≤18.13) values indicated a fairly good flowability of powder mixture. As the tablet powder mixture was free flowing, tablets produced were of uniform weight with acceptable weight variation (≤4.68%) due to uniform die fill. Hardness (3.63-4.31 kg/cm^2) and friability loss (0.15-0.72 %) indicated that tablets had a good mechanical resistance. Drug content was found to be high (≥96.2%) and uniform (coefficient of variation between 0.89-2.56%) in all the tablet formulations.

The most important parameter that needs to be optimized in the development of fast dispersible tablets is the disintegration time of tablets. In the present study, all the tablets disintegrated in ≤57.5 sec fulfilling the official requirements (<3 min) for dispersible tablets[18]. Fig. 1 depicts the disintegration behavior of the tablets in water. It is observed that the disintegration time of the tablets decreased (from 28.25 to 17 sec) (P<0.05) with increase in the level of croscarmellose sodium. In case of tablets containing crospovidone, increasing level of crospovidone had no effect (P>0.05) on the disintegration times of the tablets. However, disintegration time increased (P<0.05) with increase in the level of sodium starch glycolate in the tablets. It indicates that increase in the level of sodium starch glycolate had a negative effect on the disintegration of the tablets. At higher levels, formation of a viscous gel layer by sodium starch glycolate[19] might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or

leakage of tablet contents. Thus, tablet disintegration is retarded to some extent with tablets containing sodium starch glycolate. Comparatively, disintegration times of the tablets containing crospovidone<croscarmellose sodium<sodium starch glycolate. The disintegration times of crospovidone containing tablets are comparatively lower than those containing croscarmellose sodium and sodium starch glycolate. The faster disintegration of crospovidone tablets may be attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation[20]. Thus, these results suggest that the disintegration times can be decreased by using wicking type of disintegrants (crospovidone).

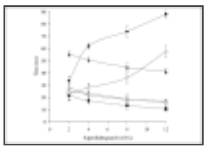


Fig. 1
Effect of concentrations of sodium starch glycolate (—◦—), croscarmellose sodium (—Δ—) and crospovidone (—□—) on disintegration time and sodium starch glycolate (—•—), ...

Since the dissolution process of a tablet depends upon the wetting followed by disintegration of the tablet, the measurement of wetting time may be used as another confirmative test for the evaluation of dispersible tablets. Fig. 1 depicts the wetting times for tablets prepared with three superdisintegrants. Wetting times of the tablets did not change (P>0.05) with increase in the croscarmellose sodium from 2-4%. However, wetting times decreased (P<0.05) with increase in the level of croscarmellose above 4%. A significant decrease (P<0.05) in the wetting times is seen with increase in the level of crospovidone (4 to 12%). It is interesting to note that wetting times increased (P<0.05) with increase in the level of sodium starch glycolate from 2% to 12% in the tablets. Thus wetting times of tablets with crospovidone<croscarmellose sodium<sodium starch glycolate. These results are in consistent with disintegration test results.

The influence of superdisintegrants on the dissolution of aceclofenac from the tablets is shown in figs. 2-4. The $t_{50\%}$ and $t_{80\%}$ (time for 50% and 80% of release) values decreased (P<0.05) with increase in the level of croscarmellose sodium. However, $t_{50\%}$ and $t_{80\%}$ values increased (P<0.05) with increase in the level of sodium starch glycolate. While $t_{50\%}$ and $t_{80\%}$ values did not change (P>0.05) with increase in the level of crospovidone. These results indicated that dissolution parameter values of croscarmellose sodium and sodium starch glycolate containing tablets are in consistent with the disintegration time values observed. However, disintegration time values observed with crospovidone tablets are not predictable of dissolution of the drug. The rapid increase in dissolution of aceclofenac with the increase in croscarmellose sodium may be attributed to rapid swelling and disintegration[20] of tablet into apparently primary particles[13] (fig. 5a). While, tablets prepared with sodium starch glycolate, disintegrate by rapid uptake of water, followed by rapid and enormous swelling[20] into primary particle but more slowly[13] (fig. 5b) due to the formation of a viscous gel layer by sodium starch glycolate[19]. Crospovidone exhibits high capillary activity and pronounced hydration with a little tendency to gel formation[20] and disintegrates the tablets rapidly but into larger masses of aggregated particles[13] (fig. 5c). Thus, the differences in the size distribution generated and differences in surface area exposed to the dissolution medium with different superdisintegrants rather than speed of disintegration of tablets may be attributed to the differences in the $t_{50\%}$ and $t_{80\%}$ values with the same amount of superdisintegrants in the tablets. Thus, although the disintegration times were lower in crospovidone containing tablets, comparatively higher $t_{50\%}$ and $t_{80\%}$ values were observed due to larger masses of aggregates.

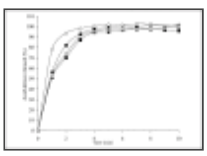


Fig. 2
Effect of croscarmellose sodium level on the release of aceclofenac.

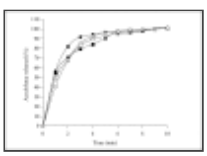


Fig. 4
Effect of crospovidone level release of aceclofenac.

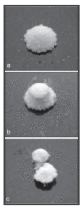


Fig. 5
Photographs showing disintegration of tablets in water after 20 sec.

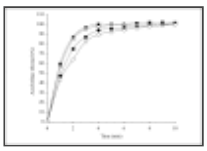


Fig. 3
Effect of sodium starch glycolate level on the release of aceclofenac

When tablets were kept at real time (30±2°/65±5% RH) and accelerated (40±2°/75±5% RH) storage conditions, both disintegration time and hardness values decreased significantly indicating that tablets have lost the mechanical integrity leading to more friability loss (Table 2). Increase in thickness of all tablets was noticed particularly pronounced in crospovidone tablets. These results indicate that, at higher relative humidity, tablets containing high concentration of superdisintegrants get softened and hence, must be protected from atmospheric moisture. As crospovidone tablets absorbed larger amount of moisture, tablets became fragile and developed cracks. After stability test period, some portion of the tablet edges was removed and hence, drug content, hardness, friability and disintegration tests could not be conducted on these tablets.

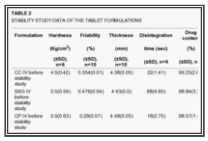


TABLE 2
STABILITY STUDY DATA OF THE TABLET FORMULATIONS

It is concluded that, although functionality differences existed between the superdisintegrants, the fast dispersible aceclofenac tablets could be prepared by using any of the superdisintegrants used. The dissolution parameters were consistent with disintegration times of croscarmellose sodium and sodium starch glycolate containing tablets. However, disintegration time values of crospovidone tablets were not correlating with dissolution profiles. Dispersible tablets prepared with superdisintegrants must be protected from atmospheric moisture.

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Research Article

DEVELOPMENT AND INVITRO EVALUATION OF FAST DISSOLVING TABLETS OF GLIPIZIDE

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ABSTRACT

In the present work, fast dissolving tablets of glipizide were prepared by direct compression method with a view to enhance patient compliance. Two superdisintegrants viz, crospovidone and croscarmellose sodium (4%, 5%, 6%) with different binders viz, pvp k-30 and pregelatinized starch (3%) were used. The prepared batches of tablets were evaluated for hardness, friability, weight variation, disintegration, wetting time, drug content and in vitro dissolution studies. Based on evaluating parameters, Formulation prepared by using 5% croscarmellose sodium with 3% PVP K30 was selected as optimized formulation. Finally, the optimized formulation was compared with marketed conventional formulation. Stability studies were carried out at 25ºC / 60% RH and 40ºC / 75% RH for optimized formulation for 2 months. Stability studies on the optimized formulation indicated that there was no significant change found in physical appearance, disintegration time and wetting time of the tablets.

Keywords: Fast Dissolving Tablets, Glipizide, Superdisintegrants, Direct Compression.

INTRODUCTION

Many patients express difficulty in swallowing tablets and hard gelatine capsules, resulting in non-compliance and ineffective therapy[1]. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach led to development of fast dissolving tablets[2-4]. Advantages of this drug delivery system include administration without water, convenience of administration and accurate dosing as compare to liquids, easy portability, ability to provide advantages of liquid medication in the form of solid preparation, ideal for paediatric and geriatric patients and rapid dissolution/absorption of the drug, which may produce rapid onset of action. Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down in to stomach and in such cases bioavailability of drug is increased, pre-gastric absorption can result in improved bioavailability and as result of reduced dosage form, improved clinical performance through a reduction of unwanted effects. Glipizide is a second-generation oral sulfonylurea hypoglycemic agent to lower the blood sugar in patients with non- insulin dependent diabetes dependent diabetes mellitus. Mechanism of action is produced by blocking potassium K^+ channels in beta cells of islets of Langerhans. The increase in calcium will initiate more insulin release from each beta cell. It increases the concentration of insulin in the pancreatic vein. By this, it decreases glucose concentration[5].

MATERIALS AND METHODS

Materials

All the materials including superdisintegrants were obtained from Lincoln pharmaceuticals Ltd, Ahmedabad. All other reagents were of analytical grade.

Methods

Formulation of fast dissolving tablets by direct compression method[6]

All the ingredients were weighed and passed through #60 mesh separately. Then the ingredients were mixed and compressed in to tablet using 6.5mm flat-faced punches on 16 station rotary tablet machine (Lincoln Pharmaceuticals Ltd, Ahmedabad.) The blend was compressed into tablets. Formulations of Glipizide FDTs by direct compression method are shown in Table 1.

Table 1: Formulation of Glipizide FDTs by direct compression method

INGREDIENTS	FD_1 (mg)	FD_2 (mg)	FD_3 (mg)	FD_4 (mg)	FD_5 (mg)	FD_6 (mg)	FD_7 (mg)	FD_8 (mg)	FD_9 (mg)	FD_{10} (mg)
Glipizide	5	5	5	5	5	5	5	**5**	5	5
MCC	-	-	-	-	-	-	85	**85**	85	85
DCP	86	85	84	86	85	84	-	**-**	-	-
Crospovidone	4	5	6	-	-	-	5	**-**	5	-
Croscarmellose sodium	-	-	-	4	5	6	-	**5**	-	5
PVP K-30	3	3	3	3	3	3	3	**3**	-	-
Pregelatinized starch	-	-	-	-	-	-	-	**-**	3	3
Aerosil	1	1	1	1	1	1	1	**1**	1	1
Mg. stearate	1	1	1	1	1	1	1	**1**	1	1

Evaluation parameters of fast dissolving tablets:

Hardness [7]

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Friability [7]

The friability of a sample of 20 tablets was measured using Roche friabilator (Electrolab, Mumbai, India). Twenty tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated. Friability below 1% was considered acceptable.

Weight variation test [7]

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

In vitro disintegration time[7]

The disintegration time of the tablet was measured in water (37±2°C) according to disintegration test apparatus with disk. The time in seconds taken for the complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds. Three tablets from each batch (formulation) were tested for the disintegration time calculations.

Wetting time[8]

A piece of tissue paper folded twice was placed in a small petridish (ID= 6.5 cm) containing 6 ml of simulated saliva pH 6.8, a tablet was put on the paper, and the time for complete wetting was measured.

In vitro dissolution profile[9]

Dissolution studies were carried out by USP paddle method at 37 ± 0.5^0 c, taking 900ml of

phosphate buffer pH 6.8 as a dissolution medium. Speed of rotation of paddle was set at 50 rpm. Absorbance of sample was measured at 276 nm by spectrometrically.

Stability studies[10]

Stability studies were carried out at 25^0c/60% RH and 40^0c/75% RH for 60 days for optimized formulation FD_8 according to ICH guidelines.

RESULT AND DISCUSSION

The present investigation was undertaken to formulate and evaluate fast dissolving tablets of glipizide by direct compression method using Croscarmellose sodium and crospovidone as a superdisintegrants. Superdisintegrants are generally used by formulation scientists for developing FDTs or for improvement of solubility for drugs. The primary requirement for both dosage forms is quicker disintegration. The amount of Superdisintegrants was optimized in the formulation of FDTs. The total 10 were formulation (FD_1-FD_{10}) prepared using different concentration of Croscarmellose sodium and crospovidone to study its effect on disintegration time.

The results for evaluation of different batches of Glipizide FDTs by direct compression method are shown in Table 2.

Table 2: Evaluation of direct compressible fast dissolving tablets

Formulation	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (%)	W.T. in Sec	D.T. in sec
FD_1	3.6	0.40	±4.5	38.00	20.16
FD_2	3.8	0.42	±4.8	36.46	18.48
FD_3	3.7	0.48	±5.6	41.11	20.11
FD_4	3.6	0.43	±5.9	34.50	20.12
FD_5	3.8	0.44	±6.0	37.30	18.32
FD_6	3.6	0.47	±4.6	42.07	19.48
FD_7	3.5	0.56	±4.9	18.19	12.12
FD_8	**3.5**	**0.58**	**±4.1**	**16.40**	**11.42**
FD_9	3.6	0.44	±5.8	28.38	16.52
FD_{10}	3.6	0.43	±5.5	24.44	16.00

Percent weight variation was observed between 4.1 and 6.0 which were well within the acceptable limit for uncoated tablets as per United States Pharmacopoeia. It is well known to formulation scientists that the tablets with more hardness show longer disintegration time. Since mechanical integrity is of paramount importance in successful formulation of FDTs, hence the hardness of tablets was determined and was found to be in the range of 3.5 to 3.8 Kg/cm^2. Friability was observed between 0.40 and 0.58%, which were below 1% indicating sufficient mechanical integrity and strength of prepared tablets. The disintegration time for all formulations was found to be 11-21 seconds and wetting time was 16-43 seconds.

The In vitro dissolution study was performed for all formulations and the results are shown in Table 3.

