S. MAJUMDAR & CO.
PATENT & TRADEMARK ATTORNEYS

Undertakings : Intellectual Property Laws, Patents, Trademarks, Designs, Copyrights, Licencing, Investigations, Litigations
DOMESTIC AND INTERNATIONAL

202, Elecon Chambers, Behind Saki Naka Tel. Ex., Off Kurla-Andheri Road, Saki Naka, Mumbai- 400 072, India
Tel. : 91-22- 91-22-2852 2903, e-mail : bom@patentindia.com

204406

The Controller of Patents
The Patent Office
Mumbai

August 5, 2010

Dear Sir,

Re: Opposition under Section 25(1) against
Patent Application No. **726/MUMNP/2009** dated **April 15, 2009**
Applicant: **Abbott Laboratories**
Opponent: **Cipla Limited.**
Our Ref No: PII-337

In connection with the aforesaid patent application we submit herewith the following documents:

ED

1. Representation under Section 25(1) in duplicate along with Annexure A, Exhibit 1, Exhibit 2, Exhibit 3, Exhibit 4, Exhibit 5, Annexure B and Annexure C.

2. Expert Evidence in support of Representation under Section 25 (1) in duplicate along with exhibits EA, EB and EC.

3. Power of Attorney in our favor.

We request you to kindly take the opposition on record under intimation to us.

Yours faithfully,

Mythili

Mythili Venkatesh
Of S. Majumdar & Co.
Opponent's Agent

Encl: a/a.

INDEX

Sr. No.	Details	Page Nos.
1.	Representation u/s 25 (1)	1-26
1	Annexure A	27-38
2	Annexure B	39-45
3	Exhibit 1	46-49
4	Exhibit 2	50-99
5	Exhibit 3	100-160
6	Exhibit 4	161-188
7	Exhibit 5	189-195
8	Annexure C	196-219
9	Expert Affidavit	220-248
10	Exhibit EA	249-275
11	Exhibit EB	276-286
12	Exhibit EC	287-295
13	Power of Attorney	296-297

5 AUG 2010

BEFORE THE CONTROLLER OF PATENTS,
MUMBAI

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

And

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

And

In the matter of patent application 726/MUMNP/2009 dated April 15, 2009 by Abbott Laboratories, DEPT. 377 Bldg AP6A-1, 100 Abbott Park Road, Abbott Park, IL 60064-6008. U.S.A.

.....Applicant

And

IN THE MATTER of opposition of the grant of a patent thereto by, Cipla Limited, Mumbai Central, Mumbai-400 008. India.

.....Opponent

REPRESENTATION UNDER SECTION 25(1)

We Cipla Limited, Mumbai Central, Mumbai-400 008. India, (hereinafter called 'opponent') make the following representation under Section 25(1) of the Act in opposing the grant of patent on the application indicated in the cause title.

1 OPPONENT'S BUSINESS AND ACTIVITIES

1.1 The opponent is a Company incorporated under the laws of India and carries on business, inter alia, of manufacture of various drugs/medicinal preparations. The opponent has access to the latest technologies relating to manufacture of the drugs and medicines. The opponent is a manufacturer of pharmaceutical products and preparations in this country and the opponent's products are sold under different brands and enjoy considerable goodwill and reputation. The opponent is very well known and has been operating in this country for several decades. The opponent is also engaged in the research and development of medicines and pharmaceutical products and preparations.

2 GROUNDS OF OPPOSITION

2.1 The application is opposed on the following grounds

a. 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 to what was used in India before the priority date of the applicant's claim; {U/S 25 (1) e}

b. that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act; {U/S 25 (1) f}

c. that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed; {U/S 25 (1) g}

d. 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. {U/S 25 (1) h}

3. PRELIMINARY OBJECTIONS

3.1 The opponent would like to bring to the notice of the Ld. Controller that the subject patent application is a divisional to 339/MUMNP/2006 (hereinafter referred as parent application). Pre grant opposition u/s 25 (1) to the parent application has been filed by the opponent and also heard by the Ld. Deputy Controller on April 15, 2009. It is further noteworthy that the subject divisional application is filed at the Mumbai Patent Office on the same day on which hearing u/s 25 (1) in respect of parent application was scheduled.

3.2 The opponent states that this is a deliberate attempt to mislead the Ld. Controller and the public at large since the claims of the parent application 339/MUMNP/2006 were amended prior to filing of the impugned application and the applicant is well aware that the claims of the impugned application are similar to that of the originally filed claims or the claims in the parent application before amendment i.e. 339/MUMNP/2006. The impugned application is thus not maintainable Under Section 16 of the Patents Act. It is stated that the present application was made with a malafide intention of filing

multiple applications for the same invention knowing very well that the invention claimed is devoid of patentable subject matter and the further application is merely a back-up application to shield the claims dropped during prosecution of parent.

3.3 The opponent has secured the copy of First examination report and Response filed by the applicant in respect of the parent application from the Patent Office on request under the RTI Act. The same is attached herewith as Annexure A. As evident from the applicant's response dated July 7, 2008, the claims of the parent application were amended. The applicant filed the divisional with the same claims as the original parent application as filed. The opponent states that filing of the divisional application under opposition is contradictory to the provisions of Section 16 of the Act.

3.4 The prosecution data (Annexure A) states that as-filed claims have been examined and pursuant to examiner's objections the applicant amended the claims. The opponent states that the act of re-filing the claims once rejected during prosecution as a divisional reflects the malafide intentions of the applicant. Moreover the impugned patent application is not truly a divisional application per Section 16 of the Act. The impugned patent application essentially reflects unhealthy attitude of the applicant towards the patent system. The applicant by this patent application 726/MUMNP/2009 therefore is making a back door entry to get a patent for the claims once refused. This is strictly against the objectives of Section 16 of Indian Patent Act. Permitting such practice would place undue strain on the patent office that would have to keep re-examining the same application over and over again.

3.5 The opponent states that the applicant has tried to misguide the Ld. Controller and the public at large. In all likelihood the wrongful act may not have come to the notice of the Ld. Controller at all in the absence of the present opposition. It is stated that this is an act of malice by the applicant as they are claiming lopinavir and ritonavir under several applications which is not

permitted by law. Such an action besides being wholly contrary to law is an act of fraud commissioned against the Government of India and the public of India as well with the wrongful intention of creating a monopoly for the alleged invention for which no patent can be granted in India since it is obvious and lacks inventive merit and falls under the mischief of section 3(d) of the Patents Act. Therefore it is stated that the impugned application merits refusal in limine without any further consideration of the grounds of opposition on which the present opposition is based.

4. PRIOR ART RELIED ON

- Exhibit 1: US6599528 entitled "Mechanically stable pharmaceutical presentations form containing liquid or semisolid surface-active substances" published on July 29, 2003.
- Exhibit 2: WO0134119 entitled "Inhibitors of Crystallization in a Solid Dispersion" published on May 17, 2001.
- Exhibit 3: WO0074677 entitled "Improved Pharmaceutical Formulations" published on December 14, 2001.
- Exhibit 4: WO199744014 entitled "Antifungal Compositions with Improved Bioavailability" published on November 27, 1997.
- Exhibit 5: "Physical Properties of Solid Molecular Dispersions of Indomethacin with Poly(vinylpyrrolidone) and Poly(vinylpyrrolidone-co-vinyl-acetate) in Relation to Indomethacin Crystallization" by Takahiro et al published in Pharmaceutical Research Volume 16, No. 11, 1999.

5. ANALYSIS OF THE APPLICANT'S SPECIFICATION

5.1 The patent application 726/MUMNP/2009 under opposition was filed on April 15, 2009 and was accompanied by a complete specification. The

impugned application was published in the Official Journal of the Indian Patent office dated May 22, 2009 under section 11(A) of the Indian Patent Act.

5.2 The impugned application is directed to solid pharmaceutical dosage form comprising an HIV protease inhibitor and a process for its preparation. The impugned application further states that HIV 1 and HIV 2 are identified as virus causing AIDS and that HIV protease is an attractive target for HIV treatment. The impugned application states that aqueous solubility of drug is an important factor affecting bioavailability of a pharmaceutical agent on page 1, lines 20-line 25.

5.3 The applicant on page 1 lines 28-30 states that solid dosage forms are preferred over liquid dosage form and that in most instances oral solid dosage form of a drug provide a lower bioavailability than oral solution of the drug. The applicant on page 2, lines 13-15 states that the need of the invention is improved oral solid dosage forms of HIV protease inhibitor with suitable oral bioavailability and stability.

5.4 The applicant on page 4, lines 25-28 admittedly states that HIV protease inhibitors of US5914332 may be formulated in the dosage form of the impugned application.

5.5 Specification of the impugned application is summarized as:

i. Page 2, lines 23-31 - 'Solid Dispersion' is defined as a system in a solid state comprising at least two components wherein one component is dispersed evenly through out the other component or components and when the system in solid dispersion is chemically and physically uniform or homogenous throughout or consists of one phase then it is referred as "solid solution" or a "glassy solution".

ii. Page 3, lines 7-15 - specifies the content of HIV protease inhibitor, water soluble polymer, surfactant and additives in terms of percentage by weight of total dosage form. The applicant then further lists out the

compounds like Ritonavir, Lopinavir, etc that may be used in impugned invention.

iii. Page 4, line 19 – the applicant gives reference to US Patent No. 5542206 and US Patent No. 5648497 which discloses ritonavir along with other HIV protease inhibitors and methods for preparation of the said compounds.

iv. Page 4, line 28 - the applicant gives reference to US Patent No. 5914332 which discloses lopinavir along with other HIV protease inhibitors and methods for preparation of the said compounds.

v. Page 6 and page 7 - list the non-ionic surfactants that may be used in the impugned invention. It further states that surfactant with HLB 4 to 10 are suitable for use in the present invention. Further, page 7, line 9, states that among various surfactants, sorbitan fatty acid mono esters like sorbitan mono laureate and sorbitan monopalmitate are particularly preferred.

vi. Page 7, line 30-states that water soluble polymers with Tg from about 80°C to about 180°C are preferred as they allow preparation of solid dispersion that are mechanically stable. Page 8, line 21-30 and page 9 of the specification lists out possible water soluble polymers that may be employed in the impugned invention.

vii. Page 9, lines 24-25 – discloses other additives like flow regulators, lubricants, bulking agent and disintegrants that may be used and further refers to the examples each known to a person skilled in art.

viii. Page 10, line 5 – reference is made to various techniques like melt-extrusion, spray drying and solution evaporation for the preparation of the solid solution wherein melt extrusion is preferred.

ix. Page 13, line 22 - provides exemplary composition for ritonavir/lopinavir in combination and ritonavir alone. It further states the composition being made by melt extrusion technique.

x. Page 15, line 11 - discloses the protocol for oral bioavailability studies. It further provides comparative example with and without surfactant and infers that surfactant with HLB 4-10 improved the bioavailability of the oral dosage form.

5.6 Problem: The applicant states that HIV protease inhibiting compounds have poor bioavailability due to poor aqueous solubility and that there is continuing need for development of improved oral solid dosage forms for HIV protease inhibitor with suitable oral bioavailability and stability.

5.7 Solution: The applicant by the impugned invention provides a solid pharmaceutical dosage form comprising solid dispersion of at least one HIV protease inhibitor in a pharmaceutically acceptable water soluble polymer and pharmaceutically acceptable surfactant. The applicant states that they have developed an improved oral solid dosage form for HIV protease inhibitor having improved oral bioavailability and stability.

6. BRIEF REVIEW OF APPLICANT'S CLAIMS

6.1 The impugned application for patent application no. 726/MUMNP/2009 dated April 15, 2009 was accompanied by a complete specification and a statement of 37 claims annexed hereto as "Annexure B" for ready reference.

6.2 Claim 1 is directed to solid pharmaceutical dosage form comprising solid dispersion of HIV protease inhibitor; surfactant; and water soluble polymer with Tg of at least 50 °C.

6.3 Claim 2 is dependent on claim 1 and is directed to glassy solution or solid solution of HIV protease inhibitor.

6.4 Claim 3 is a dependent on claim 1 and directed to surfactant with HLB value from about 4 to 10.

6.5 Claim 4 is dependent on claim 1 and is directed to combination of a pharmaceutically acceptable surfactant having HLB value from about 4 to 10 and another pharmaceutically acceptable surfactant.

6.6 Claim 5 is specifically directed sorbitan fatty acid ester as the surfactant.

6.7 Claim 6 is dependent on claim 1 and relative to the weight of the dosage form comprises about 5 to about 30 % by weight of HIV protease inhibitor, from about 50 to about 85 % by weight of said water-soluble polymer, from about 2 to about 20 % by weight of surfactant, and from about 0 to about 15 % by weight of additives.

6.8 Claim 7 is dependent on claim 1 and is directed to known HIV protease inhibitors.

6.9 Claim 8 is dependent on claim 1, and is specifically claims ritonavir as the HIV protease inhibitor.

6.10 Claim 9 is dependent on claim 8 and is directed to dosage form showing dose-adjusted AUC of ritonavir in dogs with plasma concentration of least about 9 ug.h/ml/100 mg.

