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9th May 2011

To,
Deputy Controller of Patents & Designs,
Intellectual Property Office,
Boudhik Sampada Bhawan,
Near Antop Hill Post Office,
S.M.Road, Antop Hill,
Mumbai - 400 037



14775

Ref: Patent Application No. 35/MUMNP/2010

Sub: Filing of Written Submission u/s 25(1) of the Act for Pre-Grant Opposition.

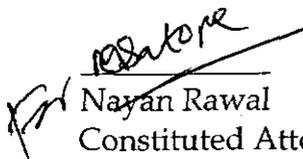
Sir,

With regards to the captioned subject and on behalf of our clients, M/s. Indian Pharmaceutical Alliance, a society registered under the Societies Registration Act, Written Submission (In duplicate) u/s 25(1) of the Patent Act for opposing the Grant of Patent Application No. 35/MUMNP/2010.

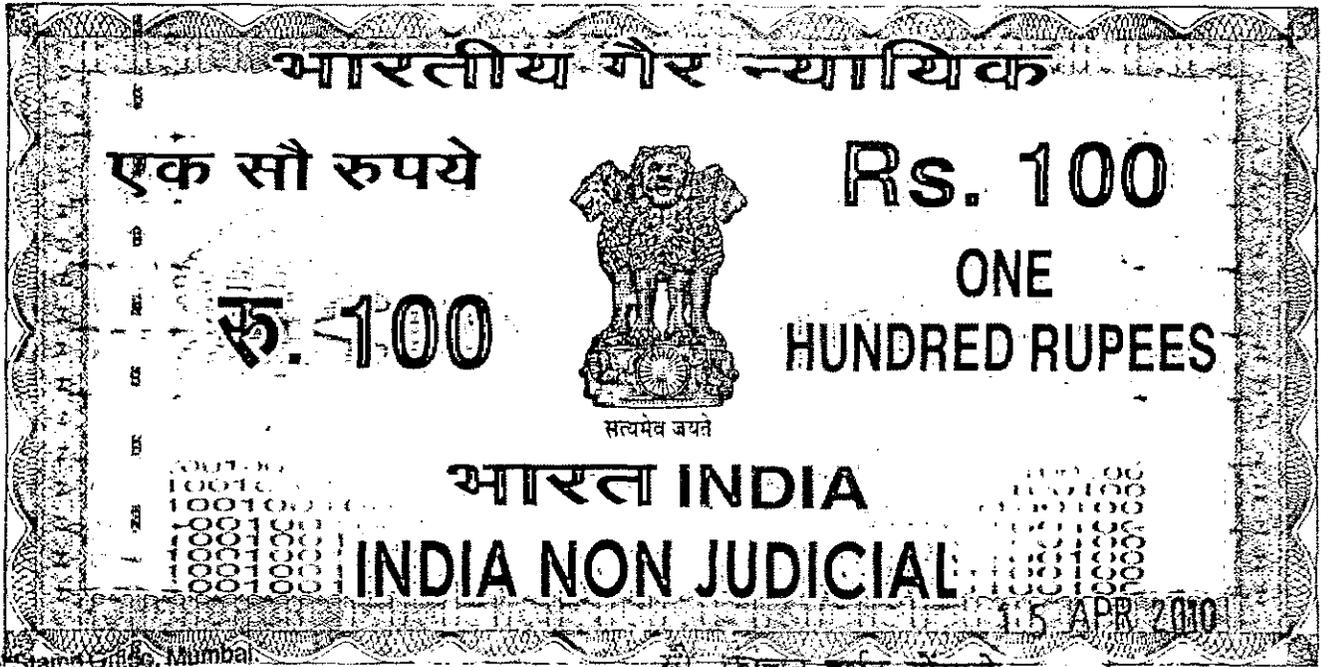
Kindly take them on record and oblige.

Thanking You,

Yours truly,


Nayan Rawal
Constituted Attorney for
the Opponent

11 MAY 2011



General Stamp Office, Mumbai

L. S. महाराष्ट्र No. 222 MAHARASHTRA

-7 APR 2010

PROPER OFFICER

SHRI. L. S. BAMBLE

श्री. फौजन हर्षद डोंगाळे

फॉरेन कॉन्सल्टिंग ग्रुप, अ. का. मार्ग
महाराष्ट्र, मुंबई - ५२.

CX 510202

15 APR 2010
Indian Pharmaceutical Alliance

यांना परवाना धारक मुद्रांक विक्रेता

परवाना धारक मुद्रांक विक्रेता

GENERAL POWER OF ATTORNEY

We, **Indian Pharmaceutical Alliance**, a Society registered under the Societies Registration Act having its mailing address as follows **C/o VISION CONSULTING GROUP, 201 Darvesh Chambers, 743 P D Hinduja Road, Khar (W), Mumbai 400 052** hereby authorize Mr. Nayan J. Rawal, Patent Agent (Agent No.654), having its Office at L-303, Panchsheel Gardens, Mahavir Nagar, Kandivli West, Mumbai 400 067, to act as our Agents and Attorneys for various Pre-Grant and Post-Grant Opposition, rectification and any other proceedings under the Patents (Amendment) Act, 1970 in respect of various Patents filed in India.

We request that all notices, requisitions and communications may be sent to the said Agents at the following address:-

Vision Consulting Group, 201 Darvesh Chambers, 743 P D Hinduja Road, Khar (W), Mumbai 400 052.

We hereby revoke all previous authorizations, if any; we hereby ratify all acts done by the said Agents

Dated this 19th day of April 2010

For **Indian Pharmaceutical Alliance**



D G Shah
Secretary General

IN THE MATTER OF THE PATENTS ACT, 1970

and

**IN THE MATTER OF THE PATENT RULES, 2003
(as amended by the Patents (Amendment) Rules 2006)**

and

**IN THE MATTER OF INDIAN PATENT APPLICATION NO. 35/MUMNP/2010
FILED BY TIBOTEC PHARMACEUTICALS.**

.....the Applicants

and

**IN THE MATTER OF A REPRESENTATION BY WAY OF AN OPPOSITION
UNDER SECTION 25(1) AND RULE 55 THERETO BY INDIAN
PHARMACEUTICALS ALLIANCE**

.....the Opponents

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

1.0 It is respectfully submitted on behalf of Indian Pharmaceutical Alliance, that a *pre-grant Opposition under Section 25(1) of the Patents Act, 1970 and rule 55(1) of the Patents Rules, 2003 (as amended by the Patents (Amendment) Rules 2006)*, is hereby presented by the “Opponents” against Indian Patent Application No. **35/MUMNP/2010** (hereinafter also referred to as the “Opposed Application”) in the name of **TIBOTEC PHARMACEUTICALS** (hereinafter referred to as the “Applicants”).

It is respectfully submitted:

2.0 The Opponents are an associations of person registered under the SOCIETIES REGISTRATION ACT, XXI OF 1860 in the name and style of “INDIAN PHARMACEUTICAL ALLIANCE” having its registered office 115/11, GROUND FLOOR, WORLD TRADE CENTRE, BABAR ROAD, CONNAUGHT PLACE, NEW DELHI – 110001, the main object of as follows:-

- (a) To support the development of international and regional policies, which seek to ensure, access to medical care for all customers.
- (b) To promote balanced and generic friendly intellectual property rights in the pharmaceuticals sector to ensure that timely access to markets is guaranteed for new and generic pharmaceutical products.
- (c) To promote the global harmonization relating to generic products.
- (d) To support the right of all governments to regulate their own pricing, substitution, prescribing and reimbursement policies.
- (e) To suggest measures for enhancing pharmaceutical research in India, both in the areas of basic as well as applied research.
- (f) To interact with the environmental protection agencies to evolve uniform standards of environmental protection measures across the country and ensure implementation of the same.
- (g) To suggest measures to strengthen the pharmaceutical pricing framework that ensures an equitable pricing system for industry and consumers.

(h) One of the further object of the society is to promote cause of generic pharmaceutical industry and to provide support for the development of competition on the off Patent pharmaceutical sector and to prepare position papers for representing India at international for a to highlight the problems face by generic pharmaceutical companies in international market. It also aims at strengthening regulatory agencies for patenting registration and quality assurance of drugs and pharmaceuticals by providing gaudiness to government and international organization in improving the regulatory and legal expertise relating to registration and marketing of drugs and pharmaceutical. It also further aims at interacting with the regulatory authorities to streamline the guidelines for clinical trials and bio-equivalence studies, to ensure expeditious registration of new as well as existing drugs.

2.1 This invention relates to solid oral dosage forms of the HIV inhibitors containing a combination of TMC114 and TMC125.

2.2 Although “any person”, “in writing” under Section 25(1) of The Patents Act, 1970; can make a representation of Opposition however, the Opponents interest in opposing this application is, substantial and real. The Opponents, therefore, have *locus standi* in opposing this application.

2.3 It is respectfully submitted that the Opposed Application entitled “**Combination Formulations Comprising Darunavir and Etravirine**” has been filed on January 07, 2010 and published in the Official Journal of the Indian Patent office on October 29, 2010. The specification of Opposed Application is attached herewith as **Document 6 (D6)**.

2.4 The Opponents are filing this Representation by way of Opposition against Indian Patent Application No. 35/MUMNP/2010 (the Opposed Application), along with documentary evidence and facts in support thereof.

2.5 In this representation by way of opposition, the following grounds enumerated in Section 25 (1) of The Patents Act, 1970 are relied upon (hereinafter referred to as the “Act”):

(a) that the applicant for the patent or the person under or through whom he claims, wrongfully obtained the invention or any part thereof from him or from a person under or through whom he claims;

(b) that the invention so far as claimed in any claim of complete specification has been published before the priority date of the claim –

i) in any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January, 1912; or

ii) in India or elsewhere, in any other document

Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub-section (2) or sub-section (3) of section 29;

(c) that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim;

(d) that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of the claim.

Explanation:- For the purpose of this clause, an invention relating to a process for which a patent is claimed shall be deemed to have been publicly known or publicly used in India before the priority date of the claim if a product made by that process had already been imported into India before that date except where such importation has been for the purpose of reasonable trial or experiment only;

(e) That the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as mentioned in clause (b) or having regard what was used in India before the priority date of the applicant's claim;

(f) that the subject matter of any claim of the complete specification is not invention within the meaning of this Act, or is not patentable under this Act;

(g) that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

(h) that the applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge;

(i) that in the case of convention application, the application was not made within twelve months from the date of the first application for protection for the invention made in a convention country by the applicant or a person from whom he derives title;

(j) that the complete specification does not disclose or wrongly mentions the source or geographical origin of biological material used for the invention;

(k) That the invention so far as claimed in any claim of the complete specification is anticipated having regard to the knowledge, oral or otherwise, available within any local or indigenous community in India or elsewhere;

The present *Representation By Way Of Opposition U/S 25(1)* takes into consideration the following documents:

Document 1 [D1] - HICKS CHARLES B: 'Report from the 13th retrovirus conference. New data on TMC114 and TMC125.' Journal of AIDS CLINICAL CARE, vol. 18, no.4, April 2006 (2006-04), page 34, ISSN: 1043-1543

Document 2 [D2] – WO 01/23362 KNOLL AKTIENGESELLSCHAFT published on 5 April 2001.

Document 3 [D3] – WO 01/22938 JANSSEN PHARMACEUTICA NV Published on 5 April 2001(2001-04-05).

Document 4 [D4] - Handbook of Pharmaceutical excipients, Raymond C Rowe, Paul J Shesky and Sian C Owen, 5th edition, 2006

Document 5 [D5] - SCH LLER-GY] RE MONIKA ET, AL: "Pharmacokinetics of darunavir/ritonavir and TMC125 alone and coadministered in HIV-negative volunteers" journal of *ANTIVIRAL THERAPY, MTM PUBLICATIONS, LONDON*, GB, vol. 12, no.5, 1 January, pages 789-796,

Document 6 [D6] - Specification of Opposed Application.

3.0 LACK OF INVENTIVE STEP

It is respectfully submitted that the alleged invention as described and claimed in the opposed specification lacks inventiveness and is obvious to a person skilled in the art. In other words, even if it is assumed without admitting that the alleged invention is novel, it is still obvious and lacks in inventive step in view of the teachings contained in the following documents:

Document 1 [D1] - HICKS CHARLES B: 'Report from the 13th retrovirus conference. New data on TMC114 and TMC125.' Journal of AIDS CLINICAL CARE, vol. 18, no.4, April 2006 (2006-04), page 34, ISSN: 1043-1543

Document 2 [D2] – WO 01/23362 KNOLL AKTIENGESELLSCHAFT published on 5 April 2001.

Document 3 [D3] – WO 01/22938 JANSSEN PHARMACEUTICA NV Published on 5 April 2001(2001-04-05).

Document 4 [D4] - Handbook of Pharmaceutical excipients, Raymond C Rowe, Paul J Shesky and Sian C Owen, 5th edition, 2006

Document 5 [D5] - SCH LLER-GY] RE MONIKA ET, AL: “Pharmacokinetics of darunavir/ritonavir and TMC125 alone and coadministered in HIV-negative volunteers” journal of *ANTIVIRAL THERAPY, MTM PUBLICATIONS, LONDON*, GB, vol. 12, no.5, 1 January, pages 789-796,

3.1 Claims 1-4 of the opposed application are obvious over D1, D2 in combination with D3, and D5

Claim 1 of the opposed patent application is, “A solid pharmaceutical oral dosage form comprising:

- (a) from about 15 mg to about 200mg of TMC1 25, or from about 25 mg to about 150 mg of TMC125, or from about 50 to about 150 mg of TMC125, or from about 80 to about 120 mg of TMC125, dispersed in a solid dispersion with a water-soluble polymer;
- (b) from about 50 to about 600 mg, or from about 50 mg to about 500 mg of free-form equivalent TMC1 14; or from about 250mg to about 450 mg of free-form equivalent TMC114, or from about 250 mg to about 350 mg of free-form equivalent of TMC1 14;
- (c) from about 200 mg to about 400 mg of a carrier; the total weight of the dosage form not exceeding 1300 mg.”

Claim 2 of the opposed patent application is, “The dosage form according to claim 1, comprising:

- (a) from about 80 to about 120 mg of TMC125, dispersed in a solid dispersion with a water-soluble polymer;
- (b) from about 250 mg to about 350 mg of free-form equivalent of TMC114; (c)

from about 200 mg to about 400 mg of a carrier;
the total weight of the dosage form not exceeding 1300 mg.”

Claim 3 of the opposed patent application is, “The dosage form according to claim 1, comprising

(a) about 100 mg of TMC125 dispersed in a solid dispersion with a water-soluble polymer;

(b) about 300 mg free-form equivalent of TMC114, or in particular about 325 mg of TMC114 monoethanolate; or about 400mg free-form equivalent of TMC114, or in particular about 434 mg of TMC114 monoethanolate;

(c) From About 200mg To About 400 Mg Of A carrier; the total weight of the dosage Form Not Exceeding 1300 mg.”

Claim 4 of the opposed patent application is, ‘The dosage form according to any of claims 1 to 3, wherein the TMC125 is present as the free form and the TMC 114 as the monoethanolate form.’

Claims 1-4 of the opposed patent application claims the dosage form is from about 15 mg to about 200mg of TMC125, or from about 25 mg to about 150 mg of TMC125, or from about 50 to about 150 mg of TMC125, or from about 80 to about 120 mg of TMC125, dispersed in a solid dispersion with a water-soluble polymer; and from about 50 to about 600 mg, or from about 50 mg to about 500 mg of free-form equivalent TMC114; or from about 250mg to about 450 mg of free-form equivalent TMC114, or from about 250 mg to about 350 mg of free-form Equivalent Of TMC114; and from about 200 mg to about 400 mg of a carrier; and the total weight of the dosage form not exceeding 1300 mg.

D1 discloses the combination of TMC114 and TMC125 has a positive effect on the viral load in HIV patient.

Furthermore, D5 also discloses the co-administration of TMC 125, 200 mg with TMC114 (Darunavir).

Further, page no.33, lines 13-22 of D3 states “*Those of skill in the treatment of HIV-infection could determine the effective daily amount from the test results*

presented here. In general, it is contemplated that an 15 effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, in particular 5 to 600 mg of active ingredient per unit dosage form, and more in particular from 200 to 400 mg per unit dosage form or from 5 to 200 mg of active ingredient per unit dosage form depending on the particular compound being used."

From above paragraph it is clear that the amount of dosage TMC125 and TMC114 as claimed in claims 1-4 of opposed patent application is (15 mg to about 200 mg of TMC125 and 50 mg to about 600 mg TMC114) falls in dosage range as discloses in D3 particular 5 to 600 mg of active ingredient per unit dosage form of formulation of antiviral formulation of HIV- infection.

Further page no.33, lines 24-34 of D3 states, "the exact dosage and frequency of administration depends on the particular compound of formula. The particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention"

Further, page no.13 in line 1-6 of D3 states that, "*The particles of the present invention are prepared as solid dispersions of the active compounds in a polymeric matrix. The term "solid dispersion" is well known in the art and means a dispersion consisting of solid components. Preferably solid dispersions are in the form of solid solutions wherein the active ingredients are molecularly dispersed in the polymeric matrix.*"

Further page no.1, line 7-13 of D3 states, "*These compositions comprise particles obtainable by melt extruding water-soluble polymers and subsequently*

milling said melt-extruded mixture. The antiviral compounds constituting the pharmaceutical compositions of the present invention are dispersed in a carrier by melt-extrusion to obtain a solid dispersion in order to improve their bio-availability."

Further, claim 8 of D3 states that, "A particle according to claim 7 wherein the water-soluble polymer is selected from the group comprising;

- alicycluloses such as methycellulose, - hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose, - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose, - carboxyalkylcelluloses such as carboxymethylcellulose, - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethyl cellulose, - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose, - carboxyalkylcellulose esters, - starches, - pectines such as sodium carboxymethylamylopectine, - chitin derivatives such as chitosan, di-, oligo- or polysaccharides such as trehalose, cyclodextrins or a derivative thereof, alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi, - polyacrylic acids and the salts thereof, - polymethacrylic acids, the salts and esters thereof, methacrylate copolymers, - polyvinylalcohol, - polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide."

Hence, on the basis of above discussion it is clear that at the time of invention the combination formulation of TMC125 and TMC114 with suitable carrier and water-soluble polymer was known in the prior art.

Further if we talk about the range of unit dosage, Generally the range of unit dosage or active ingredient depend upon patient compliance that how much dosage effective or comfortable for patient, so claims 1-4 of opposed patent application claims total weight of dosage 1300 mg is not inventive skill. So, according patient convenience or compliance evaluate effective amount of dosage is routine practice or experimentation in medical field.

Therefore, in the teaching of D1, D3, and D5 claims 1-4 of opposed patent application are obvious.

3.2 Claim 5 of the opposed application is obvious over D1, D3.

Claim 5 of the opposed patent application is, “The dosage form according to any of claims 1 to 4, wherein the total weight of the dosage form does not exceed 1100 mg.

Page no. 4, lines 17-21 of D3 states, “as mentioned above, an effective antiviral dose of a compound of formula (I-A), (I-B) or (I-C) ranges from about 1 mg to about 1000 mg per unit dosage form, and preferably is about 200 to 400 mg or 5 to 200 mg per unit dosage form depending on the particular compound being used”

As discussed earlier, opposed patent application claims the combination of TMC125 and TMC114 was known from D1.

Further page no.33, lines 24-34 of D3 states, “the exact dosage and frequency of administration depends on the particular compound of formula. The particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention”

Furthermore the total weight of dosage form comprising the weight of API and excipient, therefore after deciding the amount of API the total weight of dosage form depend on amount of excipient,

Generally, in the formulation of pharmaceutical ingredient wherein decide the amount of excipient is knowledge of formulation development (F&D) person,

wherein skilled person decide the required amount of excipient on the basis of trial & error method,

Therefore, according patient convenience or compliance evaluate effective or optimum amount of dosage for patient requirement is routine practice or experimentation in medical field.

In claim 5 of opposed patent application doesn't an inventive merite and obvious to person skill in the art.

Therefore in view of D3 and D1, the subject matter claimed in the claim 5 of the opposed patent application doesn't involve an inventive merit and obvious to person skilled in the art.

3.3 Claim 6 to 8 of the opposed application are obvious over D4,

Claim 6 of the opposed patent application is, "The dosage form according to any of claims 1 to 5, wherein the TMC 125 is dispersed in from about 100 to about 500mg of a water-soluble polymer."

Claim 7 of the opposed patent application is, "The dosage form according to any of claims 1 to 5, wherein the TMC125 is dispersed in from about 200 to about 400 mg of a water-soluble polymer."

Claim 8 of the opposed patent application is, "The dosage form according to any of claims 1 to 5, wherein the TMC 125 is dispersed in about 300 mg of a water-soluble polymer."

Claim 6-8 of the opposed patent application claims the TMC 125 is dispersed in from about 100 to about 500mg of a water-soluble polymer."

Now page no. 346 in point -7 of D4 states "*Hypromellose (HPMC) is widely used in oral ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film coating and as a matrix for use in extended – release tablet formulations, concentration*

between 2% and 5% w/w may be used as binder in either wet or dry-granulation process.” Further information from FDA –side “The Inactive Ingredients Database provides information on inactive ingredients present in FDA-approved drug products. This information can be used by industry as an aid in developing drug products. For new drug development purposes, once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and may require a less extensive review the next time it is included in a new drug product.”

Hence, based on above evident, it is obvious for the person skilled in the art to decide the range of suitable excipient for pharmaceutical formulation.

Therefore, claim 6-8 of the present application do not involve an inventive skill and obvious over D4.

3.4 Claim 9 of the opposed application is obvious over D4,

Claim 9 of the opposed patent application is, “The dosage form according to any of claims 1 to 8, wherein the solid dispersion of TMC125 comprises from about 10 mg to about 100 mg, or from about 20mg to about 80 mg, or from about 30mg to about 70 mg, or from about 40mg to about 60 mg, or about 50mg, of microcrystalline cellulose.”

Now D4 page, 132 in point 7 states that, “*Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrate properties that make it useful in Tableting.*” Further D4 in page 132 in table -1 also provided the use and concentration of microcrystalline cellulose.

Table -1 use of microcrystalline cellulose

Adsorbent	20-90
Antiadherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder/diluent	20-90

Table -1 of D1

Further information from FDA –side “*The Inactive Ingredients Database provides information on inactive ingredients present in FDA-approved drug products. This information can be used by industry as an aid in developing drug products. For new drug development purposes, once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and may require a less extensive review the next time it is included in a new drug product.*”

Hence, based on above evident, it is obvious for the person skilled in the art to decide the range of suitable excipient for pharmaceutical formulation.

Therefore, claim 9 of the present application doesn't involve an inventive skill and obvious over D4.

3.4 Claims 10 and 11 of the opposed application are obvious over D3

Claim 10 of the opposed patent application is “The dosage form according to any of claims 1 to 9, wherein the weight/weight ratio between the TMC125 and the water-soluble polymer is in the range from about 1:1 to about 1:5.”

Claim 11 of the opposed patent application is, “The dosage forms according to any of claims 1 to 9, wherein the weight/weight ratio between the TMC125 and the water-soluble polymer is about 1:3.”

Claim 10 and 11 of the present application claims the weight/weight ratio between the TMC125 and the water-soluble polymer is in the range from about 1:1 to about 1:5.

Now page no. 37, lines 1-3 of D3 states “the weight- by weight ratio of (a) (i.e. the antiviral compound) :(b) (i.e. the water-soluble polymer) is in the range of **1:1 to 1: 899**, more preferably **1:1 to 1: 100**. More preferably, **1:1 to 1:5**”

On the basis above evident claims 10 and 11 of opposed patent application claimed the ratio of TMC125 and water soluble polymer is fall under the ratio of the antiviral compound and the water-soluble polymer discloses in D3.

Therefore, in the teaching of D3, claims 10 and 11 of the opposed application don't involve an inventive merit and obvious to person skilled in the art.

3.4 Claim 12 of the opposed application is obvious over D3,

Claim 12 of the opposed patent application is The dosage form according to any of claims 1 to 9, wherein the water-soluble polymer is HPMC.

Claim 9 of D3 discloses the water-soluble polymer is hydroxyl propyl methylcellulose (**HPMC**).

Hence, in view of D3 claim 12 of the present application claims the water-soluble polymer, as (HPMC) is not inventive skill its routine practice in the field of formulation and development.

Therefore, claim 12 of opposed patent application is obvious .

4.0 NON-PATENTABLE SUBJECT MATTER

4.1 Section 3(d)

According to Section 3(d) of the Indian Patent Act, *“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 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 purpose 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.”

4.2.1 Claim 1-12 of the opposed patent application is not patentable under Section 3(d) of the Act

According to Section 3(d) of Indian Patent Act, mere discovery of new formulation is not patentable unless there is increase in efficacy. Applicant of patent has not showing any surprising effect to prove better efficacy or comparison data of formulation of TMC125 and TMC114 and pharmaceutical acceptable excipient with closest prior art formulation discloses. Further, opposed patent application does not provide any data to prove better properties over closest prior art.

Therefore, the formulation of TMC125 and TMC114 and pharmaceutical acceptable excipient is not patentable under section 3(d) of the Indian patent act.

According to Intellectual Property Appellate Board (IPAB) decision dated 26th June 2009, a new formulation of a known substance can be patentable provided they show substantial improvement in the therapeutic efficacy as compared to prior art. This means there has to be an improvement in the therapeutic content or capacity in the same amount of drug compound of the present invention vis-à-vis prior art compound or marketed drug. Thus according to the decision of Intellectual Property Appellate Board (IPAB) pharmacokinetics or bioavailability increase is not related to therapeutic efficacy.

Therefore, the present invention as claimed in claims 1-12 of the present application constitute non-patentable subject matter as per the provisions of section 3(d) of the Indian Patent Act.