Table 3: Dissolution parameters of directly compressible fast dissolving tablets

Formulation	% Release after 2.5min	% Release after 5min	% Release after 10min	% Release after 15min	% Release after 20min
FD_1	40.11	58.95	82.93	92.81	96.21
FD_2	39.37	56.19	81.26	91.26	95.37
FD_3	39.93	57.43	81.74	91.43	95.11
FD_4	43.54	58.68	83.37	93.51	97.47
FD_5	41.13	56.70	80.24	90.67	94.58
FD_6	42.39	58.41	83.98	93.23	94.69
FD_7	46.75	59.96	88.02	98.89	99.00
FD_8	**51.35**	**62.70**	**89.74**	**99.28**	**99.89**
FD_9	49.96	59.67	85.78	96.68	98.00
FD_{10}	49.76	58.78	84.91	97.41	98.79

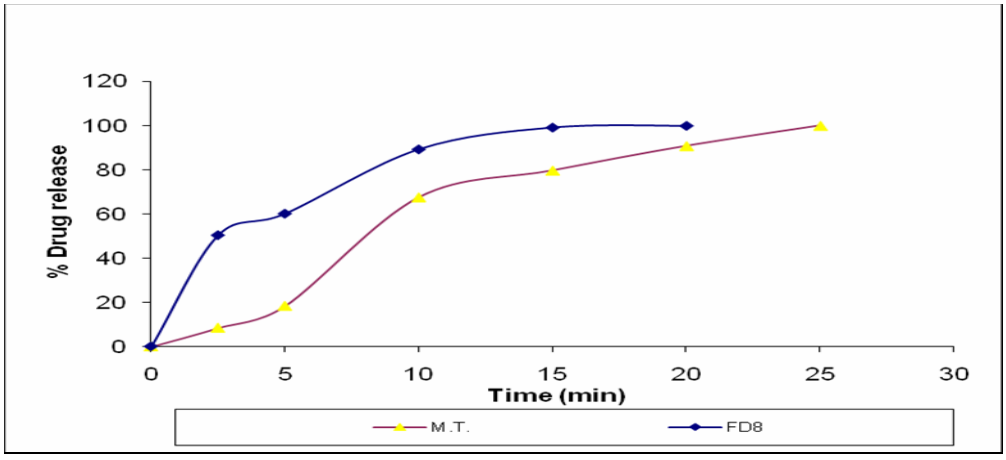
In vitro dissolution studies showed that more than 50% of the drug was released from the all formulations within 5 minutes. The FD_8 formulation containing croscarmellose sodium in concentration of 5% showed minimum disintegration time of 11.42 seconds, wetting time of 16.40 seconds and 51.35% drug and 99.89% drug was released within 2.5 and 20 minutes respectively.

The optimized formulation of FD_8 was compared with marketed tablet (Glucotrol 5mg) and the dissolution parameters of both formulations are shown in Table 4 and Fig 1.

Table 4: Comparison of dissolution profiles of Optimized formulation FD_8 with marketed tablet (Glucotrol 5mg)

Time (min)	% release of FD_8	% release of M.T.
2.5	50.32	8.47
5	60.08	18.36
10	89.16	67.50
15	99.01	79.61
20	99.78	90.68
25	-	99.87

Fig. 1: Comparison of dissolution profiles of Optimized formulation FD_8 with marketed tablet (Glucotrol 5mg)



From the dissolution studies, it was confirmed that the more than 99% drug release for optimized formulation was within 15 minutes, where as the marketed tablet showed the maximum release at 25 minutes.

Stability studies for optimized formulation FD_8 was carried out at 25^0c/60% RH and at 40^0c/75% RH and the results are shown in Table 5.

Table 5: Stability studies parameters for Optimized formulation FD_8

Time in Days	At 25ºC / 60% RH		At 40ºC / 75% RH	
	DT	WT	DT	WT
0	11.42	16.40	11.42	16.40
15	11.40	16.12	11.55	16.02
30	11.56	16.21	11.40	16.04
45	11.35	16.15	11.29	16.12
60	11.58	16.14	11.38	16.19

There was no significant variation found in physical appearance, disintegration time and wetting time of the tablets.

CONCLUSION

Fast dissolving tablets of Glipizide were prepared by direct compression method using Croscarmellose sodium and crospovidone as a superdisintegrants. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. In vitro drug release from the tablets shows significantly improved drug dissolution. It was concluded that in direct compression method, croscarmellose sodium was best superdisintegrant with pvpk-30 as binding agent. Hence it could be concluded that the superdisintegrant based fast dissolving tablets of Glipizide would providing quick onset of action without need of water for swallowing or administration. Further investigations are needed to confirm the in vivo efficiency.

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Development of a rapidly dispersing tablet of a poorly wettable compound—formulation DOE and mechanistic study of effect of formulation excipients on wetting of celecoxib

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Abstract

Celecoxib has extremely poor aqueous wettability and dispersibility. A dispersibility method was developed to study the effects of formulation excipients and processing methods on wetting of celecoxib. In this method, a tablet or powder was placed in water and the turbidity of the resulting "dynamic" suspension was measured. Higher turbidity values reflect better dispersibility. Results show that wet granulation facilitates better drug dispersion than does dry granulation or direct compression. Results from a screening formulation statistical design of experiments (DOE) show that sodium lauryl sulfate (SLS), an anionic surfactant, gives higher celecoxib dispersibility than polysorbate 80, a neutral surfactant. Polyplasdone XL as a disintegrant results in better celecoxib dispersibility than sodium starch glycolate. The binder Kollidon 30 leads to better dispersibility, but slower disintegration than Kollidon 12. Jet-milling celecoxib with excipients not only improves dispersibility of the drug but also the ease of material handling. The method of microcrystalline cellulose addition does not significantly impact tablet properties. The effect of critical formulation variables on the wettability of celecoxib was further examined in prototype formulations. It is found that ionic surfactant resulted in better dispersibility than a neutral surfactant, probably due to charge dispersion. Kollidon 30 gives better drug dispersion than hydroxypropylmethyl cellulose and hydroxypropyl cellulose. This may be explained through a surface energy calculation, where the spreading coefficients between Kollidon 30 and celecoxib indicate formation of open porous granules in which pores can facilitate water uptake. The mode of disintegrant addition also impacts dispersibility of the drug. Dense granules were formed when the disintegrant, Polyplasdone, was added intra-granularly. As the extra-granular portion of the disintegrant increases, the dispersibility of the drug increases as well. The drug initial dispersibility (turbidity at 5 min during the dispersibility test) increases as the tablet porosity increases. A 3-factor face-centered experimental design was conducted to optimize the levels of surfactant (SLS), binder (Kollidon 30) and disintegrant (Polyplasdone). Within the range that was studied, the dispersibility of micronized drug increases as the amount of SLS and Kollidon 30 increases. The level of Polyplasdone has no significant impact on the dispersibility of micronized drug; however, higher levels of Polyplasdone lead to significantly harder tablets.

Keywords: Wetting; Celecoxib; Dispersion; Disintegration; Surface energy; Porosity; Poorly soluble; Agglomeration

1. Introduction

According to the biopharmaceutical classification system (BCS), celecoxib is a BCS class II compound (Amidon et al., 1995) with an aqueous solubility of less than 5 μg/ml, and it is non-ionizable over the physiologic pH range. Earlier human pharmacokinetic studies suggested that dissolution of celecoxib is the rate-limiting step for its absorption (unpublished data). It is desirable to enhance the dissolution rate of the drug to increase its rate of absorption. According to the Noyes–Whitney equation

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(Noyes and Whitney, 1897), the rate at which a solid dissolves is directly proportional to the surface area of drug exposed to the dissolution medium. One common method of enhancing the dissolution rate, especially for poorly soluble compounds, is to increase the surface area of a drug through particle size reduction (Amidon et al., 2003). In this paper, we describe how fluid-bed jet milling can be used to reduce the drug particle size from a D50 of 7 μm to a D50 of 2 μm (50% of the mass of the particles in a sample are less than the diameter defined by D50). An early pharmacokinetic study in dogs showed that the bioavailability of a suspension containing jet-milled celecoxib is significantly enhanced (unpublished data). However, initial attempts to formulate jet-milled celecoxib into a tablet failed to match the *in vivo* performance of the suspension formulation. This is believed to be due to the fact that celecoxib is poorly wettable and tends to aggregate upon contact with water. The aggregation reduces the effective surface area of the drug, thereby diminishing or negating the benefit of particle size reduction. This is a common problem associated with formulating small particles of poorly wettable materials. Very often, a surfactant is added to a formulation to aid in wetting the drug (Buckton, 1995a). However, addition of a surfactant is not sufficient to solve the wetting problem of celecoxib. Despite the general importance of wetting on bioavailability of the poorly wettable compounds, methods to overcome the wetting problem by formulation manipulation are not well understood. The objectives of this study are three-fold. The first goal is to identify critical processing and formulation variables that influence the wetting properties of celecoxib. The second goal is to obtain a mechanistic understanding as to why certain excipients improve the dispersibility/wetting of celecoxib. The third goal is to optimize the excipient levels through statistical design of experiments (DOE) to maximize the dispersion of celecoxib.

2. Material and methods

2.1. Materials

Celecoxib, supplied by Pfizer, Inc. as is, has a particle size with a D50 of 7 μm and D90 of 16.7 μm. The drug was milled, either with or without excipients, using a fluid-bed jet mill (Alpine AFG-100, Hosakawa Micron, Summit, NJ) to achieve a particle size distribution with a D50 of 2 μm and a D90 of less than 4 μm. The following excipients are present in at least one of the formulations used in this study: spray dried lactose monohydrate (Foremost Farms USA, Baraboo, WI), sodium lauryl sulfate (SLS) (Stepan, Northfield, IL), polysorbate 80 (Uniquema, Newcastle, DE), cetrimide (Aldrich, Milwaukee, WI), sodium bicarbonate (SB) (Mallinkcrodt Baker Inc., Paris, KT), sodium starch glycolate (SSG) (Penwest Pharmaceuticals, Cedar Rapids, IA), microcrystalline cellulose (MCC), Avicel PH 101 (FMC, Philadelphia, PA), a variety of grades of povidone, including Kollidon 12, and Kollidon 30 (BASF Inc., Ludwigshafen, Germany), hydroxypropyl cellulose EXF NF (HPC) (Hercules Aqualon, Wilmington, DE), hydroxypropylmethyl cellulose (HPMC) 2910 3 cps (Biddle Sawyer, New York, NY), crosslinked povidone or Polyplasdone XL (ISP Inc., Wayne, NJ) and magnesium stearate (Mallinkrodt Inc., St. Louis, Missouri).

2.2. Manufacturing procedure

2.2.1. Effect of processing methods on celecoxib dispersibility

Three different processing methods were used to prepare a single tablet formulation, containing jet-milled celecoxib, lactose, SLS, povidone, MCC and Polyplasdone. These methods are: direct compression (DC), dry granulation (DG) and wet granulation (WG).

In the direct compression process, formulation components were mixed well in a bag prior to compression. In the dry granulation process, intra-granular components were mixed well in a plastic bag, then processed on a roller compactor (Model TF Mini, Freund Industrial Corp., Tokyo, Japan) at a screw feed rate of 52 rpm, roller speed of 8 rpm and a roller pressure of 65 kg/cm^2 (equivalent to 65 bar) to form ribbons. The ribbons were hand-screened through a 20-mesh screen and mixed with extra-granular excipients. In the wet granulation process, intra-granular excipients were mixed well in a bag, and placed into a mortar. A surfactant was dissolved in water (0.042 g surfactant per g of water) and sprayed onto the powder bed. An appropriate amount of solution was sprayed so that the sprayed surfactant is about 0.4% (w/w) of the final formulation. The resulting wet granules were hand-screened through a 20-mesh screen then dried in a vacuum oven (Model 5851, Napco Scientific Corp., Tualatin, Oregon) at room temperature for 2 h. The moisture level in the granules was tested with a Computrac Moisture Analyzer (Model MA-5A, Compu-Trac Inc., Tempe, AZ). The final moisture level ranged from 0.9% to 1.9% by weight. After drying, the granules were mixed with an appropriate amount of extra-granular excipients.

Prior to compression, upper and lower punches along with the die were lubricated with magnesium stearate to prevent sticking. Formulated powder was compressed into two sets of tablets with 14/32 in. round tooling with a standard concave punch using a Carver Press (Carver Inc., Wabash, Indiana). In one set, compression force was adjusted to achieve a target tablet hardness of 70.1 N; in the other set, tablets were manufactured to have the same porosity ($\sim 0.175 \pm 0.003$), defined as follows:

$$\text{porosity} = 1 - \frac{W}{V \times \rho} \quad (1)$$

where W is the tablet weight, V the tablet volume, ρ is the true density, which was measured by helium pyconometry (AccuPyc 1330, Micromeritics Inc., Norcross, GA). The tablet volume was determined from the physical dimensions of the tablet. Compression pressure was varied to create desired tablet thickness, while the tablet porosity remained the same for each lot. Tablets with the same porosity were analyzed by hardness and turbidity tests, while tablets with the same hardness were subject to a disintegration test.

Table 1
Prototype formula used in the screening formulation design of experiments

Material	Tablet (mg)	Percentage of the tablet (%, w/w)	Batch size (g)
Intra-granular			
Co-mill or blend[a]	392.90	78.9	20.0
Binder: Kollidon 12 or Kollidon 30	20.80	4.2	1.06
Surfactant: SLS or polysorbate 80[b]	2.00	0.4	0.10
Microcrystalline cellulose (MCC)	0 or 20.60	0 or 4.1	0 or 1.05
Extra-granular			
MCC	41.20 or 20.60	8.2 or 4.1	2.10 or 1.05
Polyplasdone XL	41.30	8.3	2.10
Total	498.20	100.0	25.36

[a] "Co-mill" refers to the mixture of celecoxib and excipients jet-milled together. "Blend" refers to the mixture where the jet-milled celecoxib alone, was blended with the same excipients present in the "co-mill" mixture. Both the "co-mill" and "blend" had the same overall formulation composition, which contained 50.9% celecoxib, 45.7% lactose, 2.9% SB and 0.5% SLS.
[b] Both SLS and polysorbate 80 were first dissolved in water (0.042 g of polysorbate 80 or SLS/g of water) and sprayed onto the powder bed.

2.2.2. Screening formulation statistical design of experiments (DOE)

A 5-factor 1/2 fraction factorial statistical design was used to study the effect of formulation components on dispersion of the jet-milled drug. The factors include:

(1) Type of surfactant: SLS (−) vs. polysorbate 80 (+).
(2) Type of binder: Kollidon 12 (−) vs. Kollidon 30 (+).
(3) Type of disintegrant: Polyplasdone XL (−) vs. SSG (+).
(4) The drug-processing method: co-mill (−) vs. blend (+), where "co-mill" refers to a process by which the mixture of drug and excipients were milled together, and "blend" refers to the process where excipients were blended with the milled drug.
(5) Method of MCC addition: EXT (−) vs. INT + EXT (+), where EXT means that MCC was only present in the extra-granular portion, and INT + EXT means that MCC was present both intra-granularly and extra-granularly.

The statistical design is comprised of 19 experiments, three of which are triplicate runs. Table 1 summarizes the prototype formula used in the DOE studies. The formulations were manufactured by a wet granulation process, following the procedure described in the Section 2.2.1.