6.11 Claim 10 is dependent on claim 1 and is directed specifically to lopinavir as the HIV protease inhibitor.

6.12 Claim 11 is dependent on claim 10 and is directed to dose-adjusted AUC, in dogs under non- fasting conditions, of lopinavir plasma concentration of at least about 20 g. h/ml/100 mg.

6.13 Claim 12 is dependent on claim 1 and specifically relates to combination of HIV protease inhibitors; lopinavir and ritonavir.

6.14 Claim 13 is dependent on claim 12 and is directed to dose-adjusted AUC of ritonavir plasma concentration as 9 μg.h/ml/100 mg and lopinavir plasma concentration as 20 μg.h/ml/100 mg in dogs.

6.15 Claim14 is dependent on claim 1 and is directed to water-soluble polymer having Tg in the range of 80 to 180 °C.

6.16 Claim 15 is dependent on claim 1 and is directed to water soluble polymer being homopolymer or copolymer of N-vinyl pyrrolidone.

6.17 Claim 16 is dependent on claim 1 and is directed to copolymer of N-vinyl pyrrolidone and vinyl acetate as the water soluble polymer.

6.18 Claim 17 is dependent on claim 1 and directed to solid dosage form containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

6.19 Claim 18 is dependent on claim 1 and is directed to content of HIV protease inhibitor on storage for about 6 weeks at 40 °C and 75% humidity which is about 98% of the initial content.

6.20 Claim 19 is dependent on claim 1, and claims a process of preparation of solid dispersion product comprising preparation of homogenous melt of HIV protease inhibitor, water soluble polymers and surfactant followed by solidification of the melt to obtain solid dispersion product.

6.21 Claim 20 is dependent claim 19 and additionally comprises grinding of the solid dispersion product of claim 19 followed by compressing to solid dispersion product as tablet.

6.22 Claim 21 is dependent on claim 1 and is directed to method of treating an HIV infection.

6.23 Claim 22 is an independent claim and is directed to solid pharmaceutical dosage form comprising ritonavir, a homopolymer of N-vinyl pyrrolidone; and a sorbitan fatty acid ester.

6.24 Claim 23 is dependent on claim 22 and is directed to solid dosage form containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

6.25 Claim 24 is an independent claim and claims solid pharmaceutical dosage form comprising lopinavir, a copolymer of N-vinyl pyrrolidone and sorbitan fatty acid ester.

6.26 Claim 25 is dependent on claim 24 and is directed to solid dosage form containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

6.27 Claim 26 is an independent claim and claims solid pharmaceutical dosage form comprising ritonavir and lopinavir, a copolymer of N-vinyl pyrrolidone and vinyl acetate and sorbitan fatty acid ester.

6.28 Claim 27 is dependent on claim 26 and is directed to solid dosage form containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

6.29 Claim 28 is an independent claim directed to solid pharmaceutical dosage form comprising ritonavir about 5 % to about 30 % by weight, a homopolymer of N-vinyl pyrrolidone from about 50 % to about 85 % by weight of the dosage form; and a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

6.30 Claim 29 is dependent on claim 28 and is directed to solid dosage form containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

6.31 Claim 30 is dependent on claim 29 and relates concentration of additive in being in the range of about 0% to 15% by weight.

6.32 Claims 31 is an independent claim directed to solid pharmaceutical dosage form comprising lopinavir about 5% to 30%, copolymer of N-vinyl pyrrolidone from about 50 % to about 85% by weight of the dosage form; and a sorbitan fatty acid ester from about 2% to about 20% by weight of the dosage form.

6.33 Claim 32 is dependent on claim 31 and is directed to solid dosage form containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

6.34 Claim 33 is dependent on claim 32 and relates concentration of additive being in the range of about 0% to 15% by weight.

6.35 Claim 34 is an independent claim and claims a solid pharmaceutical dosage form comprising ritonavir and lopinavir at about 5 % to about 30 % by weight, a copolymer of N-vinyl pyrrolidone and vinyl acetate from about

50% to about 85% by weight of the dosage form; and a sorbitan fatty acid ester from about 2% to about 20% by weight of the dosage form.

6.36 Claim 35 is dependent on claim 34 and is directed to solid dosage form containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

6.37 Claim 36 is dependent on claim 35 and relates concentration of additive being in the range of about 0% to 15% by weight.

6.38 Claim 37 is directed to method of treating an HIV infection.

7. OBVIOUSNESS AND LACK OF INVENTIVE STEP (U/s 25 1 (e))

7.1 The opponent relies on US6599528 annexed hereto as Exhibit-1. Exhibit 1 is published on July 29, 2003 and therefore is a permissible and a valid prior art. The opponent states that mechanically stable oral pharmaceutical composition of active ingredients along with a melt-processable matrix-forming excipient and surface-active substance with an HLB value of about 2 to 18 is taught in Exhibit 1. Exhibit 1 teaches solid dispersions with active ingredients in the form of molecular dispersions in excipient as advantageous for increasing the bioavailability. Exhibit 1 on column 2, lines 3-10 states that it is crucial to achieve optimal absorption rate for active ingredients of low solubility that crystallize readily and to achieve rapid and sufficiently long lasting solubilization in the aqueous medium of the digestive tract without instance of recrystallization. This can be achieved by addition of surface active substance and that this is generally known per se.

7.2 The opponent states that active ingredients of exhibit 1 are the ones with low solubility or low bioavailability (column 2, line 51-53) and includes protease inhibitors. Exhibit 1 on column 1, last 3 paragraphs teaches characteristics of an active ingredient with regards to solubility and bioavailability in solid dispersion. Moreover the active ingredients of resulting drug forms of exhibit

1 as per column 4, lines 52-58 are amorphously embedded. The preferable drug form is a solid dispersion wherein the active ingredient is in the form of molecular dispersion. Secondly, the surface active agents of Exhibit 1 have HLB value of 2 to 18 in the range of 10% to 40%. The surface active agents of Exhibit 1 as per column 3, lines 3 include sorbitan fatty acid esters. Moreover sorbitan fatty acid esters are known to have HLB value of 2- 10. The third aspect of the Exhibit 1 is referred as "melt-processable matrix excipient." The matrix forming polymers *homo- and copolymers of N-vinylpyrrolidone such as polyvinylpyrrolidone with vinyl carboxylates such as vinyl acetate or vinyl propionate, for example copovidone (VP/VAc-60/40)* are taught in Exhibit 1. The opponent therefore states that melt processable matrix excipient is similar to the matrix forming polymer component of the impugned application.

7.3 The process of preparation of drug forms of Exhibit 1 involves melt process carried out in kneader or screw extruder (column 3, line 65). The starting material of Exhibit 1 are processed together to form a melt which is then passed through open extruder head, and after solidification, followed by grinding and compression on tablet press (column 4, line 34-36). The opponent states that the solid dosage form of the impugned application are also prepared by preparing a homogenous melt of HIV protease inhibitor, water soluble polymer and surfactants followed by melting and solidification to give a solid dispersion product. The resulting solid dispersion is then compressed into tablet after grinding.

7.4 The opponent further states that Exhibit 1 and the impugned application have following features in common:

- Poorly soluble active ingredients (includes protease inhibitor).

- Surface active agent with HLB 2-18; 10% to 40%; sorbitan fatty acid esters (HLB from 2 to about 10) and ethoxylated sorbitan fatty acid esters (HLB from about 10 to 18).
- Matrix forming polymer; homopolymers and copolymers N-vinylpyrrolidone, or copolymers with vinyl carboxylates.
- Process of preparation of solid dispersion by melt extrusion followed by compression in to tablet after solidification and grinding.

7.5 Claim 1 of the impugned application claims, "A solid pharmaceutical dosage form which comprises a solid dispersion of *at least one HIV protease inhibitor* and *at least one pharmaceutically acceptable water-soluble polymer* and at least *one pharmaceutically acceptable surfactant*, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C". The opponent states that all attributes of the claimed invention are present in Exhibit 1.

7.6 The opponent further states that both Exhibit-1 and the application under opposition are assigned to same applicant and have common inventors. The present application is therefore a mere extrapolation of teachings of exhibit 1 to protease inhibitors. The only difference between Exhibit 1 and the impugned patent application is that Exhibit 1 does not exemplify the protease inhibitors claimed in the impugned application. The said document however undoubtedly teaches application of the technology to protease inhibitors in general. Also in light of remarkable resemblance between the formulation of Exhibit 1 and the impugned application, the impugned application is devoid of inventive merit.

7.7 The opponent states that Exhibit 1 teaches enhancement of bioavailability of poorly soluble drugs including HIV protease inhibitors by preparing solid dispersion of active along with surfactant and melt processable polymer. This according to the opponent is the key feature of the impugned application;

already known in the art. The opponent states that variation in the concentration of the ingredient is within the purview of the skilled artisan

7.8 The opponent states that the HIV protease inhibitors disclosed in Exhibit 1 have poor aqueous solubility and thereby low bioavailability. This is addressed by formulating the drug as solid dispersion in a water soluble polymer and a surfactant with HLB 2-18 prepared by melt extrusion. The impugned application too encounters the same problem of low bioavailability of poorly soluble HIV protease inhibitor which is addressed by preparing solid dispersion in a manner similar to that in Exhibit 1.

7.9 The opponent states that the active ingredient viz. poorly soluble HIV protease inhibitors, water soluble polymers, surfactant/solubilizing agent, process of preparation on which the impugned application is based is already taught in prior art by way of Exhibit 1. Thus solution to the problem of enhancing bioavailability of poorly soluble actives is disclosed in the prior art. The impugned application is therefore a mere application of the teachings of prior art to specific HIV protease inhibitors and is therefore devoid of inventive merit.

7.10 WO200134119 entitled "Inhibitors of Crystallization in a Solid Dispersion" is annexed herewith as Exhibit 2. Exhibit 2 is published on May 17, 2001 and is therefore permissible as a valid prior art. Exhibit 2 discloses solid dispersion comprising HIV protease inhibitors-ritonavir and/or lopinavir in water soluble carrier polyethylene glycol and polyvinylpyrrolidone and surfactant. Exhibit 2 on line 3-5, page 6 states the need of a stable solid dispersion of pharmaceutical formulation which demonstrates lack of crystallization. Exhibit 2 specifically relates to dispersion of amorphous drug within the matrix that does not crystallize. Crystallization is undesirable as it causes loss of desired properties and reduces the shelf life (on page 10 line 10-16). The opponent states that the polymer matrix of Exhibit 2 involves two components viz. polyethylene glycol (PEG) as hydrophilic matrix and

polyvinylpyrrolidone (PVP) as hydrophilic amorphous polymer. In other words dispersion in Exhibit 2 is brought about by PEG and PVP together. Moreover, as per Exhibit 2 addition of PVP is beneficial as it increases the amorphous volume of the matrix where the drug reside.

7.11 Exhibit 2 teaches preparation of solid (molecular) dispersion on page 11 and 12; comprising HIV protease inhibitor by dissolving/dispersing the HIV protease inhibitor in an organic solvent followed by dispersion in to a suitable water soluble carrier (PEG/PVP). The organic solvent after evaporation leaves the drug dispersed in the molten matrix, which is allowed to solidify. The drug is dispersed in the resultant matrix. The solid mass is further grounded, sized and dispensed as gelatin capsules or potentially compressed into a tablet. The opponent further states that ABT-538 (ritonavir) is disclosed as compound of formula I on page 14 last paragraph and on page 19 as example 1 A as ritonavir dispersion preparation. The other HIV protease inhibitor of Exhibit-2 is ABT-378 (i.e. lopinavir), disclosed on page 20 as Example B. The solid dispersion of example B is prepared in 10% to 20% of PVP. Thus solid dispersion of HIV protease inhibitors comprising ritonavir and lopinavir are taught by Exhibit 2. The opponent further states that method of preparation using an organic solvent like ethanol as Exhibit 2 is referred as 'solution evaporation' in the impugned application on page 10, line 5-6. The opponent states that solid dispersion of HIV protease inhibitor lopinavir and ritonavir by matrix forming polymer that may be compressed as a tablet is known in prior art from Exhibit 2. Also addition of surfactant and water soluble polymer as PVP is taught in Exhibit 2.

7.12 The opponent further states that solid dispersion of Exhibit 2 is prepared with PVP and PEG as matrix in which the amorphous drug is dispersed. The formulation of Exhibit 2 as per the abstract can be made as tablet and hard/soft gelatin capsules. The same is also stated on page 12, lines 19-23 as "By improving the dissolution of poorly water soluble drug, the drug in a

suitable carrier may be filled into a gelatin capsule as solid, or the matrix may potentially be compressed into a tablet." Replacement of PVP of Exhibit 2 with other water soluble polymers like copovidone to make solid dispersion cannot impart inventive merit. However, the opponent contends that solid dosage forms of HIV protease inhibitors are already been known in the prior art as soft gelatin capsule and oral solutions manufactured by the applicant itself. The applicant has come up with alternative dosage form as tablet. Thus in lieu of teaching of Exhibit 2 the impugned invention is devoid of inventive merit.