4.2 Section 3(e)

According to Section 3(e) of the Indian Patent Act, "*a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance;*

4.2.1 Claim 1-12 of the opposed patent application is not patentable under Section 3(e) of the Act

Claims 1 and 12 of the opposed patent application describe the combination formulation of TMC125 and TMC114 with one or more pharmaceutically acceptable excipients like hydroxypropyl methylcellulose (HPMC) and microcrystalline cellulose (MCC) or combination of both. In absence of any data to the contrary such formulation will be consider a substance obtained by a mere admixture and therefore is not patentable under Section 3(e) of the Indian Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

Therefore, in absence of any synergistic effect of TMC125 and TMC114 with pharmaceutically acceptable excipients (water soluble polymer) is not patentable under Section 3(e) of the Indian Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

5.0 LACK OF CLARITY AND SUFFICIENCY - Section 25(1)(g)

5.1 Claim 1-3 and 6-11 of the opposed application is ambiguous as well as indefinite

Claim 1-3 and 6-11 of the opposed patent application is ambiguous as well as indefinite for following reason.

The relative terms “**about**” used in claims 1-3 and 6-11, respectively, have no well-recognized meaning because applicant does not provide exact dosage of TMC125 and TMC114; further applicant also does not provided the accurate amount of pharmaceutical acceptable excipient, which require for the combination formulations of TMC114 and TMC125. Hence, the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject matter of said claims **unclear**.

Hence Claims 1-3 and 6-11 of the opposed application is ambiguous, indefinite and is not supported by disclosure therefore it lacks clarity and sufficiency.

6.0 **Section 25(1)(h)**

It is respectfully prayed that the controller should check whether the Applicant of the opposed application has dutifully informed the status of their co-pending applications their prosecutions in other convention countries as required under Section 8 of the Patents Act, 1970. If such information is not provided, it is respectfully submitted that the opposed patent under opposition is liable to be rejected on this ground alone.

7.0 The Opponents hereby submit that Claims 1-12 contained in the opposed Indian Patent Application No. 35/MUMNP/2010 are not patentable under the Act.

8.0 The Opponents further submits that Claims 1-12 contained in the opposed Indian Patent Application No. 35/MUMNP/2010 are neither novel nor inventive or are otherwise not patentable under the Act. The Opposed Application does not fulfill the patentability criteria under the Act. The subject matter of the claims are lack of inventive step over the prior art. The Opposed Application also does not sufficiently and clearly describe the alleged invention for it to be carried out by a person skilled in the art.

09.0 In view of the aforementioned submissions, it is respectfully submitted that the Opposed Application lacks clarity and sufficiency, i.e. the description of the

Opposed Application does not enable a person reasonably skilled in the art to achieve the results of the present invention as claimed, without inventive merit.

10.0 Accordingly, it is respectfully submitted that the Opposed Application does not contain sufficient information to enable the person skilled in the art to perform the invention disclosed and claimed in opposed Indian Patent Application No. 35/MUMNP/2010. Therefore, this ground of opposition has been established and the entire Opposed Application ought to be rejected on this ground alone.

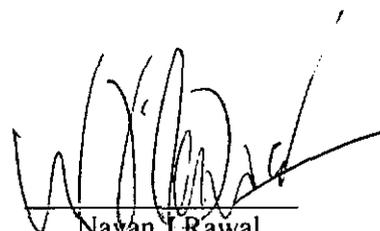
CONCLUSION

11.0 In view of the submissions presented above, we humbly pray that:

- i) the Indian Patent Application No. 35/MUMNP/2010 be dismissed *in toto*;
- ii) any other relief as the Learned Controller may deem fit be awarded in favor of the Opponents.

As a matter of precaution we request the Learned Controller to grant us an oral hearing before disposing of this application.

Dated this the ^{9th} day of May 2011


Nayan J Rawal
Constituted Attorney
for the Opponent
IPA NO 654



Report from the 13th Retrovirus Conference

Many results presented at the 2006 Retrovirus Conference could have an immediate and direct effect on HIV clinical care.

This year's Retrovirus Conference was held in downtown Denver at the sparkling new Colorado Convention Center. The sheer size of the site was a far cry from the original meetings 13 years ago, which took place in a much more intimate Washington, DC, hotel, but the increased scale of the meeting has only solidified it as the leading venue for presenting HIV-related research to both clinical and basic-science audiences.

As always, the focus of our meeting report is on new study results that could have an immediate and direct effect on HIV clinical care. All abstracts, as well as webcasts of the symposia, are available at the meeting website: www.retroconference.org. — Paul E. Sax, MD

INTEGRASE INHIBITORS ON THE WAY

Both Merck and Gilead have investigational integrase inhibitors in clinical development. With the Merck drug, MK-0518, about to enter phase III testing, researchers presented interim 16-week results from an ongoing phase II study [[Abstract 159LB](#)]. A total of 167 triple-class-experienced patients were randomized to receive an optimized background regimen plus MK-0518 (200 mg, 400 mg, or 600 mg orally, twice daily) or placebo. At enrollment, the median duration of prior antiretroviral experience was about 10 years, mean viral loads ranged from 4.6 log copies/mL to 4.8 log copies/mL, and mean CD4 counts were between 220 cells/mm³ and 283 cells/mm³. At week 16, all three doses of MK-0518 were superior to placebo; 56% to 72% of MK-0518 recipients achieved viral loads <50 copies/mL, compared with 19% of placebo recipients. Overall, regimens containing MK-0518 were well tolerated, and adverse events were comparable to those observed with placebo-containing regimens. The most common side effects in the study (occurring in at least 5% or a minimum of 2 patients in any treatment group) were diarrhea, nausea, fatigue, injection-site reaction, headache, and itching. The upcoming phase III trials (BENCHMRK-1 and -2) are designed to evaluate MK-0518 in both treatment-experienced and treatment-naïve patients.

Initial data were also presented on the new Gilead integrase inhibitor, GS-9137 [[Abstract 160LB](#)]. These data came from a phase I/II dose-escalation study conducted in 40 HIV-infected patients, 15 of whom were treatment-naïve. Subjects were randomized to receive GS-9137 (200 mg, 400 mg, or 800 mg twice daily; 800 mg once daily; or 50 mg boosted with 100 mg of ritonavir once daily) or placebo with food for 10 days. Mean baseline viral load was 4.75 log copies/mL, and mean CD4 count was 442 cells/mm³. At all doses, GS-9137 monotherapy demonstrated significant antiviral activity compared with placebo; the greatest reduction (–2.03 log copies/mL) was seen with the ritonavir-boosted dose. Overall, 25 of 30 patients in the GS-9137 arms had a viral load decline ≥ 1.0 log copies/mL; no placebo recipient had such a decline. Adverse events were mostly mild (none above grade 2); only fatigue was more common with GS-9137 than with placebo. A longer phase II study is being developed with more patients.

Both MK-0518 and GS-9137 appear to be highly promising for the treatment of HIV infection. The Merck drug will likely be developed as a twice-daily agent given without ritonavir (because MK-0518 is metabolized through

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glucuronidation, and ritonavir does not affect its pharmacokinetics), whereas the Gilead drug will probably be a once-daily agent requiring ritonavir-boosting. We eagerly await further studies on both agents. — *Charles B. Hicks, MD*

NEW DATA ON TMC114 AND TMC125

Patients with triple-class antiretroviral experience have had promising treatment responses to the investigational PI darunavir (TMC114). However, data have been sparse on resistance and correlates of virologic response. To address this, researchers evaluated pooled data from the previously described POWER-1 and -2 studies ([ACC Feb 1 2006](#)), as well as additional data from the as-yet-unpresented POWER-3 study [[Abstract 157](#)]. Diminished virologic response to darunavir was seen in patients with at least 10 primary PI mutations. The mutations that particularly affected response in these patients included V32I, L33F, I47V, I54L, and L89V. Notably, viruses that were susceptible to tipranavir at baseline remained so, even after darunavir failure.

One major issue with the clinical use of darunavir is the availability of additional active antiretrovirals to pair with it. To evaluate whether potential drug-drug interactions preclude using TMC125 (a next-generation NNRTI) as a second active agent, investigators assigned 11 patients with triple-class resistant infection to receive darunavir + TMC125 + an optimized background regimen [[Abstract 575c](#)]. Although TMC125 levels were about 30% lower when the two drugs were given together, the concurrent use of TMC125 did not affect darunavir levels. The combination was associated with a median viral-load reduction of 2.76 log copies/mL, and all patients experienced a decline of at least 2 log copies/mL.

Additional information about TMC125 came from the C223 study, which assessed the influence of baseline resistance on virologic response [[Abstract 154](#)]. In contrast to the "all or none" pattern of resistance seen with currently licensed NNRTIs, TMC125 exhibited gradations of virologic response. The greatest reductions were observed among patients with no baseline NNRTI mutations (–1.82 log copies/mL), followed by those with one mutation (–1.65 log copies/mL), two mutations (–1.00 log copies/mL), or at least three mutations (–0.66 log copies/mL). These data suggest that TMC125 might be most effective when used before multiple NNRTI mutations accumulate.

Finally, investigators studied the effects of adding TMC125 to a regimen containing lopinavir/ritonavir, saquinavir, and at least two NRTIs [[Abstract 575b](#)]. TMC125 was associated with significantly reduced lopinavir AUC_{12h} and C_{max} but did not appear to affect lopinavir C_{min} . No significant change was seen for saquinavir or ritonavir, and the use of these PIs did not affect TMC125 concentrations. — *Charles B. Hicks, MD*

VICRIVIROC LESS EFFECTIVE THAN EFAVIRENZ IN TREATMENT-NAIVE PATIENTS

In the fall of 2005, Schering-Plough terminated its phase II comparison of vicriviroc and efavirenz in treatment-naive patients because the vicriviroc arm had a higher rate of virologic failure ([ACC Nov 8 2005](#)). Now, the company has provided additional details on the study, which included 92 treatment-naive subjects with CCR5-tropic virus and baseline CD4 counts >150 cells/mm³ [[Abstract 161LB](#)]. Patients were randomized to receive vicriviroc (25 mg, 50 mg, or 75 mg once daily) or placebo for 14 days. At day 15, AZT/3TC was added to all

regimens, and the placebo was replaced with efavirenz. At that time, the vicriviroc-treated patients showed an approximate 1-log copies/mL decline in viral load, consistent with earlier phase I studies. However, by study closure, a much higher proportion of patients in the vicriviroc arm (26 of 68) than in the efavirenz arm (1 of 24) had experienced virologic failure, especially at the two lower doses of vicriviroc. Furthermore, all 22 patients with virologic failure and obtainable genotypes in the vicriviroc arm showed the M184V mutation. The reason for this disappointing result is not yet clear; no consistent pattern of mutations was seen in envelope sequences, and tropism switches — seen in three placebo recipients and five vicriviroc recipients — did not explain the virologic rebounds. Overall, these results raise important questions about the use of CCR5 antagonists in treatment-naïve subjects — a concern further enhanced by the closing of the once-daily treatment arm of a maraviroc study in a similar patient population. Notably, the twice-daily arm of that study is ongoing, as are vicriviroc and maraviroc studies in treatment-experienced patients.

Further information on vicriviroc was released on March 3, 2006, detailing the occurrence of five cases of malignancy (4 lymphoma, 1 adenocarcinoma of the stomach) in ACTG 5211. This study involves 118 treatment-experienced patients, randomized to receive one of three doses of vicriviroc or placebo in addition to an optimized background regimen. All cases occurred in the vicriviroc-treated group. The study has been unblinded, and further investigation of the cases is ongoing. —Paul E. Sax, MD

TREATMENT INTERRUPTION, INTERRUPTED

Six studies presented at the conference advanced our knowledge of treatment interruption (TI) for the management of chronic HIV infection in patients who have good viral control and preserved CD4-cell counts while on antiretroviral therapy. As shown in Table 1, the studies fall into three categories: natural history of TI, TI based on fixed intervals, and TI driven by CD4-cell count.

Table 1: Summary of six treatment-interruption trials

Study	TI strategy	Months of prior therapy	Number of subjects	Nadir CD4-cell count*	Baseline CD4-cell count*	Key findings
<i>Natural History of TI</i>						
ACTG 5170	Therapy restarted at the discretion of the patient & physician	54	167	436	833	Safe in terms of HIV disease progression, but 5 deaths occurred, raising questions about the advisability of this TI strategy

Fixed-Interval TI

ISS PART	3 mos on / 1–3 mos off	26	CT = 137 TI = 136	420	740	CT and TI arms similar; 30% resistance in TI arm
ANRS 106	8 wks on / 8 wks off	63	CT = 194 TI = 197	280	741	CT and TI arms similar; no difference in resistance

CD4-Based TI

ANRS 1269	Therapy restarted at CD4 count <250 cells/mm ³	7	CT = 110 TI = 216	273	459	TI arm stopped because of increased risk for morbidity (RR, 2.3)
SMART	Therapy restarted at CD4 count <250 cells/mm ³	72	CT = 2752 TI = 2720	253	598	TI arm stopped because of increased risk for disease progression or death (RR, 2.2)
STACCATO	Therapy restarted at CD4 count <350 cells/mm ³	15	CT = 146 TI = 284	260	490	No difference in proportion suppressed

TI=treatment interruption, CT=continuous therapy, RR=relative risk. * in cells/mm³

The natural-history study, ACTG 5170, demonstrated that TI was generally safe in terms of HIV disease progression among patients with a nadir CD4 count >350 cells/mm³; it also showed that patients could remain off therapy for an extended duration (median interruption, 96 weeks) [Abstract 101]. Although the CD4-cell count fell rapidly during the first 8 weeks of interruption (20 cells/mm³/week), the rate of decline subsequently slowed to 2 cells/mm³/week. There were five deaths in the study, one case of acute retroviral syndrome, and four cases of severe thrombocytopenia. Nadir CD4-cell count was the best predictor of CD4-cell decline or adverse events during TI.

In the two studies of fixed-interval TI, the TI and continuous-therapy groups had similar results [Abstracts 103 and 104]. Elevated rates of resistance were noted in the TI arm of the ISS PART study (which suggests a need for caution when using NNRTI-based regimens), and 5% of TI patients had a low platelet count in ANRS 106.

Results from the three studies of CD4-driven TI are particularly illuminating: They strongly suggest that the CD4 count should not be allowed to fall below 350 cells/mm³ because of an increased risk for serious morbidity. In ANRS 1269, which was conducted in Africa, most of the conditions seen in the CD4-based TI arm were serious bacterial infections (non-AIDS-defining) [Abstract 105LB]. Although this arm of the trial was halted, a comparison of continuous therapy and fixed-interval TI is ongoing. In the SMART study, 47 deaths and 46 confirmed AIDS-defining events occurred in the TI arm versus 29 deaths and 15 AIDS-defining events in the continuous-therapy arm [Abstract 106LB]. Most of the deaths and many of the serious disease events were not due to standard AIDS-defining conditions. This observation, along with data from the other trials, suggests that stopping effective antiretroviral therapy might trigger HIV-related immune deficiency or inflammation that could lead to a range of serious conditions affecting vital organs (such as the heart, liver, kidneys, and bone marrow). In the STACCATO trial, the threshold for reinitiation (CD4 count <350 cells/mm³) was higher than in the other studies, and most participants used ritonavir-boosted saquinavir-based therapy (80%) [Abstract 102]. After patients in the TI arm reinitiated treatment, the two arms had similar proportions of subjects with a viral load <50 copies/mL and similar proportions with CD4 counts >350 cells/mm³.

One wonders what the long-term outcome of the SMART study (the largest HIV randomized clinical trial ever) might have been if the study had been allowed to continue with longer follow-up. One also wonders about the level of high-risk behavior and HIV transmission to sexual partners during TI; none of the presentations provided this important public-health information. Overall, the results of the CD4-based TI trials suggest that the door is essentially closed to TI studies that enroll patients with AIDS and that allow the CD4 count to fall below 350 cells/mm³. Further, the findings make the CD4-based TI strategy undesirable in resource-poor countries. For patients with high CD4 nadirs, TI remains a useful experimental strategy for evaluating therapeutic vaccination or immune-based therapies that might be antiretroviral-sparing at higher CD4-cell counts. —Keith Henry, MD

SHOULD WE BE STARTING TREATMENT EARLIER?

Several analyses from well-known cohort studies suggested that it might be beneficial to start HIV treatment at higher CD4-cell counts. In the ART Cohort Collaboration, researchers followed 10,855 patients for a median of 2.7 years after treatment initiation [Abstract 525]. Not surprisingly, patients who started therapy at CD4 counts < 200 cells/mm³ were significantly more likely to progress to AIDS or death than those who started at 201–350 cells/mm³ (hazard ratio, 2.93). More importantly from a policy standpoint, a strong trend was seen across even higher CD4-cell counts, favoring treatment initiation at 351–500 cells/mm³ versus 201–350 cells/mm³ (HR, 1.26). Two particular strengths of this analysis were the relatively large study population and the investigators' avoidance of lead-time bias by accounting for the time before treatment initiation in patients who delayed therapy. Investigators with the HIV Outpatient Study evaluated the risk for antiretroviral toxicity among treatment-naive patients and found that the incidence rates of renal insufficiency, neuropathy, and lipodystrophy decreased as CD4-cell counts at treatment initiation increased. [Abstract 769]. Finally, in the Hopkins HIV Cohort and Athena National Cohort, researchers found that the absolute increase in CD4-cell count over time was greatest in patients who started therapy at lower values, but the likelihood of achieving a normal CD4-cell count was greatest

in those who started at higher values [[Abstracts 529](#) and [530](#)]. The results of these studies, along with implicit messages from the SMART study, cumulatively move the pendulum toward an earlier optimal time to start therapy in asymptomatic patients. — *Paul E. Sax, MD*

METABOLIC COMPLICATIONS AND CARDIOVASCULAR DISEASE

Although many antiretrovirals can cause dyslipidemia and insulin resistance, research on metabolic complications is increasingly focused on how chronic HIV infection and host factors contribute to these complications. Several studies at this year's Retrovirus Conference demonstrated a lower prevalence of diabetes among HIV-infected adults than among population-based controls. In each of these studies, traditional risk factors (e.g., body-mass index and age) overshadowed the effect of antiretroviral therapy on diabetes risk [[Abstracts 759, 760, and 761](#)]. During the past several years, many clinicians have focused on minimizing cardiovascular risk by addressing these risk factors, and that focus seems to be paying off. Several large cohort studies suggested that rates of myocardial infarction (MI) and coronary heart disease in HIV-infected adults are stabilizing or even declining [[Abstracts 735, 737, and 144](#)]. Although the shifting rates have been attributed to changing patterns of antiretroviral use and increased attention to lipid-lowering and antihypertensive therapy, there is still plenty of room for improvement: In the Swiss HIV Cohort Study, only one third of patients with dyslipidemia or hypertension were receiving lipid-lowering or antihypertensive therapy [[Abstract 740](#)]. Randomized trials in HIV-infected patients demonstrated the efficacy of two new options for managing hypertriglyceridemia: salmon oil (3 g daily) [[Abstract 756](#)] and fish oil with or without fenofibrate [[Abstract 146](#)]. Despite the clear role of traditional risk factors in metabolic complications, antiretrovirals are not completely off the hook. In the Multicenter AIDS Cohort Study, the metabolic syndrome was more common in HIV-positive than HIV-negative men, and the use of potent combination antiretroviral therapy (especially PI use) seemed to be an important contributor [[Abstract 747](#)]. Researchers with the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study previously reported an association between longer exposure to combination antiretroviral therapy and increased risk for MI (*N Engl J Med* 2003; 349:1993). Now, observations from that study have been extended to an analysis of specific drug classes and MI risk [[Abstract 144](#)]. During nearly 95,000 person-years of follow-up, each additional year of PI exposure increased the risk for MI by 16%. Although a longer duration of NNRTI exposure also increased the risk for MI slightly, the effect was not statistically significant after adjustment for NRTI use. In a matched cohort study, the 3-year rate of progression of carotid intima-media thickness (IMT) was not significantly greater in PI-treated patients than in non-PI-treated patients, but there was some suggestion of a PI effect [[Abstract 145](#)]. In another study, cytomegalovirus-specific T-cell responses and high-sensitivity C-reactive protein levels (but not levels of T-cell activation) were significantly correlated with cross-sectional measures of carotid IMT [[Abstract 741](#)].

Pulmonary hypertension was a recognized complication of HIV infection before the advent of potent combination antiretroviral therapy, and the problem does not seem to have diminished. In one prospective study, HIV-infected patients had an increased risk for pulmonary hypertension [[Abstract 743](#)], and in another, the prevalence of pulmonary hypertension (0.21%) remained similar to that reported in the 1990s [[Abstract 744](#)]. Treatment with the

oral endothelial antagonist bosentan appears to be well tolerated in HIV-infected patients [Abstract 745], and clinicians are reminded to consider pulmonary hypertension in HIV-infected patients with a differential diagnosis of dyspnea.

The management of lipodystrophy and fat accumulation continues to be a challenging clinical issue. News from this year's conference confirms that antiretroviral substitutions (switching from AZT or d4T to either abacavir or a nucleoside-sparing regimen) are the best currently available options for managing lipodystrophy [Abstract 755]. Placebo-controlled studies of pioglitazone [Abstract 151LB] and rosiglitazone [Abstract 147] showed small but statistically significant increases in limb fat; in both studies, the effect of the glitazone was diminished in the presence of d4T. Neither metformin nor replacement doses of testosterone significantly reduced visceral fat in controlled trials [Abstracts 147, 148, and 149]. — *Judith Currier, MD, MSc*

RENAL TENOFOVIR DEBATE CONTINUES

Given the frequent development of nephrotoxicity with adefovir and didanosine, concerns about the potential for nephrotoxicity with tenofovir are well founded. Several new studies highlighted the frequency of this problem in tenofovir-treated patients and the potential importance of drug-drug interactions.

In the ESS40006 study, patients receiving tenofovir experienced significant declines in glomerular filtration rate (GFR) at 24 and 48 weeks, whereas patients receiving efavirenz did not [Abstract 777]. In another study of patients initiating tenofovir, 4% developed renal insufficiency within one year, and 13% developed hypophosphatemia [Abstract 778]. Renal insufficiency seemed to occur with cumulative exposure to tenofovir, whereas hypophosphatemia developed acutely. Risk factors for nephrotoxicity included being treatment-naïve and having previously received amphotericin B. In a much larger study, CDC investigators analyzed longitudinal data from 11,362 HIV-infected patients, all of whom had GFR >90 mL/min at baseline [Abstract 779]. Mild renal impairment (GFR, 60–89 mL/min) was seen in 35.1% of patients, moderate impairment (GFR, 30–59 mL/min) was seen in 6.4% of patients, and severe impairment (GFR, <30 mL/min) was seen in 2.6% of patients. Tenofovir treatment was significantly associated with mild and moderate renal insufficiency, but not with more severe renal impairment. In an observational study of 497 patients initiating tenofovir, 87 patients (17.5%) developed renal dysfunction [Abstract 780]. Most experienced moderate declines in GFR (<60 mL/min), but eight had more severe declines (>80 mL/min) that were associated with concomitant treatment with ritonavir-boosted regimens containing either amprenavir or lopinavir. In stark contrast to these reports were combined data from the tenofovir expanded-access program and postmarketing safety reports, which did not suggest a high incidence of serious renal adverse events in tenofovir-treated patients [Abstract 781].

Taken collectively, these findings suggest that clinicians should be concerned about the development of renal dysfunction in patients receiving tenofovir. Routine laboratory monitoring of patients on this drug should include calculation of GFR and assessment of serum phosphate. For the most part, renal dysfunction appears to be reversible when the agent is discontinued expediently. The incidence and risk factors for tenofovir-induced

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nephrotoxicity still need to be defined in large studies that control for antiretroviral regimen and associated comorbidities. In addition, more data are needed on drug-drug interactions and the possible role of boosted PIs in potentiating tenofovir-associated renal toxicity. — *G. Sonia Nagy, MD*

EXTENDING THE ROLE OF ATAZANAVIR

The PI atazanavir is increasingly popular for both treatment-naïve and treatment-experienced patients because of its low pill count, tolerability, and favorable effects on lipid levels. Although many clinicians routinely offer boosted atazanavir to their treatment-naïve patients, there have been no prospective data on this practice. In the first study to address this, researchers randomized 200 treatment-naïve individuals to receive a nucleoside backbone of 3TC and extended-release d4T with either unboosted atazanavir (400 mg) or boosted atazanavir (300 mg plus 100 mg of ritonavir) once daily [Abstract 107LB]. The 48-week intent-to-treat analysis showed no significant differences in the proportion of subjects achieving a viral load <400 copies/mL (86% in the boosted arm and 85% in the unboosted arm) or <50 copies/mL (75% and 70%, respectively). Although study-drug discontinuation rates were similar in both arms, the boosted arm had a higher rate of discontinuation for adverse events; it also had a greater proportion of subjects (59%, compared with 20% in the unboosted arm) experiencing a rise in total bilirubin to greater than 2.5 times the upper limit of normal. As expected, changes in total cholesterol, LDL cholesterol, and triglyceride levels were more pronounced in the boosted arm. More virologic failures occurred in the unboosted arm (10 vs. 3), and three patients in this arm developed the signature mutation for atazanavir resistance, I50L. No PI resistance was seen in the boosted group.