2.2.3. Mechanistic studies

Following the screening formulation DOE, more prototype formulations were made to study the effect of surfactants and binders on the wettability of celecoxib using the wet granulation procedure described in Section 2.2.1. In the surfactant study, three formulations were made containing SLS, polysorbate 80 or cetrimide (Table 2). In the binder study, three formulations were made containing Kollidon 30, HPMC or HPC (Table 3). In the disintegration study, four formulations were prepared where the ratio of intra- to extra-granular proportions of Polyplasdone was varied (Table 4). These were 100% intra-granular; 50% intra-granular and 50% extra-granular, 20% intra-granular and 80% extra-granular, or 100% extra-granular. The combined level of intra- and extra-granular Polyplasdone was always equal to 8.3% of the formulation.

Table 2
Prototype formulations containing different types of surfactants

Materials	Amount per tablet (mg)	Percentage of the tablet (%, w/w)
Intra-granular		
Jet-milled celecoxib[a]	200.00	55.6
Lactose	79.00	21.9
Surfactant[b]	3.00	0.8
Kollidon 30	18.00	5.0
Extra-granular		
MCC	30.00	8.3
Polyplasdone XL	30.00	8.3
Total tablet weight (mg)	360.00	100.0

[a] Celecoxib jet-milled without excipients present.
[b] Surfactant could be SLS, polysorbate 80 or cetrimide.

The effect of tablet porosity on the drug dispersion was also studied. The formula is shown in Table 3, where Kollidon 30 was used as a binder. Tablets were made under appropriate compression force to achieve a target porosity, ranging from 0.340 (most porous) to 0.115 (least porous) (Table 5).

Table 3
Prototype formulations containing different types of binders

Materials	Amount per tablet (mg)	Percentage of tablet (%, w/w)
Intra-granular		
Co-milled celecoxib[a]	392.90	78.8
SLS	1.95	0.4
Binder[b]	20.83	4.2
Extra-granular		
MCC	41.57	8.3
Polyplasdone XL	41.57	8.3
Total tablet weight (mg)	498.82	100.0

[a] Co-milled celecoxib is a mixture of celecoxib and excipients jet-milled together. It was composed of 50.9% celecoxib, 45.7% lactose, 2.9% SB and 0.5% SLS.
[b] Binder could be Kollidon 30, HPMC or HPC.

Table 4
Prototype formulations containing different ratios of intra- to extra-granular disintegrants

Materials	Amount per tablet (mg)	Percentage of tablet (%, w/w)
Intra-granular		
Jet-milled celecoxib[a]	200.00	55.6
Lactose	79.00	21.9
SLS	3.00	0.8
Kollidon 30	18.00	5.0
Polyplasdone XL[b]	Varied	Varied
Extra-granular		
MCC	30.00	8.3
Polyplasdone XL[b]	Varied	Varied
Total tablet weight (mg)	360.00	100.0

[a] Celecoxib jet-milled by itself.
[b] The intra- to extra-granular portions of Polyplasdone in the prototype formulation could be 100% intra-granular; 50% intra-/50% extra-; 20% intra-/80% extra-; 100% extra-granular. The combined level of intra- and extra-granular Polyplasdone was equal to 8.3% of the formulation.

Table 5
Tablet porosity and tablet hardness in the porosity study

Tablet porosity[a]	Tablet hardness[b] (N)
0.115	210.2
0.175	140.1
0.259	70.1
0.340	35.0

[a] The standard deviation for tablet porosity ($n = 3$) is typically less than 0.003.
[b] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.

2.2.4. Optimization design of experiments (DOE)

Using the appropriate excipients identified in the studies described above, a 3-factor face-centered design was utilized to optimize the level of these excipients in tablets containing jet-milled drug. The design is outlined in Table 6. Prototype formulations used in the DOE are shown in Table 7. The analytical measurements representing response factors in the study were turbidity, granule moisture level and tablet hardness. Design Expert (Stat-Ease, Inc., Minneapolis, MN) was used to analyze the results.

Table 7
Prototype formulations of micronized celecoxib tablets

Material	Amount per tablet (mg)
Intra-granular portion	
Jet-milled celecoxib	200.00
Spray dried lactose	80.00
SLS (surfactant)	Varied from 3.60 to 25.20 mg
Kollidon 30 (binder)	Varied from 3.60 to 32.40 mg
Extra-granular portion	
MCC	30.00
Polyplasdone XL (disintegrant)	Varied from 7.20 to 36.00 mg
Total tablet weight	

2.3. Analytical methods

2.3.1. Turbidity test

A turbidity method was developed to quantitatively assess how well the jet-milled celecoxib dispersed into finely divided particles upon tablet disintegration in water. If a formulation disperses into small particles, the resulting 'dynamic' suspension will be more turbid than that resulting from a formulation that disperses into larger particles. Higher turbidity reflects better dispersion. The method was developed as a substitute for dissolution testing. Efforts to develop a discriminating dissolution test were not successful because the necessary addition of surfactant to the media to provide sink conditions suppresses the discriminatory ability of the method. The dispersion characteristics of

Table 6
Design of experiments—optimization studies (3-factor face-centered design)

Run	A: Polyplasdone XL (mg)	B: SLS (mg)	C: Kollidon 30 (mg)	Fixed excipients[a] (mg)	Total tablet weight (mg)
1	36.00	25.20	32.40	310.00	403.60
2	7.20	3.60	32.40	310.00	353.20
3	36.00	25.20	3.60	310.00	374.80
4	21.60	14.40	18.00	310.00	364.00
5	36.00	3.60	3.60	310.00	353.20
6	7.20	14.40	18.00	310.00	349.60
7	21.60	14.40	18.00	310.00	364.00
8	21.60	25.20	18.00	310.00	374.80
9	21.60	14.40	3.60	310.00	349.60
10	21.60	14.40	18.00	310.00	364.00
11	21.60	14.40	32.40	310.00	378.40
12	36.00	3.60	32.40	310.00	382.00
13	21.60	14.40	18.00	310.00	364.00
14	36.00	14.40	18.00	310.00	378.40
15	21.60	3.60	18.00	310.00	353.20
16	21.60	14.40	18.00	310.00	364.00
17	7.20	25.20	3.60	310.00	346.00
18	7.20	3.60	3.60	310.00	324.40
19	7.20	25.20	32.40	310.00	374.80

[a] Every tablet contained 200.00 mg jet-milled drug, 80.00 mg spray dried lactose in the intra-granular portion and 30.00 mg of MCC in the extra-granular portion.

the formulations were tested in a USP II dissolution apparatus (SR8 Plus, Hanson Research Corporation, Chatsworth, CA, USA or Dissolution System 2100, Distek, North Brunswick, NJ, USA) containing 500 ml of de-ionized water at 37 °C and 50 rpm paddle speed. The tablet or powder sample was placed into the dissolution flask at the start of the test. At selected time points (typically 5, 20 and 35 min), 8 ml samples were manually withdrawn 0.75 in. from the water/air interface with a 10 ml syringe fitted with a stainless steal cannula. The first 4 ml of the sample was filtered through an acrylic copolymer membrane filter, collected in a vial, representing the "filtered" sample. The membrane pore size was selected such that what passed through the filter membrane were mostly primary particles. For the jet-milled drug (D50: 2 μm, D90: 4 μm), a filter membrane with 5 μm pore size was chosen (Acrodisc 25 mm Syringe Filter, Part no. 4489T, Gelman Sciences, Ann Arbor, MI, USA). The remaining 4 ml of sample was retained in a vial as "unfiltered" sample. The turbidity (a unitless quantity) of both filtered and unfiltered samples was measured using a spectrophotometer (Cinitra 40, GBC Scientific Equipment, Dandenong, Victoria, Australia) at 650 nm using a 1 cm quartz cuvette and reported as the log of the ratio of the incident and transmitted light intensity. The placebo ingredients in the formulation had negligible contribution to the turbidity measurement (turbidity < 0.0001) because the excipients were either water-soluble or swelled quickly and sank to the bottom of the vessel. Therefore, the turbidity results accurately reflected how well the drug was dispersed. Note that because of the low solubility, very little (<0.5% of the total dose) of the drug being tested dissolved in the media.

2.3.2. Contact angle analysis

To measure the contact angle, microscope slides were sprayed with a thin coating of adhesive. A solid (in powder form) of unknown surface energy was sprinkled onto the slide to create a uniform layer of coverage. Excess powder was removed by tapping the slide. Equilibrium contact angle between the test liquid and the solid was used for surface energy calculations. The contact angle was measured using the Dynamic Contact Angle Instrument (Model No. FTÅ 200, First Ten Ångstrom Inc., Portsmouth, VA) which was equipped with a high speed camera.

2.3.3. Microscopy test

Either a tablet or test powder was placed in a beaker containing 50 ml of water. If the sample was a tablet, it was allowed to fully disintegrate. The sample was then shaken for a minute prior to withdrawing an aliquot to observe under the microscope (Axioplan2, Carl Zeiss Inc., Thornwood, NY), equipped with a MC100 Spot Camera (Carl Zeiss Inc., Thornwood, NY). Photos were taken at 100× and 400× magnifications.

3. Results and discussions

3.1. Contact angle analysis

The contact angle between water and the drug is 127°, indicating that the drug has very poor wettability in water. The drug powder tends to form agglomerates in water and the agglomerates cannot be re-dispersed into small particles even with manual shaking.

3.2. Effect of the processing method on celecoxib dispersibility

The choice of processing method has a significant effect on drug dispersion in an aqueous environment. During disintegration testing (USP <701>, with disks, using water as medium), tablets made by dry granulation and direct compression disintegrated into large aggregates that quickly sank to the bottom of the flask, yielding a clear disintegration medium. However, tablets made by the wet granulation process produced a fine turbid dispersion in the disintegration test. This agrees well with the turbidity results (Table 8), where wet-granulated tablets have much higher turbidity in both filtered and unfiltered samples than those made from dry granulation and direct compression. Microscopy observations of samples from the disintegration medium indicate that the particle size of samples from the wet granulation process is much smaller than that of the dry granulation and direct compression processes. It is hypothesized that wet granulation facilitates an intimate contact between the poorly wettable drug and wetting agents such as surfactant and binder, thereby enhancing the wettability of the drug. Based on these results, the wet granulation processes was chosen to further study the effect of excipients on the dispersibility of celecoxib.

3.3. Screening formulation DOE

The statistically significant factors (with a p-value < 0.05) are summarized in Table 9.

3.3.1. Surfactant

Both "co-mill" and "blend" celecoxib formulations contained 0.4% anionic surfactant-SLS. To investigate the effect of surfactant type on drug dispersion, an additional 0.4% SLS or

Table 8
Effect of processing methods on celecoxib dispersion[a]

	Wet granulation	Dry granulation	Direct compression
Turbidity of filtered sample	0.291 (0.004)	0.097 (0.018)	0.048 (0.002)
Turbidity of unfiltered sample	1.950 (0.031)	0.540 (0.027)	0.365 (0.030)

[a] Tablets with the same porosity were used in these experiments. Values in parentheses are standard deviation.

Table 9
Summary of significant effects of screening formulation design of experiments[a]

Factors	Surfactant	Binder	Disintegrant	Method of MCC addition	Drug process
Tablets with the same porosity					
Turbidity of filtered sample	−	+	−		
Turbidity of unfiltered sample	−		−		−
Tablet hardness	−		−		−
Tablets with the same hardness					
Disintegration time		+	+		−

[a] Factors with p-value less than 0.05 are considered statistically significant. "−" means the low level variable results in a statistically significant higher value in the corresponding response. For example, SLS (−) results in a higher turbidity than polysorbate 80 (+); similarly, "+" means a high level variable results in a significant higher value in the corresponding factor. The key for "−" or "+" is described in Section 2.2.2.

polysorbate 80 was added to the formulation. Tablets containing 0.8% SLS (total) produced significantly higher turbidity values than those containing 50/50 mixture of SLS and polysorbate 80 (Table 9). In addition, tablets containing 0.8% SLS were also significantly harder than those containing polysorbate 80–SLS combination. Neutral surfactants such as polysorbate 80 are not expected to interact with ionic surfactants to adversely affect dispersion (Buckton, 1995). Thus, SLS appears to be a better surfactant than polysorbate 80 in terms of improving dispersibility of celecoxib. The effect of anionic, cationic and neutral surfactants on celecoxib dispersion is compared in a later study described in Section 3.4.1.

3.3.2. Binder

For tablets made at the same porosity, tablets containing Kollidon 30 as a binder produce significantly higher turbidity in filtered samples than those containing Kollidon 12, indicating that the formulation containing Kollidon 30 disperses celecoxib more readily into primary particles. For tablets made at the same hardness, tablets containing Kollidon 30 disintegrate significantly slower than those containing Kollidon 12. This is probably due to the higher molecular weight and solution viscosity of Kollidon 30.

3.3.3. Disintegrant

Tablets containing Polyplasdone XL as a disintegrant give significantly higher turbidity in both filtered and unfiltered samples than those containing SSG, indicating that Polyplasdone XL promoted better celecoxib dispersion. The poor dispersibility of tablets containing SSG may be due to the fact that SSG tends to form a gel at high concentrations. The gel formation can trap the celecoxib particles and slow drug release into the test medium. This hypothesis is consistent with visual observation that tablets containing SSG seem to "flake off" and released more coarse particles than those containing Polyplasdone XL. In addition to improving the overall dispersibility of celecoxib, tablets containing Polyplasdone XL are harder than those containing SSG, when the tablet porosity is controlled, or have a shorter disintegration time, when the tablets hardness is controlled. These data suggest that Polyplasdone XL should be selected as the tablet disintegrant.

3.3.4. Drug processing

Two drug-processing methods are examined. In one scenario, celecoxib and excipients were mixed and then jet-milled together; this is referred to as the "co-milled" process. In the other scenario, celecoxib was first jet-milled by itself and then the milled celecoxib was blended with un-milled excipients; this is referred to as the "blended" process. Tablets containing co-milled celecoxib disperse significantly better than those containing blended celecoxib, although both formulations have comparable turbidity for filtered samples. Since the excipient particle size in the co-milled celecoxib formulations is much smaller than that in the blended celecoxib formulations, the co-milled celecoxib formulations require a higher compaction pressure to achieve the same porosity as those containing blended celecoxib, and as a result, produced much harder tablets. In addition to giving better dispersion, co-milling celecoxib also enhances the ease of handling during the milling process. It was observed that the feed material has much less sticking and enhanced flowability when the excipients were milled together with celecoxib.

3.3.5. Microcrystalline cellulose formulation variables

Microcrystalline cellulose, added to the formulation either as a 100% extra-granular excipient or a 50% intra-granular/50% extra-granular, has no significant effect on dispersion, disintegration or hardness.