7.13 The opponent relies on WO00/74677 entitled "Improved Pharmaceutical Formulations"; annexed herewith as Exhibit 3. Exhibit 3 is published on December 14, 2000 and is permissible as a valid prior art. Exhibit 3 specifically relate to pharmaceutical composition of ritonavir and other protease inhibitors like lopinavir, indinavir, saquinavir, nelfinavir. The pharmaceutical compositions of Exhibit 3 are dispensed as soft elastic gelatin capsule (bridging paragraph of pg 14-15).

7.14 The opponent states that the impugned application is therefore just an alternative solid dosage form of known substances without any surprising properties over the existing formulation. The opponent states that preparation of solid dispersion of protease inhibitor as tablet formulation can only be regarded as workshop improvement and not a patentable subject matter. The opponent therefore states that the impugned application is obvious and devoid of inventive merit.

7.15 WO199744014 entitled "Antifungal Compositions with Improved Bioavailability" is annexed herewith as Exhibit 4. Exhibit 4 is published on November 27, 1997 and is therefore permissible as a valid prior art. Exhibit 4 relates to antifungal compositions with improved bioavailability as once daily dose independent of the food intake. The composition of exhibit 4 is obtained by melt-extruding a mixture comprising itraconazole and appropriate water

soluble polymer followed by milling of the melt-extruded mixture. Also the active ingredient of Exhibit 4 is practically insoluble in water (page 1, line 14). The opponent states that the object of Exhibit 4 is to prepare a pharmaceutical dosage form that can be administered to a patient at any time independently of the food taken i.e. can be administered in a fasted state (page 3, line 13) and that it does not convert in to a crystalline form which is not readily bio-available (page 3, line 25-26). This object is achieved by preparing a solid dispersion comprising water soluble polymers. Also the itraconazole of Exhibit 4 is in non-crystalline phase as this has intrinsically faster dissolution rate than its microcrystalline or crystalline form. The opponent states that the description of the invention of Exhibit 4 bear surprising resemblance with the impugned application in terms of definition of term 'solid dispersion,' (page 4, lines 5 to7) and various techniques for preparation of solid dispersion (page 4, lines 31-32). Moreover the process of preparation of solid dispersion as claimed in claim 19 of the impugned application is taught in Exhibit 4 on page 4, lines 35-38 and page 5, lines 1-2 , reproduced as

"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,
d) forcing the thus obtained melt through one or more nozzles; and
e) cooling the melt till it solidifies."

7.16 The opponent states that preferable water soluble polymers of Exhibit 4 include polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate (page 7, line 14). Exhibit 4 on page 14 lines 25-29 states an observation on food effect with Sporonox (itraconazole) capsules and tablets of Exhibit 4. It was observed that the difference between taking the medication after the meal or in fasted state was significantly less when tablet of Exhibit 4 was administered than with Sporonox Capsules.

7.17 The opponent states that Exhibit 4 teaches solid pharmaceutical dosage form (tablets) of a poorly soluble drug (that does not crystallize when formulated) by solid dispersion technique. The impugned application too teaches solid pharmaceutical dosage form of poorly soluble drug in non crystalline form prepared by solid dispersion technique.

7.18 Exhibit 4 teaches that the solid dispersion is in the form of a solid solution comprising drug (a) and water soluble polymers (b). As regards to water soluble polymers, polyvinylpyrrolidone and copolymers of polyvinylpyrrolidone with vinyl acetate have been stated to be suitable in terms of physico-chemical properties. Exhibit 4 thus teaches every aspect of the impugned patent application. Exhibit 4 teaches beyond doubt that capsule form of an active to be taken after meals may be replaced by a tablet made by melt extrusion of a solid solution of the active in a water soluble polymer and that the said tablet would be independent of the fed condition of the patient.

7.19 The opponent relies on "Physical Properties of Solid Molecular Dispersions of Indomethacin with Poly(vinylpyrrolidone) and Poly(vinylpyrrolidone-co-vinyl-acetate) in Relation to Indomethacin Crystallization" by Takahiro et al published in Pharmaceutical Research Volume 16, No. 11, 1999; annexed herewith as Exhibit 5. The opponent states that Exhibit 5 relates to amorphous molecular dispersions of poorly water soluble drug with PVP, PVP/VA as polymers. The introduction of Exhibit 5 affirms that crystalline drugs exhibit very poor water solubility and have inadequate bioavailability when administered as a solid dosage form and that conversion of such a drug to amorphous state offers improved dissolution and bioavailability. Exhibit 5 further states that amorphous state being metastable, the drug tends to crystallize under certain conditions of temperature and relative humidity during storage (on page 1722, paragraph 1 of right column). Exhibit 5 further states that from a pharmaceutical perspective it is necessary to add excipient to retard tendencies of instability. Also, mechanism of crystallization

inhibition is taught on page 1722, paragraph 2 of right column as "*The basic premise is that the molecular dispersion will have Tg greater than that of the drug alone, and hence that the molecular mobility of drug will be reduced, therefore reducing tendencies for crystallization. In particular, polymeric excipients with high Tg values would appear to provide the basis for accomplishing these objectives.*" Exhibit 5 also teaches on last paragraph on page 1722 that amorphous system tends to exhibit optimal conditions for nucleation and crystal growth above Tg where molecular mobility is greater and that crystal form is to be inhibited during storage. Further more, teaching of Exhibit 5 is directed to facilitate storage at room temperature as low temperature storage is not practical.

7.20 The opponent states that behavioral pattern of the drug of Exhibit 5 is similar to that of the impugned application. The opponent further states that Exhibit 5 teaches PVP/VA as the polymers for solid dispersion for poorly soluble drug to arrest/inhibit crystallization of the drug. In other words, exhibit 5 is addressing similar set of problems as purportedly faced by the impugned application as regards to formulation, stability and storage. The opponent contends that it is the teachings of Exhibit 5 that are one of the crucial elements affecting inventive merit of the impugned application.

7.21 It is stated that soft gelatin capsules of lopinavir/ritonavir as known by Exhibit 3 required refrigeration. In view of disclosures of exhibit 5, application of its teachings to Exhibit 3, a person skilled in the art will arrive at the impugned application. The opponent, therefore, states that the impugned applicant lacks inventive merit on the face of teachings of Exhibit 5 alone and in combination with other Exhibits specifically Exhibit 3.

7.22 The opponent further states that the contention of the applicant as regards the BCS classification status of HIV protease inhibitors (Class IV drugs) is an after thought raised by the applicant in reply statement and during the hearing of the parent application to escape non-inventiveness of the alleged invention.

Had this been the case, the same ought to have been reflected in the specification. A person skilled in the art will certainly carry out experiments to see if known techniques help to resolve problems rather than exploring unknown avenues. Evidently Exhibit 4 identifies the problem similar to the one faced by the applicant and the solution sought in the prior art is nothing but the same as that resorted to by the applicant by way of the impugned application. Thus, the impugned application is devoid of inventive merit with regards to disclosure of Exhibit 4. The opponent craves leave to rely on written arguments and reply statement in respect of parent application at the time of hearing.

7.23 The opponent further states that Exhibit 1 teaches mechanically stable solid oral pharmaceutical compositions (tablets) of HIV protease inhibitors having low aqueous solubility comprising pharmaceutically acceptable polymers and surface active agents prepared by process of molecular dispersion/melt extrusion. Exhibit 2 teaches solid dispersion of lopinavir and/or ritonavir having low solubility hence low bioavailability. Exhibit 4 teaches solid dosage form (tablet) of practically insoluble drug in non-crystalline form prepared by solid dispersion/melt extrusion irrespective of food intake. Exhibit 5 specifically teach inhibition of crystallization with PVP/VA as solid dispersion polymers and its storage at room temperature. The opponent states that it is obvious for a person skilled in the field of pharmaceutics to formulate solid dispersion of poorly soluble HIV protease inhibitors like ritonavir and lopinavir by combining the teaching of Exhibit 1 alone and / or in combination with Exhibit 2, Exhibit 3, Exhibit 4 and Exhibit 5.

7.24 The opponent therefore states that the impugned applicant is devoid of inventive merit over multiple documents singularly and in combination with one another as shown above. It is further stated that given the fact that these teachings were available to a skilled artisan prior to the priority date of

application under opposition; the claims of the impugned application are obvious and devoid of inventive step and ought to be rejected outrightly.

8. NOT AN INVENTION /NOT PATENTABLE (U/S 25 (1) (f))

8.1 The impugned application claims an invention not patentable as per 25 (1) (f) and Section 3 (d). The opponent states that the impugned application is directed to solid dosage form of HIV protease inhibitors like lopinavir, ritonavir, indinavir, saquinavir, nelfinavir. The opponent states that pharmaceutical formulations of HIV protease inhibitors as stated in the impugned application were known and disclosed in Exhibit 3 before the date of priority. Moreover US-FDA approved Kaletra (lopinavir/ritonavir) capsule on September 15, 2000. The label is annexed herewith as Annexure C. The soft gelatin capsules of HIV protease inhibitor viz. lopinavir and ritonavir were thus available before the date of priority of the impugned application.

8.2 Section 3 (d) of the Act states that "*the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant. Explanation.- For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.*"

8.3 The opponent states that as per the statutory requirement of Section 3 (d) of the Patent Act, the applicant of the impugned application will need to demonstrate enhanced therapeutic efficacy with respect to known

pharmaceutical formulations of Exhibit 3. In absence of which the impugned application cannot be held as patentable.

8.4 The opponent states that presentation of the same combination of the active ingredients albeit through a new type of formulation, that too without any enhancement in therapeutic efficacy cannot be held patentable under the provisions of section 3(d) of the Act.

8.5 The impugned application claims an invention not patentable as per section 3 (e). The opponent states that the claimed invention falls under the mischief of section 3(e) which clearly states that a substance obtained by a mere admixture resulting only in the aggregation of properties of components thereof are not patentable. Evidently, the applicant has failed to demonstrate any satisfactory synergy between the actives of the composition. In absence of any data on synergy, the composition is thus a mere admixture of known active agents. The application is therefore liable to be rejected on this ground alone.

8.6 The opponent states that claim 37 of the impugned application relates to administration of solid dosage form to a mammal in need of treatment for HIV infection. The opponent therefore states that the claimed invention clearly falls under the mischief of Section 3 (i) which states that "any process for the medicinal, surgical, curative, prophylactic diagnostic, therapeutic or other treatment of human beings or any process for similar treatment of animals to render them free of disease or to increase their economic value or that of their products" is not patentable. The application is liable to be rejected on this ground also.

8.7 The opponent states that the claimed invention does not meet the requirement of Section 2(1)(ja) being devoid of inventive step as according to definition of Inventive step, the invention should be a technical advancement over the prior art or it should show economical significance or both and should not be obvious to a person skilled in the art. The opponent states that the applicant's

invention is neither a technical advancement for the reasons apparent from the pleadings under the ground of lack of inventive step which is adopted herein and not repeated here for the sake of brevity.

9. INSUFFICIENCY (U/S 25 1 (i))

9.1 The claims of the impugned application are not fairly based on the disclosures of the impugned application. The opponent states that claim 1 of the impugned application is directed to HIV protease inhibitor. The dependent claim, claim 7 claims around 24 HIV protease inhibitors. The description provides only two exemplary compositions viz, lopinavir/ritonavir and ritonavir. The claims are therefore not fairly based. Also the embodiment of the impugned application does not provide the specific process parameters followed for a particular active ingredient. It is thus implied that the invention will work in ways more than one.

9.2 The opponent states that a disclosure has to have enablement. In other words the disclosure has to be such as to enable the public to make or obtain the invention. This is not the case with the impugned application. Therefore, the ground of insufficiency is established and application is liable to be rejected on this ground also.

10. SECTION 8 (U/S 25 1 (h))

10.1 The applicant is required to provide all the information regarding the prosecution of his equivalent applications till the grant of his Indian application to the Controller in writing from time to time and also within the prescribed time which the applicant has failed to do.

10.2 The opponent states that the corresponding equivalent of the impugned application in major patent offices viz. European Patent Office is under

prosecution. It is to be noted that US2005048112 has been abandoned due to failure to reply to office action.

10.3 The applicant has not furnished statement and undertaking under section 8, therefore the applicant has failed to comply with the requirements of the section 8 of the Act and the opponent demands rejection on this ground also.

11. RELIEF SOUGHT

11.1 The opponent states that it has established and made out a case on each of the aforesaid grounds of opposition and pray to the Ld. Controller for the following relief(s),

1) Take the representation on record
2) A copy of reply statement and amended claims, if any to be furnished;
3) Leave to file supplementary representation in the event that such amendments are made to the application which are not adequately covered in the present representation;
4) Leave to file further evidence;
5) Grant of hearing;
6) Refusal of the application in toto;
7) Such other relief or reliefs as the Controller may deem appropriate.