In a small pilot study, lopinavir/ritonavir was effective as sole maintenance therapy in patients who were previously fully suppressed after triple-drug therapy that included lopinavir/r (*J Acquir Immune Defic Syndr* 2005; 40:280). In ACTG 5201, a single-arm pilot study, researchers evaluated whether boosted atazanavir alone might also be an effective maintenance therapy [Abstract 108LB]. The study involved 36 subjects with a CD4 count \geq 250 cells/mm³ who had achieved a viral load <50 copies/mL on PI-based combination therapy for at least 48 weeks and had no history of virologic failure. After study entry, participants were all switched to ritonavir-boosted atazanavir plus two NRTIs for 6 weeks. If the viral load remained fully suppressed, the two NRTIs were discontinued, and subjects continued on boosted atazanavir alone for 48 weeks. At 24 weeks, 91% of subjects achieved a viral load <200 copies/mL. The eight subjects who provided semen samples for viral-load testing all had values <150 copies/mL. None of the three participants with virologic failure had any resistance, and two of the three had no detectable plasma atazanavir levels. The results of this pilot study suggest that ritonavir-boosted atazanavir should now be thoroughly evaluated in a larger, randomized trial. — *Judith Feinberg, MD*

ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS

This year's Retrovirus Conference featured a marked and gratifying increase in presentations related to HIV in resource-limited settings. Two summary talks were of particular importance and are available as [webcasts](#). The first, by Dr. Tony Harries, was a comprehensive and thoughtful review of the epidemiologic convergence of HIV and tuberculosis (TB) in sub-Saharan Africa [Abstract 9]. The second, by Dr. Tom Quinn, was a tour-de-force

presentation of the epidemiologic, biologic, research, and policy issues surrounding male circumcision as a strategy for HIV prevention [[Abstract 120](#)].

Antiretroviral therapy has now been available long enough in resource-limited settings to explore and document its effectiveness. Initial concerns about adherence have decreased, examples of biologic and clinical benefit have been documented, and now reports are emerging about the cumulative side effects and toxicities in large-scale national rollout programs. In rural Uganda, researchers evaluated early clinical toxicity among more than 1000 adults receiving an initial regimen, most commonly d4T + 3TC + nevirapine [[Abstract 142](#)]. The overall rate of toxicity was 4.5 per 100 person-months, and the rate of severe toxicity was 1.3 per 100 person-months. Most adverse events were grade 1 or 2. Neuropathy and rash were the most common events and were manageable by single drug substitutions. A smaller but more detailed study from Nairobi, using the same regimen, yielded similar conclusions [[Abstract 143](#)]. In this study, most adverse events occurred within 6 months of follow-up, were of grade 1 or 2 in severity, and were resolved with regimen switches. In Cape Town, South Africa, approximately 11% of patients on an initial regimen of d4T + 3TC + nevirapine had a substitution for toxicity in the first 36 months of treatment [[Abstract 66](#)]. Most substitutions were for d4T and were related to the appearance of peripheral neuropathy and, more disturbingly, lactic acidosis. The latter appeared at a higher rate than anticipated based on research in developed countries and is of particular concern because of its vague clinical symptoms and the difficulty of documenting lactate levels. Women were at particularly high risk for developing lactic acidosis on d4T, as were patients weighing more than 75 kg.

These caveats aside, the emerging data indicate that, overall, adverse events related to commonly used first-line regimens are not a significant barrier to provision of antiretroviral therapy in government rollouts. — *Gerald H. Friedland, MD*

THE NEW ABCS: ANTIRETROVIRALS, BARRIERS, AND CIRCUMCISION

During the keynote lecture, Dr. James Curran told us that "prevention is not as simple as ABC," referring to *Abstinence, Being faithful, and using Condoms*. However, at this meeting, we became familiar with the "second-generation ABCs": Antiretrovirals, Barriers (condoms and microbicides), and Circumcision. Will this new generation of ABCs gain more respect than the last one as a viable set of HIV prevention tools?

Antiretrovirals are now used routinely for nonoccupational postexposure prophylaxis (nPEP) [[Abstract 54](#)]. However, there is no clinical evidence of benefit, and often the therapy is not initiated within 72 hours of exposure as recommended by CDC guidelines. In a review of 880 calls placed to a national PEP hotline following sexual exposures, researchers found that 28% of the calls came in more than 72 hours after exposure [[Abstract 906](#)]. Although many countries now have guidelines for PEP [[Abstract 904](#)], it is still uncertain which regimen is best. Data from a prospective study in France suggest that AZT/3TC + LPV/rifonavir might be the combination with the best tolerability [[Abstract 905](#)]. Pre-exposure prophylaxis is also being evaluated, with five trials under way in humans. To date, the animal data seem promising: in a study of nonhuman primates, tenofovir/FTC offered

100% protection against repeated rectal SHIV challenge [[Abstract 32LB](#)]. Ultimately, the drugs of choice for pre- and post-exposure prophylaxis may be determined by the penetration of antiretrovirals into genital secretions [[Abstracts 129, 396, and 569](#)].

Barrier methods beyond condoms are necessary to protect women from HIV. The growing consensus is that a highly effective female-controlled barrier requires a combination of products or methods; one compelling approach is a cervical barrier with microbicides [[Abstract 55](#)].

The potential value of circumcision in HIV prevention received widespread attention last year, when a randomized trial in South Africa demonstrated a 60% reduction in HIV acquisition among circumcised men compared with uncircumcised men (*PLoS Med* 2005; 2:e298). Now, data from the Rakai Community Cohort Study suggest that male circumcision also reduces the incidence of HIV infection among female partners [[Abstract 128](#)]. Incidence rates were 6.6 per 100 person-years among the wives of infected *circumcised* men and 10.3 per 100 person-years among the wives of infected *uncircumcised* men. An ongoing controlled trial in Rakai will yield more information later this year on how male circumcision affects HIV acquisition in female partners. — *Carlos del Rio,*

MD

MORE ON FALSE-POSITIVE RESULTS IN RAPID HIV TESTING

In late 2005, counselors at several HIV testing programs (mainly in New York City and San Francisco) reported an unusually high number of false-positive results from the OraQuick Advance Rapid HIV-1/2 Antibody Test with oral fluid ([ACC Jan 4 2006](#)). Since then, CDC investigators have analyzed data from four prospective studies that involved simultaneous testing of whole blood and oral fluid between 2000 and 2005 [[Abstract 34LBb](#)]. They found that the specificity of OraQuick was 99.9% with whole blood and 99.6% with oral fluid; in comparison, the specificity of serum EIA was 99.7%. These data suggest that the specificity of HIV rapid testing is slightly lower with oral fluid than with whole blood, but is still well above the FDA minimum threshold (98%) for both specimen types. At three testing sites, the excess number of false-positive results appeared to be related to unidentified host- or site-specific factors; CDC investigators found no evidence of a lot- or device-related problem.

Investigators also evaluated an algorithm that was adopted in New York and San Francisco in late 2005. According to this algorithm, a positive result on an oral-fluid rapid test should be followed up with a whole-blood HIV rapid test using a fingerstick. When this algorithm was used, positive results from both oral fluid and fingerstick were almost always followed by a positive Western blot result, whereas a positive result from oral fluid followed by a negative fingerstick was almost always followed by a negative Western blot result. These data suggest that performing a fingerstick test after a reactive oral-fluid test might reduce the number of people who receive false-positive results. However, confirmatory testing is still required for all reactive rapid tests. — *Carlos del Rio, MD*

EXPANDING HIV TESTING

The incidence of HIV in the U.S. is holding steady at about 40,000 new cases per year, with the epidemic being fueled largely by the 250,000 HIV-infected people who are unaware of their serostatus. Studies show that these

individuals are more likely than those who know their serostatus to practice unprotected sex with HIV-negative partners ([ACC Sep 14 2005](#)). To address this problem, the CDC developed an initiative in 2003 called "Advancing HIV Prevention: New Strategies for a Changing Epidemic." One strategy, "Prevention for Positives," focuses on changing the behavior of those already infected. Another is designed to expand HIV testing by making it a routine, voluntary part of care for all individuals aged 13 to 64 [[Abstract 164](#)]. This approach is feasible because 22% of all testing is currently done in hospitals, emergency rooms, and outpatient clinics, and 27% of all positive tests occur in these settings. The CDC is currently revising its testing recommendations and may propose that HIV testing be included in an individual's overall consent to receive care. Under such a policy, a person who did not want to be tested for HIV would have to opt out — a distinct departure from the current policy of opting in, which requires that patients give explicit, signed consent for HIV testing when it is offered. Hopefully, this approach will result in more HIV-infected people being identified, referred for care, and placed on antiretroviral therapy as appropriate; this should, in turn, reduce transmission through both serostatus awareness and controlled viral replication.

Another strategy by the CDC is to accept only name-based HIV test results from state and local health departments, so that classic public health strategies, such as contact tracing, can be used to identify more infected individuals. If health departments do not implement name-based reporting, they risk losing federal HIV/AIDS funds. Apparently, the threat is working: Shortly after the Retrovirus Conference, California health officials announced that they would move to confidential name-based testing. — *Judith Feinberg, MD*

CONCLUSION

As the year unfolds, we'll eagerly await follow-up information from many of the studies presented at the Retrovirus Conference. On the treatment front, we hope to see accelerated approval of TMC114 (darunavir), additional data on integrase inhibitors, and more information on the risks and benefits of CCR5 antagonists in treatment-naïve and treatment-experienced patients. On the prevention front, we'll look to Rakai for more data on male circumcision and to the CDC for new recommendations on HIV testing. — *Paul E. Sax, MD*

D2

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/23362 A2

(51) International Patent Classification: C07D 239/48,
251/18, 239/50, 403/12, 521/00, 405/14, A61K 31/505,
A61P 35/00

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(21) International Application Number: PCT/EP00/09149

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(22) International Filing Date:
19 September 2000 (19.09.2000)

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
199 45 982.7 24 September 1999 (24.09.1999) DE

(84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

(71) Applicant (for all designated States except US): KNOLL AKTIENGESELLSCHAFT [DE/DE]; 67061 Ludwigshafen (DE).

Published:
— Without international search report and to be republished upon receipt of that report.

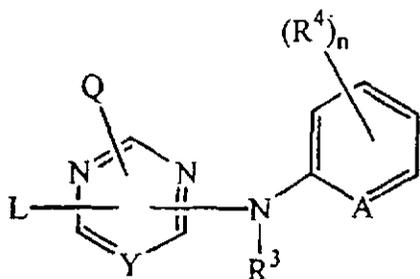
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



(54) Title: RATE-CONTROLLED PARTICLES



(I)

(57) Abstract: Rate-controlled particles, comprising compounds of formula (I) as a solid dispersion.

WO 01/23362 A2

11 MAY 2001

Rate-controlled particles

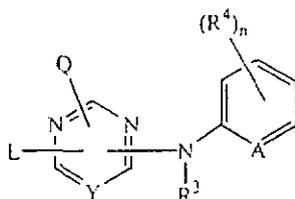
Specification

5

The present invention concerns pharmaceutical compositions in the form of rate-controlled particles, comprising compounds of the formula (I) to (VI)

10 (I) is an antiviral compound of formula

15



(I)

an N-oxide, a pharmaceutically acceptable addition salt or a
20 stereochemically isomeric form thereof, wherein

Y is CR⁵ or N;

A is CH, CR⁴ or N;

n is 0, 1, 2, 3 or 4;

25 Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen;

R¹ and R² are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)-amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of
30 the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxy-C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or
35 di(C₁₋₆alkyl)amino, aryl and Het; or

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;

R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy-carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and
40 each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethoxy, or when Y is CR⁵ then R⁴ may also represent C₁₋₆alkyl substituted with cyano or aminocarbonyl;

45 R⁵ is hydrogen or C₁₋₄alkyl;

L is -X¹-R⁶ or -X²-Alk-R⁷ wherein

The particles of the present invention are prepared as solid dispersions of the active compounds in a polymeric matrix. The term "solid dispersion" is well known in the art and means a dispersion consisting of solid components. Preferably solid
5 dispersions are in the form of solid solutions wherein the active ingredients are molecularly dispersed in the polymeric matrix.

Such solid dispersion is preferably obtained by forming a homogeneous mixture of the components in the form of a melt,
10 extruding said melt and shaping of the extrudate. The melting is effected by the input of thermal and/or mechanic energy.

Depending on the composition of the matrix, the melting takes place in the range of from 40°C to 190°C, preferably 50 to 150°C.
15 The suitable temperature range depends on the glass transition temperature of the polymer component, the properties of the active ingredients and further additives. The optimal temperature range can be established by a few simple tests.

20 The mixing of the active substances with the polymer and additional components of the matrix can take place before or after the melting of the polymer. Preferably the process is solvent-free which means that no additional organic solvents or water are added.

25 The plastification and melting preferably can take place in an extruder, a kneader or a mixing reactor, preferably in an extruder having one or more screws which may rotate in the same direction or opposite directions, especially in a twin screw
30 extruder. The latter can be operated with or without kneading elements, but use of kneading elements is preferred because mixing is better.

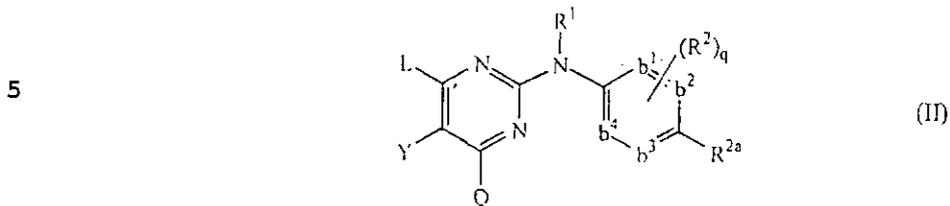
The still plastic material is extruded through a die or a breaker
35 plate and then shaped into particles. This may be effected by milling and subsequent sieving the cooled extrudate. The preferred particle size for instant release forms lies in the range of from 0.5 to 1.5 mm.

40 The particles, optionally together with conventional pharmaceutically acceptable excipients, may be further processed to conventional pharmaceutical dosage forms such as tablets, pastilles, suppositories, or be packed in capsules.

45 It is possible and particularly advantageous to produce pharmaceutical forms with rate-controlled release and improved dissolution rates of the active ingredients. This was not to be

C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR⁵ then R⁶ and R⁷ may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethoxy and trihalomethyl; or when Y is N then R⁶ and R⁷ may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; X¹ and X² are each independently -NR³-, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or -S(=O)₂-; Alk is C₁₋₄alkanediyl; or when Y is CR⁵ then L may also be selected from C₁₋₁₀alkyl, C₃₋₁₀alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, or C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, C₁₋₆alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethoxy and C₁₋₆alkylcarbonyl; aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro and trifluoromethyl; Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,

or a compound of formula



10 the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

-b¹=b²-C(R^{2a})-b³-b⁴= represents a bivalent radical of formula

- 15
- CH=CH-C(R^{2a})=CH-CH= (b-1);
 - N=CH-C(R^{2a})=CH-CH= (b-2);
 - CH=N-C(R^{2a})=CH-CH= (b-3);
 - N=CH-C(R^{2a})=N-CH= (b-4);
 - N=CH-C(R^{2a})=CH-N= (b-5);
 - CH=N-C(R^{2a})=N-CH= (b-6);
 - 20 -N=N-C(R^{2a})=CH-CH= (b-7);

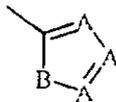
q is 0, 1, 2; or where possible q is 3 or 4;

R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl;

25 R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)amino-carbonyl, C₁₋₆alkyl substituted with cyano, amino-carbonyl or mono- or di(methyl)aminocarbonyl, C₂₋₆alkenyl substituted with cyano, or C₂₋₆alkynyl substituted with cyano;

30 each R² independently is hydroxy, halo, C₁₋₆alkyl optionally substituted with cyano or -C(=O)R⁶, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more halogen atoms or cyano, C₁₋₆alkyloxy, 35 C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or a radical of formula

40



(c)

45

wherein each A independently is N, CH or CR⁶;

B is NH, O, S or NR⁶;

p is 1 or 2; and

R⁶ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

5

L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C₃₋₇cycloalkyl,

10

* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C₁₋₆alkyl-carbonyl,

15

* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or

20

L is -X-R³ wherein

R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and

25

X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;

Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or -NR⁴R⁵; and

30

R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or

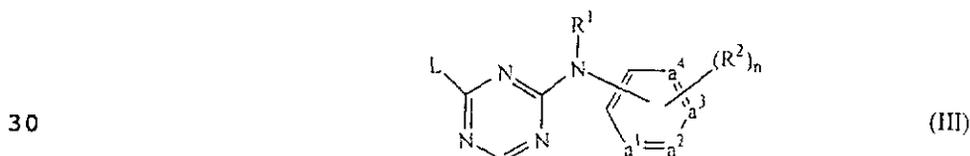
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40

R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;

45

- Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or
- 5 -C(=O)R⁶, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;
- 10 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;
- Het is an aliphatic or aromatic heterocyclic radical;
- 15 said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said
- 20 aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,
- 25 or a compound of formula



- a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof,
- 35 wherein

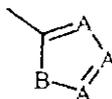
-a¹=a²-a³=a⁴- represents a bivalent radical of formula

- CH=CH-CH=CH- (a-1);
- N=CH-CH=CH- (a-2);
- N=CH-N=CH- (a-3);
- 40 -N=CH-CH=N- (a-4);
- N=N-CH=CH- (a-5);

n is 0, 1, 2, 3 or 4; and in case -a¹=a²-a³=a⁴- is (a-1), then n may also be 5;

- R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and
- 45

each R^2 independently is hydroxy, halo, C_{1-6} alkyl optionally substituted with cyano or $-C(=O)R^4$, C_{3-7} cycloalkyl, C_{2-6} alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6} alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6} alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, $-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula



(c)

wherein each A independently is N, CH or CR^4 ;
 B is NH, O, S or NR^4 ;
 p is 1 or 2; and
 R^4 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{4-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

- * C_{3-7} cycloalkyl,
- * indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6} alkyl, hydroxy, C_{1-6} alkyloxy; cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethoxy and C_{1-6} alkyl-carbonyl,
- * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2 ; or

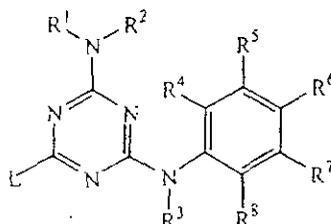
L is $-X-R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in R^2 ; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, cyano, nitro, polyhalo C_{1-6} alkyl and polyhalo C_{1-6} alkyloxy,

or a compound of formula



(IV)

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R¹ and R² are each independently selected from hydrogen;

hydroxy; amino; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl;

C₁₋₆alkyloxycarbonyl; Ar¹; mono- or di(C₁₋₆alkyl)amino;

mono- or di(C₁₋₆alkyl)aminocarbonyl; dihydro-2(3H)-fura-

none; C₁₋₆alkyl substituted with one or two substituents each independently selected from amino, imino, amino-

carbonyl, aminocarbonylamino, hydroxy, hydroxyC₁₋₆alkyl-

oxy, carboxyl, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxy-

carbonyl and thienyl; or
R¹ and R² taken together may form pyrrolidinyl; piperidinyl, morpholinyl, azido or mono- or di(C₁₋₆alkyl)aminoC₁₋₄-alkylidene;

R³ is hydrogen, Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy-carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and

R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

L is C₁₋₁₀alkyl; C₃₋₁₀alkenyl; C₃₋₁₀alkynyl; C₃₋₇cycloalkyl; or

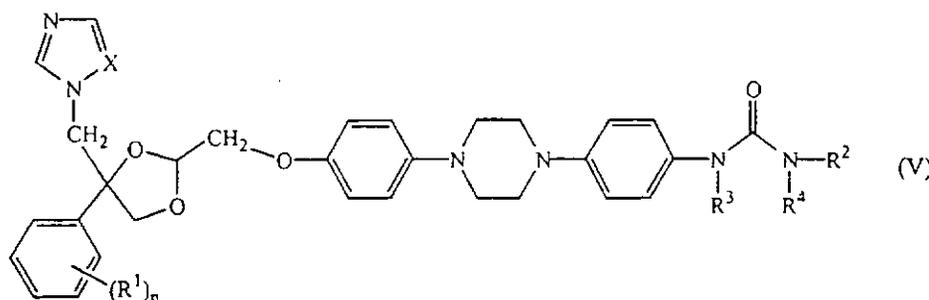
L is C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; and,

Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

Co. No.	Alk	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH ₃	H	H	H	H
b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO ₂	H	H
c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C ₆ H ₅	H	H	H	H	H
d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO ₂	H	CH ₃	H	H
e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH ₂	H	H
f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF ₃	H	H	H
g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
n	Phenylmethyl	H/H	H	CH ₃	H	H	H	H
o	Phenylmethyl	H/H	H	H	H	H	H	H

are not included,

or a compound of formula



the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

n is zero, 1, 2 or 3;

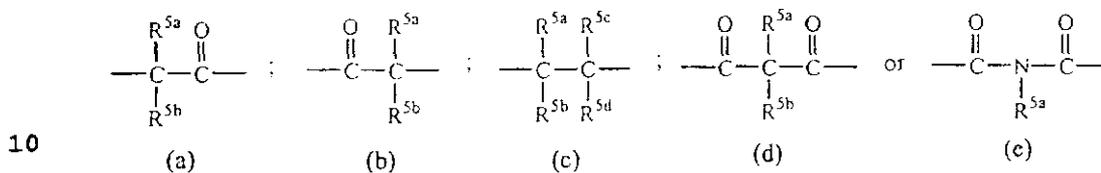
X is N or CH;

each R¹ independently is halo, nitro, cyano, amino, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy or trifluoromethyl;

R² is hydrogen; C₃₋₇alkenyl; C₃₋₇alkynyl, aryl; C₃₋₇cycloalkyl; C₁₋₆alkyl or C₁₋₆alkyl substituted with hydroxy, C₁₋₄alkyloxy, C₃₋₇cycloalkyl or aryl;

R^3 and R^4 each independently are hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl; or
 R^3 and R^4 taken together form a bivalent radical $-R^3-R^4-$ of formula:

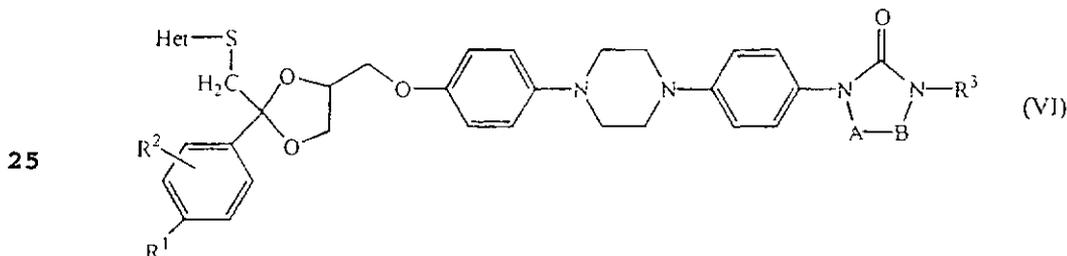
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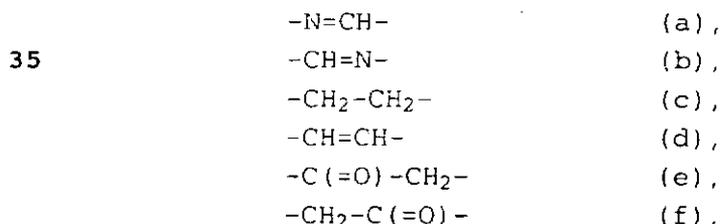
15 wherein R^{5a} , R^{5b} , R^{5c} , R^{5d} each independently are hydrogen, C_{1-6} alkyl or aryl; and aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxy or trifluoromethyl,

or a compound of formula

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30 the *N*-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :



40 in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6} alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6} alkyl;

R^1 is hydrogen, C_{1-6} alkyl or halo;

45 R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8} alkyl; C_{3-6} cycloalkyl; or C_{1-8} alkyl substituted with hydroxy, oxo, C_{3-6} cycloalkyl or aryl;

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino or aryl;
5 pyrimidine; pyrimidine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino or aryl; tetrazole; tetrazole substituted with C₁₋₆alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; thia-
10 diazole; thiadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-
15 amino; oxadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; thia-
20 zole; thiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalo-
methyl, amino, mono- or di(C₁₋₆alkyl)amino; oxazole; oxazole substituted with one or two substituents selected
25 from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino;
aryl is phenyl or phenyl substituted with C₁₋₆alkyl or halo,
and the heterocyclic radical "Het" is bound to the sulfur
atom via a carbon atom,

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as a solid dispersion in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone.

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2. Particles according to claim 1, wherein the copolymer of N-vinylpyrrolidone is a copolymer with vinyl acetate.

3. Particles according to claim 1 or 2, further comprising a surfactant.

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4. Particles according to claim 3, wherein the surfactant is a PEG-n-hydrogenated castor oil.

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5. Particles according to any of the claims 1 to 3, wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

6. Particles according to any of the claims 1 to 3, further comprising citric acid in amounts of up to 5 % b.w.
7. Particles according to any of the claims 1 to 6, wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 40 to 70 % b.w. of the total weight of the dosage form.
8. Particles according to claim 7, wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 50 to 65 % b.w..
9. Particles according to any of the claims 1 to 8, wherein the controlled release is an instant release of the drug.
10. Particles according to any of the claims 1 to 8, wherein the controlled release is a sustained release.
11. Particles according to claim 10, further comprising hydroxypropyl methyl cellulose in amounts of from 5 to 10 % b.w..
12. Particles according to any of the claims 1 to 11, obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said mixture and shaping of the extrudate.
13. Particles according to any of the claims 1 to 11, comprising a compound selected from the group consisting of
- 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile;
- 4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzotrile;
- 4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzotrile;
- 4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzotrile;
- 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-amino]benzotrile;
- 4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile;
- 4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-amino]benzotrile;
- 4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzotrile;
- 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzotrile;

- 4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]-amino]benzotrile;
- 4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzotrile;
- 5 4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzotrile;
- 1-[[4-[[4-[[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;
- 10 (-)-[2S-[2alpha,4alpha(S*)]]-4-[[4-[[4-[[2-(4-chlorophenyl)-2-[[[4-methyl-4H-1,2,4-triazol-3-yl]thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,
a N-oxide, a pharmaceutically acceptable addition salt or a
- 15 stereochemically isomeric form thereof.
14. Pharmaceutical dosage form, comprising particles according to any of the preceding claims.
- 20 15. Pharmaceutical dosage forms according to claim 13, further comprising one or more pharmaceutically acceptable excipients.