3.4. Mechanistic understanding on effect of excipients on wetting of celecoxib

3.4.1. Surfactant study

Surfactant is a very important pharmaceutical excipient that aids in wetting/dispersion of poorly wettable drugs. Surfactant may promote wetting by adsorbing onto the surface of a hydrophobic particle and reducing the interfacial tension between hydrophilic and hydrophobic phases. Results from the screening formulation DOE indicate that SLS may be a better surfactant than polysorbate 80. However, the results are not entirely clear since the formulations which were used for comparison all contained a different level of SLS.

To further study the effect of types of surfactants on wetting of celecoxib, prototype formulations (shown in Table 2) containing anionic surfactant (SLS), cationic surfactant (cetrimide) or neutral surfactant (polysorbate 80) were prepared.

Table 10
The effect of types of surfactants on dispersion of drug in water[a]

Formulation/types of surfactant	Compaction pressure (MPa)	Tablet hardness (N)[b]	Turbidity in water
SLS	10.0	64.4	1.620 ± 0.011
Cetrimide	10.0	86.9	1.037 ± 0.044
Polysorbate 80	6.89	21.0	0.200 ± 0.046

[a] Dispersion at tablet porosity = 0.175 ± 0.003.
[b] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.

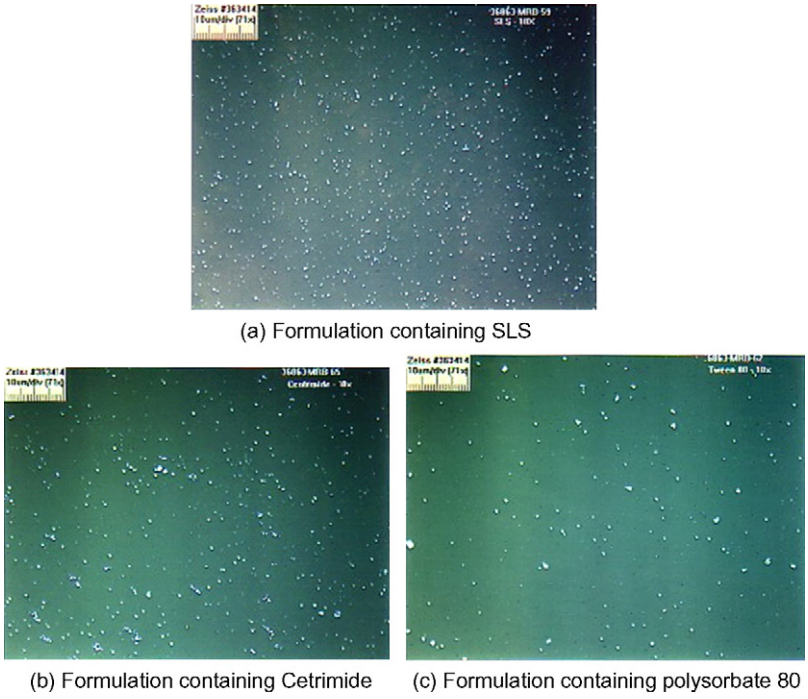


Fig. 1. Photomicrographs of dispersion medium of granules containing different types of surfactants.

As shown in Table 10, turbidity follows the rank order of SLS > cetrimide ≫ polysorbate 80, indicating that ionic surfactants disperse celecoxib more efficiently than neutral surfactants. Visual observations agree well with the turbidity data. The SLS formulation has the largest numbers of primary particles per sample. The cetrimide formulation has a medium number of primary particles, and polysorbate 80 formulation has the least primary particles per sample (Fig. 1). Furthermore, wettability of both the SLS and the cetrimide formulation using contact angle analysis is found to be similar (Fig. 2). It is hypothesized that celecoxib particles covered with negatively charged SLS or positively charged cetrimide were less likely to form agglomerates as compared to particles without any surface charge due to charge repulsion. However, this conclusion would not necessarily hold for an ionizable compound, due to the potential ionic interaction with the surfactant.

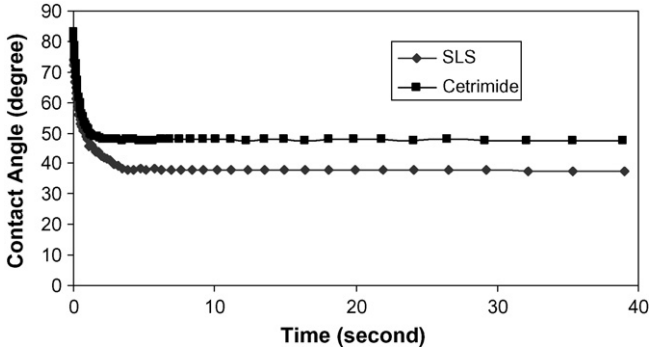


Fig. 2. Contact angles of water on formulations containing SLS or cetrimide.

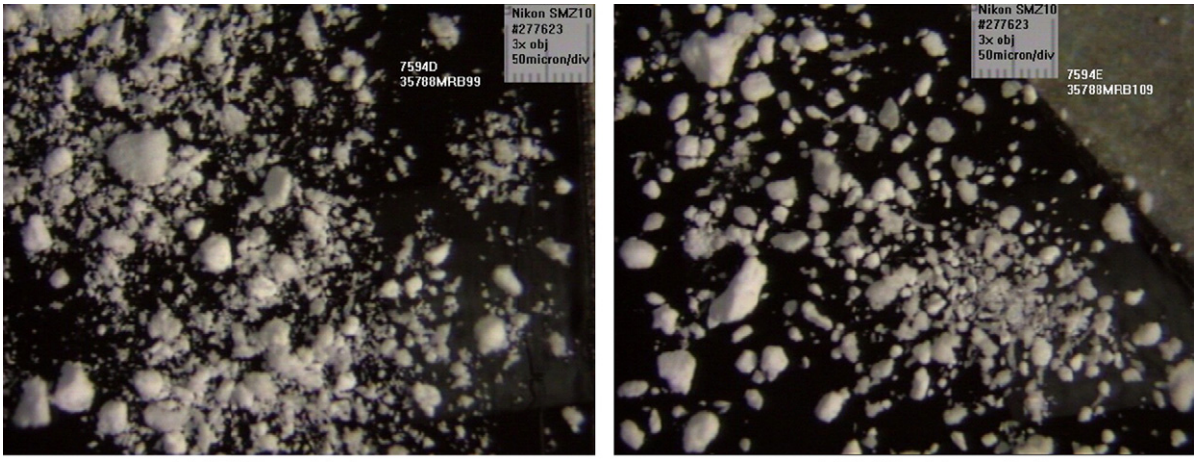
3.4.2. Binder study

As shown in Table 11, turbidity results suggest that the dispersibility of celecoxib follows the rank order of Kollidon 30 > HPC > HPMC. Scanning electron microscopy of formulated powders containing Kollidon 30 and HPMC show that

Table 11
The effect of types of binders on the dispersion of drug in water[a]

Types of binders	Tablet hardness (N) [b]	Turbidity
Kollidon 30	141.5	2.003 ± 0.026
HPMC	105.8	1.260 ± 0.066
HPC	98.1	1.320 ± 0.067

[a] Dispersion in water at tablet porosity = 0.175.
[b] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.



(a) HPMC as a binder (b) Kollidon 30 as a binder

Fig. 3. Microscopic view of granules containing Kollidon 30 or HPMC.

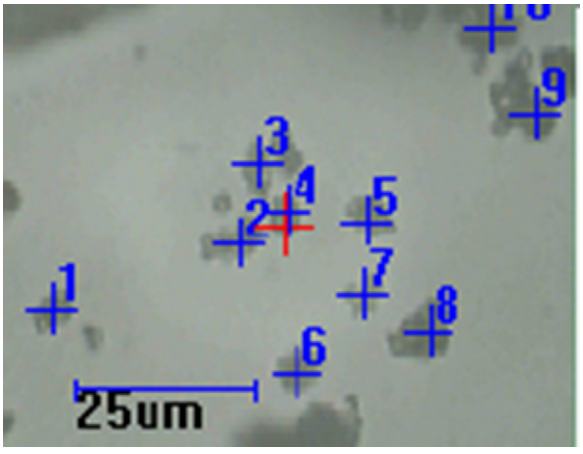


Fig. 4. Photomicrographs view with point map definition superimposed.

the HPMC formulation has a higher percentage of fine particles than the Kollidon 30 formulation (Fig. 3). The fine particles were characterized by the Almega® Raman microscope with point map capability (Fig. 4). Most of the particles analyzed are drug particles (<10 μm in size).

To gain an in-depth understanding on why the Kollidon formulation gives higher drug dispersion than the HPMC formulation, the spreading coefficient of the drug over Kollidon or HPMC is calculated to study the interactions between the drug and the binder.

The interfacial forces between any two phases are given by Young's equation (Young, 1855):

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos\theta \tag{2}$$

where γ_{SV}, γ_{SL} and γ_{LV} are the surface tensions of the solid–vapor, solid–liquid and liquid–vapor interfaces, respectively, and θ is the contact angle between the liquid and the solid.

Wu (Wu, 1971) derived a relationship that allows the calculation of the dispersion and polar components of the surface energy of a solid from two liquids with known dispersion and polar surface energy,

$$\gamma_{LS} = \gamma_{LV} + \gamma_{SV} - 4\left[\frac{\gamma_L^d \gamma_S^d}{\gamma_L^d + \gamma_S^d} + \frac{\gamma_L^p \gamma_S^p}{\gamma_L^p + \gamma_S^p}\right] \tag{3}$$

where γ_L^d and γ_L^p are the dispersion and polar components of the liquid surface tension, respectively, γ_S^d and γ_S^p are the dispersion and polar components of the solid surface, respectively.

Combining Wu's equation with Young's to get Eq. (4)

$$\gamma_{LV}(1 + \cos\theta) = 4\left[\frac{\gamma_L^d \gamma_S^d}{\gamma_L^d + \gamma_S^d} + \frac{\gamma_L^p \gamma_S^p}{\gamma_L^p + \gamma_S^p}\right] \tag{4}$$

where γ_{LV} is the surface tension of the liquid. An Excel program (Microsoft Excel® 2000, Microsoft Corp. Redmond, WA) was written to solve Eq. (4) iteratively.

Table 12
Surface energy of drug and several solvents

	θ (°)	γ_S (mN/m)[c]	γ_S^d (mN/m)	γ_S^p (mN/m)
Formamide[a]	–	58.30	32.30	26.00
Ethylene glycol[a]	–	48.90	33.40	15.50
Drug[b]	44.84° (formamide), 26.83° (ethylene glycol)	43.84	31.45	12.39

[a] Data was obtained from reference (Zografi and Tam, 1976).
[b] Surface energy of Drug was calculated using Eq. (4) (Young, 1855; Wu, 1971).
[c] γ_S is defined as the surface tension of the test substance.

Table 13
Surface energy and spreading coefficients of drug and binders

	γ_S (mN/m)[c]	γ_S^d (mN/m)	γ_S^p (mN/m)	S_{21} (binder over drug)[d]	S_{12} (drug over binder)[d]
HPMC[a]	48.40	18.40	30.00	−15.29	−6.71
Kollidon 30[b]	53.60	28.40	25.20	−14.28	5.24
Celecoxib	43.84	31.45	12.39		

[a] Data was obtained from reference (Rowe, 1989).
[b] Data was obtained from references (Krycer et al., 1983a,b).
[c] γ_S is defined as the surface tension of the test substance.
[d] Spreading coefficients of binder over drug (S_{12}) and drug over binder (S_{21}) were calculated using Eq. (5).

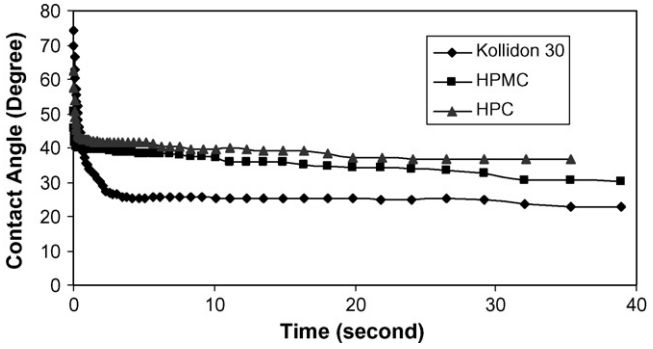


Fig. 5. Contact angle comparisons of formulations containing different binders.

The spreading tendencies between solids can then be predicted by Eq. (5) (Buckton, 1995b).

$$S_{12} = 4\left[\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d} + \frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p}\right] - 2\gamma_1 \quad (5)$$

where S_{12} is the spreading coefficient of solid 1 onto solid 2, γ_1 is the surface energy of solid 1, γ_1^d and γ_1^p are the dispersive and polar components, respectively, of solid 1, and γ_2^d and γ_2^p are the dispersive and polar components, respectively, of solid 2. A positive value of the spreading coefficient indicates that spreading is energetically favored while a negative value indicates that spreading is not favored. The more positive the number the more the spreading is favored.

The contact angles of two test liquids, formamide and ethylene glycol, on the drug powder were measured. These, combined with the polar and dispersive surface energies of the test liquids, which are known from the literature (Zografi and Tam, 1976), allow one to calculate the polar and dispersive surface energies of the drug using Eq. (4) (Table 12). The polar and dispersive surface energies of the drug, combined with those of HPMC and Kollidon 30, which are also known from the literature (Rowe, 1989; Krycer et al., 1983a,b), allow one to calculate the spreading coefficients of celecoxib over binder and binder over celecoxib using Eq. (5) (Table 13). According to Rowe's work (Rowe, 1989), the spreading coefficient can be used to predict the type of granules formed. Positive spreading coefficient of substrate over binder (S_{12}) indicates that the substrate tends to spread over the binder to form an open porous granule. A negative S_{12} combined with positive S_{21} (binder over substrate) indicates a tendency to form strong granules with the binder film covering the substrate. The spreading coefficients of celecoxib over HPMC (S_{12}) and HPMC over celecoxib (S_{21}) are both negative, indicating that there is not a favorable interaction between celecoxib and HPMC (Table 13). This may explain why the granules containing HPMC as a binder have a high percentage of fine granules (Fig. 3), where the fine particles are characterized to be primarily celecoxib particles (Fig. 4). The positive S_{12} of celecoxib over Kollidon 30 and negative S_{21} of Kollidon 30 over celecoxib indicates that celecoxib has a tendency to spread over Kollidon, creating open porous granules in which pores may facilitate water uptake. This finding may explain why the formulation containing Kollidon 30 results in the highest celecoxib dispersion.