Dated this the 5th day of August 2010

Mythili Venkatesh
Of S. Majumdar & Co.
Opponent's Agent

To,
The Controller of Patents
The Patent Office
Mumbai

Enclosures: Annexure A

Annexure B

Exhibit 1

Exhibit 2

Exhibit 2

Exhibit 3

Exhibit 4

Exhibit 5

Annexure C

ANNEXURE-A 27

बौद्धिक सम्पदा भारत
एकस्व /अभिकल्प /व्यापार चिन्ह /
भौगोलिक संकेत
INTELLECTUAL
PROPERTY **INDIA**
PATENTS / DESIGNS / TRADEMARKS /
GEOGRAPHICAL INDICATIONS

सत्यमेव जयते
भारत सरकार
पेटेंट कार्यालय - बौद्धिक सम्पदा भवन
एस.एम. रोड, अन्टॉप हिल डाकघर, अन्टॉप हिल, मुंबई - **400037**
Government of India
Patent Office - Bouddhik Sampada Bhawan
Beside Antop Hill Post office, S.M. Road,
Mumbai - 400037

दूरभाष Tel: 022-24140145
Extn: 199
फॅक्स Telefax: 022-24156393
Email: skesharwani.ipo@nic.in
Website: www. ipindia.nic.in

संख्या /**Letter No.** RTI ACT 2005/POM/2009/4341 दिनांक /**Date: 09.07.2009.**

To,

M/s S. Majumdar & Co.
202, Elecon Chambers, Behind Sakinaka Tel. Ex
Off Kurla –Andheri Road
Saki Naka, Mumbai 400072

RECEIVED
10 JUL 2009

SUBJECT: RTI application seeking information regarding

REFERENCE : Your RTI request dated 29.06.2009

Sir,

It is to inform you that as per your RTI request dated 29.06.2009 the requisite information is given below:

Application No : 339/ MUMNP/2006

Date of filing :24/.03/.2006

a) Fist examination report issued on dated 9.10.2007 response filed on 17.07.2008

b) Further process of per- grant opposition under process

2) Copies of examination reports issued-- provided

3) Copies of the response filed-- provided

Encl: As above

(A.T. Patre)
Assistant Controller of Patents & Designs
Central Public Information Officer

5 AUG 2010

28

(1)

INTELLECTUAL PROPERTY INDIA

PATENTS / DESIGNS / TRADE MARKS
GEOGRAPHICAL INDICATIONS

GOVERNMENT OF INDIA
PATENT OFFICE
INTELLECTUAL PROPERTY BUILDING
Boudhik Sampada Bhavan, Near Antop Hill Post Office,
S.M. Road, Antop Hill, Mumbai- 400037, India
Phone:24137701 Fax:24130387
E-mail:mumbai-patent@nic.in
Website:http://ipindia.nic.in

No. 339/MUMNP/2006 Q.936 - 09/10/07

Dated the :

To

CRAWFORD BAYLEY & CO., STATE BANK BUILDINGS, N.G.N. VAIDYA MARG, MUMBAI-400023 MAHARASHTRA INDIA INDIA.

To
ANAND and ANAND,
ADVOCATES
B-41, NIZAMUDDIN EAST,
NEW DELHI - 13

SUB : First Examination Report

REF :- Patent Application No.339/MUMNP/2006

NAME OF APPLICANT :- ABBOTT LABORATORIES

With reference to request no.870/RQ-MUM/2006 dt.24/03/2006 by you for examination, the above quoted application has been examined under section 12 of the Patent Act,1970 as amended and the First Examination Report containing a statement of objection is forwarded herewith for compliance thereof.

The documents enclosed shall be resubmitted within 12(Twelve) months from the date of issue of the said report together with your observation if any, in connection with the compliance of the requirements of this First Examination Report.

The application referred to will be deemed to have been abandoned under section 21(1) unless all the requirements imposed by the said Act and the rules there under are complied with within the above said prescribed period.

The pages of the complete specification should be freshly typed wherever corrections of interpolation are made. The typed pages in duplicate should be on white pages in order that clear photocopies of the specification can be prepared.The original pages in that case should be returned to this office duly cancelled.

It is in the interest of the applicant to comply with the requirements at the earliest.

(Dr.Sharana Gowda)
Examiner of Patents & Designs
For Controller of Patents & Designs

Encl:-
1. Application for Grant of Patent
2. Provisional/Complete Specification

NOTE : All Communications to be sent to the Controller of Patents at the above address.

29

ANAND AND ANAND

Mailing Address
B-41, NIZAMUDDIN EAST, NEW DELHI-110013 (INDIA)

Office Location
Plot No. 17A, Sector 16A, FILM CITY, NOIDA - 201301 (UP) (INDIA)
PHONES : 91-120-4059300 (100 Lines) FAX : 91 -120-4243056 - 058
email@anandandanand.com www.anandandanand.com

LAST DATE: October 9, 2008

Our Ref: 14050 (P-12) **July 17, 2008**

The Controller of Patents
The Patent Office
Mumbai

Kind attn.: Dr. Sharana Gowda
Examiner of Patents & Designs

Re.: Indian patent application number 339/MUMNP/2006
Applicant: Abbott Laboratories
Title: "Solid Pharmaceutical Dosage Form"

We write in continuation of our response to the First Office Action Dated 7th July 2008.

The first examination report with respect to said application was issued on 9th October 2007. There was a pre-grant oppositions raised by I-MAK and Cipla. The response to both the oppositions and evidence was couriered and faxed to the patent office on 8th January 2008 and 5th March 2008 respectively. The response to the examination report was couriered and faxed to the patent office on 7th July 2008. A hearing was requested as part of the response to the first examination report as well as the pre-grant oppositions.

We request the learned Controller to appoint us a hearing in the aforesaid matter and advice us accordingly.

Yours faithfully,

Archana Shanker

5 AUG 2010

30

ANAND AND ANAND

Mailing Address
B-41, NIZAMUDDIN EAST, NEW DELHI-110013 (INDIA)

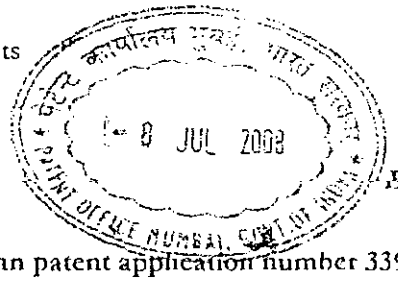
Office Location
Plot No. 17A, Sector 16A, FILM CITY, NOIDA - 201301 (UP) (INDIA)
PHONES : 91-120-4059300 (100 Lines) FAX : 91-120-4243056 - 058
email@anandandanand.com www.anandandanand.com

LAST DATE: October 9, 2008

Our Ref: 14050 (P-12)

July 7, 2008

The Controller of Patents
The Patent Office
Mumbai



Kind attn.: Dr. Sharana Gowda
Examiner of Patents & Designs

Re.: Indian patent application number 339/MUMNP/2006
Applicant: Abbott Laboratories
Title: "Solid Pharmaceutical Dosage Form"

Sir,

Thank you for the first examination report dated 9th October 2007 in respect of the above application. Our submissions to the objections raised by the Learned Examiner are as follows:

Para 1:

At the outset, we submit that the claims have been revised and request the Learned Controller to consider and allow the revised set of claims.

The Examiner has held the subject matter of the claims under section 2(1)(j) of the Indian Patents (Amendment) Act, 2005 are not novel, in view of PCT application no. WO 01/34119. The Learned Examiner has pointed to page 7 of the citation being directed to a stable solid dispersion pharmaceutical formulation comprising a pharmaceutical compound such as HIV protease inhibitor, a water soluble carrier and a crystallization inhibitor such as PVP or HPMC and additionally pharmaceutically acceptable carriers, diluents or excipients. We beg to disagree with the Learned Examiner and humbly submit that the claims of the instant application are novel in view of said citations.

We humbly submit that WO 01/34119 discloses a solid dispersion comprising ritonavir and/or lopinavir in a water-soluble carrier polyethylene glycol (PEG), a crystallization inhibitor polyvinylpyrrolidone (PVP) and surfactants. However, WO 01/34119 does not teach or suggest the solid dispersion disclosed in the present invention.

We would like to bring to the kind attention of the Learned Examiner that:

- The solid dispersion of the present invention employs a water-soluble polymer (e.g., copovidone or PVP) to form an amorphous matrix in which ritonavir and

surfactant(s) are distributed. For instance, the polymer(s) employed in the present invention has a Tg of at least about 50°C. As appreciated by those skilled in the art, Tg (glass transition temperature) only applies to polymers in amorphous state, not polymers in crystalline state. The addition of surfactant(s) to this amorphous matrix significantly improves the bioavailability of ritonavir, which is demonstrable on a comparison between examples 1-7 and to the comparative example on pages 15-16 of the present application. In contrast, the solid dispersion system of WO 01/34119 employs a crystalline matrix formed by PEG (or other suitable non-amorphous polymers), and ritonavir resides in this crystalline matrix. PEG, when in amorphous state, has extremely low Tg. For example, PEG 8000 used in WO01/34119 has a Tg of – 55°C. See Table 2 of *A. Foster et.al "Selection Of Excepirnts For Melt Extrusion With Two Poorly Water-Soluble Drugs By Solubility Parameter Calculation And Thermal Analysis", International Journal Of Pharmaceutics226 (2001) 147-161* (**Annexure 1**).

In WO 01/34119, PVP functions as a crystallization inhibitor, as opposed to a matrix builder. Therefore, the solid dispersion of the present invention is entirely different from that of WO 01/34119.

- Specifically, WO 01/34119 on page 11, lines 7-8, states that the "benefits of incorporating PVP into the PEG matrix are two fold." .
- WO 01/34119 on page 11, lines 11-16 further states that one "benefit of adding PVP is an increase in amorphous volume of the polymer matrix where drugs reside" and "since polyethylene glycols tend to be highly crystalline, this increase in amorphous volume could be important for fast dissolution."

  Nor does WO 01/34119 suggest that the crystalline matrix *could be replaced with an amorphous matrix.*

- Moreover, in all the Examples of WO 01/34119, the PVP over PEG ratio is no more than 20:80, indicating that crystalline PEG, not amorphous PVP, is primarily responsible for the formation of the matrix. See, e.g., page 17, line 21("PEG:PVP (95:5)"); page 20, line 13/14 ("in 85:15 PEG8000:PVP"); page 20, line 15/16 ("dispersions of 10 or 20% PVP 17PF in PEG 8000 without drug"); page 21, line 8/9 ("to the 90:10 PEG 8000:PVP control dispersion"); page 22, line 8/9 ("using the 80:20 PEG8000:PVP control dispersion" and page 23, line 21 ("for PEG:PVP (95:5)").
- Therefore, the formulation of WO 01/34119 is crystalline matrix-based, which is fundamentally different from the amorphous matrix-based formulation of the present application. WO 01/34119 neither teaches nor suggests that ritonavir can be stabilized in an amorphous matrix, such as a matrix formed by PVP or another amorphous polymer.

In fact, WO 01/34119 teaches away from the present invention which is supported by the following facts:

- WO 01/34119 actually teaches away from using PVP matrix to stabilize ritonavir. On page 11, lines 7-8, WO 01/34119 states that the "benefit of incorporating PVP into the PEG matrix are two fold," indicating that using PVP alone would not enjoy the "two fold" benefits.

- WO 01/34119, on page 11, lines 8-10, further explains the "benefit of incorporating PVP into PEG" as follows:

  > Firstly, processing PVP can be difficult due to its hygroscopicity. Secondly, when PVP dissolves a viscous layer at the solid-liquid interface forms. This viscous region can hinder dissolution of the drug.

- Accordingly, WO 01/34119 teaches away from using PVP alone because of the above-cited disadvantages. Apparently, these disadvantages had not been resolved at the time WO 01/34119 was filed. One of ordinary skill in the art would consider that these benefits teach against using PVP as the principle carrier to form a drug-supporting matrix for the enhancement of bioavailability.

Thus, in the light of above submissions the invention is clearly novel. We humbly request the learned examiner to kindly waive off said objection.

Para 2:

The examiner has held claims 1-37 obvious under section 2(1)(j) in view of documents D1-D4. We do not agree with the learned Examiner's objection.

The submission of para 1 clearly indicate that **D1 (WO 01/34119)** teaches away from the use of PVP in solid dosage formulations and therefore thus the instant invention cannot be held obvious in light of D1.

Also combining U.S. Patent No. 4,769,236 (D2) with WO 01/34119 (D1) would also not remedy the deficiency of WO 01/34119. Like WO 01/34119, the '236 patent does not teach or suggest using a crystallization inhibitor such as PVP to form an amorphous matrix to stabilize ritonavir.

- The '236 patent on column 2, lines 3-6 states that "according to the invention the concentration of the inhibiting agent present at the time of spraying is comprised between 1 and 50% with respect to the active principle (weight/weight)." Example 1 of the '236 patent uses only 10% of PVP with respect to the weight of the active principle. Example 2 of the '236 patent uses no more than 35% of PVP with respect to the weight of the active principle.
- Claim 1 of the '236 patent also prescribes the use of "a stabilizing and crystal-formation-inhibiting amount of between about 1 to 50% w/w with respect to the active principle of polyalkyleneglycol-polyvinylpyrrolidone."
- Because the amount of the crystallization inhibitor used in the '236 patent is less than 50% of the amount of the active principle, the crystallization inhibitor cannot form a matrix in which the active principle is dispersed and stabilized.

> Accordingly, like W01/34119, the formulation of the '236 patent is fundamentally different from the solid dispersion of the present application.