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/22938 A1

- (51) International Patent Classification⁷: A61K 9/14, 31/505, 31/53
- (74) Agent: ALLARD, Susan, Joyce; Boulton Wade Tennant, Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).
- (21) International Application Number: PCT/EP00/08522
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: 31 August 2000 (31.08.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 99203128.6 24 September 1999 (24.09.1999) EP
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
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Published:
With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/22938 A1

(54) Title: ANTIVIRAL COMPOSITIONS

(57) Abstract: The present invention is concerned with pharmaceutical compositions of antiviral compounds which can be administered to a mammal, in particular a human, suffering from a viral infection. These compositions comprise particles obtainable by melt-extruding a mixture comprising one or more antiviral compounds and one or more appropriate water-soluble polymers and subsequently milling said melt-extruded mixture.

11 MAY 2011

ANTIVIRAL COMPOSITIONS

- 5 The present invention concerns pharmaceutical compositions of antiviral compounds which can be administered to a mammal, in particular a human, suffering from a viral infection. These compositions comprise particles obtainable by melt-extruding a mixture comprising one or more antiviral compounds and one or more appropriate water-soluble polymers and subsequently milling said melt-extruded mixture.
- 10 The antiviral compounds constituting the pharmaceutical compositions of the present invention are dispersed in a carrier by melt-extrusion to obtain a solid dispersion in order to improve their bio-availability.
- 15 Compounds structurally related to the present antiviral compounds are disclosed in the prior art.
- Pharmazie (1990), 45(4), p 284 discloses trisubstituted derivatives of 2,4,6-trichloro-1,3,5-triazine having anti-bacterial activity.
- 20 Chem. Abstr. (1990), 112, no. 1 concerns synthesis of fluorinated derivatives of 1,3,5-triazine as potential bactericidal agents.
- Chem. Abstr. (1988), 108, no. 15 describes 2,4,6-mixed functional substituted 1,3,5-triazines as anti-convulsives.
- Chem. Abstr. (1983), 98, no. 11 concerns the preparation of *p*-(2,4-diarylamino-6-*S*-triazinylamino)-benzaldehyde/acetophenone thiosemicarbazones as potential
- 25 tuberculostatic agents.
- Chem. Abstr. (1981), 95, no. 4 describes the preparation of polypyromellitimides containing dialkylamino-type melamine units.
- Chem. Abstr. (1975), 83, no. 23 describes optically active *S*-triazine derivatives.
- 30 FR-A-2099730 concerns diamino-, and dinitro-*S*-triazines, which can be used for the preparation of polymeric material and colorants.
- EP-A-0795549 discloses bis-aryloxy(amino)-triazinyl-oxy(amino)aryl derivatives as antiviral agents.
- Ashley et al. (J. Chem. Soc. (1960), January 1, pp 4525-4532) describes
- 35 amidinoanilino-1,3,5-triazines having potential trypanocidal activity.
- WO 91/18887 discloses diaminopyrimidines as gastric acid secretion inhibitors.
- EP-A-0588762 concerns the use of *N*-phenyl-2-pyrimidinamine derivatives as proteinkinase C-inhibitors and anticancer agents.

formula (I-A), (I-B) or (I-C) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I-A), (I-B) or (I-C) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds to prepare compounds of formula (I-A), (I-B) or (I-C) may need to be blocked by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydropyranyl. Suitable protecting groups for amino include *tert*-butyloxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C₁₋₆alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after a reaction step.

The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis' 2nd edition, T W Greene & P G M Wutz, Wiley Interscience (1991).

The compounds of formula (I-A), (I-B) and (I-C) and the intermediates of formula (II'-a) unexpectedly show antiretroviral properties, in particular against Human Immunodeficiency Virus (HIV), which is the aetiological agent of Acquired Immune Deficiency Syndrome (AIDS) in humans. The HIV virus preferentially infects human T-4 cells and destroys them or changes their normal function, particularly the coordination of the immune system. As a result, an infected patient has an everdecreasing number of T-4 cells, which moreover behave abnormally. Hence, the immunological defense system is unable to combat infections and neoplasms and the

HIV infected subject usually dies by opportunistic infections such as pneumonia, or by cancers. Other conditions associated with HIV infection include thrombocytopaenia, multiple sclerosis, Kaposi's sarcoma and infection of the central nervous system characterized by progressive demyelination, resulting in dementia and symptoms such as, progressive dysarthria, ataxia and disorientation. HIV infection further has also been associated with peripheral neuropathy, progressive generalized lymphadenopathy (PGL) and AIDS-related complex (ARC).

The compounds of formula (I-A), (I-B) and (I-C) also show activity against HIV-1 strains that have acquired resistance to art-known non-nucleoside reverse transcriptase inhibitors. They also have little or no binding affinity to human α -1 acid glycoprotein.

Those of skill in the treatment of HIV-infection could determine the effective daily amount from the test results presented here. In general it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, in particular 5 to 600 mg of active ingredient per unit dosage form, and more in particular from 200 to 400 mg per unit dosage form or from 5 to 200 mg of active ingredient per unit dosage form depending on the particular compound being used..

The exact dosage and frequency of administration depends on the particular compound of formula (I-A), (I-B) or (I-C) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines and are not intended to limit the scope or use of the invention to any extent.

The compounds of formula (I-A), (I-B) or (I-C) can also be used in the present invention in combination with another compound of formula (I-A), (I-B) or (I-C) or with another antiretroviral compound. Thus, the present invention also relates to a pharmaceutical composition containing (a) a compound of formula (I-A), (I-B) or

(I-C), (b) another compound of formula (I-A), (I-B) or (I-C) or another antiretroviral compound, and (c) one or more water-soluble polymers, as a combined preparation for anti-HIV treatment. Said other antiretroviral compounds may be known antiretroviral compounds such as nucleoside reverse transcriptase inhibitors, e.g. zidovudine
5 (3'-azido-3'-deoxythymidine, AZT), didanosine (dideoxy inosine; ddI), zalcitabine (dideoxycytidine, ddC) or lamivudine (3'-thia-2'-3'-dideoxycytidine, 3TC) and the like; non-nucleoside reverse transcriptase inhibitors such as suramine, foscarnet-sodium (trisodium phosphono formate), nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b : 2',3'-e] [1,4]diazepin-6-one), sustiva (efavirenz), tacrine
10 (tetrahydroaminoacridine) and the like; compounds of the TIBO (tetrahydroimidazo[4,5,1-jk][1,4]-benzodiazepine-2(1H)-one and thione)-type e.g. (S)-8-chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo-[4,5,1-jk][1,4]benzodiazepine-2(1H)-thione; compounds of the α -APA (α -anilino phenyl acetamide) type e.g. α -[(2-nitro-phenyl)amino]-2,6-dichlorobenzene-acetamide
15 and the like; TAT-inhibitors, e.g. RO-5-3335 and the like; protease inhibitors e.g. indinavir, ritanovir, saquinovir and the like; NMDA receptor inhibitors e.g. pentamidine; α -glycosidase inhibitor e.g. castanospermine and the like; RNase H inhibitor e.g. dextran (dextran sulfate) and the like; or immunomodulating agents, e.g. levamisole, thymopentin and the like.

20

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically
25 uniform or *homogenous throughout or consists of one phase as defined in thermodynamics*, such a solid dispersion will be called "a solid solution" hereinafter. Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered. This advantage can probably be explained by the ease with which said solid solutions can form liquid
30 solutions when contacted with a liquid medium such as gastric juice. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of components from a crystalline or microcrystalline solid phase.

35 The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase. For example, the term "a solid

dispersion" also relates to particles having domains or small regions wherein amorphous, microcrystalline or crystalline (a), or amorphous, microcrystalline or crystalline (b), or both, are dispersed more or less evenly in another phase comprising (b), or (a), or a solid solution comprising (a) and (b). Said domains are regions within
5 the particles distinctively marked by some physical feature, small in size compared to the size of the particle as a whole, and evenly and randomly distributed throughout the particle.

As described hereinabove, the particles of the present invention also comprise one or
10 more water-soluble polymers.

The water-soluble polymer in the particles according to the present invention is a polymer that preferably has an apparent viscosity, when dissolved at 20°C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa.s more preferably of 1 to 700 mPa.s,
15 and most preferred of 1 to 100 mPa.s. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- 20 - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- 25 - carboxyalkylcellulose esters,
- starches,
- pectines such as sodium carboxymethylamylopectine,
- chitin derivatives such as chitosan,
- di-, oligo- and polysaccharides such as trehalose, cyclodextrins and derivatives thereof, alginic acid, alkali metal and ammonium salts thereof, carrageenans,
30 galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids, the salts and esters thereof, methacrylate copolymers,
- 35 - polyvinylalcohol,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

Preferred water-soluble polymers are Eudragit E[®] and hydroxypropyl methylcelluloses (HPMC).

5 Said Eudragit E[®] (Röhm GmbH, Germany) is an aminoalkyl methacrylate copolymer, more in particular poly(butyl methacrylate, (2-dimethylaminoethyl)methacrylate, methyl methacrylate) (1:2:1). This basic polymethacrylate is soluble in gastric fluid up to pH 5. Eudragit E[®] 100, which is a solvent-free Eudragit E[®] solid substance is preferred.

10 Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxy-
15 propyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). In the four digit number "2910", the first two digits represent the approximate percentage of methoxyl
20 groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups : 5 mPa.s is a value indicative of the apparent viscosity of a 2 % aqueous solution at 20°C.

The molecular weight of the HPMC normally affects both the release profile of the
25 milled extrudate as well as its physical properties. A desired release profile can thus be designed by choosing an HPMC of an appropriate molecular weight ; for immediate release of the active ingredient from the particles, a low molecular weight polymer is preferred. High molecular weight HPMC is more likely to yield a sustained release pharmaceutical dosage form. The molecular weight of a water-soluble cellulose ether
30 is generally expressed in terms of the apparent viscosity at 20°C of an aqueous solution containing two percent by weight of said polymer. Suitable HPMC include those having a viscosity from about 1 to about 100 mPa.s, in particular from about 3 to about 15 mPa.s, preferably about 5 mPa.s. The most preferred type of HPMC having a
35 viscosity of 5 mPa.s., is the commercially available HPMC 2910 5 mPa.s, because this yields particles from which superior oral dosage forms of compounds of formula (I-A), (I-B) or (I-C) can be prepared as will be discussed hereunder and in the experimental part.

The weight-by-weight ratio of (a) (i.e. the antiviral compound) : (b) (i.e. the water-soluble polymer) is in the range of 1 : 1 to 1 : 899, preferably 1 : 1 to 1 : 100, more preferably 1 : 1 to 1 : 5. In the case of (compound of formula (I-A), (I-B) or (I-C)) : (HPMC 2910 5 mPa.s), said ratio preferably ranges from about 1 : 1 to about 1 : 3, and
5 optimally is about 1 : 1.5 (or 2 : 3). The most appropriate weight by weight ratio of a compound of formula (I-A), (I-B) or (I-C) to water-soluble polymer(s) may be determined by a person skilled in the art by straightforward experimentation. The lower limit is determined by practical considerations. Indeed, given the therapeutically effective amount of a compound of formula (I-A), (I-B) or (I-C) (from about 1 mg to
10 about 1000 mg per unit dosage form, preferably about 200 mg to 400 mg or 5 to 200 mg per unit dosage form), the lower limit of the ratio is determined by the maximum amount of mixture that can be processed into one dosage form of practical size. When the relative amount of water-soluble polymer is too high, the absolute amount of mixture needed to reach the therapeutic level will be too high to be processed into one
15 capsule or tablet. Tablets, for example, have a maximum weight of about 1 g, and the extrudate can account for maximally about 90 % (w/w) thereof. Consequently, the lower limit of the amount of a compound of formula (I-A), (I-B) or (I-C) over water-soluble polymer will be about 1 : 899 (1 mg of a compound of formula (I-A), (I-B) or (I-C) + 899 mg water-soluble polymer).

20
On the other hand, if the ratio is too high, this means the amount of the compound of formula (I-A), (I-B) or (I-C) is relatively high compared to the amount of water-soluble polymer, then there is the risk that the compound of formula (I-A), (I-B) or (I-C) will not dissolve sufficiently in the water-soluble polymer, and thus the required
25 bioavailability will not be obtained. The degree to which a compound has dissolved into a water-soluble polymer can often be checked visually : if the extrudate is clear then it is very likely that the compound will have dissolved completely in the water-soluble polymer. It will be appreciated that the upper limit of 1 : 1 may be underestimated for particular compounds of formula (I-A), (I-B) or (I-C) and particular
30 water-soluble polymers. Since this can be established easily but for the experimentation time involved, solid dispersions wherein the ratio (a) : (b) is larger than 1 : 1 are also meant to be comprised within the scope of the present invention.

35
The particles according to the present invention can be prepared by first preparing a solid dispersion of the components, and then optionally grinding or milling that dispersion. Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation, melt-extrusion being preferred.

The melt-extrusion process comprises the following steps :

- a) mixing the components (a) and (b),
- b) optionally blending additives with the thus obtained mixture,
- c) heating the thus obtained blend until one obtains a homogenous melt,
- 5 d) forcing the thus obtained melt through one or more nozzles; and
- e) cooling the melt till it solidifies.

The terms "melt" and "melting" should be interpreted broadly. For our purposes, these terms not only mean the alteration from a solid state to a liquid state, but can also refer
10 to a transition to a glassy state or a rubbery state, and in which it is possible for one component of the mixture to get embedded more or less homogeneously into the other. In particular cases, one component will melt and the other component(s) will dissolve in the melt thus forming a solution, which upon cooling may form a solid solution having advantageous dissolution properties.

15

One of the most important parameters of melt extrusion is the temperature at which the melt-extruder is operating. It was found that the operating temperature can easily range between about 20°C and about 300°C, more preferably about 70°C and 250°C. The lower temperature limit depends on the solubility of a compound of formula (I-A),
20 (I-B) or (I-C) in the water-soluble polymer and on the viscosity of the mixture. When the compound of formula (I-A), (I-B) or (I-C) is not completely dissolved in the water-soluble polymer, the extrudate will not have the required bioavailability; when the viscosity of the mixture is too high, the process of melt extrusion will be difficult. At temperatures of more than 300°C the water-soluble polymer may decompose to an
25 unacceptable level. It may be noted that there is no need to fear decomposition of a compound of formula (I-A), (I-B) or (I-C) at temperatures up to 300°C. A person skilled in the art will easily recognize the most appropriate temperature range to be used.

30 The throughput rate is also of importance because even at relatively low temperatures the water-soluble polymer may start to decompose when it remains too long in contact with the heating element.

It will be appreciated that the person skilled in the art will be able to optimize the
35 parameters of the melt extrusion process within the above given ranges. The working temperatures will also be determined by the kind of extruder or the kind of configuration within the extruder that is used. Most of the energy needed to melt, mix and dissolve the components in the extruder can be provided by the heating elements.

However, the friction of the material within the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogenous melt of the components.

- 5 A person skilled in the art will easily recognize the most appropriate extruder, such as, for example, a single screw, a twin screw extruder or a multi-screw extruder, for the preparation of the subject-matter of the present invention.

10 Spray-drying of a solution of the components also yields a solid dispersion of said components and may be a useful alternative to the melt-extrusion process, particularly in those cases where the water-soluble polymer is not sufficiently stable to withstand the extrusion conditions and where residual solvent can effectively be removed from the solid dispersion. Yet another possible preparation consists of preparing a solution
15 of the components, pouring said solution onto a large surface so as to form a thin film, and evaporating the solvent therefrom.

The solid dispersion product is milled or ground to particles having a particle size of less than 1500 μm , preferably less than 400 μm , more preferably less than 250 μm , and most preferably less than 125 μm . The particle size proves to be an important factor
20 determining the speed with which a particular dosage form can be manufactured on a large scale. For instance, for capsules, the particle size may range preferably from 100 to 1500 μm ; for tablets the particle size is preferably less than 250 μm . The smaller the particles, the faster the tableting speed can be without detrimental effects on their quality. The particle size distribution is such that more than 70% of the particles
25 (measured by weight) have a diameter ranging from about 50 μm to about 1400 μm , in particular from about 50 μm to about 200 μm , more in particular from about 50 μm to about 150, and most in particular from about 50 μm to about 125 μm . Particles of the dimensions mentioned herein can be obtained by sieving them through nominal standard test sieves as described in the CRC Handbook, 64th ed., page F-114. Nominal
30 standard sieves are characterized by the mesh/hole width (μm), DIN 4188 (mm), ASTM E 11-70 (No), Tyler® (mesh) or BS 410 (mesh) values. Throughout this description, and in the claims hereinafter, particle sizes are designated by reference to the mesh/hole width in μm and to the corresponding Sieve No. in the ASTM E11-70
35 standard.

Preferred are particles wherein the compound of formula (I-A), (I-B) or (I-C) is in a non-crystalline phase as these have an intrinsically faster dissolution rate than those

wherein part or all of the compound of formula (I-A), (I-B) or (I-C) is in a microcrystalline or crystalline form.

Preferably, the solid dispersion is in the form of a solid solution comprising (a) and (b).

- 5 Alternatively, it may be in the form of a dispersion wherein amorphous or microcrystalline (a) or amorphous or microcrystalline (b) is dispersed more or less evenly in a solid solution comprising (a) and (b).

Preferred particles are those obtainable by melt-extrusion of the components and
10 grinding, and optionally sieving. More in particular, the present invention concerns particles consisting of a solid solution comprising two parts by weight of a compound of formula (I-A), (I-B) or (I-C) and three parts by weight of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s, obtainable by blending said components, melt-extruding the blend at a temperature in the range of 20°C - 300°C, grinding the
15 extrudate, and optionally sieving the thus obtained particles. The preparation is easy to perform and yields particles of a compound of formula (I-A), (I-B) or (I-C) that are free of organic solvent.

The particle as described hereinabove may further comprise one or more
20 pharmaceutically acceptable excipients such as, for example, plasticizers, flavors, colorants, preservatives and the like. Said excipients should not be heat-sensitive, in other words, they should not show any appreciable degradation or decomposition at the working temperature of the melt-extruder.

25 In the current formulations (compound of formula (I-A), (I-B) or (I-C):HPMC 2910 5 mPa.s), the amount of plasticizer is preferably small, in the order of 0 % to 15 % (w/w), preferably less than 5 % (w/w). With other water-soluble polymers though, plasticizers may be employed in much different, often higher amounts because plasticizers as mentioned hereinbelow lower the temperature at which a melt of (a), (b) and plasticizer
30 is formed, and this lowering of the melting point is advantageous where the polymer has limited thermal stability. Suitable plasticizers are pharmaceutically acceptable and include low molecular weight polyalcohols such as ethylene glycol, propylene glycol, 1,2 butylene glycol, 2,3-butylene glycol, styrene glycol; polyethylene glycols such as diethylene glycol, triethylene glycol, tetraethylene glycol; other polyethylene glycols
35 having a molecular weight lower than 1,000 g/mol; polypropylene glycols having a molecular weight lower than 200 g/mol; glycol ethers such as monopropylene glycol monoisopropyl ether; propylene glycol monoethyl ether; diethylene glycol monoethyl ether; ester type plasticizers such as sorbitol lactate, ethyl lactate, butyl lactate, ethyl

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glycolate, allyl glycollate; and amines such as monoethanolamine, diethanolamine, triethanolamine, monoisopropanolamine; triethylenetetramine, 2-amino-2-methyl-1,3-propanediol and the like. Of these, the low molecular weight polyethylene glycols, ethylene glycol, low molecular weight polypropylene glycols and especially propylene glycol are preferred.

Once the extrudate is obtained, it can be milled and sieved, and it can be used as ingredient to make pharmaceutical dosage forms.

- 10 The particles of the present invention can be formulated into pharmaceutical dosage forms comprising a therapeutically effective amount of particles. Although, at first instance, pharmaceutical dosage forms for oral administration such as tablets and capsules are envisaged, the particles of the present invention can also be used to prepare pharmaceutical dosage forms e.g. for rectal administration. Preferred dosage
- 15 forms are those adapted for oral administration shaped as a tablet. They can be produced by conventional tableting techniques with conventional ingredients or excipients and with conventional tableting machines. As mentioned above, an effective antiviral dose of a compound of formula (I-A), (I-B) or (I-C) ranges from about 1 mg to about 1000 mg per unit dosage form, and preferably is about 200 to 400
- 20 mg or 5 to 200 mg per unit dosage form depending on the particular compound being used. When one considers that the weight-by-weight ratio of (a) : (b) is maximally about 1 : 1, then it follows that one dosage form will weigh at least 10 to 800mg. In order to facilitate the swallowing of such a dosage form by a mammal, it is advantageous to give the dosage form, in particular tablets, an appropriate shape.
- 25 Tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape. Especially preferred are biconvex oblate tablets. As discussed hereunder in more detail, a film coat on the tablet further contributes to the ease with which it can be swallowed.
- 30 Tablets that give an immediate release of a compound of formula (I-A), (I-B) or (I-C) upon oral ingestion and that have good bioavailability are designed in such a manner that the tablets disintegrate rapidly in the stomach (immediate release) and that the particles which are liberated thereby are kept away from one another so that they do not coalesce, give local high concentrations of a compound of formula (I-A), (I-B) or (I-C)
- 35 and the chance that the drug precipitates (bioavailability). The desired effect can be obtained by distributing said particles homogeneously throughout a mixture of a disintegrant and a diluent.

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Comp No.	Ex. No.	X	R ^a	R ^b	R ^c	Physical Data
1	3.B1	-NH-	CH ₃	CH ₃	CH ₃	mp. 248-249°C
2	3.B2	-O-	CH ₃	CH ₃	CH ₃	mp. 220-221°C
3	3.B2	-O-	CH ₃	Br	Cl	mp. 221-222°C
4	3.B3	-S	CH ₃	CH ₃	CH ₃	mp. 256-257°C
5	3.B2	-O-	Br	CH ₃	Br	mp. 255-257°C
6	3.B1	-NH-	Br	CH ₃	Br	mp. 285-286°C
7	3.B1	-NH-	CH ₃	Br	CH ₃	mp. 248-249°C

3.C. Pharmacological example

Example 3.C.1

- The same test as described above for the compounds of formula (I-A) (example 1.C.1) was used for the *in vitro* evaluation of the anti-HIV agents of formula (I-C). The compounds of formula (I-C) were shown to inhibit HIV-1 effectively. Particular IC₅₀, CC₅₀ and SI values of compounds of formula (I-C) are listed in Table 8 hereinbelow.

Table 8

Co. No.	IC ₅₀ (μM)	CC ₅₀ (μM)	SI
1	0.0004	9.1	22722
2	0.0006	>100	>166666
3	0.0011	56.2	53536
4	0.0022	>100	>46511

Co. No.	IC ₅₀ (μM)	CC ₅₀ (μM)	SI
5	0.0016	10.1	6452
6	0.0005	1.0	1901
7	0.0007	27.8	39722

10

4. Preparation of the particles of the present invention

- 8 g of compound 17 of formula (I-A) and 12 g hydroxypropyl methylcellulose 2910 5 mPa.s (HPMC 2910 5 mPa.s) were mixed until the mixture was homogenous. The mixture was fed into a Gimac single screw extruder L/D 24:1 having the following operating parameters : screw rate was 30 revolutions per minute, the temperature ranged from 70°C to 235°C. Yield was 17 g (85 %). The melt extrudate was milled and fractions with particle size below 150 μm (condition I in point 6) and between 500 and 850 μm (condition II in point 6) were collected.

5. Thermal stability of the antiviral compound in the melt extrudate

The thermal stability of compound 17 of formula (I-A) after melt extrusion was determined by HPLC (high performance liquid chromatography). No degradation of

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the antiviral compound could be detected, which confirms the thermal stability of said compound after melt extrusion.

6. Dissolution study

- 5 *In-vitro* dissolution studies were performed on the melt extrudate fractions described under point 4. 375 mg of each fraction was directly added to the dissolution medium. The fraction with particle size between 500 and 850 μm was also filled in a gelatin capsule nr. 0 EL, which was then added to the dissolution medium (III). The dissolution medium was 900 ml of 0.1 N HCl at 37°C in Apparatus 2 (USP 23, <711> 10 Dissolution, pp. 1791-1793) (paddle, 100 rpm). The concentration of the active ingredient compound 17 of formula (I-A) dissolved in the test medium was determined by removing a 3 ml sample at the indicated time, filtering the sample over a millex-LCR filter, measuring its absorbance at 286 nm and calculating the concentration therefrom.
- 15 The following results were obtained :

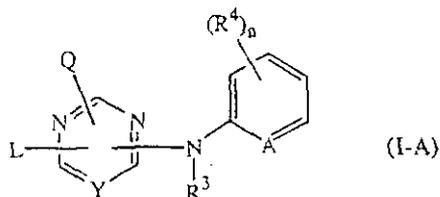
Time (min)	Percentage dissolved active ingredient		
	I	II	III
0	0.00	0.00	0.00
5	64.32	33.96	12.90
15	76.44	69.18	52.02
30	82.74	79.50	79.08
45	91.50	84.84	88.98
60	98.34	92.40	92.28

- I : compound 17 of formula (I-A):HPMC 2910 5 mPa.s (1:1.5 (w/w)); fraction with particle size below 150 μm
- 20 II : compound 17 of formula (I-A):HPMC 2910 5 mPa.s (1:1.5 (w/w)); fraction with particle size between 500 and 850 μm
- III : compound 17 of formula (I-A):HPMC 2910 5 mPa.s (1:1.5 (w/w)); fraction with particle size between 500 and 850 μm filled in a gelatin capsule nr. 0 EL

- 25 The *in vitro* dissolution study from the melt extrudate fractions and the fraction filled in a gelatine capsule shows that the drug release reached at least 85% after 60 minutes.