The aqueous wettability of formulated powders containing different binders are also compared using dynamic contact angle measurement (Fig. 5). The formulation containing Kollidon 30 as a binder has the best wettability because the contact angle in water is the lowest among the three formulations. In addition, the contact angle of the Kollidon 30 formulation reaches

Table 14
The effect of disintegrant location on the dispersion of celecoxib in water[a]

Formulation/disintegrant location	Tablet hardness (N)[b]	Turbidity
100% intra	–	–
50%:50% intra:extra	59.5	0.690 ± 0.008
20%:80% intra:extra	62.3	1.395 ± 0.055
100% extra	64.4	1.620 ± 0.011

[a] Dispersion in water at tablet porosity = 0.175; all formulations contain 8.33% disintegrant.
[b] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.

Table 15
Hardness and porosity of a tablet when all of the disintegrant is added intra-granularly

Tablet weight (mg)	Compation pressure (MPa)	Thickness (mm)	Porosity	Hardness (N)[a]
360.4	10.00	3.56	0.097	26.6
360.1	6.89	3.65	0.126	21.7
359.9	4.14	3.72	0.148	10.5

[a] Hardness was obtained with three tablets. The standard deviation is typically less than 7.0 N.

Table 16
Summary of significant effects (p-value < 0.05)[a]

Response	Disintegrant level	Surfactant level	Surfactant^2 level[b]	Binder level	Binder^2 level[c]	Disintegrant*binder[d]
Turbidity		+ <0.0001	− 0.0026	+ 0.0010		
Moisture				+ (<0.0001)		
Hardness	+ (0.0121)	− (<0.0001)		+ (<0.0001)	− (0.0006)	+ (0.0269)

[a] Factors with p-value less than 0.05 are considered statistically significant.
[b] Surfactant^2: quadratic term for surfactant binder.
[c] Binder^2: quadratic term for binder.
[d] Disintegrant*binder: the interaction term between extra-granular disintegrant.

equilibrium more quickly than those of the HPMC and HPC formulations, indicating a quick and uniform wetting of the Kollidon 30 formulation. These data suggest one could use contact angle analysis as a quick way to screen formulations for which wetting is a concern.

3.4.3. Disintegrant study

The mode of disintegrant addition has long been a topic of interest in solid formulation development. It is often thought that adding disintegrants intra-granularly helps break the granules apart, thereby leading to a faster drug release. However, the turbidity results indicate that as more Polyplasdone is added intra-granularly, celecoxib dispersibility decreases (Table 14). This is probably because intra-granular Polyplasdone can adsorb a large amount of water during the wet granulation process, which leads to the formation of dense granules. Such is the case when all of the Polyplasdone is added intra-granularly, the granules are so dense that it is difficult to achieve the target tablet porosity of 0.175 even with minimum compression force (Table 15). Since porous granules are likely to give higher drug dispersibility, fluid-bed granulation may be a good granulation method because it is known to produce fluffy and porous granules.

3.4.4. Porosity study

The tablet porosity significantly impacts the initial wetting and dispersion of celecoxib (Fig. 6) at $t = 5$ min, but not at later times ($t = 20$ and 35 min). The higher the tablet porosity, the higher the initial dispersibility of the drug. Therefore, one should make tablets as porous as possible to achieve

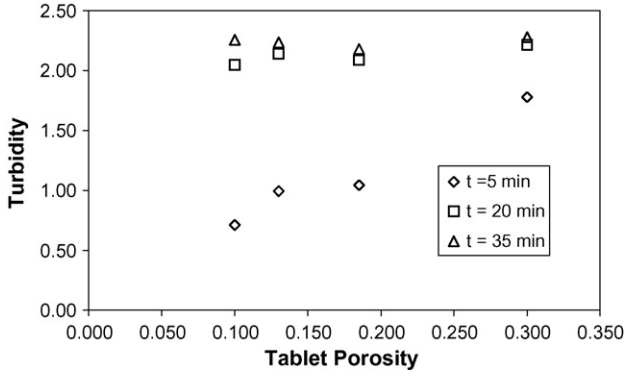


Fig. 6. Effect of tablet porosity on turbidity of celecoxib.

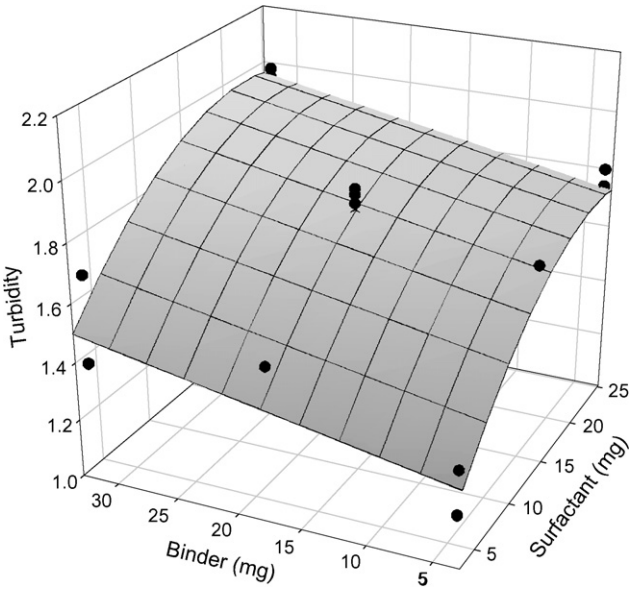


Fig. 7. Surface response plots of turbidity as a function of surfactant and binder levels.

rapid dispersion, as long as the tablet hardness criteria are met.

3.5. DOE optimization study

Statistical analysis shows that the dispersibility of drug increases as the amount of SLS and Kollidon 30 increases (Table 16). No optimum is found within the range that was studied (Fig. 7). Formulations with a higher binder level lead to granules with higher moisture level, and harder tablets (Table 16). Higher disintegrant levels result in harder tablets, while having little impact on dispersibility of the drug.

4. Conclusions

In order to formulate a poorly wettable compound such as celecoxib (the contact angle with water is 127°) into a rapidly dispersible formulation, one has to use optimum excipients to facilitate wetting and dispersion of the drug. It is found that ionic surfactants such as sodium lauryl sulfate can facilitate dispersion/wetting of celecoxib through the charge dispersion

effect. Granule and tablet porosity play an important role in celecoxib dispersion. In general, higher porosity leads to more water uptake and better wetting/dispersibility of the drug. Therefore, fluid-bed granulation may be a desirable way to produce porous granules. Using Kollidon 30 as a binder facilitates dispersion of celecoxib as compared to HPMC and HPC. This may be due to the fact that the surface interaction between celecoxib and Kollidon 30 favors the formation of an open porous granule. Addition of Polyplasdone intra-granularly results in the formation of dense granules that lead to poor dispersibility. Therefore, Polyplasdone should be added in the extra-granular portion of the formulation.

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Effect of the Mode of Super Disintegrant Incorporation on Dissolution in Wet Granulated Tablets

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Abstract □ The effect of the mode of super disintegrant incorporation in wet granulated tablets was investigated with three super disintegrants: sodium starch glycolate, crospovidone, and croscarmellose sodium. The disintegrants were incorporated extragranularly or intragranularly or distributed equally between the two phases. Lactose, naproxen, or dibasic calcium phosphate was used as the principal tablet component to provide various degrees of solubility to the formulations. The formulations were dried to three different levels of moisture content. The results indicated that, for the formulations studied, extragranular incorporation resulted in faster dissolution than did equal distribution intragranularly and extragranularly, which in turn was superior to intragranular incorporation. Granulation moisture content was found to have a formulation-specific impact on tablet dissolution, with each main tablet component behaving in a different fashion. When all other factors were kept constant, there was a tendency for croscarmellose sodium to produce faster tablet dissolution than sodium starch glycolate or crospovidone. The super disintegrants tended to promote faster dissolution in a neutral pH medium than in an acidic medium.

An important variable in any tablet system is the rate at which the drug substance dissolves. Dissolution of the pharmacologically active agent must occur if the agent is to pass through biological membranes and into systemic circulation. For many solid dosage forms, disintegration precedes drug dissolution. Super disintegrants,[1] such as croscarmellose sodium, sodium starch glycolate, and crospovidone, are now frequently used in tablet formulations to improve the rate and extent of tablet disintegration and thereby increase the rate of drug dissolution. The wet granulation technique is often used to prepare blends that are to be compressed into tablets. The disintegrant may be incorporated during the wet granulation technique by one of three methods: intragranular or extragranular incorporation or distribution in both phases. A review of the literature revealed that although a number of investigators have examined super disintegrants in wet granulated tablets by using a single mode of incorporation,[2-13] the effect of the mode of super disintegrant addition on drug dissolution has not been fully investigated. Mendell[14] used tablet disintegration as the evaluating criterion and concluded that the method of incorporation appears to have little effect. Although tablet disintegration is frequently a necessary prerequisite for drug dissolution, it in no manner assures that a drug will dissolve and hence have the potential for satisfactory bioavailability. Therefore, it is important to examine the effectiveness of a super disintegrant in the context of how the rate of dissolution of a drug from a tablet is affected. Miller et al.[15] used an acetaminophen–microcrystalline cellulose tablet to compare croscarmellose sodium distributed extragranularly versus distributed equally between the intragranular and extragranular phases. They found that the latter results in faster dissolution. Lang[16] stated, without presenting supporting information, that an equal distribution of a super disintegrant in the intragranular and extragranular phases resulted in better dissolution than did incorporating it totally in either phase. A prednisone tablet with a lactose base was used by Van Kamp et al.[17] to show that apportioning a super disintegrant intragranularly or extragranularly generally had little impact on the dissolution characteristics of a tablet. Using a naproxen-based tablet, Gordon et al.[18] demonstrated that incorporating croscarmellose sodium in the intragranular phase resulted in faster tablet dissolution than did incorporating it in the extragranular phase or in both phases. Therefore, there are contradictions in the literature as to which granulation phase a super disintegrant should be distributed in for tablet dissolution to be optimized.

It has been noted by Shangraw et al.[1] that super disintegrants, when not incorporated in tablets, can behave differently in acidic and neutral dissolution media, both at microscopic and at macroscopic levels. Botzolakis and Augsburger[19] showed that changing from dilute acid to water alters the liquid uptake and swelling or the swelling efficiency of pure sodium starch glycolate, crospovidone, and croscarmellose sodium. However, Vadas et al.[20] examined the disintegration times of directly compressed lactose tablets containing croscarmellose sodium and showed that these tablets were insensitive to changes in medium pH. Sakr and Sidhom[21] found that when croscarmellose sodium was included in a microcrystalline cellulose–dibasic calcium phosphate tablet, there was a pH-related effect only at very low levels of the disintegrant. It has been shown that the disintegration of acetaminophen and aspirin tablets containing sodium starch glycolate is influenced by whether gastric juice or water is used.[22] Caramella et al.[23] found that although pure super disintegrants behaved differently in isotonic saline versus 0.1 N HCl solutions, when they were incorporated into aspirin tablets, they acted similarly with respect to the disintegrating force development rate and the disintegration time. However, there is a dearth of information on whether a pH-related effect exists when super disintegrants are incorporated into tablets and then examined via dissolution testing.

The purpose of this study was to determine the optimum mode of super disintegrant incorporation and to test whether this was affected by the overall solubility of the tablet base, the granulation moisture content, the specific super disintegrant that was used, or the pH of the dissolution medium. It is important to determine the optimum mode of super disintegrant incorporation so that tablets can be formulated in a manner that maximizes tablet dissolution and thereby maximizes the potential bioavailability of the medicament.

Experimental Section

Materials—Sodium starch glycolate (Explotab; Edward Mendell Co.), crospovidone (Polyplasdone XL; GAF Corp.), croscarmellose

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Table I—Generalized Tablet Formulation for All Batches

Component	%, w/w
p-Aminobenzoic acid	1.00
Intragranular super disintegrant (crospovidone, sodium starch glycolate, or croscarmellose sodium)	0, 1.00, or 2.00[a]
Extragranular super disintegrant (crospovidone, sodium starch glycolate, or croscarmellose sodium)	0, 1.00, or 2.00[a]
Povidone K-29-32	5.00
Main tablet component (lactose, naproxen, or dibasic calcium phosphate)	91.50
Magnesium stearate	0.50

[a] Except for control formulations, the quantity of the super disintegrant always totalled 2.00%. Control formulations contained 2% additional main tablet component instead of the super disintegrant.

Table II—Main Tablet Component Solubility[a] in Dissolution Test Media

Component	Solubility, mg/mL, in:	
	0.01 M HCl	pH 7.4 Buffer
Lactose	153	203
Naproxen	Not Tested	6
Dibasic calcium phosphate	2	<1

[a] Solubility was determined by stirring a solution with excess test component for at least 3 h at room temperature and then filtering, drying, and weighing the amount of excipient that had dissolved. Values for controls (solutions without test component) were subtracted out.

sodium (Ac-Di-Sol; FMC Corp.), dibasic calcium phosphate, dihydrate (VWR Scientific; notated as "calcium phos." in all figures), regular lactose monohydrate (Foremost Whey Products), naproxen (Syntex, Inc.), povidone K-29-32 (Plasdone; GAF), and magnesium stearate (Mallinckrodt Inc.) were all USP or NF grade. *p*-Aminobenzoic acid (Aldrich Chemical Co.) was at least 99% pure. *p*-Aminobenzoic acid has solubilities at room temperature of 12.1 mg/mL in pH 7.4 buffer and 6.5 mg/mL in 0.01 M HCl.

Powder Blend—The intragranular super disintegrant (if required by the experimental design), *p*-aminobenzoic acid (which was the dissolution tracer), and the major component (which consisted of lactose, naproxen, or dibasic calcium phosphate, to vary the solubility) were passed through a 30-mesh screen before being mixed. In each formulation, the super disintegrant and *p*-aminobenzoic acid were geometrically diluted with the major component before dry blending, which was performed with a high-shear mixer (Gral 10; Machines Collette) for 3 min.

Binder Preparation—In each formulation, the binder consisted of povidone K-29-32 dissolved in an appropriate amount of water for granulating the major component of the formulation. The amounts of granulating water used (as a percentage of the total dry weight of the formulation) were 14% (lactose formulations), 17% (naproxen formulations), and 18% (dibasic calcium phosphate formulations). Since the mixing time was kept constant for all formulations, it was necessary to vary the percentage of water to achieve similar granulations.