Even assuming without admitting that the crystallization inhibitor employed in the '236 patent forms an amorphous matrix, the formulation of the '236 patent would not work for ritonavir. The formulation of the '236 patent does not include any surfactant. As demonstrated by the Comparative Example of the present application, ritonavir in such an amorphous matrix (without surfactant) would have poor bioavailability.

Furthermore, it is humbly submitted that there is no magic formulation that works for all drugs. This is particularly true for ritonavir, a Class IV compound under the Biopharmaceutics Classification System (BCS). See page 119, right column, of Rochele C. *Rossi et. al. "Development And Validation Of Dissolution Test For Ritonavir Soft Gelatin Capsules Based On In Vivo Data", International Journal Of Pharmaceutics 338 (2007) 119-124* (**Annexure 2**) Class IV compounds have low aqueous solubility as well as low membrane permeability and therefore have poor bioavailability and are not well absorbed by gastro intestinal mucosa. Ibid *"Absorption and Drug Development, by Alex Avdeef, pp. 20-21 (John Wiley & Sons, Inc., Hoboken, New Jersey, 2003) pp. 20-21* (**Annexure 3**). For this reason, the improvement in dissolution does not correlate with the improvement in bioavailability for a Class IV compound such as ritonavir. Ibid Figure 2.9 on page 20 of **Annexure 3**, which states that "No IVIV (in vitro - in vivo) correlation [is] expected" for Class IV compounds. See also page 119, right column, of **Annexure 2**, which states that Class IV compounds "are less likely to show IVIV than class II". Therefore, Class IV compounds are the most difficult of being formulated into a solid form so as to provide both adequate solubility and acceptable permeability to achieve satisfactory bioavailability. There is no general formulation for Class IV compounds. A high variability in formulation is expected for different Class IV compounds. A person skilled in the art cannot reasonably predict, without actually testing, if a given formulation would work for a Class IV compound. Extensive research must be conducted for each Class IV compound in order to identify formulations that can provide adequate bioavailability. The traditional trial-and-error process, though often time-consuming and labor-intensive, does not guarantee the identification of a suitable formulation for a Class IV compound. Considerable technical challenges must be resolved in order to formulate a Class IV compound into a solid dosage form.

Without actual testing, one of ordinary skill in the art cannot predict with any certainty if a particular formulation would work for a Class IV compound. Solid dispersion technology was originally designed to improve solubility and/or dissolution, but not membrane permeability. This is because solid dispersion converts drug into a high-energy phase, thereby facilitating the dissolution of the drug. However, a Class IV compound, such as ritonavir, is not only poorly soluble but also poorly permeable. Therefore, one of ordinary skill in the art would not be able to predict if solid dispersion could provide adequate bioavailability to a Class IV compound.

The solid pharmaceutical composition of the present invention was the result of years of intense research. The composition confers markedly improved bioavailability to ritonavir and has been used in the commercial product Kaletra® tablet since 2005. Ibid *"Melt Extrusion Can Bring New Benefits to HIV Therapy - The Example of Kaletra® Tablets," Am. J. of Drug Delivery, 4(2), 61-64 (2006)* (**Annexure 4**), page 62, right column, which states that "[n]early 10 years of research and equipment modification were required to successfully

incorporate the active ingredients of Kaletra® into a tablet with satisfactory bioavailability and storage requirements." **Annexure 4** in the Abstract on page 61 also states that "[t]he incorporation of poorly soluble drugs into convenient oral dosage forms is one of the biggest challenges encountered in drug formulation." *Abu T.M. Serajuddin," Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs"* (**Annexure 5**), at page 1064, right column, also recognizes that "Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, as exemplified by the recent withdrawal of ritonavir capsules from the market, so future research needs to be directed to address various stability issues." Therefore, extensive and time-consuming research, as well as substantial inventive steps, had been performed to develop a solid dispersion of the present invention.

Ritonavir is practically insoluble in water, and traditional mixtures of ritonavir, surfactants, and other excipients do not significantly improve the solubility of Ritonavir. Ibid page 1 of Y Zhu et. at. *'New Tablet Formulation Of Lopinavir/Ritonavir Is Bioequivalent To The Capsule At A Dose Of 800/200 Mg'* ("Incorporation of surfactants, acids or other wetting agents with traditional technologies failed to provide adequate bioavailability for [ritonavir/lopinavir] solid formulations") (**Annexure 6**). It was not expected that amorphous polymer-based solid dispersion technology would work for ritonavir. The first attempts to use the solid dispersion technology to improve ritonavir bioavailability had failed. These attempts are exemplified in the Comparative Example of the present application. Ritonavir formulated as a mere solid dispersion in an amorphous polymer matrix showed poor bioavailability.

Because ritonavir is a Class IV compound which is both poorly soluble and poorly permeable, and solid dispersions were originally designed to improve solubility and/or dissolution but not permeability, one of ordinary skill in the art would not have expected that further modifications of the original solid dispersion formulation would lead to improved bioavailability of ritonavir. Therefore, one of ordinary skill in the art would more likely have abandoned the solid dispersion formulation, and pursued other formulation strategies or selected non-Class IV drug candidates that have the same therapeutic effect as ritonavir.

It was totally unexpected that surfactants can significantly improve the bioavailability of ritonavir in an amorphous polymer matrix. Those skilled in the art would not have any reasonable expectation of success that the addition of surfactants to an amorphous polymer matrix could improve the bioavailability of ritonavir or another Class IV compound. Prior to the present application, those skilled in the art did not know, and could not predict, what effect a surfactant might have on the bioavailability of a Class IV compound in an amorphous polymer matrix. All the references cited by the Examiner do not teach or suggest, in any way, that the addition of surfactant to an amorphous solid dispersion may improve the bioavailability of ritonavir or another Class IV compound.

Accordingly, though solid dispersion technology had been known, its application to produce a pharmaceutical composition comprising a Class IV compound proved complicated and technically challenging, thereby making the application of the same not obvious to a person skilled in the art.

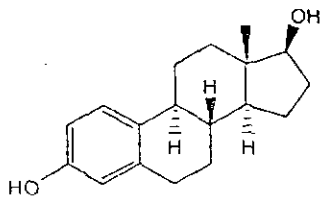
(Please see the above arguments in blue that beef up the deleted arguments)

Hence D2 also does not hint or indicate that PVP along with a surfactant would work for a class IV compound (Ritonavir). Therefore even combining D1 and D2 would not result in the present invention.

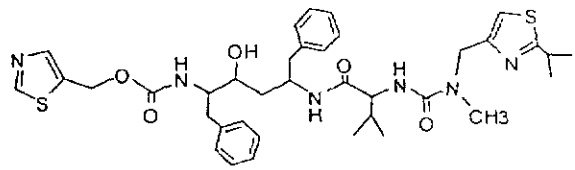
Eur. J. Pharma. & Biopharma., 554,2002, Pages 107-117 (D3):

The third citation, D3, describes a solid dispersion comprising 10% 17-Estradiol, 50% PVP and 40% Geluciree 44/14 which has a 30-fold increase in dissolution rate. However, like all other references cited D3 does not suggest that one of ordinary skill in the art would have a reasonable expectation of success that the same formulation would work for ritonavir. As noted, there is no magic formulation that works for all drugs, particularly Class IV drugs such as ritonavir. The application of melt extrusion to the manufacturing of tablets is relatively new, complex, and is technically challenging and till date, only four drugs have been successfully manufactured using melt extrusion technology.

Moreover, as appreciated by one of ordinary skill in the art, the fact that a formulation works for one compound does not give rise to any reasonable expectation of success that the same or similar formulation would work for a structurally very different compound. In this case, the structural difference between 17-Estradiol and ritonavir is substantial. This can be clearly seen as below:



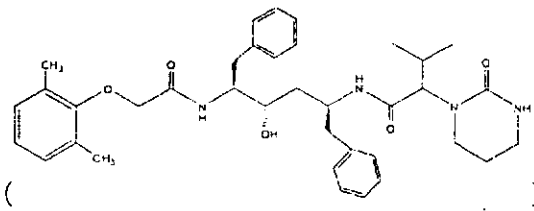
17-Estradiol



Ritonavir

Therefore, those skilled in the art would not have any reasonable expectation of success that the 17-Estradiol formulation described in D3 would also work for ritonavir. More importantly, it is further submitted that 17-Estradiol is a Class II compound under the Biopharmaceutics Classification System, which means that it has low aqueous solubility but high membrane permeability. Class II compounds are often the best candidate for using formulations, such as solid dispersions, to improve solubility and thereby bioavailability. This is because the improvement in solubility of a Class II compound directly correlated with the improvement in its bioavailability. This is in contrast to Class IV compounds such as ritonavir, where improvement in solubility does not necessarily correlate with improvement in bioavailability.

We would like to bring to the kind attention of the Learned Examiner that melt extrusion, as well as other solid dispersion technologies, were originally designed to improve solubility and/or dissolution rates, but not membrane permeability. The effect of solid dispersion formulation on the bioavailability of 17-Estradiol, a Class II compound, is therefore not indicative of whether the same or similar formulation would work for a Class IV compound such as ritonavir. A person skilled in the art would not have any reasonable expectation of success that a formulation which works for a Class II compound would also work for a Class IV compound.



Furthermore, lopinavir ( ), a compound much more similar to ritonavir than 17-Estradiol, does not have good bioavailability when formulated using a solid dispersion similar to those described in D3. See Examples 3 and 4 of WO2004/032903 (equivalent to US20060257470 (**Annexure 7**), which describe a solid dispersion comprising lopinavir, 68.17% water-soluble polymer (Kollidon VA-64) and 7% surfactant (Cremphor RH-40). However, Examples 3 and 4 show that this solid dosage form has poor water dissolution profile ("The extrudates dissolved in water only after several hours.") Thus, Examples 3 and 4 of WO2004/032903 (US20060257470) teaches away from using amorphous water-soluble polymers to build a matrix for the dispersion of ritonavir.

The third citation (D3) also cannot be combined with any other citation to come up with the instant invention.

J. Pharma. Sci. Vol. 88(10), 1999, pages 1058-1066 (D4):

Like all other cited references, D4 does not teach or suggest that ritonavir, a Class IV compound, can be formulated and stabilized in a matrix made from PVP or other water-soluble polymers. Moreover, as demonstrated in the Comparative Example of the present application, such a matrix would not work for ritonavir without the addition of surfactants.

Quoting from the citation itself,
D4 states at page 1064, right column:

> "Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, as exemplified by the recent withdrawal of ritonavir capsules from the market, so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problems that might not be seen in other types of solid dosage forms. Predictive methods will be necessary for the investigation of any potential crystallization of drugs and its impact on dissolution and bioavailability. Possible drug-carrier interactions must also be investigated."

Therefore, D4 does not provide any suggestion to one of ordinary skill in the art that ritonavir can be formulated and stabilized in a matrix formed by PVP or another like water-soluble polymer. Instead, D4 merely points to "future research" to resolve the ritonavir formulation issue. This further demonstrates that the formulation of the present application was not obvious to those skilled in the art.

Hence none of the documents cited alone or in combination suggest the present invention. We therefore request the learned examiner to waive off the objection.

Para 3:

The Examiner has held that the method claimed in claims 21 and 37 is not patentable u/s 3(i) of the Patents Act. We agree with the Learned Examiner, and the claims 21 and 37 have been deleted in view of section 3(i) of the Indian Patents (Amendment) Act, 2005.

Para 4:

Form 1 has been corrected as indicated by the Learned Examiner.

Para 5

Please find enclosed the General Power of Attorney

Paras 6 and 7:

We have already complied with these objections vide our letter dated February 1, 2008. Petitions u/r 137 and 138 is enclosed.

In view of the above submissions and revisions, we request the Learned Examiner to allow the application to proceed for grant.

Yours faithfully,

Archana Shanker

Encl.: Application Form
Complete Specification
GPA
Petition u/r 137 and 138 (2)
Cancelled pages
Retyped pages
Prescribed fee of Rs. 12,000

38

INTELLECTUAL
PROPERTY INDIA
बौद्धिक सम्पदा भारत
एकस्व /अभिकल्प /व्यापार चिन्ह /
भौगोलिक संकेत
PATENTS/DESIGNS/
TRADEMARKS/
GEOGRAPHICALINDICATIONS

सत्यमेव जयते
भारत सरकार/Government of India
पेटेन्ट कार्यालय / The Patent Office
बौद्धिक सम्पदा भवन / Boudhik Sampada Bhavan
नजदीक अन्टॉप हिल डाकघर / Near Antop Hill PostOffice
एस.एम. रोड / S. M. Road
अन्टॉप हिल / Antop Hill
मुम्बई - ४०० ०३७ / Mumbai – 400 037

दूरभाष /Tel : 022-24141026
022-24150381
:022-24137701
फॅक्स / Fax 022-2413 0387
Email: mumbai-patent nic.in
Website www. ipindia.nic.in

संख्या /No: 339/MUMNP/2006 6035. 03/10/07. दिनांक /Date: 03/10/07

To,
Anand And Anand
Advocates
B-41, Nizamudin East,
New Delhi-110013.