Claims

1. A particle consisting of a solid dispersion comprising
 (a) a compound of formula



5

a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

Y is CR⁵ or N;

A is CH, CR⁴ or N;

10 n is 0, 1, 2, 3 or 4;

Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen;

R¹ and R² are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl,

C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the

15 aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C₁₋₆alkyl)amino, aryl and Het; or

20 R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄alkylidene;

R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and

each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, amino-

25 carbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is CR⁵ then R⁴ may also represent C₁₋₆alkyl substituted with cyano or aminocarbonyl;

R⁵ is hydrogen or C₁₋₄alkyl;

L is -X¹-R⁶ or -X²-Alk-R⁷ wherein

30 R⁶ and R⁷ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR⁵ then R⁶ and R⁷ may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy

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and trihalomethyl; or when Y is N then R⁶ and R⁷ may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxy carbonyl,

5 formyl, cyano, nitro, amino, and trifluoromethyl;

X¹ and X² are each independently -NR³-, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or -S(=O)₂-;

Alk is C₁₋₄alkanediyl; or

when Y is CR⁵ then L may also be selected from C₁₋₁₀alkyl, C₃₋₁₀alkenyl, C₃₋₁₀alkynyl,

10 C₃₋₇cycloalkyl, or C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl,

indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl,

15 C₁₋₆alkyloxy, cyano, aminocarbonyl, C₁₋₆alkyloxy carbonyl, formyl, nitro, amino, trihalomethyl, trihalomethoxy and C₁₋₆alkylcarbonyl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro and trifluoromethyl;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is

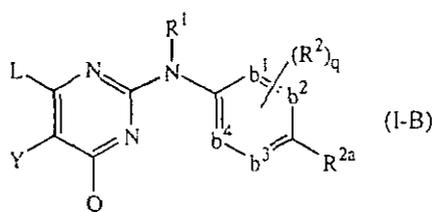
20 selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic hetero-

cyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may

25 optionally be substituted with hydroxy;

or

a compound of formula



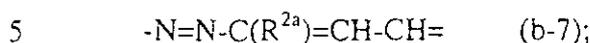
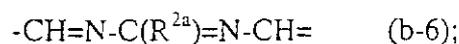
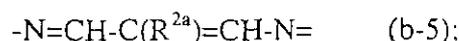
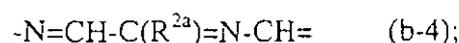
30 the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

-b¹=b²-C(R^{2a})=b³-b⁴= represents a bivalent radical of formula

-CH=CH-C(R^{2a})=CH-CH= (b-1);

-N=CH-C(R^{2a})=CH-CH= (b-2);

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q is 0, 1, 2; or where possible q is 3 or 4;

R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy carbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxy carbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C₁₋₆alkyl substituted

10 with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C₂₋₆alkenyl substituted with cyano, or C₂₋₆alkynyl substituted with cyano;

each R² independently is hydroxy, halo, C₁₋₆alkyl optionally substituted with cyano or

-C(=O)R⁶, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more

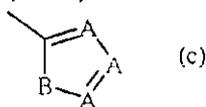
halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more

15 halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxy carbonyl, carboxyl, cyano,

nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy,

polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H,

-C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or a radical of formula



20 wherein each A independently is N, CH or CR⁶;

B is NH, O, S or NR⁶;

p is 1 or 2; and

R⁶ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said

25 aliphatic group may be substituted with one or two substituents independently selected from

* C₃₋₇cycloalkyl,

* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy,

30 C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl,

polyhalomethoxy and C₁₋₆alkylcarbonyl,

* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or

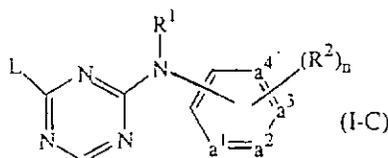
35 L is -X-R³ wherein

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- R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;
- 5 Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or -NR⁴R⁵; and R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the
- 10 aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or
- 15 R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄alkylidene;
- Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or -C(=O)R⁶, C₁₋₆alkyloxy,
- 20 C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;
- aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each
- 25 independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;
- Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranlyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic
- 30 radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy;
- or
- 35 a compound of formula

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the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

5 -a¹=a²-a³=a⁴- represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

-N=CH-CH=CH- (a-2);

-N=CH-N=CH- (a-3);

-N=CH-CH=N- (a-4);

10 -N=N-CH=CH- (a-5);

n is 0, 1, 2, 3 or 4; and in case -a¹=a²-a³=a⁴- is (a-1), then n may also be 5;

R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl,

C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and

each R² independently is hydroxy, halo, C₁₋₆alkyl optionally substituted with cyano or

15 -C(=O)R⁴, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more

halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more

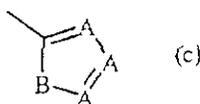
halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro,

amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy,

polyhalomethylthio,

20 -S(=O)_pR⁴, -NH-S(=O)_pR⁴, -C(=O)R⁴, -NHC(=O)H, -C(=O)NHNH₂,

-NHC(=O)R⁴, -C(=NH)R⁴ or a radical of formula



wherein each A independently is N, CH or CR⁴;

B is NH, O, S or NR⁴;

25 p is 1 or 2; and

R⁴ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said

aliphatic group may be substituted with one or two substituents independently

selected from

30 * C₃₋₇cycloalkyl,

* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy,

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C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethoxy and C₁₋₆alkylcarbonyl,

- * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or

L is -X-R³ wherein

R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and

- X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;

with the proviso that compounds wherein

- * L is C₁₋₃alkyl; R¹ is selected from hydrogen, ethyl and methyl; -a¹=a²-a³=a⁴- represents a bivalent radical of formula (a-1); n is 0 or 1 and R² is selected from fluoro, chloro, methyl, trifluoromethyl, ethyloxy and nitro; or
- * L is -X-R³, X is -NH-; R¹ is hydrogen; -a¹=a²-a³=a⁴- represents a bivalent radical of formula (a-1); n is 0 or 1 and R² is selected from chloro, methyl, methyloxy, cyano, amino and nitro and R³ is phenyl, optionally substituted with one substituent selected from chloro, methyl, methyloxy, cyano, amino and nitro;

and the compounds

- * *N,N'*-dipyridinyl-(1,3,5)-triazine-2,4-diamine;
- * (4-chloro-phenyl)-(4(1-(4-isobutyl-phenyl)-ethyl)-(1,3,5) triazin-2-yl)-amine
- are not included;

and

(b) one or more pharmaceutically acceptable water-soluble polymers.

30

2. A particle according to claim 1 having a particle size of less than 1500 μm.
3. A particle according to claim 1 or 2 wherein the compound of formula (I-A), (I-B) or (I-C) is in a non-crystalline phase.

35

4. A particle according to claim 3 wherein the solid dispersion is in the form of a solid solution comprising (a) and (b), or in the form of a dispersion wherein amorphous or

microcrystalline (a) or amorphous or microcrystalline (b) is dispersed more or less evenly in a solid solution comprising (a) and (b).

5. A particle according to the preceding claims wherein the compound of formula (I-A), (I-B) or (I-C) is 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzotrile (R165335), 4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile (, 4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile (4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzotrile (4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile (4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile (4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzotrile (4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzotrile (or 4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzotrile .
6. A particle according to the preceding claims wherein the compound of formula (I-A) is 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile .
7. A particle according to the preceding claims wherein the water-soluble polymer is a polymer that has an apparent viscosity of 1 to 5000 mPa.s when dissolved at 20°C in an aqueous solution at 2 % (w/v).
8. A particle according to claim 7 wherein the water-soluble polymer is selected from the group comprising
- alkylcelluloses such as methylcellulose,
 - hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
 - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
 - carboxyalkylcelluloses such as carboxymethylcellulose,
 - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
 - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
 - carboxyalkylcellulose esters,
 - starches,

- pectines such as sodium carboxymethylamylopectine,
 - chitin derivatives such as chitosan,
 - di-, oligo- or polysaccharides such as trehalose, cyclodextrins or a derivative thereof, alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
 - polyacrylic acids and the salts thereof,
 - polymethacrylic acids, the salts and esters thereof, methacrylate copolymers,
 - polyvinylalcohol,
 - polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.
9. A particle according to claim 8 wherein the water-soluble polymer is hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.
10. A particle according to claim 9 wherein the weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 899.
11. A particle according to any one of the preceding claims obtainable by melt-extrusion of the components and grinding, and optionally sieving.
12. A particle according to any one of the previous claims consisting of a solid solution comprising two parts by weight of a compound of formula (I-A), (I-B) or (I-C) and three parts by weight of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s, obtainable by blending said components, extruding the blend at a temperature in the range of 20°C - 300°C, grinding the extrudate, and optionally sieving the thus obtained particles.
13. A particle according to the preceding claims further comprising one or more pharmaceutically acceptable excipients.
14. A pharmaceutical dosage form comprising a therapeutically effective amount of particles as claimed in any one of the preceding claims.
15. A dosage form according to claim 14 adapted for oral administration shaped as a tablet.

D4

11 1 MAY 2011

**Handbook of
Pharmaceutical Excipients**

Handbook of Pharmaceutical Excipients

FIFTH EDITION

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11 MAY 2011

Hypromellose

1 Nonproprietary Names

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Hypromellosum
USP: Hypromellose

2 Synonyms

Benecel, *MHPC*, *E464*, *hydroxypropyl methylcellulose*; *HPMC*, *Methocel*, *methylcellulose propylene glycol ether*, *metil hidroksi propil selulosa*, *Mellose*, *Islopar*.

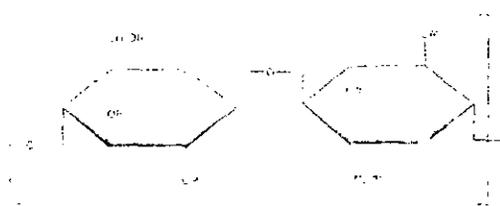
3 Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

4 Empirical Formula and Molecular Weight

The PhEur 2005 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa.s, of a 2% w/w aqueous solution at 20 °C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name; e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH₃). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH₂CH(OH)CH₃), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the types of hypromellose stated in Table I. Molecular weight is approximately 1000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2900, and 2910, respectively.

5 Structural Formula



where R is H, CH₃, or CH₂CH(OH)CH₃.

6 Functional Category

Coating agent; film-former; excipient; polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder,⁽¹⁾ in film-coating,^(2–7) and as a matrix for use in extended-release tablet formulations.^(8–12) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include *AnyCoat C*, *Spectracel*, and *Pharmacoat*.

Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

8 Description

Hypromellose is an odorless and tasteless, white or cream-white fibrous or granular powder. See also Section 10.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.

Ash: 1.5–3.0%, depending upon the grade and viscosity.

Autoignition temperature: 360 °C

Density (bulk): 0.341 g/cm³

Density (tapped): 0.557 g/cm³

Density (true): 1.326 g/cm³

Melting point: browns at 190–200 °C; chars at 225–230 °C.

Glass transition temperature is 170–180 °C.

Moisture content: hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air. See Figure 1.

SEM: 1

Excipient: Hypromellose
 Manufacturer: Dow Chemical Co.
 Lot No.: ME20012N11
 Magnification: 600x
 Voltage: 5kV



SEM: 2

Excipient: Hypromellose
 Manufacturer: Dow Chemical Co.
 Lot No.: ME20012N11
 Magnification: 60x
 Voltage: 5kV



Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. See *also* Section 11.
Specific gravity: 1.26

Table 1: Pharmaceutical specifications for hypromellose

Test	JP 2001	PhEur 2005	USP 28
Identification	—	—	—
Characteristics	—	—	—
Appearance of solution	—	—	—
pH (1% w/w solution)	5.0–8.0	5.5–8.0	—
Apparent viscosity	—	—	—
Loss on drying	≤ 5.0%	≤ 10.0%	≤ 5.0%
Residue on ignition	≤ 1.5%	—	—
For viscosity grade	—	—	≤ 1.5%
50 mPa·s	—	—	—
For viscosity grade	—	—	≤ 3.0%
≤ 50 mPa·s	—	—	—
For type 1828 of cellulosines	—	—	≤ 5.0%
Sulfated ash	—	≤ 1.0%	—
Chlorides	≤ 0.284%	≤ 0.5%	—
Heavy metals	≤ 10 ppm	≤ 20 ppm	≤ 0.001%
Iron	≤ 100 ppm	—	—
Arsenic	≤ 2 ppm	—	—
Organic volatile impurities	—	—	—
Methoxy content	—	—	16.5–20.0%
Type 1828	—	—	19.0–24.0%
Type 2208	19.0–24.0%	—	27.0–30.0%
Type 2906	27.0–30.0%	—	28.0–30.0%
Type 2910	28.0–30.0%	—	—
Hydroxypropoxy content	—	—	23.0–32.0%
Type 1828	—	—	4.0–12.0%
Type 2208	4.0–12.0%	—	4.0–7.5%
Type 2906	4.0–7.5%	—	7.0–12.0%
Type 2910	7.0–12.0%	—	—

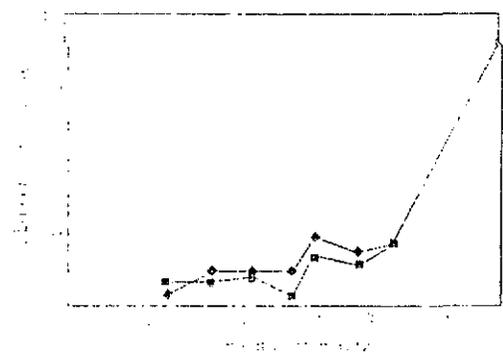


Figure 1: Adsorption-desorption isotherm for hypromellose
 ◆ Adsorption
 ■ Desorption

Viscosity (dynamic): a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloroethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared

using organic solvents tend to be more viscous, increasing concentration also produces more viscous solutions; see Table II.

Table II: Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.). Viscosities measured at 20°C.

Methocel product	USP 28 designation	Nominal viscosity (mPa s)
Methocel K100 Premium (VEP)	2208	160
Methocel K4M Premium	2208	400
Methocel K10M Premium	2208	1000
Methocel K100M Premium	2208	10000
Methocel E4M Premium	2910	200
Methocel F50 Premium	2906	50
Methocel E10M Premium CE	2906	10000
Methocel E3 Premium IV	2906	3
Methocel E5 Premium IV	2906	5
Methocel E6 Premium IV	2906	6
Methocel E15 Premium IV	2906	15
Methocel E50 Premium IV	2906	50
Methocel 60SH	2910	50, 1000, 10000
Methocel 65SH	2906	50, 100, 1000, 4000
Methocel 90SH	2208	100, 400, 2000, 15000

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, then the remaining hypromellose should be added. Sufficient cold water should then be added to produce the required volume.

When a water-miscible organic solvent such as ethanol (95%), glycol, or mixture of ethanol and dichloromethane are used, the hypromellose should first be dispersed into the organic solvent at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

11 Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3–11, but very low temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transition upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.^{11,12} However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions. Benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving, the coagulum, however, must be redispersed on cooling by shaking.

Hypromellose powder should be stored in a well closed container in a cool, dry place.

12 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

13 Method of Manufacture

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

14 Safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.^{13,14} The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.¹⁵

LD₅₀ (mouse, IP): 5 g/kg^{16a}

LD₅₀ (rat, IP): 5.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hypromellose phthalate, methylcellulose.

18 Comments

Powdery (or granular, surface-treated grades of hypromellose are also available that are dispersible in cold water. These are not recommended for oral use. A specification for hypromellose is contained in the Food Chemicals Codex (FCC).

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21 Authors

RJ Harwood.

22 Date of Revision

17 August 2005.

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Cellulose, Microcrystalline

1 Nonproprietary Names

BP: Microcrystalline cellulose
 JP: Microcrystalline cellulose
 PhEur: Cellulosum microcristallinum
 USPNF: Microcrystalline cellulose

2 Synonyms

Avicel PH; *Cellex*; cellulose gel; *Celphere*; *Ceolus KG*; crystalline cellulose; *F460*; *Emcocel*; *Ethospheres*; *Fibrocel*; *Pharmacel*; *Tabulose*; *Vivapur*.

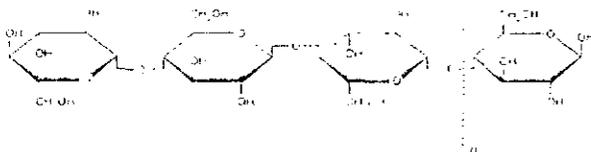
3 Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n \approx 36,000$
 where $n \approx 220$.

5 Structural Formula



6 Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.¹¹⁻¹² In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant¹³ and disintegrant¹⁴ properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products; see Table I.

8 Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20-90
Antiadherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder/diluent	20-90

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for microcrystalline cellulose.

Test	JP 2001	PhEur 2005 (Suppl 5.1)	USPNF 23
Identification	-	+	+
Characteristics	-	-	-
pH	5.0-7.0	5.0-7.5	5.0-7.5
Bulk density	-	-	+
Loss on drying	≤7.0%	≤7.0%	≤7.0%
Residue on ignition	≤0.05%	-	≤0.1%
Conductivity	-	-	+
Sulfated ash	-	≤0.1%	-
Ether-soluble substances	≤0.05%	≤0.05%	≤0.05%
Water-soluble substances	-	≤0.25%	≤0.25%
Heavy metals	10 ppm	10 ppm	≤0.001%
Organic volatile impurities	-	-	-
Microbial limits	-	-	+
Aerobia	-	≤10 ² /g	≤1000 cfu/g
Molds or yeasts	-	10 ² /g	≤100 cfu/g
Solubility	-	-	-
Particle size distribution	-	-	+

10 Typical Properties

Angle of repose:

49° for *Ceolus KG*;
 31.4° for *Emcocel 90M*.¹⁰¹

Density (bulk):

0.337 g/cm³;
 0.32 g/cm³ for *Avicel PH-101*.¹⁰⁰
 0.27 g/cm³ for *Emcocel 90M*.¹⁰¹
 0.27 g/cm³ for *VivaPar 101*.

Density (tapped):

0.478 g/cm³;
 0.45 g/cm³ for *Avicel PH-101*;
 0.35 g/cm³ for *Emcocel 90M*.¹⁰¹

Density (true): 1.512-1.668 g/cm³

Flowability: 1.41 g/s for *Emcocel 90M*.¹⁰¹

Melting point: chars at 260-270°C.

Moisture content: typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.^{11,12} See Table III.

SEM: 1

Excipient: Microcrystalline cellulose
 Manufacturer: JRS Pharma LP
 Lot No.: 98662
 Magnification: 100x



SEM: 2

Excipient: Microcrystalline cellulose
 Manufacturer: JRS Pharma LP
 Lot No.: 98662
 Magnification: 300x



Particle size distribution: typical mean particle size is 20–200 μm . Different grades may have a different nominal mean particle size; see Table III.

SEM: 3

Excipient: Microcrystalline cellulose
 Manufacturer: FMC Biopolymer
 Magnification: 100x



Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Specific surface area:

1.06–1.12 m^2/g for *Avicel PH-101*;

1.21–1.30 m^2/g for *Avicel PH-102*;

0.78–1.18 m^2/g for *Avicel PH-200*.

11 Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

13 Method of Manufacture

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of α -cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14 Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Table III: Properties of selected commercially available grades of microcrystalline cellulose.

Grade	Nominal mean particle size (μm)	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel PH-101 ^(a)	50	60	≤ 1.0	≤ 5.0
		200	≤ 30.0	
Avicel PH-102 ^(a)	100	60	≤ 8.0	≤ 5.0
		200	≤ 45.0	
Avicel PH-103 ^(a)	50	60	≤ 1.0	≤ 3.0
		200	≤ 30.0	
Avicel PH-105 ^(a)	20	200	≤ 1.0	≤ 5.0
Avicel PH-112 ^(a)	100	60	≤ 8.0	≤ 1.5
Avicel PH-113 ^(a)	50	60	≤ 1.0	≤ 1.5
		200	≤ 30.0	
Avicel PH-200 ^(a)	180	60	≤ 10.0	≤ 5.0
		100	≤ 50.0	
Avicel PH-301 ^(a)	50	60	≤ 1.0	≤ 5.0
		200	≤ 30.0	
Avicel PH-302 ^(a)	100	60	≤ 8.0	≤ 5.0
		100	≤ 45.0	
Cellex 101 ^(b)	75	60	≤ 1.0	≤ 5.0
		200	≤ 30.0	
Ceflus KG-802 ^(c)	50	60	≤ 0.5	≤ 0.0
		200	≤ 30.0	
Emcocel 50M ^(d)	50	60	≤ 0.25	≤ 5.0
		200	≤ 30.0	
Emcocel 90M ^(d)	90	60	≤ 8.0	≤ 5.0
		200	≤ 45.0	
Vivapur 101 ^(d)	50	60	≤ 1.0	≤ 5.0
		200	≤ 30.0	
Vivapur 102 ^(d)	90	60	≤ 8.0	≤ 5.0
		200	≤ 45.0	
Vivapur 12 ^(d)	180	58	≤ 1.0	≤ 5.0
		54	≤ 50.0	

Suppliers

^(a) FMC Biopolymer^(b) International Specialty Products^(c) Asahi Kasei Corporation^(d) Retenauer & Sonne GmbH

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.¹²

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the occupational exposure limits for cellulose have been set at 10 mg/m^3 for 9-h (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3 .⁽¹³⁾

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral

medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Microcrystalline cellulose and carrageenan; microcrystalline cellulose and carboxymethylcellulose sodium; microcrystalline cellulose and guar gum; powdered cellulose; sified microcrystalline cellulose.

Microcrystalline cellulose and carrageenan

Synonyms: *Lustre Clear*.

Comments: *Lustre Clear* (FMC Biopolymer) is an aqueous film coating combining microcrystalline cellulose and carrageenan.

Microcrystalline cellulose and carboxymethylcellulose sodium

Synonyms: *Avicel CL-611*; *Avicel RC-581*; *Avicel RC-591*; colloidal cellulose; dispersible cellulose.

Appearance: white, odorless and tasteless, hygroscopic powder. Acidity/alkalinity: pH = 6–8 for a 1.2% w/v aqueous dispersion.

Moisture content: not more than 6.0%, w/w.

Particle size distribution:

Avicel CL-611: $\leq 0.1\%$ retained on a #60 mesh and $\leq 50\%$ retained on a #325 mesh;

Avicel RC-581: $\leq 0.1\%$ retained on a #60 mesh and $\leq 35\%$ retained on a #200 mesh;

Avicel RC-591: $\leq 0.1\%$ retained on a #60 mesh and $\leq 45\%$ retained on a #325 mesh.

Solubility: practically insoluble in dilute acids and organic solvents. Partially soluble in dilute alkali and water (carboxymethylcellulose sodium fraction).

Viscosity (dynamic):

5–20 mPa s (5–20 cP) for a 1.2% w/v aqueous dispersion of *Avicel CL-611*;

72–168 mPa s (72–168 cP) for *Avicel RC-581* at the same concentration.

39–91 mPa s (39–91 cP) for *Avicel RC-591* at the same concentration.

Comments: mixtures of microcrystalline cellulose and carboxymethylcellulose sodium that are dispersible in water and produce thixotropic gels are suitable as suspending vehicles in pharmaceutical formulations. The amount of carboxymethylcellulose present can vary between 8.3% and 18.8% w/w depending upon the grade of material.

Microcrystalline cellulose and guar gum

Synonyms: *Avicel CE-15*.

Comments: *Avicel CE-15* (FMC Biopolymer) is a coprocessed mixture of microcrystalline cellulose and guar gum used in chewable tablet formulations.

18 Comments

Several different grades of microcrystalline cellulose are commercially available that differ in their method of manufacture,^(14,15) particle size, moisture, flow, and other physical properties.^(16,28) The larger-particle-size grades generally provide better flow properties in pharmaceutical machinery. Low-moisture grades are used with moisture-sensitive materials. Higher-density grades have improved flowability.

Several coprocessed mixtures of microcrystalline cellulose with other excipients such as carrageenan, carboxymethylcellulose sodium, and guar gum are commercially available; see Section 17.

Celphere (Asahi Kasei Corporation) is a pure spherulized microcrystalline cellulose available in several different particle size ranges.

A specification for microcrystalline cellulose is contained in the Food Chemicals Codex (FCC).

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22 Date of Revision

20 August 2005.

Pharmacokinetics of darunavir/ritonavir and TMC125 alone and coadministered in HIV-negative volunteers

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The results of this study have been orally presented at the XVIth International AIDS Conference, Toronto, Canada, 13-18 August 2006, Poster TUPE0086.

Objective: To evaluate the pharmacokinetics of TMC125 (etravirine) and darunavir (DRV) with low-dose ritonavir (DRV/r).

Design: Open-label, randomized, two-way crossover Phase I trial.

Methods: Thirty-two HIV-negative volunteers were randomized 1:1 to two panels. All received TMC125 100 mg twice daily for 8 days and, after 14 days washout, DRV/r 600/100 mg twice daily for 16 days. During days 9-16, TMC125 100 or 200 mg twice daily was coadministered (Panel I or II, respectively).

Results: Twenty-three volunteers completed the trial. With DRV/r coadministration, mean exposure (area under the plasma concentration-time curve from 0 to 12 h [AUC_{12h}]) to TMC125 given as 100 mg twice daily was decreased by 37%; maximum and minimum plasma concentrations (C_{max} and C_{min}) were decreased by 32% and 49%, respectively. For TMC125 200 mg twice daily

coadministered with DRV/r, AUC_{12h} , C_{max} and C_{min} of TMC125 were 80%, 81% and 67% greater, respectively, versus TMC125 100 mg twice daily alone. DRV pharmacokinetics were unchanged except a 15% increase in AUC_{12h} when given with TMC125 200 mg twice daily.