Granulation—After the 3 min of dry blending, the binder solution was added to the mixing bowl during the initial 15 s of a 5-min mixing period. To ensure even and complete granulation, we thoroughly scraped the mixing blades and the bowl with a spatula before we allowed the formulation to be mixed for an additional 5 min (the total mixing time after binder addition was 10 min). The granulated mixtures were then dried at 60 °C in a tray dryer, and the moisture content was determined by the loss-on-drying (LOD) method at 105 °C with a Compu-Trac moisture analyzer (model MA-5A; Arizona Instrument Corp.). Each formulation was dried to a moisture content of 0.5% (±0.2%), 1.25% (±0.25%), and 2.25% (±0.25%) LOD. Because the dibasic calcium phosphate tablet batches could not be manufactured at 0.5% LOD owing to poor compressibility, these batches were also dried to 3.25% (±0.25%)

Table III—Dissolution Results for Tablets with a Moisture Content of 0.5% ± 0.2%[a]

Main Component	Disintegrant	Mode of Incorporation	Tablet Weight ± SD, mg	Tablet Hardness ± SD, kilopond	% Dissolved ± SD at 15 min[b]
Lactose	Crospovidone	Control	507 ± 3.0	8.5 ± 0.5	47.6 ± 0.6
		Intragranular	518 ± 11.0	8.4 ± 0.4	64.0 ± 1.2
		Intragranular + extragranular	522 ± 2.0	8.3 ± 0.5	101.8 ± 1.6
		Extragranular	551 ± 6.0	8.6 ± 0.5	105.2 ± 0.7
	Sodium starch glycolate	Control	507 ± 3.0	8.5 ± 0.5	47.6 ± 0.6
		Intragranular	523 ± 7.0	8.9 ± 0.5	54.7 ± 1.5
		Intragranular + extragranular	508 ± 5.0	8.4 ± 0.4	63.5 ± 0.8
		Extragranular	544 ± 9.0	8.3 ± 0.4	100.7 ± 2.9
	Croscarmellose sodium	Control	507 ± 3.0	7.5 ± 0.5	47.5 ± 0.6
		Intragranular	494 ± 3.0	8.1 ± 0.3	99.8 ± 2.2
		Extragranular	494 ± 4.0	8.1 ± 0.6	105.7 ± 1.2
		Intragranular + extragranular	505 ± 4.0	8.0 ± 0.2	106.9 ± 0.9
Naproxen	Crospovidone	Control	507 ± 5.0	5.6 ± 0.5	6.1 ± 0.2
		Intragranular	504 ± 3.0	5.5 ± 0.7	6.3 ± 0.2
		Intragranular + extragranular	501 ± 5.0	6.8 ± 0.6	16.3 ± 0.9
		Extragranular	504 ± 6.0	5.3 ± 0.4	85.9 ± 7.0
	Sodium starch glycolate	Control	507 ± 5.0	5.6 ± 0.5	6.1 ± 0.2
		Intragranular	502 ± 3.0	6.7 ± 0.8	15.7 ± 0.7
		Intragranular + extragranular	494 ± 3.0	6.6 ± 0.7	53.9 ± 6.3
		Extragranular	499 ± 2.0	4.9 ± 0.4	89.9 ± 2.1
	Croscarmellose sodium	Control	507 ± 5.0	5.6 ± 0.5	6.1 ± 0.2
		Intragranular + extragranular	498 ± 3.0	7.7 ± 0.5	85.9 ± 2.5
		Extragranular	496 ± 4.0	5.1 ± 0.3	93.9 ± 1.2
		Intragranular	502 ± 2.0	6.3 ± 0.3	98.4 ± 0.8

[a] At 15 min in pH 7.4 buffer. Tablets were sorted by main tablet component, type of disintegrant, and increasing dissolution. [b] Mean for six tablets. Statistical significance was calculated by the least-significant-difference method at the p = 0.05 level; a bracket connecting data indicates that the results were not significantly different.

Table IV—Dissolution Results for Tablets with a Moisture Content of 1.25% ± 0.25%[a]

Main Component	Disintegrant	Mode of Incorporation	Tablet Weight ± SD, mg	Tablet Hardness ± SD, kilopond	% Dissolved ± SD at 15 min[b]
Lactose	Crospovidone	Control	505 ± 3.0	8.0 ± 0.5	42.4 ± 2.4
		Intragranular	516 ± 6.0	7.9 ± 0.7	63.4 ± 4.0
		Intragranular + extragranular	501 ± 4.5	8.2 ± 0.5	103.3 ± 1.3
		Extragranular	512 ± 6.0	7.1 ± 0.5	105.1 ± 0.4
	Sodium starch glycolate	Control	505 ± 3.0	8.0 ± 0.5	42.4 ± 2.4
		Intragranular	491 ± 5.0	7.1 ± 0.5	50.7 ± 1.6
		Intragranular + extragranular	499 ± 7.0	7.3 ± 0.6	61.8 ± 1.5
		Extragranular	493 ± 6.0	6.7 ± 0.4	98.5 ± 2.9
	Croscarmellose sodium	Control	505 ± 3.0	8.0 ± 0.5	42.4 ± 2.4
		Intragranular	502 ± 3.0	7.7 ± 0.3	97.5 ± 1.6
		Extragranular	499 ± 4.0	7.9 ± 0.8	103.8 ± 4.1
		Intragranular + extragranular	505 ± 3.0	8.1 ± 0.2	104.0 ± 0.8
Naproxen	Crospovidone	Control	501 ± 3.0	8.2 ± 0.6	6.0 ± 0.2
		Intragranular	502 ± 2.0	7.7 ± 0.6	6.6 ± 0.3
		Intragranular + extragranular	501 ± 2.0	8.0 ± 0.6	31.8 ± 2.5
		Extragranular	497 ± 2.0	8.2 ± 0.4	43.5 ± 3.3
	Sodium starch glycolate	Control	501 ± 3.0	8.2 ± 0.6	6.0 ± 0.2
		Intragranular	495 ± 2.0	7.7 ± 0.9	17.6 ± 1.0
		Extragranular	495 ± 2.0	8.1 ± 0.5	54.2 ± 2.5
		Intragranular + extragranular	496 ± 2.0	8.2 ± 0.6	56.8 ± 0.9
	Croscarmellose sodium	Control	501 ± 3.0	8.2 ± 0.6	6.0 ± 0.2
		Intragranular	499 ± 4.0	8.1 ± 0.5	66.1 ± 1.5
		Extragranular	497 ± 2.0	8.4 ± 0.8	83.6 ± 5.4
		Intragranular + extragranular	502 ± 3.0	7.4 ± 0.7	85.0 ± 7.2
Dibasic calcium phosphate	Crospovidone	Control	504 ± 6.0	8.2 ± 0.8	22.0 ± 0.3
		Intragranular	496 ± 2.0	8.0 ± 1.0	24.8 ± 1.3
		Intragranular + extragranular	498 ± 2.0	7.9 ± 0.5	29.9 ± 4.5
		Extragranular	500 ± 5.0	7.6 ± 0.5	62.7 ± 4.2
	Sodium starch glycolate	Control	504 ± 6.0	8.2 ± 0.8	22.0 ± 0.3
		Intragranular	499 ± 7.0	8.1 ± 0.9	31.1 ± 0.7
		Intragranular + extragranular	510 ± 8.0	8.6 ± 0.9	39.0 ± 2.8
		Extragranular	497 ± 5.0	8.1 ± 0.5	49.2 ± 5.2
	Croscarmellose sodium	Control	504 ± 6.0	8.2 ± 0.8	22.0 ± 0.3
		Intragranular	—[c]	—	60.9 ± 1.3
		Extragranular	510 ± 4.0	6.9 ± 0.7	64.8 ± 3.8
		Intragranular + extragranular	501 ± 3.0	7.5 ± 0.5	98.8 ± 1.1

[a] See Table III, footnote *a*. [b] See Table III, footnote *b*. [c] —, Not available.

LOD to maintain three moisture content levels. The dried granulated mixtures were passed through a 16-mesh screen with an oscillator (Erweka AR400) and stored in a tightly closed plastic bag.

Final Blending—The milled granules were mixed with the extragranular super disintegrant (if required by the experimental design) in the high-shear mixer for 3 min (batches without the extragranular super disintegrant were mixed for 3 min as well). The final blend was then mixed with magnesium stearate (which served as a tablet lubricant) for 2 min and stored in a tightly closed plastic bag.

Compression—The moisture content of the granulated mixtures was retested just before compression to ensure that it had not changed during processing. The tablets were compressed with a single-punch machine (Stokes F-4) to a targeted hardness of 8 kiloponds (±1 kilopond) (see below), except for the 0.5% LOD naproxen formulations, which could only be compressed to a hardness of 6 kiloponds (±1 kilopond). The tablets were manufactured to a targeted weight of 500 mg (±50 mg). See Tables III through VI for the actual hardnesses and weights of the tablets. A 1.11-cm standard concave punch and die set was used. The tablets were doubly bagged in tightly closed bags for storage.

Hardness Determination—Tablet hardness was determined immediately after compression with an instrument (model HT-300; Key International) that uses the principle of strain-gauge linear force to ascertain the degree of tablet hardness. Twenty tablets were tested for each batch, and the mean ± standard deviation were calculated. Hardness was measured in kiloponds (1 kilopond = 1.4 Strong-Cobb units = 9.8 N).

In Vitro Dissolution—Dissolution of the tablets was performed in accordance with USP XXI by use of apparatus 1. Testing of the tablets was accomplished within 1 week from the time that the tablets were compressed. The medium was 900 mL of deaerated phosphate buffer (pH 7.4) or 0.01 M HCl (pH 2.0) at a temperature of 37.0 ± 0.5 °C. The basket rotated at 100 rpm. Automated sampling equipment removed the samples through a filter and analyzed them spectrophotometrically at 226 nm for the acidic medium or at 266 nm for the neutral medium, with sampling every 5 min for 45 min. Lactose and dibasic calcium phosphate tablets were examined for the amount of *p*-aminobenzoic acid released, whereas naproxen tablets were monitored for the combined amount of naproxen and *p*-aminobenzoic acid that was liberated from the tablets, with 95% of the spectrophotometric response being due to the naproxen.

Table V—Dissolution Results for Tablets with a Moisture Content of 2.25% ± 0.25%[a]

Main Component	Disintegrant	Mode of Incorporation	Tablet Weight ± SD, mg	Tablet Hardness ± SD, kilopond	% Dissolved ± SD at 15 min[b]
Lactose	Crospovidone	Control	500 ± 3.0	7.2 ± 0.6	42.6 ± 1.4
		Intragranular	503 ± 3.0	8.0 ± 0.3	64.8 ± 2.4
		Intragranular + extragranular	495 ± 2.0	8.2 ± 0.5	90.8 ± 1.6
		Extragranular	503 ± 2.0	8.4 ± 0.4	107.3 ± 0.7
	Sodium starch glycolate	Control	500 ± 3.0	7.2 ± 0.6	42.6 ± 1.4
		Intragranular	504 ± 4.0	8.8 ± 0.5	45.5 ± 1.2
		Intragranular + extragranular	499 ± 4.0	8.3 ± 0.5	57.9 ± 1.1
		Extragranular	499 ± 4.0	7.9 ± 0.7	86.6 ± 2.1
	Croscarmellose sodium	Control	500 ± 3.0	7.2 ± 0.6	42.6 ± 1.4
		Intragranular	499 ± 3.0	7.9 ± 0.5	87.4 ± 2.2
		Intragranular + extragranular	490 ± 3.0	8.5 ± 0.6	99.5 ± 1.2
		Extragranular	510 ± 4.0	8.3 ± 0.3	102.8 ± 2.1
Naproxen	Crospovidone	Control	499 ± 3.0	5.9 ± 0.4	5.8 ± 0.1
		Intragranular	500 ± 2.0	8.0 ± 0.3	20.9 ± 1.5
		Intragranular + extragranular	505 ± 2.0	8.1 ± 0.3	75.5 ± 1.5
		Extragranular	497 ± 2.0	8.2 ± 0.4	89.6 ± 3.6
	Sodium starch glycolate	Control	499 ± 3.0	5.9 ± 0.4	5.8 ± 0.1
		Intragranular	499 ± 4.0	7.3 ± 0.4	18.3 ± 1.0
		Intragranular + extragranular	494 ± 2.0	7.5 ± 0.3	51.0 ± 3.3
		Extragranular	495 ± 3.0	8.4 ± 0.4	59.9 ± 0.8
	Croscarmellose sodium	Control	499 ± 3.0	5.9 ± 0.4	5.8 ± 0.1
		Intragranular	499 ± 4.0	8.1 ± 0.4	72.0 ± 0.7
		Intragranular + extragranular	497 ± 2.0	8.4 ± 0.8	81.5 ± 0.9
		Extragranular	500 ± 3.0	8.3 ± 0.6	84.7 ± 2.1
Dibasic calcium phosphate	Crospovidone	Control	498 ± 5.0	8.2 ± 0.6	21.7 ± 0.5
		Intragranular	493 ± 4.0	8.3 ± 0.4	29.5 ± 1.4]
		Intragranular + extragranular	498 ± 3.0	8.0 ± 0.4	33.6 ± 1.7]
		Extragranular	498 ± 3.0	7.5 ± 0.2	50.7 ± 10.0
	Sodium starch glycolate	Control	498 ± 5.0	8.2 ± 0.6	21.7 ± 0.5
		Intragranular	503 ± 3.0	7.6 ± 0.5	32.7 ± 1.3
		Intragranular + extragranular	497 ± 3.0	8.0 ± 0.9	51.3 ± 2.7
		Extragranular	498 ± 4.0	8.2 ± 0.4	62.1 ± 1.5
	Croscarmellose sodium	Control	498 ± 5.0	8.2 ± 0.6	21.7 ± 0.5
		Intragranular	500 ± 5.0	8.0 ± 0.5	67.0 ± 1.2]
		Extragranular	496 ± 4.0	8.4 ± 0.6	67.7 ± 3.0]
		Intragranular + extragranular	497 ± 3.0	7.9 ± 0.7	74.4 ± 4.5

[a] See Table III, footnote *a*. [b] See Table III, footnote *b*.

Table VI—Dissolution Results for Tablets with a Moisture Content of 3.25% ± 0.25%[a]

Disintegrant	Mode of Incorporation	Tablet Weight ± SD, mg	Tablet Hardness ± SD, kilopond	% Dissolved ± SD at 15 min[b]
Crospovidone	Control	496 ± 4.0	6.6 ± 0.4	21.4 ± 1.1
	Intragranular	501 ± 4.0	7.9 ± 0.3	35.5 ± 2.3
	Intragranular + extragranular	514 ± 7.0	6.7 ± 0.5	52.8 ± 4.0
	Extragranular	505 ± 3.0	7.1 ± 0.4	56.4 ± 2.9
Sodium starch glycolate	Control	496 ± 4.0	6.6 ± 0.4	21.4 ± 1.1
	Intragranular	513 ± 18.0	8.3 ± 0.9	35.7 ± 2.0]
	Intragranular + extragranular	509 ± 17.0	8.3 ± 0.8	36.7 ± 2.3]
	Extragranular	502 ± 6.0	8.7 ± 0.5	69.7 ± 2.1
Croscarmellose sodium	Control	496 ± 4.0	6.6 ± 0.4	21.4 ± 1.1
	Intragranular	509 ± 7.0	7.2 ± 0.2	75.0 ± 5.4
	Intragranular + extragranular	501 ± 3.0	9.2 ± 0.4	80.4 ± 3.4]
	Extragranular	500 ± 2.0	8.6 ± 0.4	81.1 ± 2.2]

[a] At 15 min in pH 7.4 buffer. The main component was dibasic calcium phosphate. Tablets were sorted by type of disintegrant and increasing dissolution. [b] See Table III, footnote *b*.