Sub: Patent Application No. **339/MUMNP/2006.**

Sir,

With reference to your letter No.14050 (P-12) Patent application No. 339/MUMNP/2006 and dated 03/09/2007. A representation by way of opposition u/s 25 (1) of the Act has been filed by I-MAK, Delhi (copy enclosed). You may submit statement and evidence within three months from date of this notice as per Rule 55.

Encl:
✓Copy of Rep.u/s 25 (1).

Yours faithfully

(Dr. Sharan Gouda)
Examiner of Patents & Designs
For Asstt. Controller of Patents & Designs

ANNEXURE-B

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

Section 10

"Solid Pharmaceutical Dosage Form"

Abbott Laboratories, a corporation organized and existing under the laws of USA, of Dept. 377 Bldg AP6A-1, 100 Abbott Park Road, Abbott Park, IL 60064-6008 USA.

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

726/MUMNP/2009

15/04/2009

We claim:

1. A solid pharmaceutical dosage form which comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C.

2. The dosage form of claim 1 comprising a glassy solution or solid solution of said HIV protease inhibitor.

3. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant has an HLB value of from about 4 to about 10.

4. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant is a combination of at least one pharmaceutically acceptable surfactant having an HLB value of from about 4 to about10 and at least one further pharmaceutically acceptable surfactant.

5. The dosage form of Claim 1 wherein said pharmaceutically acceptable surfactant is a sorbitan fatty acid ester.

6. The dosage form of Claim 1 which comprises, relative to the weight of the dosage form, from about 5 to about 30 % by weight of said HIV protease inhibitor, from about 50 to about 85 % by weight of said water-soluble polymer, from about 2 to about 20 % by weight of said surfactant, and from about 0 to about 15 % by weight of additives.

7. The dosage form of claim 1, wherein said HIV protease inhibitor is selected from the group consisting of: 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir); (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir); N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-

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

8. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

9. The dosage form of Claim 8 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of ritonavir plasma concentration of at least about 9 μg.h/ml/100 mg.

10. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)-amino-3-hydroxy-5-[2S-(l-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl]amino-1,6-diphenylhexane (lopinavir).

11. The dosage form of claim 10 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of lopinavir plasma concentration of at least about 20 μg.h/ml/100 mg.

12. The dosage form of claim 1 wherein said HIV protease inhibitor is a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydropyrimid-2-onyl)-3-methylbutanoyl] amino-1,6-diphenylhexane (lopinavir).

13. The dosage form of claim 12 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of ritonavir plasma concentration of at least 9 about μg.h/ml/100 mg and a dose-adjusted AUC of lopinavir plasma concentration of at least about 20 μg.h/ml/100 mg.

14. The solid dosage form of Claim 1 wherein said water-soluble polymer has a Tg of from about 80 to about 180 °C.

15. The solid dosage form of Claim 1 wherein said water-soluble polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.

16. The solid dosage form of Claim 1 wherein said water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate.

17. The solid dosage form of Claim 1 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

18. The solid dosage form of Claim 1 which contains, upon storage for about 6 weeks at about 40 °C and about 75% humidity, at least about 98 % of the initial content of HIV protease inhibitor.

19. A method of preparing a solid dosage form of claim 1 which comprises:
    i. preparing a homogeneous melt of said HIV protease inhibitor(s), said water-soluble polymer(s) and said surfactant(s), and
    ii. allowing the melt to solidify to obtain a solid dispersion product.

20. The method of claim 19 additionally comprising grinding said solid dispersion product and compressing said solid dispersion product into a tablet.

21. A method of treating an HIV infection comprising administering the solid dosage form of claim 1 to a mammal in need of such treatment.

22. A solid pharmaceutical dosage form comprising,

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

a homopolymer of N-vinyl pyrrolidone; and

a sorbitan fatty acid ester.

23. The solid dosage form of Claim 22 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

24. A solid pharmaceutical dosage form comprising,

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

a copolymer of N-vinyl pyrrolidone; and

a sorbitan fatty acid ester.

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

26. A solid pharmaceutical dosage form comprising,

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

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

a sorbitan fatty acid ester.

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

28. A solid pharmaceutical dosage form comprising,

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

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

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

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

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

31. A solid pharmaceutical dosage form comprising,

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

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

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

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

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

34. A solid pharmaceutical dosage form comprising,

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

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

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

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

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

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

EXHIBIT. 1

46

US006599528B1

(12) **United States Patent**
Rosenberg et al.

(10) **Patent No.: US 6,599,528 B1**
(45) **Date of Patent: Jul. 29, 2003**

(54) **MECHANICALLY STABLE PHARMACEUTICAL PRESENTATIONS FORM CONTAINING LIQUID OR SEMISOLID SURFACE-ACTIVE SUBSTANCES**

(75) Inventors: **Jörg Rosenberg**, Ellerstadt (DE); **Gunther Berndl**, Herxheim (DE); **Bernd Liepold**, Mannheim (DE); **Jörg Breitenbach**, Mannheim (DE)

(73) Assignee: **Abbott GmbH & Co. KG**, Ludwigshafen (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/936,349**

(22) PCT Filed: **Mar. 17, 2000**

(86) PCT No.: **PCT/EP00/02381**

§ 371 (c)(1),
(2), (4) Date: **Sep. 11, 2001**

(87) PCT Pub. No.: **WO00/57854**

PCT Pub. Date: **Oct. 5, 2000**

(30) **Foreign Application Priority Data**

Mar. 25, 1999 (DE) 199 13 692

(51) **Int. Cl.**[7] **A61K 9/48**; A61K 9/20
(52) **U.S. Cl.** **424/451**; 424/464
(58) **Field of Search** 424/451, 464

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,801,460	A	1/1989	Goertz et al.	424/465
4,880,585	A	11/1989	Klimesch et al.	264/141
4,904,699	A	2/1990	Bauer	514/972
5,695,784	A	12/1997	Pollinger et al.	424/495
5,707,648	A *	1/1998	Yiv	424/450
5,834,472	A	11/1998	Sangekar et al.	514/252

FOREIGN PATENT DOCUMENTS

EP	240 904	10/1987
EP	240 906	10/1987
EP	272 336	6/1988
EP	551 820	7/1993

OTHER PUBLICATIONS

Voigt "Pharmazeutische Technologie" (1993) pp. 80–85.

* cited by examiner

Primary Examiner—Carlos Azpuru
(74) *Attorney, Agent, or Firm*—Keil & Weinkauf

(57) **ABSTRACT**

The present invention relates to mechanically stable pharmaceutical presentations for oral administration, comprising in addition to one or more active ingredients and at least one melt-processable matrix-forming excipient more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C.

6 Claims, No Drawings

47

MECHANICALLY STABLE PHARMACEUTICAL PRESENTATIONS FORM CONTAINING LIQUID OR SEMISOLID SURFACE-ACTIVE SUBSTANCES

BACKGROUND OF THE INVENTION

The present invention relates to mechanically stable pharmaceutical presentations for oral administration, comprising in addition to one or more active ingredients and at least one melt-processable matrix-forming excipient more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C. A process for producing such forms has also been found.

The production of pharmaceutical preparations by the melt extrusion process is known per se. Thus, the process described, for example, in EP-A 240 904 or EP-A 240 906 makes it possible, by a specific selection and defined mixtures of the excipients employed, to control specifically the properties of the formulations to be produced.

For example, it is possible to produce, by selecting suitable matrix polymers, preparations which release the active ingredient continuously over a lengthy period. On the other hand, it may be desirable, for example in the case of analgesics, for the active ingredient to dissolve rapidly and be released quickly. The melt extrusion process has proven to be suitable for producing rapid release and slow release formulations.

A basic requirement is, however, that the active ingredient is able to dissolve sufficiently in the aqueous medium in the digestive tract. Absorption of the active ingredient is possible only if it is in dissolved form, because only dissolved active ingredients can cross the intestinal wall. Active ingredients of low solubility may therefore not be absorbed sufficiently and, associated with this, have a low bioavailability.

There have been no lack of attempts to improve the bioavailability of active ingredients of low solubility (cf. R. Voigt; "Pharmazeutische Technologie", published by Ullstein Mosby, 7th edition, 1993, pages 80–85). In particular, the production of coevaporates or so-called solid dispersions, in which the active ingredient is in the form of a molecular dispersion in an excipient matrix, has frequently proved advantageous for increasing the bioavailability. When the drug form dissolves in the body, the active ingredient can be released in molecular form from such solid dispersions directly and without supplying energy of salvation.

However, the use of solid dispersions has a beneficial effect on the bioavailability of the active ingredient only if the active ingredient can also undergo rapid absorption. However, if the absorption process is slow, the active ingredient of low solubility recrystallizes in the aqueous medium of the intestinal lumen because a supersaturated solution of active ingredient may be produced on dissolution of the drug form. For this reason, the bioavailabilities which can be achieved even with solid dispersions are often unsatisfactory.

The absorption of the active ingredient is often insufficient also because the active ingredient is released too slowly from the tablet. Absorption of most active ingredients into the blood circulation takes place in the upper sections of the small intestine, i.e. relatively soon after passing through the stomach. Active ingredients which have not been

adequately solubilized on reaching this region of the small intestine can be absorbed to only a limited extent.

It is therefore crucial for achieving optimal absorption rates, especially of active ingredients of low solubility which readily crystallize, to achieve rapid and sufficiently long-lasting solubilization in the aqueous medium of the digestive tract without recrystallization occurring.

The addition of surface-active substances is appropriate for this. The addition of surface-active substances to formulations of active ingredients of low solubility is generally known per se.

U.S. Pat. No. 5,834,472 discloses, for example, that the bioavailability of an antifungal agent can be improved by using a nonionic surface-active substance.

However, since most surface-active substances are liquid or semisolid at room temperature, the preparations produced to date are usually oily liquids or semisolids used to fill hard or soft gelatin capsules. However, in the case of soft gelatin capsules, interactions between excipients and the gelatin shell of the capsule are frequent and lead to leakage from the capsule.

The use of surface-active substances in tablet formulations is not possible without problems either because the liquid or semisolid surface-active substances impede compressibility in the conventional tableting process, especially when larger amounts of surface-active substances in the region of more than 10% by weight are needed to solubilize the active ingredient.

It is an object of the present invention to find mechanically stable solid formulations for oral use which can be used in particular for rapid and nevertheless long-lasting solubilization of active ingredients of low solubility after they have been liberated from the drug form.

BRIEF SUMMARY OF THE INVENTION

We have found that this object is achieved by the pharmaceutical formulations defined at the outset, and a process for producing them.

DETAILED DESCRIPTION OF THE INVENTION

The active ingredients which can be used are in principle all human and veterinary pharmaceutical substances, and active ingredients used in food supplements.

Particularly suitable active ingredients are immunosuppressants, protease inhibitors, reverse transcriptase inhibitors, cytostatics or antimycotics, in addition to CNS-active substances or dihydropyrimidine derivatives.

It is possible in particular to formulate active ingredients of low solubility or low bioavailability according to the invention. Low solubility means that the solubility in an aqueous medium is less than 1 mg/ml. Such active ingredients are also referred to in USP XXII, page 8, as scarcely soluble or practically insoluble.

Examples of active ingredients of low solubility are esuprone, nifedipine, ciclosporin or Taxol.

Suitable and preferred surface-active substances are low molecular weight substances which have an HLB (HLB—hydrophilic lipophilic balance) and are liquid at 20° C. or have a drop point in the range from 20° C. to 50° C., preferably up to 40° C. Preferred substances have an HLB of from 7 to 18, particularly preferably 10 to 15.

Examples of suitable surface-active substances are saturated and unsaturated polyglycolized glycerides, semisyn-

thetic glycerides, fatty acid esters or ethers of fatty alcohols as long as they have the properties stated above.

The corresponding sorbitan fatty acid esters or ethoxylated sorbitan fatty acid esters are particularly suitable, such as, for example, polyoxyethylene 20 sorbitan monolaurate, polyoxyethylene 20 sorbitan monopalmitate, polyoxyethylene 20 sorbitan monostearate, polyoxyethylene 20 sorbitan monooleate, polyoxyethylene 20 sorbitan tristearate, polyoxyethylene 20 sorbitan trioleate, polyoxyethylene 4 sorbitan monostearate, polyoxyethylene 4 sorbitan monolaurate or polyoxyethylene 4 sorbitan monooleate. Also suitable are macrogol 6 cetylstearyl ether or macrogol 25 cetylstearyl ether.

Particular preference is given to polyoxyethylene glycerol ricinoleate 35, polyoxyethylene glycerol trihydroxystearate 40, PEG 660 12-hydroxystearate (polyglycol ester of 12-hydroxystearic acid (70 mol%) with 30 mol% ethylene glycol).

The surface-active substances are present in the preparations in amounts of more than 10% by weight based on the total weight of the preparation, and up to 40% by weight, preferably 15 to 25% by weight and particularly preferably 20 to 25% by weight.

The preparations according to the invention also comprise at least one melt-processable matrix excipient. Particularly suitable matrix-forming excipients are water-soluble pharmaceutically acceptable polymers or sugar alcohols or mixtures thereof as long as they can be melted without decomposition.