Conclusions: No clinically relevant changes in DRV pharmacokinetics were observed when combined with TMC125; therefore DRV dose adjustment is not required. Coadministration of TMC125 100 mg twice daily with DRV/r decreased TMC125 exposure by 37%. The increase of TMC125 exposure by 80% when given as 200 mg twice daily reflects the higher dose and the interaction with DRV/r. The magnitude of this interaction is comparable to TMC125 interactions with other boosted PIs observed in Phase IIb trials in HIV-1-infected patients. As these trials demonstrated TMC125 efficacy, no dose adjustment of TMC125 is needed when combined with DRV/r.

Introduction

Full suppression of HIV RNA replication requires multiple active antiretrovirals (ARVs) [1]. In treatment-experienced patients, both the Department of Health and Human Services (DHHS) and the International AIDS Society (IAS) guidelines recommend addition of at least two fully active drugs to an optimized background ARV regimen (OBR): a drug with activity against drug-resistant virus (for example, a potent ritonavir-boosted protease inhibitor [PI]); and a drug with a new mechanism of action or with distinct resistance patterns and activity against drug-resistant viruses. Emphasis is placed on the long list of known interactions of ARV drugs that potentially lead to toxicities, suboptimal

responses and the development of resistance due to suboptimal doses. Physicians are advised to take these effects into consideration when designing regimens with combinations of these agents [1,2].

Darunavir (DRV) is a new PI with activity against both wild-type and PI-resistant HIV [3]. DRV in combination with low-dose ritonavir (DRV/r) at a dose of 600/100 mg twice daily has been approved for treatment-experienced HIV-infected patients in several countries including the US, on the basis of the efficacy and safety data observed in the POWER 1 and 2 Phase IIb trials [4-7]. DRV/r has been shown to be generally safe and well tolerated.

TMC125 (etravirine) is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against both wild-type and NNRTI-resistant HIV [8,9]. TMC125 showed promising antiviral effects in short-term monotherapy trials of treatment-naïve HIV-1-infected individuals and subjects with NNRTI-resistant virus [10,11]. Sustained efficacy of the drug has also been demonstrated in a controlled Phase IIb dose-ranging trial in HIV-infected patients with documented genotypic resistance to the NNRTI and PI classes after 24 and 48 weeks of treatment [12,13]. Treatment with TMC125 was generally safe and well tolerated [12,13].

DRV is a substrate and inhibitor of cytochrome P450 3A4 (CYP3A4) [14]. Ritonavir is a potent inhibitor of CYP3A4 and increases DRV exposure approximately 14-fold when used at low doses (that is, 100 mg twice daily). Coadministration with low-dose ritonavir increases the elimination half-life of DRV to approximately 15 h. DRV exposure is further increased by 30% in the presence of food, regardless of the type of meal taken, and it is therefore recommended that DRV be taken with food [5,16].

In vitro, TMC125 is mainly metabolized by CYP3A4 and CYP2C_{12C9}, 2C18 and 2C19). *In vivo*, the most important metabolic pathway for TMC125 is methyl hydroxylation, with subsequent glucuronidation of the metabolites. Most TMC125 is excreted unchanged in the faeces [17,18]. *In vitro*, TMC125 is an inducer of CYP3A4 and a mild inhibitor of CYP2C9 and P-glycoprotein. Its *in vivo* interaction potential (induction) has been demonstrated for CYP3A4 substrates [19]. It has a terminal elimination half-life in plasma of ~30–40 h [11,17]. TMC125 should also be taken with food, to enhance oral bioavailability [20].

Recently, a new 100 mg formulation of TMC125 has been developed, which at a dose of 200 mg twice daily provides comparable pharmacokinetics to the selected dose of the formulation used in the Phase IIb trials. This new formulation was used for the present study, and is the formulation being investigated in ongoing clinical trials of TMC125.

The virological and efficacy profiles of TMC125 and DRV/r indicate a strong theoretical rationale for combining these agents in an ARV regimen. On the basis of the interaction potential of all three agents and their shared pathways of hepatic metabolism, the presence of interactions could be anticipated. In order to assess these, a pharmacokinetic interaction trial was conducted in HIV-negative volunteers with the objective of determining the effect of DRV/r 600/100 mg twice daily on the pharmacokinetics of TMC125 100 mg or 200 mg twice daily and vice versa. The safety and tolerability of the coadministration of TMC125 and DRV/r were also evaluated.

Methods

The protocol for this trial (TMC125-C176) was reviewed and approved by an Independent Ethics Committee (IEC) according to specifications outlined in the applicable regulations (for example, International Conference on Harmonisation Good Clinical Practice (GCP) and US Code of Federal Regulations). The trial was performed in accordance with the principles of GCP and the Declaration of Helsinki. All volunteers gave their written, informed consent prior to any trial-related procedure.

Trial population

Thirty-two volunteers between 18 and 55 years of age with a body mass index (BMI) between 18.0 and 30.0 kg/m² were enrolled in the trial. Females of non-childbearing potential and with a negative serum pregnancy test could be included. All volunteers needed to be in good health as determined by medical history, physical examination and clinical laboratory assessments. Volunteers needed to test negative for HIV antibody and could not have participated in trials of investigational drugs within the previous 30 days. Volunteers with a history of alcohol and/or drug abuse, tobacco use of more than 10 cigarettes, two cigars or two pipes per day, or a known allergy to any trial medication or their excipients were excluded. During the trial, volunteers were not allowed to use any vitamin or herbal supplements, or prescription or over-the-counter medication other than the trial medication, except for ibuprofen and hormone replacement therapy in postmenopausal women.

Trial design

This was an open-label, randomized, two-way crossover, Phase I trial consisting of two treatment sessions separated by a washout period of at least 14 days (Figure 1). Thirty-two volunteers were randomized to two panels (Panel I and Panel II) in a 1:1 ratio and received two treatment sessions; Sessions A and B1 for Panel I and Sessions A and B2 for Panel II. Within each panel, half of the volunteers were randomized to start in Session A and half were randomized to start in Session B1 (Panel I) or Session B2 (Panel II). In Session A, volunteers received TMC125 100 mg twice daily for 7 days with an additional morning dose on day 8. The pharmacokinetics of TMC125 were assessed on day 8. In Session B1 (Panel I) and Session B2 (Panel II) volunteers received DRV/r 600/100 mg twice daily for 15 days with an additional morning dose on day 16; TMC125 100 mg twice daily (Session B1) or 200 mg twice daily (Session B2) was coadministered from day 9 to day 15 with an additional morning dose on day 16.

Pharmacokinetics of DRV and ritonavir were determined on days 8 and 16. TMC125 pharmacokinetics were assessed on day 16.

Pharmacokinetic and statistical analyses

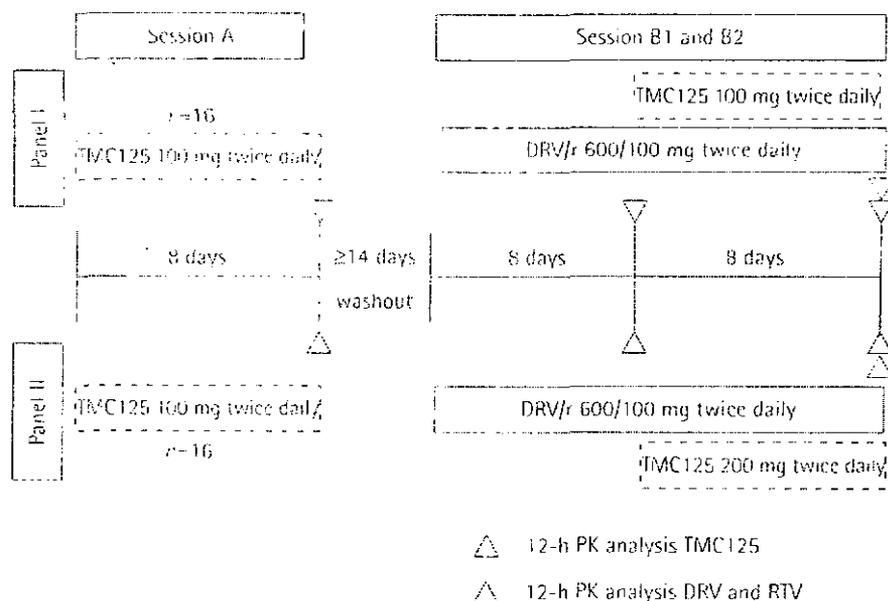
For pharmacokinetic analyses of all three compounds, blood was collected before dosing and 0.5, 1, 1.5, 2, 3, 4, 6, 9 and 12 h after dosing. Plasma samples were stored at $\leq 18^{\circ}\text{C}$ until assayed. Plasma concentrations of TMC125, DRV and ritonavir were determined using validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) methods [21].

For determination of TMC125, an aliquot of heparinized plasma sample (0.3 ml) was diluted with water and spiked with the stable-isotope-labelled internal standard (IS). Isocratic chromatographic separation was achieved at 40°C on a $3.5\ \mu\text{m}$ Waters Symmetry Shield RP 18 chromatographic column (2.1 I.D. \times 50 mm; Waters, Taunton, MA, USA) at a flow rate of 0.3 ml/min. A mixture of 0.1% (v/v) formic acid and acetonitrile (20/80, v/v) was used as elution mixture. Detection was done by tandem mass spectrometry (MS/MS) in the electrospray positive mode (ESI+, multiple reaction monitoring [MRM]). The following transitions were monitored for TMC125 and the IS m/z 435 ± 0.5 to 163 ± 0.5 and m/z 440 ± 0.5 to 164 ± 0.5 on an API-3000 instrument (Applied Biosystems, Foster City, CA, USA). The effective linear range was 2,00–5,000 ng/ml for undiluted samples.

For determination of DRV and RTV levels 0.05 ml aliquots of heparinized human plasma were diluted with ammonium acetate 0.01 M and spiked with stable-isotope-labelled internal standards for DRV and RTV. Quantitative detection was carried out on an API-4000 MS/MS instrument (Applied Biosystems) using ESI+ MRM. The following MRM transitions were monitored: m/z 548.2 to 392.0 for DRV and m/z 721.3 to 296.0 for RTV. For the ISs the following transitions were monitored: m/z 552.2 to 396.0 (IS DRV) and m/z 727.4 to 302.0 (IS RTV). Linearity of the calibration curve ranged from 5 to 10,000 ng/ml. The lower limit of quantification (LLOQ), defined as the lowest spiked standard of the calibration curve prepared in the same matrix as the study samples, was 5 ng/ml for undiluted samples.

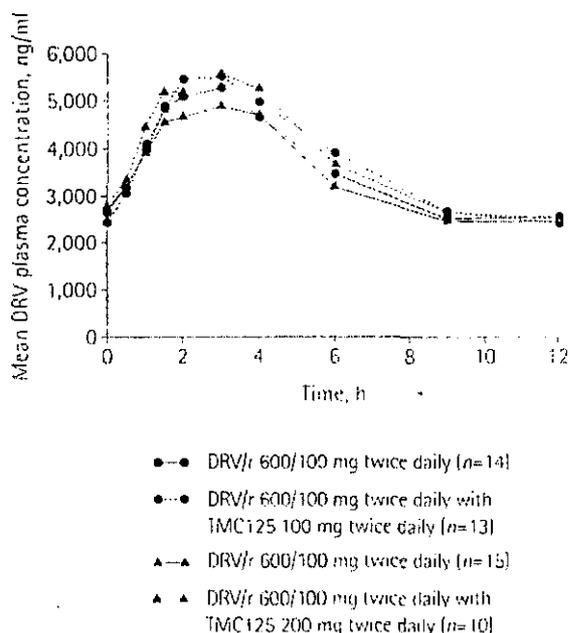
No interfering peaks occurred near the retention times of TMC125 and darunavir. The accuracy and precision for both TMC125 and darunavir quality control samples complied with the pre-specified criteria at all concentrations (accuracy: overall bias $\leq 20\%$ for the LLOQs and $\leq 15\%$ for all other concentrations; precision: total coefficient of variation $\leq 20\%$ for the LLOQs and $\leq 15\%$ for all other concentrations). Recovery of TMC125 and darunavir was consistent over the evaluated concentration range (TMC125: 90.7% at 6.0 ng/ml, 78.0% at 250 ng/ml and 89.9% at 4,000 ng/ml; darunavir: 98.7% at 20.0 ng/ml, 96.1% at 500 ng/ml and 95.4% at 10,000 ng/ml). Both

Figure 1. Schematic representation of the study design



DRV/r, ritonavir boosted darunavir; PK, pharmacokinetic; RTV, ritonavir.

Figure 2. Mean plasma concentration–time curves for DRV 600 mg twice daily, administered with ritonavir 100 mg twice daily, with or without TMC125



DRV, darunavir; DRV/r, ritonavir-boosted DRV.

methods met the validation criteria regarding stability (mean bias $\leq 15\%$ of the reference concentration).

Pharmacokinetic and statistical analyses of DRV, TMC125 and ritonavir plasma concentrations and pharmacokinetic parameters were performed using SAS System for Windows[®] version 8.2 (SAS Institute Inc., Cary, NC, USA). A non-compartmental model with extravascular input was used for the pharmacokinetic analysis. The trough, minimum and the maximum plasma concentrations (C_{tr} , C_{min} and C_{max} , respectively) and time to reach C_{max} (t_{max}) were obtained by inspection of the plasma concentration–time profiles. The minimum plasma concentration (C_{min}) was the lowest plasma concentration observed within a dosing interval. The area under the plasma concentration–time curve from 0 to 12 h (AUC_{12h}) was determined using the linear trapezoidal rule.

Descriptive statistics were calculated for the pharmacokinetics of TMC125, DRV and ritonavir. Statistical analyses were performed for TMC125 using treatment with DRV/r as the test, and treatment without DRV/r as the reference. Similarly, statistical analyses were performed for DRV and ritonavir using treatment with TMC125 as the test and treatment without TMC125 as the reference. The primary pharmacokinetic parameters used in the statistical

analysis were C_{tr} , C_{max} and AUC_{12h} on the logarithmic scale. All available observations were included in the statistical analysis. The least squares means (LSM) of the primary parameters for each treatment were estimated with a linear mixed-effects model, controlling for period (for TMC125 only) and randomization group as fixed effects and subject (nested in treatment sequence) as a random effect. A 90% confidence interval (CI) was constructed around the difference between the LSMs of test and reference. Both the difference between the LSM and the 90% CI were retransformed to the original scale. Period effects were considered significant at the 5% level and sequence effects were considered significant at the 10% level.

Results

The trial enrolled 32 volunteers with a mean age of 42 years (range: 18–55 years). Overall, 28 (88%) were male, 30 (94%) were Caucasian and two (6%) were Hispanic. The median BMI was 23.6 kg/m² (range: 19–29 kg/m²). The demographic characteristics of the two panels were comparable (data not shown). Ingestion of trial medication by the volunteers was witnessed by trial personnel at the research unit or was recorded by the volunteers in the trial diary if tablets were taken at home. Of the 32 volunteers, 23 completed the trial (13 in Panel I and 10 in Panel II). Five volunteers were withdrawn due to adverse events as per protocol (four because of a grade 2 morbilliform rash and one because of grade 3 headache). One volunteer with a grade 1 morbilliform rash was withdrawn as a result of an investigator decision, one volunteer was withdrawn because of poor adherence to trial medication and two volunteers withdrew their consent during the trial.

DRV pharmacokinetics

The mean plasma concentration–time curves of DRV in the presence and absence of TMC125 are displayed in Figure 2. Summary results for DRV pharmacokinetics are shown in Table 1. The pharmacokinetics of DRV were similar after administration of DRV/r with or without TMC125. No significant treatment effects were observed in Panel I for any of the primary pharmacokinetic parameters of DRV when comparing the administration of DRV/r with or without TMC125 100 mg twice daily. In Panel II an increase of DRV AUC_{12h} by 15% was observed, with no significant differences in DRV C_{max} or C_{min} when combined with TMC125 200 mg twice daily. The 90% CI for the LSM ratio of AUC_{12h} was just outside the 80–125% limits, but the magnitude of this increase in DRV AUC_{12h} is not considered to be clinically relevant. No significant period or sequence effects were observed.

Table 1. Pharmacokinetics of DRV/r

Pharmacokinetic parameter	Panel I			Panel II		
	DRV/r reference ^a	DVR/r plus TMC125 test ^b	LSM ratio test/ ^c reference (90% CI)	DRV/r reference ^a	DVR/r plus TMC125 test ^b	LSM ratio test/ ^c reference (90% CI)
<i>n</i>	14	11	-	15	10	-
Darunavir						
<i>t</i> _{max} , h	2.0 (1.5–4.0)	3.0 (1.0–4.0)	-	3.0 (1.0–4.0)	3.0 (1.0–3.0)	-
<i>C</i> _{max} , ng/ml	5599 ± 1104	5804 ± 1269	1.03 (0.98–1.09)	5234 ± 1060	5746 ± 1232	1.11 (1.01–1.22)
<i>C</i> _{min} , ng/ml	2254 ± 834	2217 ± 541	1.02 (0.89–1.17)	2337 ± 631	2301 ± 738	1.02 (0.90–1.17)
AUC _{0–12} , ng·h/ml	42982 ± 12666	45199 ± 11583	1.06 (1.00–1.13)	41135 ± 9579	45449 ± 10864	1.15 (1.05–1.26)
<i>C</i> _{trough} , ng/ml	2625 ± 934	2429 ± 631	-	2683 ± 820	2805 ± 758	-
Ritonavir						
<i>t</i> _{max} , h	4.0 (1.5–6.0)	4.0 (1.0–6.0)	-	4.0 (3.0–6.0)	4.0 (3.0–4.0)	-
<i>C</i> _{max} , ng/ml	830 ± 230	766 ± 184	0.93 (0.80–1.08)	1061 ± 461	974 ± 351	0.90 (0.74–1.08)
<i>C</i> _{trough} , ng/ml	163 ± 86	142 ± 56	0.91 (0.81–1.02)	192 ± 85	206 ± 85	1.01 (0.86–1.17)
AUC _{0–12} , ng·h/ml	5217 ± 1763	4296 ± 1087	0.86 (0.76–0.97)	6129 ± 2218	5742 ± 1970	0.89 (0.82–0.98)
<i>C</i> _{min} , ng/ml	226 ± 135	190 ± 70	-	269 ± 120	275 ± 130	-

Values are shown as mean ± SD except time to reach maximum plasma concentration (*t*_{max}) [*t*_{max}], which is shown as median [range]. ^aReference dosage: ritonavir-boosted darunavir (DRV/r) 600/100 mg twice daily. ^bTest dosage: DRV/r 600/100 mg twice daily plus TMC125 100 mg twice daily. ^cTest dosage: DRV/r 600/100 mg twice daily plus TMC125 200 mg twice daily. AUC_{0–12}, area under the plasma concentration-time curve from 0 to 12 h; *C*_{max}, trough plasma concentration; CI, confidence interval; *C*_{trough}, minimum plasma concentration; LSM, least squares means.

Ritonavir pharmacokinetics

Summary data for ritonavir pharmacokinetics are shown in Table 1. The AUC_{0–12} of ritonavir was 14% and 11% lower in Panel I and II, respectively, when DRV/r was coadministered with TMC125. These decreases are not considered to be clinically relevant. No significant period or sequence effects were observed.

TMC125 pharmacokinetics

The mean plasma concentration-time curves of TMC125 are shown in Figure 3. Summary data for TMC125 pharmacokinetics are shown in Table 2. In both panels, significant treatment effects were observed for all primary pharmacokinetic parameters. In Panel I, after the concomitant administration of TMC125 100 mg twice daily and DRV/r 600/100 mg twice daily, the exposure to TMC125 was decreased by 37%, compared with TMC125 administered alone. *C*_{max} and *C*_{trough} were decreased by 32% and 49%, respectively. No significant period or sequence effects were observed.

After the concomitant administration of TMC125 200 mg twice daily and the same dose of DRV/r in Panel II, a less than twofold increase in AUC_{0–12}, *C*_{max} and *C*_{trough} has been observed compared to those obtained in Session A, where the dose of TMC125 was 100 mg twice daily. In Panel II, significant period effects for *C*_{max} and sequence effects for all pharmacokinetic parameters were observed. Because of the low number of subjects per sequence group and substantial intersubject variability, no clear assessment of these effects could be performed.

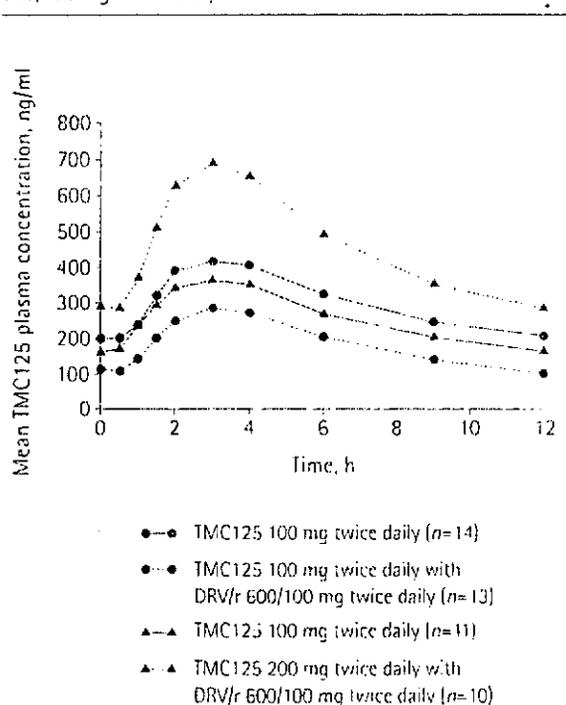
Safety

No serious adverse events were reported during the trial. The most frequently reported adverse events were headache (41%), rash (31%), fatigue (28%) and nasopharyngitis (19%). All adverse events were mild or moderate in severity, with the exception of one case of grade 3 headache and one case of grade 3 increased low density lipoprotein. Six volunteers (19%) prematurely discontinued treatment because of adverse events: five per protocol (four due to grade 2 morbilliform rash and one due to grade 3 headache) and one volunteer with a grade 1 morbilliform rash, who was withdrawn as a result of an investigator decision. Four of the five cases of rash occurred during the combined administration of DRV/r and TMC125 and were considered to be probably related to both trial medications. All events resolved within 2 weeks. There were no consistent or clinically relevant changes in vital signs or electrocardiogram parameters and no clinically relevant individual abnormalities.

Discussion

The results of this study show that, when TMC125 100 mg twice daily was coadministered with DRV/r, exposure to TMC125 was decreased by 37% with no effect on the pharmacokinetics of DRV. A similar decrease in TMC125 exposure of approximately 30% could be observed when comparing the mean TMC125 exposure (±SD) obtained after coadministration of TMC125 as 200 mg twice daily with DRV/r in this trial (5319 ± 2452 ng·h/ml) with the exposure observed in

Figure 3. Mean plasma concentration-time curves for TMC125 100 or 200 mg twice daily with or without DRV/r 600/100 mg twice daily



DRV/r, ritonavir-boosted DRV.

HIV-negative volunteers after the administration of TMC125 200 mg twice daily alone (7,638 ±2,254 ng·h/ml, historical data; Table 2) [22].

The intersubject variability of the exposure to TMC125 when given alone was comparable to that observed in other trials with healthy volunteers [22]. A slight increase in variability was noted when TMC125 was coadministered with DRV/r. In general, greater

intersubject variability has been demonstrated in HIV-1 infected subjects, without a notable difference between volunteers with or without ritonavir-boosted PIs in their background regimen [23]. Detailed analysis of the pharmacokinetics of TMC125 in HIV-1 infected subjects will be performed in the currently ongoing Phase III trials.

The magnitude of the interaction with DRV/r observed in this pharmacokinetic study of TMC125 is comparable to that observed in the above mentioned Phase IIb dose-ranging trial, demonstrating an approximately 30% difference in exposure between HIV-infected subjects using ritonavir-boosted PIs (LPV/r, mean ±SD, 6,074 ±6,380 ng·h/ml) and patients who did not have a PI in their ARV regimen (7,964 ±5,850 ng·h/ml), without a difference in antiviral efficacy [23].

In another study, when patients with high viral resistance were treated with a combination of DRV/r 600/100 mg twice daily and TMC125 200 mg twice daily (Phase III formulation) encouraging response rates were observed over 12 weeks of therapy. Exposure to TMC125 was similar to that observed in patients using the selected dose of the Phase II formulation of TMC125 and ritonavir-boosted PIs in the dose ranging trial [24]. After 24 weeks of therapy a median decrease of 2.7 log₁₀ copies/ml in plasma viral load was observed in 10 HIV-1 infected volunteers treated with the combination of DRV/r and TMC125 plus a background regimen. Nine of these subjects achieved a plasma HIV-1 RNA level <50 copies/ml [24].

A further recent study has examined the efficacy of the combination of TMC125 200 mg twice daily and DRV/r 600/100 mg twice daily and found promising activity in treatment-experienced patients [25]. Pharmacokinetic parameters of TMC125 were comparable in both above-mentioned studies.

A decrease in exposure to TMC125 due to the pharmacokinetic interaction with ritonavir-boosted

Table 2. Pharmacokinetics of TMC125

Pharmacokinetic parameter	Panel I			Panel II			Historical control [22]*
	TMC125 reference*	DRV/r plus TMC125 test†	LSM ratio test/reference (90% CI)	TMC125 reference*	DRV/r plus TMC125 test†	LSM ratio test/reference (90% CI)	
n	14	13	-	11	10	-	23
t _{max} , h	3.0 (1.5-6.0)	3.0 (2.0-4.0)	-	3.0 (1.5-6.0)	3.0 (1.5-4.0)	-	-
C _{max} , ng/ml	452 ±122	313 ±118	0.68 (0.57-0.82)	405 ±118	734 ±305	1.81 (1.56-2.11)	876 ±233
C _{min} , ng/ml	189 ±95	94 ±49	0.51 (0.44-0.61)	156 ±50	268 ±151	1.67 (1.38-2.03)	426 ±155
AUC ₀₋₁₂ , ng·h/ml	3607 ±1394	2204 ±952	0.63 (0.54-0.73)	3062 ±816	5519 ±2452	1.80 (1.56-2.08)	7638 ±2254
C _{trough} , ng/ml	198 ±101	112 ±67	-	161 ±48	289 ±157	-	461 ±171

Values are shown as mean ±SD except time to reach maximum plasma concentration (t_{max}) (t_{max}), which is shown as median (range). *Reference dosage: TMC125 100 mg twice daily. †Test dosage: ritonavir-boosted darunavir (DRV/r) 600/100 mg twice daily plus TMC125 100 mg twice daily. Test dosage: DRV/r 600/100 mg twice daily plus TMC125 200 mg twice daily. ‡Historical control: TMC125 200 mg twice daily, administered for 8 days in HIV-negative volunteers [22]. AUC₀₋₁₂, area under the plasma concentration-time curve from 0 to 12 h; C_{min}, trough plasma concentration; CI, confidence interval; C_{max}, maximum plasma concentration; LSM, least squares means.