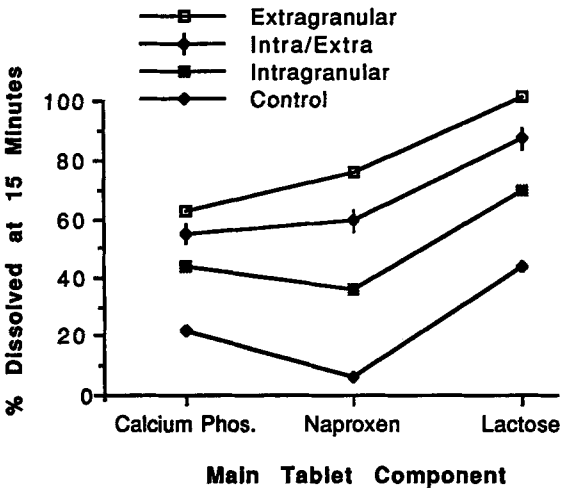

Figure 1—Effect of different modes of super disintegrant incorporation on dissolution.

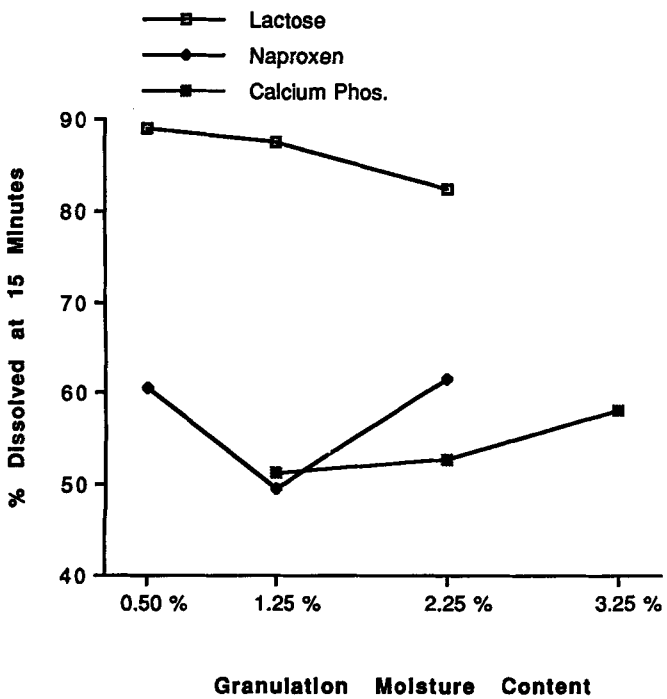

Figure 2—Effect of granulation moisture content on dissolution for tablets that contained super disintegrants but had different main components.

Results and Discussion

Table I shows the generalized tablet formulation used in this study. Each formulation contained one of the three principal excipients, so that the solubilities of the formulations varied. The solubilities of the main tablet components in the dissolution media used are presented in Table II. Each formulation contained one of three different super disintegrants or no super disintegrant as a control batch. Each formulation was dried to three different granulation moisture contents. Dissolution results at the 15-min time point for the 90 tablet batches are presented in Tables III through VI. The trends seen at 15 min were also evident at other time points. The first trend that was apparent in the tables and that is graphically shown in Figure 1 was that dissolution rates were generally enhanced as more super disintegrant was incorporated extragranularly, regardless

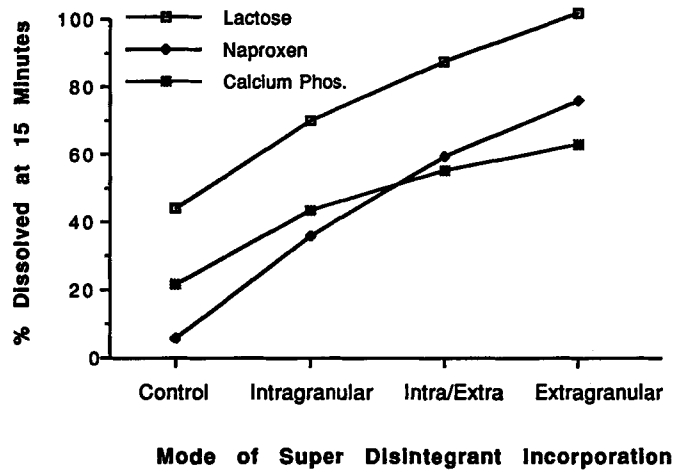

Figure 3—Effect of the main tablet component on dissolution.

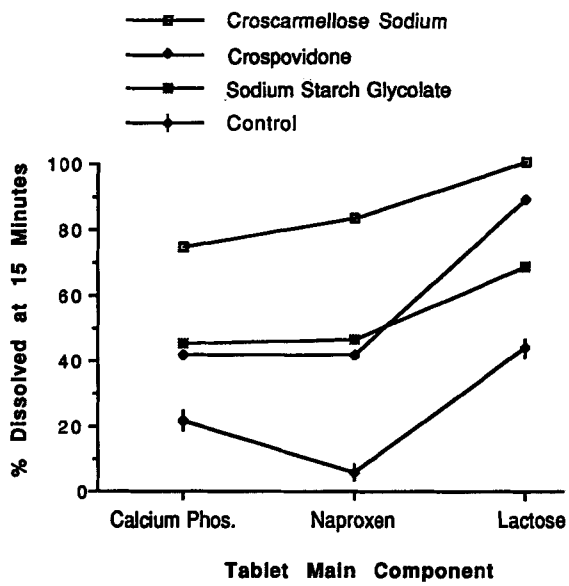

Figure 4—Effect of the type of super disintegrant on dissolution.

of the solubility of the main tablet component used and the moisture content. In tablet lots in which all factors were the same except for the mode of super disintegrant incorporation, extragranular incorporation resulted in statistically significantly faster dissolution than intragranular incorporation for 93% (25 of 27) of the batches, with statistically similar results in another 1 of the 27 batches. Formulations with extragranular incorporation outperformed those with the super disintegrant distributed equally between the two phases in 70% (19 of 27) of the batches, and an additional 22% (6 of 27) of the batches showed equivalent results. When equal distribution of the super disintegrant between the two phases was compared with intragranular inclusion, it was found that the former produced quicker dissolution in 89% (24 of 27) of the batches and that 7% (2 of 27) of the batches showed similar dissolution results. The common factor in the few instances in which either intragranular inclusion or an equal distribution of the super disintegrant produced the most rapid dissolution rate was that croscarmellose sodium was always the super disintegrant. This result may indicate that the croscarmellose sodium was less sensitive to the mode of incorporation than were the other two super disintegrants.

Table VII—Dissolution Results at 15 min in pH 7.4 Buffer versus pH 2.0 HCl for Tablets with a Moisture Content of 2.25% ± 0.25%[a]

Main Component	Mode of Incorporation	Disintegrant	% Dissolved at 15 min at the Following pH[b]:		% Dissolved at pH 7.4 Minus % Dissolved at pH 2.0
			7.4	2.0	
Lactose	None	Control (none)	42.6	39.9	2.7
	Intragranular	Sodium starch glycolate	45.5	32.8	12.7
		Croscarmellose sodium	87.4	74.4	13.0
		Crospovidone	64.8	46.3	18.5
	Intragranular + extragranular	Sodium starch glycolate	57.9	42.8	15.1
		Croscarmellose sodium	99.5	79.4	20.0
		Crospovidone	90.8	69.6	21.2
	Extragranular	Crospovidone	107.3	92.1	15.2
		Sodium starch glycolate	86.6	63.6	23.0
		Croscarmellose sodium	102.8	—[c]	—
Dibasic calcium phosphate	None	Control (none)	21.7	22.3	0.6
	Intragranular	Sodium starch glycolate	32.7	27.8	4.9
		Crospovidone	29.5	24.0	5.5
		Croscarmellose sodium	67.0	45.8	21.2
	Intragranular + extragranular	Crospovidone	33.6	37.2	−3.6
		Croscarmellose sodium	67.7	—	—
		Sodium starch glycolate	51.3	42.2	9.1
	Extragranular	Croscarmellose sodium	74.4	—	—
		Sodium starch glycolate	62.1	50.3	11.8
		Crospovidone	50.7	31.4	19.3

[a] Tablets were sorted by main tablet component, mode of incorporation, and increasing differences in dissolution at the two pHs. [b] Mean for six tablets. [c] —, Not available.

The effect of moisture content on tablet dissolution appeared to be weakly dependent on the main tablet component used (Figure 2). When all factors except for the main tablet component were controlled, there was a weak trend in the lactose tablets, in which lower LODs produced the fastest dissolution (significantly at the $p = 0.05$ level in six of nine sets, in which each set consisted of three batches for which all variables were the same except for the LODs), whereas in the dibasic calcium phosphate tablets, the opposite weak trend was evident, that is, higher LODs tended to produce the most quickly dissolving tablets (significant in six of nine sets of batches). Tablets manufactured with naproxen did not exhibit any trend at all. Further study is required to determine whether highly soluble and insoluble tablet bases typically behave in opposite fashions with regard to their dissolution response to granulation moisture content or whether the differences observed here were simply due to the particular main tablet components chosen for this investigation. When either the type of disintegrant or the mode of incorporation was isolated as a factor, no consistent interactions with moisture content could be identified.

When the impact of varying the main tablet components was examined, it was evident that the lactose tablets, with or without super disintegrants, always dissolved significantly faster than either the naproxen or the dibasic calcium phosphate tablets (Figure 3). It is not clear what the second fastest dissolving base was because the tablets containing naproxen dissolved faster than the tablets containing dibasic calcium phosphate roughly half the time, and the opposite was also true approximately half the time.

Figure 4 shows another trend: when all of the variables except for the super disintegrant used were kept constant, tablets that included croscarmellose sodium tended to dissolve faster than did tablets that incorporated either crospovidone or sodium starch glycolate. Statistically, at the $p = 0.05$ level, tablets that contained croscarmellose sodium dissolved significantly faster than tablets that incorporated either crospovidone or sodium starch glycolate in 21 of the 27 sets of batches. In cases in which croscarmellose sodium did not facilitate faster dissolution than crospovidone or sodium starch glycolate, a common factor for all was that the disintegrants were incorporated extragranularly. In general, crospovidone and sodium starch glycolate appeared to be roughly equally effective. However, crospovidone always caused quicker dissolution in the lactose tablets than did sodium starch glycolate, whereas there was a tendency for sodium starch glycolate to perform better than crospovidone in the naproxen tablets (in five of nine batch sets) and dibasic calcium phosphate tablets (in six of nine batch sets). None of the super disintegrants was influenced by the granulation moisture content.

As noted above, two investigations concluded that the method of super disintegrant incorporation into wet granulated tablets has little effect.[14,17] Two other reports indicated that apportioning super disintegrants equally between the two phases yields the best results.[15,16] Yet another investigation found that intragranular incorporation results in the fastest tablet dissolution.[18] One of the variables that differed among the reports was composite tablet solubility. It has been hypothesized[18] that the divergent findings of these investigations are due at least in part to variations in the composite solubilities of the tablet systems examined. The purposes of this study were to test this hypothesis and additionally to examine whether the

type of super disintegrant or the granulation moisture content was also a contributing factor. This study indicated that these three variables were not responsible for the lack of agreement in the previous investigations regarding the optimum mode of super disintegrant incorporation. Furthermore, this work demonstrated that, for the tablet systems tested, extragranular incorporation yielded the best dissolution. Therefore, other factors (granule size and density, for example) need to be the subject of future investigations so that the source of the differences can be identified; such identification should allow the optimum mode(s) of super disintegrant incorporation to be established, as long as the variables of a tablet system are accounted for.

Dissolution results showing the performance of the super disintegrants when they were tested at acidic and neutral pHs are presented in Table VII. Although the dissolution rates for the control tablets were not influenced by the pH of the medium, it is clear that when super disintegrants were used, dissolution was generally faster at the neutral pH than at the acidic pH. When all other factors were controlled, the three super disintegrants more often than not behaved similarly with respect to the reduction in dissolution at the acidic pH. The trend was more definite for the lactose tablets than for the dibasic calcium phosphate tablets. These results indicated that, with regard to medium pH, for most purposes a single dissolution medium should be sufficient for screening various super disintegrants for formulation efficacy. Medium selection may be based on factors such as the simplicity of the test methodology, the site of absorption for the drug, and drug solubility.

Conclusions

The results of this study showed that for lactose, naproxen, and dibasic calcium phosphate tablets, when the same amounts of super disintegrants were used, extragranular incorporation resulted in faster dissolution rates than did distribution of the disintegrants half intragranularly and half extragranularly, and both of these produced more rapid rates than did intragranular incorporation. The effect of moisture content on tablet dissolution appeared to be dependent on the main tablet component used, so moisture content therefore must be optimized for each tablet formulation. There were no consistent interactions between the moisture content and the type of disintegrant or the mode of incorporation in the tablet systems studied. The lactose tablets, with and without a disintegrant, always dissolved significantly faster than did either the naproxen or the dibasic calcium phosphate tablets. However, neither the naproxen nor the dibasic calcium phosphate tablets consistently dissolved faster than the other. All other factors being equal, there was a trend for faster tablet dissolution with croscarmellose sodium than with crospovidone or sodium starch glycolate. It was found, regardless of the super disintegrant used, that the super disintegrants usually facilitated faster dissolution in a neutral pH dissolution medium than in an acidic pH one.

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Annexure - 9

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Research Paper

The Effect of Different Superdisintegrants and their Concentrations on the Dissolution of Topiramate Immediate Release Tablets

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ABSTRACT: The purpose of this study was to investigate the efficiency of superdisintegrants: sodium starch glycolate, croscarmellose sodium and crospovidone in promoting tablet disintegration and drug dissolution of Topiramate immediate release tablets. The efficiency of superdisintegrants was tested, by considering four concentrations, viz., like 2%, 3%, 4% and 5% in the formulations. The dissolution was carried out in USP apparatus II at 50 rpm with distilled water as a dissolution medium. The dissolution rate of the model drug topiramate was found highly dependent on the tablet disintegration, on the particle size of the superdisintegrant, on the solubility of the drug and also on the type of superdisintegrant in the dissolution medium. There was no effect of the diluent (Lactose monohydrate) on the disintegration of different concentrations of superdisintegrants. These results suggest that, as determined by the *f2* metric (similarity factor), the dissolution profile of the formulation containing 4% sodium starch glycolate and lactose monohydrate as a diluent was similar to that of a marketed product.