Pharmaceutically acceptable polymers are, in particular, homo- and copolymers of N-vinylpyrrolidone such as polyvinylpyrrolidone with Fikentscher K values of from 12 to 100, in particular K 17 to K 30, or copolymers with vinyl carboxylates such as vinyl acetate or vinyl propionate, for example copovidone (VP/VAc-60/40).

Also suitable are polyvinyl alcohol or polyvinyl acetate, which may also be partially hydrolyzed, or acrylate polymers of the Eudragit type.

Also suitable are cellulose derivatives such as hydroxyalkylcelluloses, for example hydroxypropylcellulose, or, if slower release is required, hydroxyalkylalkylcelluloses which swell in water, for example hydroxypropylmethylcellulose (HPMC), preferably with degrees of methoxy substitution in the region of 22% and degrees of hydroxypropoxy substitution in the region of 8%, particularly preferably HPMC types with viscosities of 4000 mPas, 15,000 mPas or 100,000 mPas, measured at 20° C. in 2% by weight aqueous solution. Also suitable are HPMC types with degrees of methoxy substitution in the range from 28 to 29% and degrees of hydroxypropoxy substitution in the range from 5 to 8.5%.

Likewise suitable are meltable sugar alcohols such as, for example, sorbitol, maltitol, isomalt, mannitol, xylitol, erythritol or mixtures thereof. Maltitol, mannitol, xylitol or isomalt is preferred.

Suitable matrix-forming polymers are also polyethylene glycols with molecular weights in the range from 1000 to 20,000,000 Dalton, preferably 4000 to 10,000 Dalton.

The preparations may additionally contain conventional pharmaceutical excipients such as flavorings, antioxidants, silicas, release agents or dyes in the amounts usual therefor.

The preparations according to the invention are produced by a melt process. The process is preferably carried out without addition of solvents.

The melt process is carried out in a kneader or a screw extruder. Examples of suitable kneaders are those supplied by Haake or Farrell.

The melt is preferably produced in a screw extruder, particularly preferably a twin screw extruder with and without kneading disks or similar mixing elements. Corotating twin screw extruders are particularly preferred.

Depending on the composition, the processing generally takes place at temperatures from 40° C. to 260° C., preferably 50 to 200° C.

The starting materials can be fed into the extruder or kneader singly or as premix. They are preferably added in the form of powdered or granulated premixes. Thus, the liquid or oily surface-active substance can previously be mixed with another starting material to give free-flowing granules. Addition of the surface-active substance in liquid form, for example by liquid pumps, which are preferably heated in the case of semisolid substances, is likewise possible.

It is also possible first to dissolve the active substance in the surface-active substance, and then to granulate this mixture with the polymer. In this case, the active ingredient must not itself melt.

It may also be advisable for temperature-sensitive active ingredients first to melt the other starting materials and only then to add the active ingredient.

The starting materials are accordingly processed together to form a melt, which is processed by input of mechanical energy, in particular in the form of shear forces, to a homogeneous composition.

The homogenous melt is then extruded through a die or a breaker plate and subjected to shaping. This can take place by pelletizing the extrudate by usual techniques, for example using rotating knives or compressed air, to result in pellets or granules. The shaping can also take place as described in EP-A 240 906, by the extrudate being passed between two counter-rotating calender rolls and being shaped directly to tablets. It is likewise possible to pass the melt through the open extruder head and, after solidification, further process where appropriate by grinding or by suitable granulation equipment such as roll mills or compacting units.

Granules or pellets can then be processed to tablets in conventional tablet presses. It is also possible for the preparations which have been initially obtained by calendering already in the form of mechanically stable tablets to be subjected to a grinding process and then to be compressed to tablets in a conventional way. If required, the tablets can then be provided with a conventional coating.

It is surprisingly possible according to the invention to obtain tablets which, despite a high proportion of liquid or semisolid surface-active substances, have good mechanical stability and are not prone to be tacky or to soften. The good dimensional stability of the preparations makes it unnecessary, according to the invention, to use them for filling capsules.

The resulting drug forms comprise the active ingredient embedded amorphously. The preferred result is solid dispersions in which the active ingredient is in the form of a molecular dispersion. The drug forms according to the invention make it possible for even active ingredients of low solubility to be sufficiently solubilized and stably dispersed in aqueous medium.

The preparations according to the invention form, after dissolving in aqueous medium, in particular at pH 1, for at least one hour a stable solubilizate or a stable dispersion, in which the active ingredient is preferably not in crystalline form.

EXAMPLE 1

50 g of a powdered mixture of 40% by weight of esuprone, 35% by weight of polyvinylpyrrolidone K 17

49

(PVP) and 25% by weight of polyoxyethylene glycerol trihydroxystearate 40 as surface-active substance were produced by initially producing a powdered premix of esupron and the PVP, into which the surface-active substance was mixed at 20° C. until homogeneous granules resulted.

EXAMPLE 2

The granules obtained in Example 1 were kneaded at a temperature of 100° C. in a heatable kneader (supplied by Haake) to a homogeneous melt. After cooling to 20° C., the melt was solid and was broken into small fragments.

EXAMPLE 3

250 g of the granules obtained in Example 1 were stirred into 50 ml of water at room temperature. There was formation after a few minutes of a cloudy suspension from which crystalline esuprone sedimented.

EXAMPLE 4

The melt granules obtained in Example 2 were stirred into water in analogy to Example 3. After only a few minutes an opalescent solution formed, and no esuprone had separated out of this even after one hour.

We claim:

1. A mechanically stable pharmaceutical presentation for oral administration, comprising one or more active ingredients, at least one melt-processable matrix-forming excipient selected from the group consisting of homo- and copolymers of N-vinylpyrrolidone, acrylate polymers and cellulose derivatives, and more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C., obtainable by mixing the starting materials in the melt without addition of solvents and subsequently shaping.

2. A preparation as claimed in claim 1, comprising from 15 to 25% by weight of surface-active substance.

3. A preparation as claimed in claim 1, comprising a surface-active substance with an HLB of from 10 to 15.

4. A preparation as claimed in claim 1, comprising a surface-active substance with a drop point in the range from 20 to 40° C.

5. A preparation as claimed in claim 1, comprising macrogol glycerol hydroxystearate, polyoxyethylene ricinoleate 35 or PEG 660 12-hydroxystearate as surface-active substance.

6. A process for producing mechanically stable pharmaceutical presentations as claimed in claim 1 by a melt process, which comprises processing one or more active ingredients, at least one melt-processable matrix-forming excipient and more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C., in the melt to a homogeneous mixture, and shaping the latter to presentations.

* * * * *

EXHIBIT 2

50

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34119 A2

(51) International Patent Classification[7]: A61K 9/14

(21) International Application Number: PCT/US00/31072

(22) International Filing Date:
10 November 2000 (10.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/438,994 12 November 1999 (12.11.1999) US

(71) Applicant: ABBOTT LABORATORIES [US/US]; D377/AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

(72) Inventors: KRILL, Steven, K.; 5133 Pembrook Court, Gurnee, IL 60031 (US). FORT, James, J.; 2700 Leafield Terrace, Midlothian, VA 23113 (US). LAW, Devalina; 835C Country Club Drive, Libertyville, IL 60048 (US). SCHMITT, Eric, A.; 310 Evergreen Court, Libertyville, IL 60048 (US). QIU, Yihong; 6118 Honeysuckle Lane, Gurnee, IL 60031 (US).

(74) Agents: SICKERT, Dugal, S. et al.; D377/AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

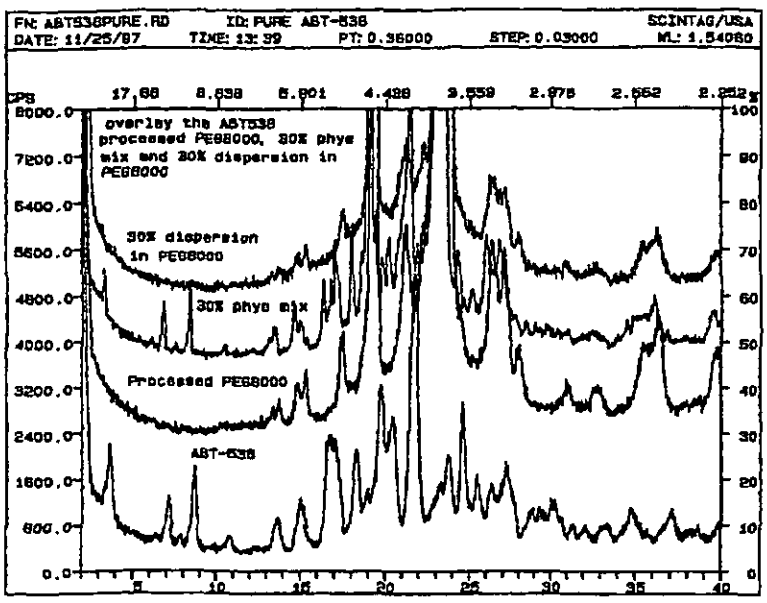
(81) Designated States *(national)*: CA, JP, MX.

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

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

(54) Title: INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION



(57) Abstract: A pharmaceutical composition is disclosed which comprises a solid dispersion of a pharmaceutical compound in a water soluble carrier, such as polyethylene glycol (PEG), and a crystallization inhibitor, such as polyvinylpyrrolidone or hydroxypropylmethylcellulose. The solid dispersion may optionally be encapsulated in hard gelatin capsules, compressed into a tablet, or may be granulated wiht a pharmaceutically acceptable granulating agent. Also disclosed are methods of making said solid dispersion and methods of treatment employing said solid dispersion.

WO 01/34119 A2

5 AUG 2010

51

INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION

Technical Field of the Invention

The instant invention relates to the fields of pharmaceutical and organic chemistry, and provides novel solid dispersion pharmaceutical formulations which demonstrate an inhibition of crystallization.

Background of the Invention

One measure of the potential usefulness of an oral dosage form of a pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength, and first pass effect. Aqueous solubility is one of the most important of these factors. When a drug has poor aqueous solubility, attempts are often made to identify salts or other derivatives of the drug which have improved aqueous solubility. When a salt or other derivative of the drug is identified which has good aqueous solubility, it is generally

identified which has good aqueous solubility, it is generally accepted that an aqueous solution formulation of this salt or derivative will provide the optimum oral bioavailability. The bioavailability of the aqueous oral solution formulation of a drug is then generally used as the standard or ideal bioavailability against which other oral dosage forms are measured.

For a variety of reasons, including patient compliance and taste masking, a solid dosage form, such as a capsule or tablet, is usually preferred over a liquid dosage form. However, oral solid dosage forms of a drug generally provide a lower bioavailability than oral solutions of the drug. One goal of the development of a suitable solid dosage form is to obtain a bioavailability of the drug that is as close as possible to the ideal bioavailability demonstrated by the oral aqueous solution formulation of the drug.

An alternative dosage form is a solid dispersion. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (or fusion), solvent, or melting-solvent methods. (Chiou and Riegelman, *Journal of Pharmaceutical Sciences*, *60*, 1281 (1971)). The dispersion of a drug or drugs in a solid diluent by

53

mechanical mixing is not included in this category. Solid dispersions may also be called solid-state dispersions.

Retroviral protease inhibiting compounds are useful for inhibiting HIV proteases *in vitro* and *in vivo*, and are useful for inhibiting HIV (human immunodeficiency virus) infections and for treating AIDS (acquired immunodeficiency syndrome). HIV protease inhibiting compounds typically are characterized by having poor oral bioavailability.

Examples of HIV protease inhibiting compounds include

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

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

N-(2(R)-hydroxy-1 (S)-indanyl)-2(R)-phenylmethyl -4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcar boxamido)-piperazinyl))-pentaneamide (indinavir);

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

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

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

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

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

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

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

While some drugs would be expected to have good solubility in organic solvents, it would not necessarily follow that oral administration of such a solution would give good bioavailability for the drug.

Polyethylene glycol (PEG) solid dispersion formulations are generally known to improve the dissolution and bioavailability of many compounds. However, Aungst *et al.* has recently demonstrated that this was unable to improve the bioavailability of an HIV protease inhibitor with a cyclic urea structural backbone, called DMP 323

55

(Aungst *et al.*, *International Journal of Pharmaceutics*, *156*, 79 (1997)).

In addition, some drugs tend to form crystals when placed in solution, which can be problematic during formulation.

Polyvinylpyrrolidone (PVP) is known to inhibit crystallization of drugs (Yohioka, M. et al., J. Pharm. Sci., 84, 983, 1995). However, prior to the instant invention, the incorporation of PVP into a second polymer matrix, such as polyethylene glycol, has never been established.

U.S. 4,610,875 teaches a process for the preparation of a stable pharmaceutical dipyridamole composition containing PVP.

U.S. 4,769,236 teaches a process for the preparation of a stable pharmaceutical composition with a high dissolution rate in the gastrointestinal tract containing PVP, wherein the pharmaceutical agent is hydroflumethiazide, dipyridamole, hydrochlorothiazide, cyclothiazide, cyclopenthiazide, polythiazide, methyldopa, spironolactone, quinidine, cyanidol, metronidazole, ibuprofen, naproxen, erythromycin, glaphenin, furosemide, suloctidil, nitrofurantoin, indomethacin, flavoxate,

phenobarbitol, cyclandelate, ketoprofen, natridrofuryl, or triamterene.