PIs did not negatively effect the efficacy of TMC125 in any of these studies and is therefore not considered to be clinically relevant.

The possible mechanism for the decrease in TMC125 exposure is thought to involve metabolic induction via ritonavir. Ritonavir is both an inhibitor of CYP3A4 and an inducer of CYP1A2, 2B6, 2C9, 2C19 and glucuronosyl transferase [26,27]. Darunavir is an inhibitor of CYP3A but is not known to induce other CYP isozymes [16]. The combined induction of CYP2C19 and glucuronosyl transferase by low-dose ritonavir might account for the decrease in TMC125 plasma concentrations seen in this study and other trials with ritonavir-boosted PIs.

The most common reason for discontinuation in this study was rash (5/32 patients). All but one case occurred during the combined administration of DRV/r and TMC125 and the relationship to both trial medications was considered to be probable. No relationship between the occurrence of rash and the pharmacokinetic parameters for DRV, ritonavir or TMC125 could be demonstrated. The design of the trial limits the clinical interpretation of rash, as the combination of TMC125 and DRV/r was administered from day 9–16. Given that rash has been reported with both DRV and TMC125 and typically occurs within the second week of dosing in HIV-negative volunteers, it is difficult to assess whether this was an effect of DRV administration only, of the introduction of TMC125, or of the combination of TMC125 and DRV/r. It is not clear whether the same incidence of rash will be observed with this ARV combination in HIV-infected patients. A previous study reported that rash was observed more frequently with amprenavir in HIV-negative volunteers than in HIV-positive subjects [28]. In clinical trials ($n=924$), rash (all grades, regardless of causality) occurred in 7% of subjects treated with darunavir [14]. The incidence of rash in HIV-1-infected subjects using TMC125 was 17–20% (all grades, irrespective of causality) [13,29]. This question should be answered by the results of the ongoing DUFF-1 and DUFF-2 Phase III trials, in which treatment-experienced patients with NNRTI and extensive PI resistance were randomized to receive optimized ARVs plus DRV/r 600/100 mg twice daily and either TMC125 200 mg twice daily or matching placebo.

In conclusion, when DRV was combined with TMC125 no clinically relevant changes in DRV pharmacokinetics were observed, so dose adjustment of DRV is not required. Co-administration of TMC125 100 mg twice daily with DRV/r decreased TMC125 exposure by 37%. The increase of TMC125 exposure by 80% when given as 200 mg twice daily reflects the twofold increase in dose and

the interaction with DRV/r. The magnitude of this interaction is comparable to interactions of TMC125 with other ritonavir-boosted PIs, as observed in Phase IIIb trials in HIV-infected patients. Because these trials demonstrated efficacy of TMC125, compensation for this interaction by dose adjustment is not necessary.

Acknowledgements

Funding for this trial was provided by Tibotec.

Disclosure

All authors are employees of Tibotec.

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Accepted for publication 4 April 2007



Complete Specification

FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

&

THE PATENTS RULES, 2003

COMPLETE SPECIFICATION

[See section 10 and rule 13]

Title: COMBINATION FORMULATIONS COMPRISING DARUNAVIR AND ETRAVIRTNE

Applicant: TIBOTEC PHARMACEUTICALS having its principal place of business at Eastgate Village, Eastgate, Little Island, Co Cork, Ireland

The following specification particularly describes the nature of the invention and the manner in which it is to

be performed:-

Field of the Invention

This invention relates to solid oral dosage forms of the HIV inhibitors containing a combination of TMC114 and TMC125.

Background of the Invention

The treatment of Human Immunodeficiency Virus (HIV) infection, known as cause of the acquired immunodeficiency syndrome (AIDS), remains a major medical challenge. HIV is able to evade immunological pressure, to adapt to a variety of cell types and growth conditions and to develop resistance against currently available drug therapies. The latter include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), HIV-protease inhibitors (Pis), fusion inhibitors, and the more recent CCR5 and integrase inhibitors.

Although effective in suppressing HIV, each of these drugs, when used alone, is confronted with the emergence of resistant mutants. This led to the introduction of combination therapy of several anti-HIV agents usually having a different activity profile. In particular the introduction of "HAART" (Highly Active Anti-Retro viral Therapy) resulted in a remarkable improvement in anti-HIV therapy, leading to a large reduction in HIV-associated morbidity and mortality. However, none of the currently available combination therapies is capable of completely eradicating HIV. Even HAART may face the emergence of resistance, often due to non-adherence and non-persistence with antiretroviral therapy. In these cases HAART can be made effective again by replacing one of its components by one of another class. If applied correctly, treatment with HAART combinations can suppress the virus for many years, up to decades, to a level where it no longer can cause the outbreak of AIDS.

Because of their pharmacokinetic properties and the need to keep plasma levels above a minimum level, currently used anti-HIV drugs require frequent administration of relatively high doses. The number and/or volume of dosage forms that need to be administered are commonly referred to as the "pill burden". A high pill burden is undesirable for many reasons, such as the frequency of intake, often combined with the inconvenience of having to swallow large dosage forms, as well as the need to store and transport a large number or volume of pills. A high pill burden increases the

risk of patients not taking their entire dose, thereby failing to comply with the prescribed dosage regimen. As well as reducing the effectiveness of the treatment, this also leads

to the emergence of viral resistance. The problems associated with a high pill burden are multiplied where a patient must take a combination of different anti-HIV agents.

The complex dosing regimens of HAART or other dosing regimens can be simplified by the application of combination dosage forms comprising two or more anti-HIV components. These could take the form of fixed dose combinations, e.g. tablets comprising predetermined doses of two or more anti-HIV agents. Most HIV inhibitors however need to be administered at relatively high doses so that often two or more doses need to be administered at once in order to reach the required quantity.

Combination dosage forms would become so large that their intake becomes inconvenient or even impossible. For reasons of convenience, a solid oral dosage form should not exceed about 1400 mg, and preferably should not exceed about 1300 mg or about 1200 mg. Providing dosage forms of relatively small size contributes to the convenience of intake and therefore also helps to overcome the problems of pill burden.

15

Therefore, it would be desirable to provide HIV inhibitory therapy that reduces pill burden in that it involves the administration of dosage forms of a practical size and additionally does not require frequent dosing.

One class of HIV drugs that is often used in HAART is that of the NNRTIs of which a number are currently on the market and several others are in various stages of development. One such NNRTI is the compound 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile, also referred to as etravirine, R 165335, or in particular as TMC125, and is currently on the market in a number of countries under the tradename Intelence™. TMC125 can be represented by the formula (TV

This compound, its properties, a number of synthetic approaches for its preparation, as well as standard pharmaceutical formulations, have been described in WO 00/27825. TMC125 not only shows pronounced activity against wild type HIV, but also against HIV strains harboring resistance-inducing mutations.

TMC125 is very insoluble in aqueous media and therefore has low bioavailability. WO 01/23362 and WO 01/22938 disclose solid dispersions of this compound in water-soluble polymers offering improved bioavailability, especially when in the form of powders prepared by spray drying. An improved spray dried formulation has been disclosed in WO 2007/141308 (published 13 December 2007). Current tablet formulations of TMC125 are based on a solid dispersion of TMC125 in hydroxy-propyl methylcellulose (HPMC) obtained by spray drying. The spray-dried powder is mixed with further ingredients and compressed to a tablet dosage form. The spray-dried solid dispersion however is difficult to compress requiring the addition of binders such as one or more of those mentioned hereinafter, in particular one or more of micro crystalline cellulose and lactose.

The current dosing regimen of TMC125 is 200 mg twice a day (b.i.d.), administered as 15 two tablets each containing 100 mg, to be taken in at once, preferably two in the morning and two at the end of the day. Because these quantity requirements and the fact that TMC125 is dispersed in a relatively large quantity of water-soluble polymer, oral dosage forms of this drug are inevitably large in size. ,

30 TMC114 as well as processes for its preparation have been disclosed in EP 715618, WO 99/67417, US 6,248,775, and in Bioorganic and Chemistry Letters, Vol. 8,

20 Another class of HIV drugs that is used in HAART is that of the PIs amongst which is TMC114 (darunavir), approved in the U.S., the E.U. and a number of other countries and available under the tradename Prezista™. TMC114 used in the form of darunavir monoethanolate, has the following chemical name: (1S,2R,3R,3aS,6aR)-{3-[(4-aminobenzenesulfonyl)isobutyl-amino]-1 -benzyl-2-hydroxypropyl} carbamic acid hexahydrofuro[2,3-b]furan-3-yl ester monoethanolate. Its molecular formula is C₂₇H₃₇N₃O₇S * C₂H₅OH, with a molecular weight of 593.73, and the following chemical structure:

pp. 687-690, 1998, "Potent HIV protease inhibitors incorporating high-affinity P?-ligands and (R) (hydroxyethylamino)sulfonamide isostere".

TMC114 is a welcome addition to the class of PI drugs because of its pronounced 5 activity against wild type virus, but in particular against many mutated variants posing a large barrier against the development of resistance.

Current HAART combinations comprise two NRTIs combined with an NNRTI or two NRTIs with a PI. In certain circumstances it is desirable to add an NNRTI to the latter 10 combination in order to increase the barrier for drug-escaping mutations, in particular where such combination is used in so-called salvage therapy. Both TMC114 and TMC125 have a high genetic barrier against drug-escaping mutations so that a combination of these two drugs is expected to create an almost insurmountable barrier. A combination of these two drugs may find use as well in experienced, in less 15 experienced or even in so called drug-naive patients and therefore provides additional therapeutic options for HIV infected patients.

In order to reduce pill-burden it would be desirable to combine TMC114 and TMC125 in one and the same dosage form. Because TMC125 dosage forms are inevitably large 20 in size, combination dosage forms with other anti-HIV drugs would take a size that surpasses the convenience barrier.

Indeed, the TMC125 tablets currently on the market in a number of countries contain 100 mg of active ingredient and have a total weight of 800 mg per tablet, are oval 25 shaped with following dimensions: length 19mm, width 9.5 mm and a radius of 7.33mm. The TMC114 tablets currently on the market contain 300 mg weight equivalents of active ingredient (corresponding to 325.25 mg of TMC114 monoethanolate), having a total weight of 625.2 mg per tablet, and are oval shaped with following dimensions: length 17.3 mm, width 8.64 mm and a radius of 7.78 mm. A 30 combination tablet therefore would weigh 1425.2 mg and would be large in size exceeding the convenience size limit so that patients will have difficulties, perceived

or real, in taking in such large tablets. This contributes to pill burden, the initial problem combination tablets were aimed to deal with.

35 Thus in one aspect, the present invention is aimed at providing more compact dosage forms that contain both TMC125 and TMC114, allowing a more convenient and acceptable size of such dosage forms. The present invention is based on the unexpected finding that the HIV inhibitor TMC114 functions as a binder, a property unique to an

active ingredient, and therefore can take over the role of such agent. This allows for the use of less binder resulting in more compact dosage forms so that TMC114 can be combined with TMC125 without exceeding the size barrier of an acceptable oral dosage form.

5

The dosage forms of this invention provide anti-HIV therapy involving the administration of combined dosage forms of acceptable size, thereby requiring less frequent dosing. Hence, present dosage forms are beneficial in terms of pill burden and drug compliance of the patient.

10

Summary of the Invention

The present invention is based on the finding that TMC114 acts as a binder in compressed solid pharmaceutical dosage forms such as for oral administration.

15 Thus, the present invention relates to a solid pharmaceutical oral dosage form comprising:

(a) from about 15 mg to about 200 mg of TMC125, or from about 25 mg to about 150 mg of TMC125, or from about 50 to about 150 mg of TMC125, or from about 80 to about 120 mg of TMC125, dispersed in a solid dispersion with a

20 water-soluble polymer;

(b) from about 50 to about 600 mg, or from about 50 mg to about 500 mg of free-form equivalent TMC114; or from about 250 mg to about 450 mg of free-form equivalent of TMC114, or from about 250 mg to about 350 mg, of free-form equivalent of TMC114;

25 (c) from about 200 mg to about 400 mg of a carrier;

the total weight of the dosage form not exceeding 1300 mg.

In one embodiment the TMC125 in the dosage forms of the invention is dispersed in from about 100 mg to about 500 mg, or from about 200 mg to about 400 mg, for 30 example 300 mg of a water-soluble polymer.

Further embodiments comprise solid pharmaceutical oral dosage forms as described above or hereinafter wherein the solid dispersion of TMC125 comprises from about 10 mg to about 100 mg, or from about 20 mg to about 80 mg, or from about 30 mg to 35 about 70 mg, or from about 40 mg to about 60 mg of microcrystalline cellulose.

In one embodiment the invention concerns a solid pharmaceutical oral dosage form comprising

(a) about 100 mg of TMC125 dispersed in a solid dispersion with a water-soluble polymer;

(b) about 300 mg free-form equivalent of TMC114, or in particular about 325 mg of TMC114 ethanolate; or about 400 mg free-form equivalent of TMC114, or in 5 particular about 434 mg of TMC114 ethanolate;

(c) from about 200 mg to about 400 mg of a carrier; the total weight of the dosage form not exceeding 1300 mg. Further embodiments comprise solid pharmaceutical oral dosage forms as described 10 above or hereinafter wherein the solid dispersion of TMC 125 comprises from about 50 mg of microcrystalline cellulose.

Description of the Invention

As mentioned above, TMC114 acts as a binder. An inactive ingredient (excipient) 15 termed a "binder" is added to help hold the tablet together and give it strength. A wide variety of binders may be used, some common ones including lactose, dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose and modified cellulose (for example hydroxymethyl cellulose). Other such materials are silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose, as well as soluble 20 materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride, and sorbitol. Such agents may sometimes also be referred to as "fillers".

The present invention provides a solid oral dosage form of TMC 114 and TMC 125 of a size below the combined size of both dosage forms. The size of the dosage forms of the 25 invention, i.e. the total weight of the dosage forms, should be below a limit of convenience which is below the size at which a number of patients starts having difficulty taking in the dosage form. The total weight of the dosage forms of the invention may be below about 1300 mg, and in particular below about 1200 mg. In particular embodiments the total weight of the dosage forms in accordance with the 30 present invention is below about 1100 mg, or is below about 1000 mg. Or alternatively, the volume of the oral dosage forms of the invention may be below about 1.3 cm³ (in particular below about 1.300 cm³ or below about 1300 mm³) and in particular below about 1.200 cm³ (in particular below about 1.200 cm³ or below about 1200 mm³). In particular embodiments the volume of the dosage forms in accordance with the present 35 invention is below about 1.100 cm³, or is below about 1.000 cm³;

The solid oral dosage forms of the present invention preferably are tablets.

The dosage forms of the invention contain the quantities of the active ingredients mentioned above. For certain patient groups certain specific quantity ranges may be recommended. For paediatric applications, lower quantities of the active ingredients may be used. In such instance, the dosage forms of the invention contain from about 15 5 to about 50 mg, or from about 20 to about 30 mg, in particular about 25 mg of TMC125 per unit of the dosage form, wherein the TMC125 is dispersed in a solid dispersion with a water-soluble polymer. Such dosage forms for paediatric applications may contain from about 50 to about 200 mg, or from about 50 mg to about 150 mg, in particular about 75 mg of TMC114 of free-form equivalent TMC114 per unit of the 10 dosage form. The total weight of the dosage forms for paediatric applications may vary, but in particular is below about 433 mg, and more in particular below about 400 mg, or below about 367 mg, or below about 333 mg. For application in adults, higher quantities of the active ingredients may be used. In such instance, the dosage forms of the invention contain from about 50 to about 200 mg, in particular from about 75 mg to 15 about 150 mg, more in particular 90 mg to about 120 mg, for example about 100 mg, of TMC125 per unit of the dosage form. Such dosage forms for application in adults may contain from about 150 to about 600

mg, or from about 200 mg to about 400 mg, in particular about 300 mg of free-form equivalent TMC114 per unit of the dosage form.

20 In an alternative embodiment, for paediatric applications, the quantities or ranges of quantities of the active ingredients TMC125 and TMC114 in the dosage forms of the invention, or the total weights or volumes of the dosage forms, or both, may be those mentioned in relation to the application for adults, divided by 3. In another alternative embodiment, for applications in adolescents, the quantities of the active ingredients 25 TMC125 and TMC114 in the dosage forms of the invention may be those mentioned in relation to the application for adults, divided by 2, by 1.7, by 1.5, or by 1.33.

The weight/weight ratio TMC125:TMC114 may vary, but in one embodiment it is in the range from about 1:1 to about 1:5, or from about 1:2 to about 1:4; in particular said 30 ratio may be about 1:3.

The active ingredients used in the formulations of the invention are the NNRTI TMC125 and the PI TMC114. Both can be used in base form or as a pharmaceutically acceptable addition salt form, in particular as an acid addition salt form, or as a 35 pharmaceutically acceptable solvate. The pharmaceutically acceptable addition salts are meant to comprise the therapeutically active non-toxic salt forms. The acid addition salt forms can be obtained by treating the base form with appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like;

sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzene-5-sulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

The term pharmaceutically acceptable solvate comprises the hydrates and the solvent addition forms that the HIV inhibitors TMC125 and TMC114 can form. Examples of 10 such forms are e.g. hydrates, alcoholates, e.g. methanolates, ethanolates and propanolates, and the like.

As used herein, the term "TMC 125" is meant to comprise the base form, any pharmaceutically acceptable acid addition salt thereof, as well as any pharmaceutically 15 acceptable solvate thereof. The pharmaceutically acceptable addition salts as mentioned hereinabove comprise the therapeutically active non-toxic acid addition salt forms, which TMC 125 is able to form. In one embodiment the term "TMC 125" is meant to comprise the base form, as well as any pharmaceutically acceptable acid addition salt thereof. Particular acid addition salts are the hydrohalic salts, e.g. the hydrochloride or 20 hydrobromide salt.

As used herein, the term "TMC114" is meant to comprise the base form, any pharmaceutically acceptable acid addition salt thereof, as well as any pharmaceutically acceptable solvate thereof. The pharmaceutically acceptable addition salts as mentioned 25 hereinabove comprise the therapeutically active non-toxic acid addition salt forms, which TMC114 is able to form. In one embodiment the term "TMC 114" is meant to comprise the base form, as well as any pharmaceutically acceptable solvate thereof. Particular solvates are the ethanolate, e.g. the

monoethanolate.

30 TMC125 preferably is used in free form, also referred to as base form, TMC114 as monoethanolate.

As used herein the term "free-form equivalent TMC114" refers to that quantity of TMC114, whether present in free form (or base form), Or as salt or solvate, that 35 corresponds to a given quantity of TMC1 14 in free form. For example 325 mg of TMC114 monoethanolate corresponds to 300 mg of free-form equivalent TMC114.

The TMC125 in the dosage forms of the invention is present in the form of a solid dispersion in a water-soluble polymer. Different types of solid dispersions exist. One type of solid dispersion is where the pharmaceutical agent is molecularly dispersed, substantially homogeneously, throughout the polymer. This is generally described as a 5 "solid solution". Another type of solid dispersion is where there are islands or clusters of crystalline or semi-crystalline pharmaceutical agent dispersed throughout the polymer. A further type of solid dispersion is where there are islands or clusters of pharmaceutical agent in amorphous form dispersed throughout the polymer. There may also be solid dispersions comprising mixtures of two or more of the above types, for 10 example a solid solution with areas where the pharmaceutical agent is crystalline or semi-crystalline, or where there are islands or clusters of the agent in amorphous form. All these types will be commonly designated hereinafter as "solid dispersions".

The TMC125 is dispersed in a water-soluble polymer present in a quantity of about 100 15 to about 500 mg, in particular about 200 to about 400 mg, more in particular about 250 to about 350 mg, for example about 300 mg, of water-soluble polymer per dosage unit. The weight/weight ratio of TMC125 to the water-soluble polymer may be in the range of about 1:1 to about 1:10, in particular of about 1:1 to about 1:5, more in particular of about 1:2 to about 1:4, for example said ratio may be about 1:3. If desired, other 20 materials may be added when preparing the solid dispersion.

In one embodiment, there is provided a solid pharmaceutical oral dosage form comprising:

(a) from about 1% to about 15% of TMC125, or from about 2% to about 12% of 25 TMC125, or from about 4% to about 12% of TMC125, or from about 6% to about 9% of TMC125, dispersed in a solid dispersion with a water-soluble polymer;

(b) from about 4% to about 45%, or from about 5% to about 40% of free-form equivalent TMC114; or from about 20% to about 35% of free-form equivalent TMC114, or from about 20% to about 27% of free-form equivalent of TMC114;

30 (c) from about 15% to about 30% of a carrier;

the total weight of the dosage form not exceeding 1300 mg and all above percentages being by weight relative to the total weight of the dosage form. In another embodiment, the above percentages are multiplied by 1.0833 and the total weight of the dosage form does not exceed 1200 mg. In still another embodiment, the above percentages are 35 multiplied by 1.18182 and the total weight of the dosage form does not exceed 1100 mg.

In one embodiment, there is provided a solid pharmaceutical oral dosage form comprising:

(a) about 7.7 % of TMC 125 dispersed in a solid dispersion with a water-soluble polymer;

5 (b) about 23 % free-form equivalent of TMC114; or in particular about 25% of TMC114 monoethanolate; or about 30% free-form equivalent of TMC114, or in particular about 33% of TMC1 14 monoethanolate; • (c) from about 15 % to about 30% of a carrier;

the total weight of the dosage form not exceeding 1300 mg and all above percentages 10 being by weight relative to the total weight of the dosage form. In another embodiment, the above percentages are multiplied by 1.0833 and the total weight of the dosage form does not exceed 1200 mg. In still another embodiment, the above percentages are multiplied by 1.18182 and the total weight of the dosage form does not exceed 1100 mg.

Particular embodiments are those wherein in the dosage forms of the previous two paragraphs the TMC 125 is dispersed in from about 8% to about 40%, or from about 15% to about 30%, or in particular in about 23% of a water-soluble polymer. Further embodiments comprise solid pharmaceutical oral dosage forms as described above or 20 hereinafter wherein the solid dispersion of TMC 125 comprises from about 1% to about 7.5%, or from about 1.5% to about 6%, or from about 2% to about 5%, or from about 3% to about 4,5%, e.g. about 3.85% of microcrystalline cellulose. The foregoing percentages being for the instance where the . total weight of the dosage form does not exceed 1300 mg and wherein all above percentages are by weight relative to the total 25 weight of the dosage form. In other embodiments, the above percentages are multiplied by 1.0833 and the total weight of the dosage form does not exceed 1200 mg. In still another embodiment, the above percentages are multiplied by }, 18)82 and the total weight of the dosage form does not exceed 1100 mg.

30 An ingredient that may be added to the spray mixture is microcrystalline cellulose (MCC) resulting in a powder of increased density thereby improving properties such as flowability.

The solid dispersion of TMC125 may be prepared using standard procedures but 35 preferably is prepared by spray drying. In this procedure, a feed mixture of a solution of a water-soluble polymer and TMC125, optionally in admixture with microcrystalline cellulose and other ingredients, is spray-dried to form a solid dispersion of the pharmaceutical agent and the polymer by introducing the feed mixture as droplets into

a; spray-drying chamber via an atomizing means. Typically a heated drying gas is used to assist removal of the solvent. The TMC125 active agent in the spray-dried formulations solid dispersion is in a highly amorphous state, with little crystallinity, thereby improving bioavailability.

5

The solid dispersion of TMC125 typically comprises particles having an average effective particle size in the range of from about 10µm to about 150µm, or about 15 µm to about 100 µm, particularly about 20 µm to about 80 µm, or 30 to about 50 µm, preferably about 40µm. As used herein, the term average effective particle size

10 has its conventional meaning as known to the person skilled in the art and can be measured by art-known particle size measuring techniques such as, for example, sedimentation field flow fractionation, photon correlation spectroscopy, laser diffraction or disk centrifugation. The average effective particle sizes mentioned herein may be related to weight distributions of the particles. In that instance, by "an

average 15 effective particle size of about 150 μm it is meant that at least 50% of the weight of the particles has a particle size of less than the effective average of 150 μm , and the same applies to the other effective particle sizes mentioned. In a similar manner, the average effective particle sizes may be related to volume distributions of the particles but usually this will result in the same or about the same value for the average effective 20 particle size.

The so-called "span" of the particles produced by the process of the invention may be lower than about 3, in particular lower than about 2.5, preferably the span is about 2. Usually the span will not be lower than about 1. As used herein the term "span" is defined by the formula $(D_{90} - D_{10})/D_{50}$ wherein D_{90} is the particle diameter corresponding to the diameter of particles that make up 90% of the total weight of all particles of equal or smaller diameter and wherein D_{50} and D_{10} are the diameters for 50 respectively 10% of the total weight of all particles.