KEYWORDS: Topiramate; Superdisintegrants; Immediate release; Sodium starch glycolate; Croscarmellose sodium

Introduction

Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants (Augsburger., 2000; Hahm., 2000). The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet. The demand for faster disintegrating formulation is increased as per time. So, pharmaceutical manufacturers needs to formulate fast disintegrating dosage forms by employing superdisintegrants which are effective at low concentrations and have greater disintegrating efficiency and are more effective intra granularly (Tagawa., 2003). But the main drawback is their hygroscopic nature, therefore not used with moisture sensitive drugs.

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Superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction which causes the tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration (Miterevej., 1982). Despite several theories proposed, still there is a lack of understanding the complete mechanism of disintegration. Proposed mechanisms for the action of disintegrants include water uptake through wicking, swelling, deformation (shape) recovery, particle repulsion, and heat of wetting, though the latter two are not well supported by researchers (Shangraw., 1980). Water penetration is an indispensable preprocessing step for disintegration. The absorption properties of various disintegrants are found essential for efficient disintegration and dissolution. If the wetting of the disintegrant particles is slowed, for example by coating the disintegrants with a hydrophobic substance (magnesium stearate) (Bolhuis., 1981), disintegration of the tablets is also slowed.

The swelling of disintegrant particles is the most widely accepted mechanism for tablet disintegration. Primarily, this is because almost all disintegrants swell to some extent. Also the concentration of the superdisintegrants and the effect of other ingredients like diluents used in the formulation of the tablets in promoting disintegration are very important in case of immediate release tablets (Caramella., 1984).

The three main classes of superdisintegrants, Primojel (sodium starch glycolate), Ac-Di-Sol (Croscarmellose sodium) and Polyplasdone XL10 (crospovidone), reportedly exhibit a broad range of intrinsic swelling capacity (Primojel > Ac-Di-Sol >> Polyplasdone XL10), yet all 3 are clearly very effective disintegrants (Gissinger., 1980).

Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. The purpose of this study is to accelerate the release and action of the drug, Topiramate. The study also includes influence of the different concentrations of superdisintegrants on a diluent, lactose monohydrate, efficiency in promoting disintegration and dissolution of active ingredient Topiramate from directly compressed tablets

Materials and Methods

Materials used in this study were Topiramate, Primojel (sodium starch glycolate), Ac-Di-Sol (Croscarmellose sodium), and Polyplasdone XL10 (crospovidone), Lactose monohydrate, Povidone K30 (Polyvinyl Pyrrolidone), Magnesium stearate, 9-fluorenyl chloroformate (9-FMOC-cl), glycine, acetonitrile, boric acid, potassium chloride, potassium hydroxide

Methods

Accurately weighed quantities of lactose monohydrate and drug were taken in a mortar and to this 2% of sodium starch glycolate and added 10% of dry binder polyvinyl pyrrrolidone; mixed thoroughly using a mortar and pestle. The mixture was passed through 40# and then the shifted quantity was mixed for 15 minutes in a polythene bag. To this, magnesium stearate was added and mixed again for 5 minutes. The mixture was then punched into 300mg tablets with 11/32 concave faced punches at a hardness of 4 to 5 kg/cm^2. The procedure was repeated for 3%, 4% and 5% of SSG. The above procedure was followed for Croscarmellose Sodium and also for Crospovidone as given in Table 1.

Table 1 Topiramate Direct Compression Formulations.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Topiramate	100	100	100	100	100	100	100	100	100	100	100	100
Lactose monohydrate	161	158	155	152	161	158	155	152	161	158	155	152
SSG (2%)	6	-	-	-	-	-	-	-	-	-	-	-
SSG (3%)	-	9	-	-	-	-	-	-	-	-	-	-
SSG (4%)	-	-	12	-	-	-	-	-	-	-	-	-
SSG (5%)	-	-	-	15	-	-	-	-	-	-	-	-
CCS (2%)	-	-	-	-	6	-	-	-	-	-	-	-
CCS (3%)	-	-	-	-	-	9	-	-	-	-	-	-
CCS (4%)	-	-	-	-	-	-	12	-	-	-	-	-
CCS (5%)	-	-	-	-	-	-	-	15	-	-	-	-
CP (2%)	-	-	-	-	-	-	-	-	6	-	-	-
CP (3%)	-	-	-	-	-	-	-	-	-	9	-	-
CP (4%)	-	-	-	-	-	-	-	-	-	-	12	-
CP (5%)	-	-	-	-	-	-	-	-	-	-	-	15
PVP K30	30	30	30	30	30	30	30	30	30	30	30	30
Mg Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Total wt (mg)	300	300	300	300	300	300	300	300	300	300	300	300

Evaluation of Tablets

The prepared tablets are evaluated for dimensions, average weight, hardness, friability, uniformity of weight along with other parameters.

Determination of Bulk Density and Tapped Density:

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and volume (Vo) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus (bulk density apparatus) .The density apparatus was set for 100 taps and after that the volume (Vf) was measured and continued operation till the two consecutive reading were equal.

Compressibility Index (Carr indexes)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more free flowing it is.

$$CI = 100(V_0 - V_f) / V_0 \qquad \text{…..(3)}$$

Hausner's Ratio

It indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density.

Disintegration and Dissolution Study

Disintegration times were measured in 900 mL of distilled water at 37 ± 0.5^{O}C using the USP disintegration apparatus. Disintegration time was the time taken by each of the six tablets to pass completely through the 10-mesh screen. The data given is the average of disintegration times of six individual tablets.

Dissolution profiles of the Topiramate tablets were determined using the paddle method of the USP II (Elico, SL 164), set with a paddle speed of 50 rpm. Dissolution was carried in distilled water as a medium The samples were withdrawn at predetermined time points 5, 10, 15, 30 45 and 60 minutes and diluted as required, analyzed spectrophometrically in UV-VIS Spectrophotometer after derivatizing with 9-FMOC-cl at 264 nm.

Method of Derivatization

To the diluted samples, 1ml of FMOC-cl in acetonitrile (500µg/ml) was added and to this 1ml of borate buffer 7.7 pH was added since the derivatization takes place at this pH.

The samples were vigorously shaked for 5 minutes and heated at 50ºC for 15 minutes in a hot mantle to maintain the constant temperature and to this glycine solution (4mg/ml) 0.5ml was added and mixed for 2 minutes to stop the derivatization and the samples were then scanned at 264nm in UV-VIS double beam spectrophotometer (Chen., 2001, Contin., 2001).

Results and Discussions

Precompression Blend Characterization

The precompression Blend of mixture containing different concentrations of three superdisintegrants was evaluated for Bulk Density, Tapped Density, Carr's Index and Hausner's Ration. There was no much difference in the precompression Blend Densities as shown in Table 2 for different superdisintegrants with same diluent Lactose.

Topiramate Tablets Characterization

Tablets were evaluated for Weight variation, Friability, Hardness, Thickness, Disintegration time, and Dissolution as shown in Table 3.

Table 2 Topiramate Precompression Blend Characterization.

Superdisintegrants (Lactose-Diluent)	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
SSG	0.523	0.566	11.67	1.082
CCS	0.525	0.551	10.57	1.049
CP	0.518	0.551	11.29	1.063

Table 3 Topiramate Tablet Characterization.

	Hardness Kg/cm2*	Thickness Mm*	Friability %	Disintegration time In min*	Weight variation
F1	4.75±0.17	3.58±0.83	< 1%	4.54±1.03	< 5%
F2	4.675±0.25	3.57±0.62	< 1%	4.33±1.02	< 5%
F3	4.825±0.95	3.57±0.44	< 1%	2.51±0.65	< 5%
F4	4.77±0.23	3.57±0.41	< 1%	2.29±0.84	< 5%
F5	5.02±0.18	3.55±0.75	< 1%	1.42±0.35	< 5%
F6	5.00±0.18	3.56±0.62	< 1%	1.26±0.53	< 5%
F7	4.77±0.12	3.56±0.25	< 1%	1.07±0.56	< 5%
F8	4.9±0.21	3.57±0.29	< 1%	0.55±0.73	< 5%
F9	5.07±0.87	3.54±0.31	< 1%	1.49±0.44	< 5%
F10	4.95±0.72	3.56±0.81	< 1%	1.22±0.77	< 5%
F11	4.9±0.621	3.567±0.51	< 1%	0.56±0.68	< 5%
F12	5.025±0.32	3.55±0.61	< 1%	0.48±0.34	< 5%

*All values represents Mean ± SD, n = 6

Discussion

From figure 1, it can be said that, an increase in the concentration of the superdisintegrant sodium starch glycolate from 2% to 5%, the disintegration rate has increased i.e. decreased the disintegration time of the tablets. And since Lactose is used as a diluent that is water soluble (Chen., 1997), the dissolution of the drug was faster (Shangraw., 1981). So it can be said that the dissolution of Topiramate is filler solubility controlled. Among all the concentrations, 4% SSG was found to be the best.

Similarly from figure 2, we notice that in Croscarmellose Sodium, the disintegration rate increased with increasing the concentration of CCS. Due to croscarmellose sodium the dissolution was even faster than sodium starch glycolate, because it is one of the disintegrant, which disintegrate and dissolves faster than that of sodium starch glycolate and crospovidone due to its fine particle size than that of other disintegrants (Van Kamp., 1986; Gissinger., 1980). All the concentration released the drug within 30 minutes itself and among them 3% CCS was the best.

From the figure 3, it can be said that, on increasing the concentration of the superdisintegrant Crospovidone from 2% to 5%, there is an increase in the disintegration rate i.e. decreased disintegration time of the tablets. But due to coarse disintegrated particle size of the superdisintegrant Crospovidone, the dissolution was slower than SSG and CCS (Shah., 2001); among them 5% CP was the best.

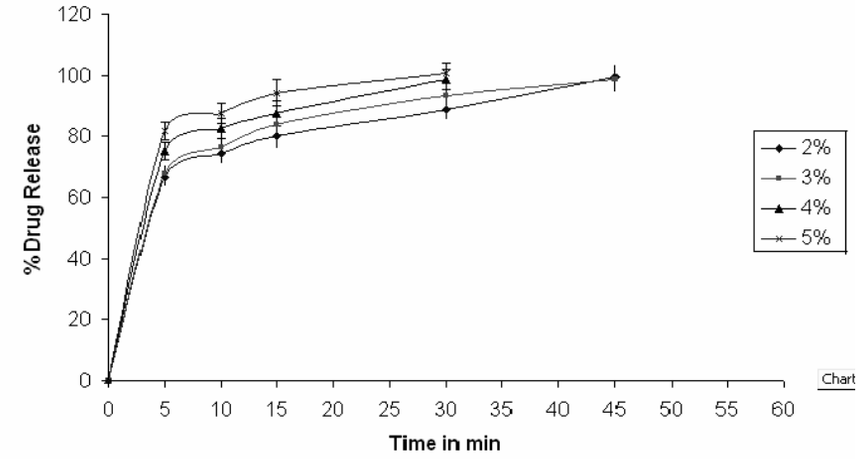

Fig. 1 Drug release profiles of topiramate tablets at different concentrations of sodium starch glycolate used when lactose monohydrate is used as a diluents.

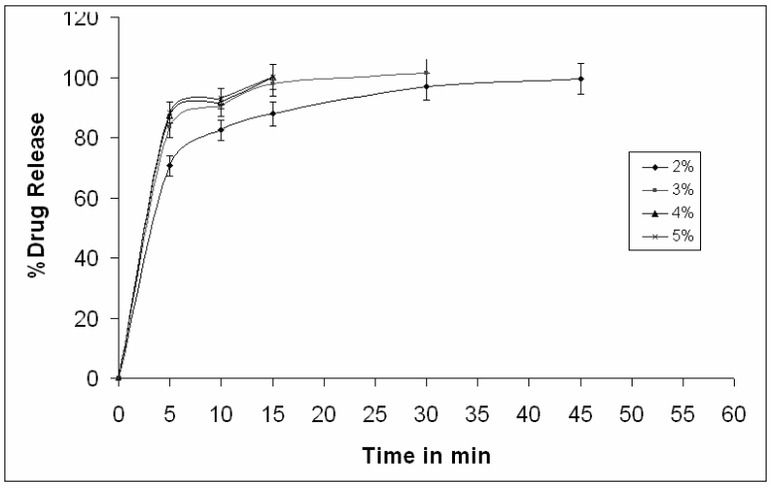

Fig. 2 Drug release profiles of topiramate tablets at different concentrations of Croscarmellose sodium used when lactose monohydrate is used as a diluents.

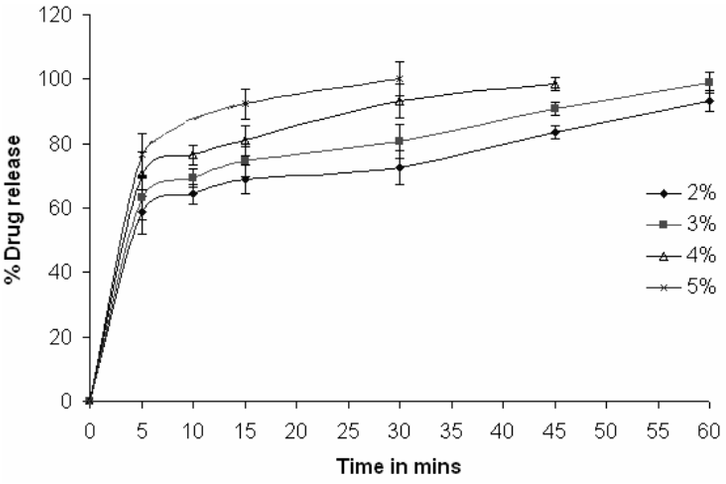

Fig. 3 Drug release profiles of topiramate tablets at different concentrations of Crospovidone used when lactose monohydrate is used as a diluents.

Conclusion

Thus, it is conducted that the immediate release tablets showed release depending on the concentration of the superdisintegrants and also on the type of mechanism of disintegration of superdisintegrants Sodium Starch Glycolate, Croscarmellose Sodium and Crospovidone. Tablet dimensions, weight, and breaking force have no significant difference between tablets with different disintegrants.

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