30 The amount of TMC125 in the spray dried product may be in the range from about 10% to about 50%, in particular about 15% to about 40%, or about 20% to about 30% or about 20% to about 25%, by weight relative to the total weight of the spray dried product comprising TMC125, water-soluble polymer, optional MCC and further optional excipients. The amount of TMC125 in the feed mixture can be calculated 35 based on these percentages and on the amount of solvent used.

The micro crystal line cellulose (MCC) that can be added to the mixture for spray-drying has an average particle size, which is selected such that when mixed into the solution of pharmaceutical agent and water-soluble polymer, the resulting feed mixture is able to

pass through the atomizing means into the spray-drying chamber without clogging or blocking the atomizer. As such, the size of the MCC is limited by the particular size of the atomizing means provided on the spray-drying chamber. For example, where the atomizing means is a nozzle, the size of the nozzle bore will affect the size range of the MCC that may be used. The average particle size of the MCC may be in the range of from 5 μm to 50 μm , in particular from 10 μm to 30 μm , e.g. about 20 μm .

Microcrystalline cellulose that can be used comprises the Avicel™ series of products available from FMC BioPolymer, in particular Avicel PH 105® (20 μm), Avicel PH 101® (50 μm), Avicel PH 301® (50 μm);

the microcrystalline cellulose products available from JRS Pharma, in particular Vivapur® 105 (20 μm), Vivapui® 101 (50 μm), Emcocel® SP 15 (15 μm), Emcocel® 50M 105 (50 μm), Prosolv® SMCC 50 (50 μm);

the microcrystalline cellulose products available from DMV, in particular 15 Pharmacel®105 (20 μm), Pharmacel®101 (50 μm);

the microcrystalline cellulose products available from Blanver, in particular Tabulose (Microcei)®101 (50 μm), Tabulose (Microcel)®103 (50 μm);

the microcrystalline cellulose products available from Asahi Kasei Corporation, such as Ceolus® PH-F20JP (20 μm), Ceolus® PH-101 (50 μm), Ceolus® PH-30] (50 μm), 20 Ceolus® KG-802 (50 μm).

A particularly preferred microcrystalline cellulose is Avicel PH 105® (20 μm).

The amount of MCC in the spray dried product may be in the range from about 0% to 25 about 25%, in particular from about 5% to about 20%, or from about 10% to about 15% or about 10% to about 12.5%, by weight relative to the total weight of the spray

dried product comprising TMCI25, water-soluble polymer, MCC and optional excipients. The weight ratio of the amounts of MCC to TMCI 25 in the spray dried product can be calculated based on these percentages and in particular may be in the range of from 30 about 2:1 to about 1:7, in particular from about 1:1 to 1:5, preferably about 1:2. The amount of MCC in the feed mixture can be calculated based on these percentages and on the amount of solvent used. In view of the desirability of keeping the concentration of pharmaceutical agent in the resulting solid pharmaceutical composition as high as possible, the amount of MCC in the feed mixture is preferably kept as low as possible.

35

Polymers suitable for use in the process of this invention are pharmaceutically acceptable, water-soluble and substantially unreactive towards the pharmaceutical agent. Preferably, the polymer is water-soluble. Suitable polymers include cellulosic polymers, such as methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxyl-ethyl cellulose, hydroxypropyl cellulose, hydroxybutyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose (HPMC), e.g. HPMC 2910, carboxymethyl cellulose, hydroxypropylmethyl cellulose phthalate (HPMCP), e.g. HP 50, hydroxypropylmethylcellulose acetate succinate (HPMCAS), cellulose 5 acetate trimellitate (CAT), hydroxypropylcellulose acetate phthalate (HPCAP), hydroxy-propylmethyl cellulose acetate phthalate (HPMCAP), methylcellulose acetate phthalate (MCAP) and mixtures thereof such as a mixture of hydroxypropyl cellulose and ethyl cellulose. Suitable polymers also include polyvinyl pyrrolidone, copolyvidone, which is polyvinyl pyrrolidone copolymerised with vinyl acetate, and 10 aminoalkyl methacrylate copolymers, such as Eudragit E® 100 (Rohm GmbH, Germany).

Preferably, the polymer is hydroxypropylmethyl cellulose (HPMC), polyvinyl pyrrolidone or copolyvidone. A particular hydroxypropylmethyl cellulose is HPMC 15 2910 5 mPa.s. A particular polyvinyl pyrrolidone is PVP K29-32, PVP K12, K30, K90, and a particular copolyvidone is PVP-co-VA64.

In one embodiment, the water-soluble polymer has a molecular weight in the range 500 D to 2 MD. The water-soluble polymer may have an apparent viscosity of 1 to 20 15,000 mPa.s, or of 1 to 5000 mPa.s, or of 1 to 700 mPa.s, or of 1 to 100 mPa.s when in a 2% (w/v) aqueous solution at 20°C.

Particular hydroxyalkyl alkylcelluloses include hydroxyethyl methylcellulose and hydroxypropyl methylcellulose (or HPMC, e.g. HPMC 2910 15 mPa.s; HPMC 25 2910 5 mPa.s). Particular vinylpyrrolidones include PVP K29-32, PVP K90.

The HPMC that can be used may contain sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 30 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide that have reacted with each anhydroglucose unit of the cellulose molecule. A preferred HPMC is hypromellose 2910 15 mPa.s or hypromellose 35 2910 5 mPa.s, especially hypromellose 2910 15 mPa.s. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose

(see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). In the four digit number "2910", the first two digits represent the approximate percentage of methoxy groups and the third and fourth

digits the approximate percentage composition of hydroxypropoxyl groups; 15 mPa.s or 5 mPa.s is a value indicative of the apparent viscosity of a 2% aqueous solution at 20°C.

5 The amount of water-soluble polymer in the spray dried product may be in the range from about 30% to about 75%, in particular about 40% to about 75%, or about 50% to about 75% or about 60% to about 70%, by weight relative to the total weight of the spray dried product comprising TMC125, water-soluble polymer, MCC and optional excipients. The amount of water-soluble polymer in the feed mixture can be calculated based on these percentages and on the amount of solvent used.

The weight:weight ratio of water-soluble polymer to TMC 25 may be in the range from 10:1 to 1:10, in particular from 10:1 to 1:1, more in particular from 5:1 to 1:1, preferably from about 3:1 to 1:1, e.g. a ratio of about 3:1 or of about 2:1. It may be desirable to reduce the amount of polymer in relation to the pharmaceutical agent in order to maximize the amount of pharmaceutical agent in the resulting pharmaceutical composition. This is the case were larger quantities of the other ingredients are used, for example were relatively large quantities of TMC 14 or TMC 125, or both, are used.

20 The solvent used in the method of the present invention may be any solvent, which is inert with respect to TMC125 and which is able to dissolve TMC 125 and the water-soluble polymer. In case MCC is added, the solvent should not dissolve the MCC. Suitable solvents include acetone, tetrahydrofuran (THF), dichloromethane, ethanol (anhydrous or aqueous), methanol and combinations thereof. Where the polymer is HPMC, the solvent preferably is a mixture of dichloromethane and ethanol, more preferably a mixture of dichloromethane and ethanol, the latter in particular being anhydrous ethanol, in a 9:1 ratio by weight. Where the polymer is polyvinyl pyrrolidone or copolyvidone, the solvent is preferably acetone.

30 Examples of feed mixtures that can be used in the process of the invention are those comprising:

(i) 200 mg TMC 125, 200 mg HPMC 2910 5 mPa.s, 100 mg microcrystalline cellulose (Avicel PH 105®) in 14.57 g dichloromethane extra pure and 1.619 g ethanol 96% (v/v);

35 (ii) 200 mg TMC125, 400 mg HPMC 2910 5 mPa.s, 100 mg microcrystalline cellulose (Avicel PH 105®) in 14.57 g dichloromethane extra pure and 1.619 g ethanol 96% (v/v);

(iii) 200 mg TMC125, 600 mg HPMC 2910 5 mPa.s, 100 mg micro crystal line cellulose (Avicel PH 105®) in 14.57 g dichloromethane extra pure and 1.619 g ethanol 96% (v/v);

(iv) 222 mg TMC125, 667 mg HPMC 2910 5 mPa.s, 111 mg microcrystalline cellulose 5 (Avicel PH 105®) in 16.19 g dichloromethane extra pure and 1.8 g ethanol absolute (100%).

The above feed mixtures can be scaled up by multiplying the quantities mentioned by a factor that is in the range of about 1 to about 105. In lab scale production the quantities may be multiplied by a factor in the range of about 1 to about 1000. For

medium or large scale production this factor may be in the range of about 500 to about 105, e.g. about 103, about 2x103, about 5x103 or about 104.

Feed mixtures (i) - (iv) can also be used without MCC. Feed mixtures (i) - (iv), with or 15 without MCC, can be scaled up by multiplying by the factors mentioned above. The solvent is removed from the droplets of the feed mixture by the spray-drying step. Preferably the solvent is volatile, with a boiling point of 150°C or less, preferably 100°C or less. The solvent should be substantially completely removed from the 20 droplets of the feed mixture during the spray-drying step.

The drying gas may be any gas. Preferably, the gas is air or an inert gas such as nitrogen, nitrogen-enriched air or argon. The temperature of the drying gas at the gas inlet of the spray-drying chamber is typically from about 60°C to about 300°C.

25

A typical spray-drying apparatus comprises a spray-drying chamber, atomizing means for introducing the feed mixture into the spray-drying chamber in the form of droplets, a source of heated drying gas that flows into the spray-drying chamber through an inlet, and an outlet for the heated drying gas. The spray-drying apparatus also comprises a 30 means for collecting the solid pharmaceutical powder that is produced.

The atomizing can be a rotary atomizer, a pneumatic nozzle, or a high pressure nozzle. A preferred atomizer is the high pressure nozzle where liquid feed is pumped to the nozzle under pressure. Pressure energy is converted to kinetic energy, and feed issues 35 from the nozzle orifice as a high-speed film that readily disintegrates into a spray as the film is unstable. The feed is made to rotate within the nozzle using a swirl insert or swirl chamber resulting in cone shaped spray patterns emerging from the nozzle orifice. Swirl insert, swirl chamber and orifice dimensions together with variation of pressure

gives control over feed rate and spray characteristics. The size of the droplets produced by high pressure nozzles depends on the operating parameters and can be in the range from about 5 to 125 µm, in particular from about 20 to 50 µm.

5 Optionally, further excipients may be included in the feed mixture. Such excipients may be included in order to improve properties of the feed mixture or the resulting solid pharmaceutical composition, such as handling or processing properties. Regardless of whether or not excipients are added to the feed mixture, which obviously results in them being incorporated in the spray-dried solid dispersion, excipients may 10 also be mixed with the resulting solid spray-dried dispersion during formulation into a desired dosage form. The spray-dried solid dispersion may be subjected to further processing steps depending on the nature of the final dosage form. For example, the pharmaceutical composition may be subjected to a post-drying process, or may undergo slugging or roller compacting prior to tableting. To improve the strength of the 15 resulting tablets, a sufficient amount of a binder can be added to the mixture that is compressed.

The spray-dried solid dispersion may be formulated into a pharmaceutical formulation. The latter comprises the spray-dried solid dispersion produced by the process of the 20 invention and a carrier, which may comprise one or more pharmaceutically acceptable Recipients. The latter include surfactants, solubilizers, disintegrants, pigments, flavoring agents, fillers, lubricants, glidants, preservatives,

thickening agents, buffering agents and pH modifiers. Typical surfactants include sodium lauryl sulphate, Cremophor RH 40, Vitamin E TPGS and polysorbates, such as Tween 20™. Typical pH modifiers are acids, such as citric acid or succinic acid, bases or buffers.

The dosage form may be coated using standard coating materials and procedures. A coating that may be used is Opadry™.

30 The administration of a dosage form in accordance with the present invention may suffice to treat HIV infection although it may be recommendable to co-administer other HIV inhibitors. The latter preferably include HIV inhibitors of other classes, in particular one or preferably two NRTIs, but also a fusion inhibitor can be added. HIV inhibitors that may be co-administered by preference are those used in HAART 35 combinations.

In certain instances, the treatment of HIV infection may be limited to only the dosage form of the invention, without co-administration of further HIV inhibitors. This option may be recommended, for example, where the viral load is relatively low, e.g. where the viral load (represented as the number of copies of viral RNA in a specified volume of serum) is below about 200 copies/ml, in particular below about 100 copies/ml, more in particular below 50 copies/ml, specifically below the detection limit of the virus.

5 This type of therapy may be applied after initial treatment with a combination of HIV drugs, such as any of the HAART combinations during a certain period of time until the viral load in blood plasma reaches the afore mentioned low viral level.

In a further aspect, the present invention relates to the use of a dosage form in 10 accordance with the invention, for the manufacture of a medicament for maintenance therapy of a subject infected with HIV. The present invention also relates to the use of a dosage form in accordance with the invention, for the manufacture of a medicament for treating a subject infected with HIV, wherein the dosage form is combined with two different NRTIs.

15

As used herein the term "treatment of HIV infection" relates to a situation of the treatment of a subject being infected with HIV. The term "subject" in particular relates to a human being.

20 The doses of TMC125 and TMC114 in the dosage forms of the invention are selected so as to keep the blood plasma concentration of these anti-HIV agents above the minimum blood plasma level between two administrations. The term "minimum blood plasma level" in this context refers to the lowest efficacious blood plasma level, the latter being that blood plasma level of both actives that provides effective treatment of 25 HIV. The plasma levels of these anti-HIV compounds should be kept above these threshold blood plasma levels because at lower levels the drugs may no longer be effective thereby increasing the risk of mutations.

The dosage forms of the present invention provide effective treatment of HIV infection 30 m that the viral load is reduced while keeping viral replication suppressed. The limited number of drug administrations adds to the patients' Compliance with the prescribed therapy.

As used herein, the word "substantially" does not exclude "completely" e.g. a 35 composition which is "substantially free" from Y may be completely free from Y.

Where necessary, the word "substantially" may be omitted from the definitions describing the invention. The term "about" in connection with a numerical value is meant to have its usual meaning in the context of the numerical value. Where necessary

the word "about" may be replaced by the numerical value $\pm 10\%$, or $\pm 5\%$, or $\pm 2\%$, or $\pm 1\%$.

All documents cited herein are incorporated by reference in their entirety.

5

Examples Example 1

10 1) Manufacturing of spray-dried powders

Feed mixtures for the spray-dried formulations were prepared by dissolving TMC 125 and the polymer in the solvent and adding microcrystalline cellulose. The polymer-type, solvent and the amounts of the components used are listed under feed mixture (iv) mentioned hereinabove. The feed mixture was then admitted to an SD-12.5-N, closed cycle spray-drying chamber via a high-pressure nozzle in co-current mode. The resulting solid pharmaceutical composition was collected from the cyclone, post-dried under vacuum at elevated temperature to decrease the residual solvent level. The dried powder was sieved and the powder fraction with a particle size between 45 and 100 micron was retained.

20

2) Manufacturing of combination tablets Table 1: composition of the combination tablets

A mixture of spray-dried TMC125 in HPMC with microcrystalline cellulose (MCC), Crosscarmellose sodium (Ac-Di-Sol™) and TMC114 was slugged and the obtained tablets were broken and sieved over a 850 μ stainless steel sieve. The rest of the external phase ingredients Colloidal anhydrous silica, Crosscarmellose sodium (Ac-Di-Sol™), 5 MCC and Magnesium stearate were sieved, added and mixed for 5 minutes using a Turbula™ mixer. The tablets were compressed on an excentric press (Courtoy AC27™).

The tablets were measured on dissolution in a medium of 0.01M HCl + 1% sodium 10 laurylsulfate (SLS), 50 rpm. The results reported in the following tables are the percentages of release drug substance. Exp 1, exp 2, etc. refer to a first, a second, etc. experiment under the same conditions.

Table 2: Dissolution of TMC125 out of combination tablet of Formula 1, obtained with 15 slugging.

time (min) 5 | 10 | 15 | 20 30 | 45 60 120 1 180

exp 1 42.13 | 57.36 j 65.87 | 71.43 78.55 | 84.65 88.07 93.89 j 96.01

exp 2 42.16 57.61 j 66.14 | 71.81 78.89 | 85.09 88.32 93.69 | 95.53

exp 2 40.98 | 56.96 | 65.80 | 71.72 78.78 85.17 88.40 94.05 | 96.05

Table 3: Dissolution of TMC114 out of combination tablet of Formula 1, obtained with slugging.

time (min) 5 10 15 20 30 45 , 60 120 180

exp 1 85.70 93.15 94.75 95.68 96.22 96.95 96.91 96.92 96.92

exp 2 86.02 92.73 94.15 94.87 95.67 96.10 95.93 95.81 95.77

exp 3 85.43 | 92.79 94.87 95.71 96.23 96.90 96.63 97.39 97.41

In the above tables, results of three experiments are listed. Example 2
25

1) Manufacturing of spray-dried powders

Spray-drying of TMC125 was performed as described in Example 1.

2) Manufacturing of the bulk blend for roller compaction

Table 7: Final blend and compression

Material in mg/tablet exp. 1 exp. 2

TMC 125 100.00 100.00

HPMC 2910 5cps -300.00 300.00

MCC 50.00 50.00

Croscarmellose Sodium 20.00 20.00

TMCI 14.EtOH 325.23 325.23

total 795.23 795.23

Croscarmellose Sodium 50.00 50.00

Colloidal anhydrous 5.00 5.00

silica

MCC 144.77 144.77

Magnesium Stearate 5.00 5.00

total 1000.00 1000.00

All ingredients except for Magnesium Stearate were sieved over a stainless steel sieve < 5 of 1 mm, and then blended in a 100 l Gally™ tumble blender at 10 rpm for 10 minutes. Then sieved magnesium stearate was added to the blend and mixed for another 4 minutes using the same speed.

The trials were performed on a 16 punch rotary press.

10

Ax compression profile study was done to evaluate tablet properties using different compression forces.

Table 8: Dissolution of TMC 125 as a function of roller compactor force (5 kN) 15.

Dissolution of TMCI 25 out of combination tablet Exp 1

time (min) 5 10 15 20 30 45 60 120 180 210

752 daN 26.16 43.32 | 54.92 70.36 74.65 85.02 90.48 97.02 99.37 100.46

1030 daN 31.67 46.35 j 57.37 65.95 75.10 80.93 84.83 93.07 96.29 98.15

1235 daN 36.99 49.05 ! 58.16 66.83 70.36 79.61 83.13 91.99 93.65 99.53

1537 daN 26.92 39.81 1 46.56

j 55.60 61.30 69.41 73.62 84.68 87.15 96.11

1775 daN 20.24 31.01 | 37.58 44.30 50.30 56.99 63.87 75.28 76.78 89.97

Table 9: Dissolution of TMC125 as a function of roller compactor force (5 kN)

Dissolution of TMCI 14 out of combination tablet Exp 1

time (min) 5 10 I 15 20 30 45 60 | 120 180 210

752 daN 1030 daN 1235 daN 1537 daN 1775 daN 34.92 50.89 74.74 63.88 49.61

53.74 165.16 66.00 | 76.00 78.53 | 83.86 74.30 1 76.94 59.09! 63.53 79.03 83.73

90.22 85.43 69.50 83.31 90.48 61.29 85.70 72.04 91.67 93.51 93.03 89.43 75.32
 95.20 | 97.26 94.87 96.66 93.16 95.06
 90.4 93.30

80.5 j 85.20 97.32 96.42 93.31 91.15 82.66 97.16 96.37 97.12 97.34 94.52

Table 10: Dissolution of TMC 125 as a function of roller compactor force (12 kN)

Dissolution of TMC125 out of combination tablet Exp 2

time (min) 5 | 10 15 20 30 45 60 120 180 210

759 daN 1051 daN 1266 daN 1496 daN 25.92 39.80 35.84 14.60 1 10.87 48.13 42.58
 20.96 13.21 54.99 49.61

28.70 16.71 .64.23 56.96 42.77 24.57 72.02 62.98 52.56 36.59 76.80 70.28 61.74
 45.84 86.94 81.14 76.12 66.54 91.85 87.60 81.10 79.12 94.65 92.40 88.90 82.30

Table 11: Dissolution of TMCI 14 as a function of roller compactor force (12 kN)

Dissolution of TMCI 14 out of combination tablet Exp 2

time (min) 5 10 15 20 30 | 45 60 120 180 210

759 daN 1051 daN 1266 daN 1496 daN 40.58 58.53 57.60 21.67 15.57 67.90 65.07
 30.69 18.44 75.48 73.32 42.99 23.37 84.13 | 89.98 79.89 | 83.59 63.22 73.73 34.54
 50.91 92.76 I 96.07 89.25 92.98 83.02 91.42 62.57 j 82.75 96.42 94.23 90.96 91.76
 96.50 95.85 95.69 91.31

The higher the compression force, the slower is the dissolution of the active ingredient. The dissolution of TMC125 appears to be more influenced by the compression force than the dissolution of TMCI 14.

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Example 3: Coating

Table 12: Dissolution of TMC125 coated and uncoated

5

time (min) 5 10 15 20 30 45 60 120 180 210

1030 daN uncoated 31.67 46.35 57.37 65.95 75.10 80.93 84.83 93.07 96.29 98.15

1266 daN uncoated 14.60 20.96 28.70 42.77 52.56 61.74 76.12 81.10 88.90

1030 daN coated 16.77 27.45 37.80 46.96 62.47 80.84 89.56 98.21 99.61 99.34

] 266 daN coated 21.99 37.79 46.23 52.07 60.11 67.31 72.54 83.87 88.91 91.43

Table 13: Dissolution of TMC114 coated and uncoated Dissolution of TMC114 out of combination tablet Exp 1

time (min) 5 . 10 15 20 30 45 60 120 180 210

1030 daN uncoated 50.59 66.00 76.00 83/73 90.48 93.51 94.87 96.66 96.42 96.37

1266 daN uncoated 21.67 30.69 42.99 63.22 73.73 83.02 91.42 90.96 95.69

1030 daN coated 21.27 30.50 39.44 50.01 64.88 82.58 90.14 95.10 95.90 98.78

1266 daN coated 41.89 63.55 71.90 77.52 84.07 87.73 90.31 93.28 93.67 91.44

Dissolution of TMC125 out of combination tablet Exp 2

10

Table 14: Formulation 2 tablet with total weight of 1100 mg 2 phase method / 75 rpm product 5 10 15 20 30 45 60 120 180 210

TMC125 uncoated 45 56 62 66 72 78 82 90 93 94
TMC125 coated 49 60 67 71 77 83 87 94 96 97
TMC114 uncoated 78 85 88 91 94 96 97 97 97 97
TMC114 coated 82 89 93 94 97 98 98 98 98 98

15 Two coating trials were performed using the tablet core samples with a compression force of 1030 daN and 1266 daN. The coating material was polyvinyl alcohol (PVA). The film coated tablets were measured on dissolution in medium 0.01 M HCl + 1% SLS, 50 rpm.

20 The release of TMC125 was somewhat faster out of the coated tablets compared to the cores. There was only a minor impact of the coating on the release of TMC114.

Claims

1. A solid pharmaceutical oral dosage form comprising:

(a) from about 15 mg to about 200 mg of TMC125, or from about 25 mg to about 5 150 mg of TMC125, or from about 50 to about 150 mg of TMC125, or from about 80 to about 120 mg of TMC125, dispersed in a solid dispersion with a water-soluble polymer;

(b) from about 50 to about 600mg, or from about 50 mg to about 500 mg of free-form equivalent TMC1 14; or from about 250 mg to about 450 mg of 10 free-form equivalent TMC1 14, or from about 250 mg to about 350 mg of free-form equivalent of TMC1 14;

(c) from about 200 mg to about 400 mg of a carrier;
the total weight of the dosage form not exceeding 1300 mg.

15 2. The dosage form according to claim 1, comprising:

(a) from about 80 to about 120 mg of TMC 125, dispersed in a solid dispersion with a water-soluble polymer;

(b) from about 250 mg to about 350 mg of free-form equivalent of TMC1 14;

(c) from about 200 mg to about 400 mg of a carrier;
20 the total weight of the dosage form not exceeding 1300 mg.

3. The dosage form according to claim 1, comprising

(a) about 100 mg of TMC 125 dispersed in a solid dispersion with a water-soluble polymer;

25 (b) about 300 mg free-form equivalent of TMC1 14, or in particular about 325 mg of

TMC1 14 monoethanolate; or about 400 mg free-form equivalent of TMC1 14, or in particular about 434 mg of TMC1 14 monoethanolate;

(c) from about 200mg to about 400 mg of a carrier;
the total weight of the dosage form not exceeding 1300 mg.

30

4. The dosage form according to any of claims 1 to 3, wherein the TMC 125 is present

as the free form and the TMC1 14 as the monoethanolate form.

5. The dosage form according to any of claims 1 to 4, wherein the total weight of the 35 dosage form does not exceed 1100 mg.

6. The dosage form according to any of claims 1 to 5, wherein the TMC125 is

dispersed in from about 100 to about 500 mg of a water-soluble polymer.

7. The dosage form according to any of claims 1 to 5, wherein the TMC125 is dispersed in from about 200 to about 400 mg of a water-soluble polymer.

5 8. The dosage form according to any of claims 1 to 5, wherein the TMC125 is dispersed in about 300 mg of a water-soluble polymer.

9. The dosage form according to any of claims 1 to 8, wherein the solid dispersion of TMC125 comprises from about 10 mg to about 100 mg, or from about 20 mg to

10 about 80 mg, or from about 30 mg to about 70 mg, or from about 40 mg to about 60 mg, or about 50 mg, of microcrystalline cellulose.

10. The dosage form according to any of claims 1 to 9, wherein the weight/weight ratio between the TMC125 and the water-soluble polymer is in the range from about 1:1

15 to about 1:5.

11 .The dosage form according to any of claims 1 to 9, wherein the weight/weight ratio between the TMC125 and the .water-soluble polymer is about 1:3.

20 12.The dosage form according to any of claims 1 to 9, wherein the water-soluble polymer is HPMC.

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