Thus, it would be a significant contribution to the art to provide a stable solid dispersion pharmaceutical formulation which demonstrates a lack of crystallization.

57

Summary of the Invention

The instant invention provides a stable solid dispersion pharmaceutical formulation comprising a pharmaceutical compound, a water soluble carrier, such as polyehtylene glycol (PEG), and a crystallization inhibitor, such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

Also provided by the instant invention is a pharmaceutical composition comprising a stable solid dispersion as described above with additional pharmaceutically acceptable carriers, diluents, or excipients.

Additionally provided by the instant invention is a method for preparing a stable solid dispersion as described above.

The instant invention still further provides methods of treatment comprising administering an effective amount of a stable solid dispersion as described above to a mammal in need of such treatment.

Brief Description of the Figures

Figure 1 illustrates the PXD patterns showing that Amorphous ABT-538 can be isolated within PEG alone.

Figure 2 illustrates the PXD patterns showing that Amorphous ABT-538 can be isolated with a PVP/PEG matrix.

Figure 3 illustrates the DSC thermograms of PEG, ABT-538, a physical mixture of the two and a solid dispersion. The absence of ABT-538 melting in the dispersion confirms the above PXD data showing amorphous ABT-538 present in the dispersion.

Figure 4 illustrates the DSC thermograms of PVP/PEG, ABT-538, a physical mixture of the two and a solid dispersion. The absence of ABT-538 melting in the dispersion confirms the above PXD data showing amorphous ABT-538 present in the dispersion.

Figure 5 illustrates the effect of PEG or PVP on the *crystallization rate of amorphous ritonavir*. The heat of fusion was used to calculate percent crystallized. In the presence of PVP the crystallization rate is slower.

Figure 6 illustrates the inhibition of crystallization using PVP.

Figure 7 illustrates PXD patterns of ABT-538 dispersions with and without PVP stored at 50°C. The data

demonstrate the improved physical stability of amorphous ABT-538 on storage.

Figure 8 illustrates PXD patterns of fenofibrate dispersions with and without PVP.

Figure 9 illustrates PXD patterns of fenofibrate dispersions with and without PVP and PEG.

Figure 10 illustrates PXD patterns of fenofibrate dispersions with and without PEG.

Figure 11 illustrates PXD patterns of fenofibrate dispersions with and without 10% PVP and PEG.

Figure 12 illustrates PXD patterns of griseofulvin dispersions with and without PEG.

Figure 13 illustrates PXD patterns of griseofulvin dispersions with and without PEG and PVP.

Figure 14 illustrates PXD patterns of griseofulvin dispersions with and without PEG.

Figure 15 illustrates PXD patterns of griseofulvin dispersions with and without PEG and PVP.

Detailed Description of the Invention

This invention pertains to the preparation of solid dispersion systems for pharmaceuticals which demonstrate a lack of crystallization.

The invention involves dispersion in a hydrophilic matrix of pharmaceuticals which exhibit poor aqueous solubility. The intent of such a formulation is to improve the aqueous dissolution properties and ultimately achieve improved bioavailability. Typically, the intent of such systems is to generate a dispersion of amorphous (high energy) drug within the matrix. The presence of the high energy drug form usually improves the dissolution rate. However, these systems are not often physically stable. The drug can crystallize over time, causing the loss of the desired properties and reduced shelf-life. The current invention enhances the physical stability of such formulations, thereby making this type of formulation more feasible.

In the instant invention, PEG 8000 is used as the hydrophilic matrix. Also employed in this formulation is polyvinylpyrrolidone (PVP), which is an example of a hydrophilic, amorphous polymer, and is used to inhibit crystallization. Other hydrophilic, amorphous polymers

61

include hydroxypropylmethylcellulose (HPMC), or other pharmaceutically acceptable hydrophilic, amorphous polymers. Specifically, PVP PF 17 is used within the PEG matrix to inhibit the crystallization of the drug of interest. A range of 1%-95% (w/w) of PVP can be employed, with a range of 1%-15% (w/w) being preferred.

The benefits of incorporating PVP into the PEG matrix are two fold. Firstly, processing PVP can be difficult due to its hygroscopicity. Secondly, when PVP dissolves a viscous layer at the solid-liquid interface forms. This viscous region can hinder dissolution of the drug. Another benefit of adding PVP is an increase in amorphous volume of the polymer matrix where drugs may reside. Since polyethylene glycols tend to be highly crystalline, this increase in amorphous volume could be important for fast dissolution. PVP has the added advantage of having a high Tg, which imparts stabilization of amorphous regions by reducing mobility. Therefore, this invention affords the benefits of the PEG properties in a dispersion along with those of PVP.

A solid (molecular) dispersion comprising an HIV protease inhibiting compound may be prepared by dissolving or dispersing the HIV protease inhibiting compound in a sufficient amount of an organic solvent followed by

dispersion into a suitable water soluble carrier. Suitable organic solvents include pharmaceutically acceptable solvents such as methanol, ethanol, or other organic solvents in which the protease inhibitor is soluble. Suitable water soluble carriers include polymers such as polyethylene glycol (PEG), pluronics, pentaeythritol, pentaeythritol tetraacetate, polyoxyethylene stearates, poly-ε-caprolactone, and the like.

The organic solvent (preferably ethanol) may then be evaporated away, leaving the drug dispersed/dissolved in the molten matrix, which is then cooled. The solid matrix has the compound finely dispersed (molecular dispersion) in such a way that dissolution of the drug is maximized, thus improving the bioavailability of a drug exhibiting dissolution rate limited absorption. Ease of manufacturing is also an attribute to this type of formulation. Once the organic solvent is evaporated to yield a solid mass, the mass may be ground, sized, and optionally formulated into an appropriate delivery system. Thus, by improving the dissolution of a poorly water soluble drug, the drug in a suitable carrier may be filled into a gelatin capsule as a solid, or the matrix may potentially be compressed into a tablet.

The delivery system of the present invention results in increased solubility and bioavailability, and improved dissolution rate of the HIV protease inhibiting compound.

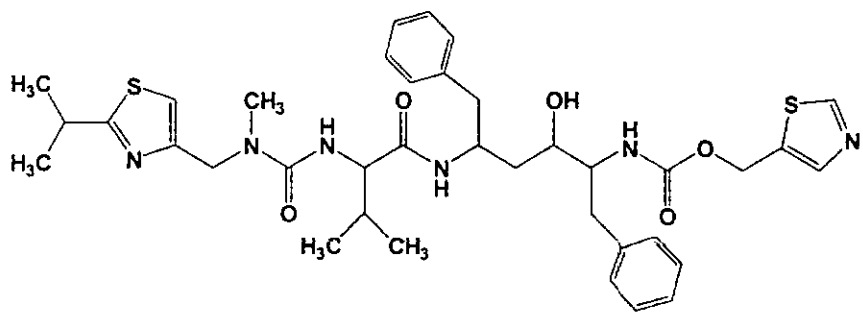
Other pharmaceutically-acceptable excipients may be added to the formulation prior to forming the desired final product. Suitable excipients include lactose, starch, magnesium stearate, or other pharmaceutically-acceptable fillers, diluents, lubricants, disintegrants, and the like, that might be needed to prepare a capsule or tablet.

The resulting composition comprising the pharmaceutical compound may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into capsules, or made into tablets for oral administration, or delivered by some other means obvious to those skilled in the art. The composition can be used to improve the oral bioavailability and solubility of said HIV protease inhibiting compound.

Total daily dosing of the pharmaceutical compound may be administered to a human in single or divided doses in amounts, for example, from 0.001 to 1000 mg/kg body weight daily, but more usually 0.1 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of

submultiples thereof to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drugs administered in combination and the severity of the particular disease undergoing therapy.

One type of pharmaceutical compound that may be employed in the practice of the present invention is an HIV protease inhibitor. An example of an HIV protease inhibitor is ABT-538 (ritonavir), the chemical structure of which is represented hereinbelow as a compound of formula I



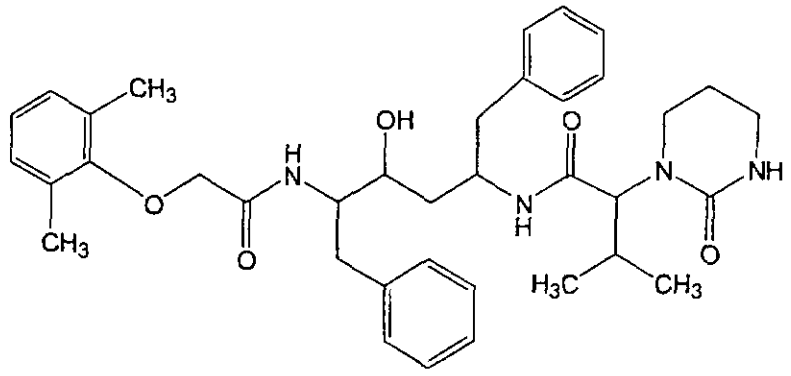
I

A compound of formula I is an HIV protease inhibitor marketed by Abbott Laboratories under the tradename Norvir®, with the common name ritonavir [(2S,3S,5S)-5-(N-(N-((N-

65

methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane]. This and other compounds as well as methods for preparing same are disclosed in U.S. Patent Nos. 5,648,497 and 5,541,206, the disclosures of which are herein incorporated by reference.

Additional HIV protease inhibitors which may be formulated into a solid dispersion of the instant invention include compounds of formula II



II

A compound of formula II is known as ABT-378 ((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane). This and other compounds, as well as methods for preparing same, are identified in U.S. Patent No. 5,914,332, the disclosure of which is herein incorporated by reference.

Other types of pharmaceutical compounds which may be employed in the practice of the present invention include but are not limited to antibacterial agents, antifungal agents such as griseofulvin, chemotherapeutic agents, agents for treating hyperlipidemia such as fenoifibrate, and the like.

The following Examples are provided to further illustrate the present invention.

EXAMPLES

Equipment:

DSC

DSC measurements were made using a Mettler DSC 30 unit. Samples (4-7mg) were sealed in standard 40 μl aluminum crucibles with a single hole punched in the lids. An empty crucible of the same type was used as a reference.

X-ray Powder Diffraction Analysis

An X-ray powder diffraction (XPD) pattern was obtained with a Scintag® XDS 2000 θ/θ diffraction system equipped with a 2 kW normal focus X-ray tube and a liquid nitrogen cooled germanium solid state detector.

Isothermal Calorimetry (TAM)

The recrystallization reactions of 30% ABT-538 in PEG or PEG:PVP (95:5) solid dispersions were monitored via isothermal calorimetry (Thermometric 2277 Calorimeter) at 40 °C. Since crystallization is an exothermic process, a positive power output indicates

crystallization. The magnitude of the power output at any time is proportional to the rate of crystallization. XPD was used to confirm crystallization.

HPLC

The potency values of all the dispersions as well as the dissolution sample concentrations were determined via HPLC.

The effect of PVP on the crystallization rate of the drug in each dispersion system (drug with polymer) was investigated with the appropriate experimental technique. The results of these studies are provided in Figures 1-15.

Three pharmaceuticals of different properties were employed to demonstrate the general applicability of the instant invention. These compounds are identified in Table 1 below:

Table 1

Model Compounds

Property/Compound	ABT-538	Fenofibrate	Griseofulvin
MW (g/mole)	720.96	360.84	352.77
T_m (°C)	124	79	218.13
T_g (°C)	45.8	-21.7	91

Example 1

Dispersion Preparations

A. Ritonavir (ABT-538) Dispersion Preparation:

The samples were prepared by dissolving ABT-538 in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The flask was vortexed and then placed in a water bath maintained at 75 °C. The PEG 8000 was added to the hot alcohol solution with continual swirling until the PEG melted. The flask was then attached to a rotary evaporator, immersed in the water bath (75 °C) under vacuum for 15 minutes to remove the ethanol. After the majority of ethanol had evaporated, the flask was immersed in an ice

bath for 15 minutes. The contents of the flask were then vacuum dried at room temperature overnight to remove residual alcohol. The dispersion was removed from the flask, gently ground, and sized to 40-100 mesh size. The drug loads used for these dispersions were 10, 20 and 30% w/w.

B. ABT-378 Dispersion Preparation:

The solid dispersion of 30% ABT-538 in 95:5 PEG8000:PVP was prepared by dissolving the ABT-538 and PVP 17 PF in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The remainder of the process was as described above. A 30% ABT-538 dispersion in 85:15 PEG8000:PVP was also prepared similarly as were dispersions of 10 or 20% PVP 17PF in PEG 8000 without drug.

C. Fenofibrate Dispersion Preparation:

15% Fenofibrate in PEG 8000:

Both fenofibrate and PEG 8000 were sized to 40-100 mesh prior to mixing with a spatula on weighing paper. The mixture was then added to a 25 ml beaker and heated to 85°C in a water bath until the all the material had

melted. The molten solution was then poured onto a chilled X-ray sample holder to rapidly solidify the solution. The solid sample was immediately used to monitor the crystallization rate via X-ray powder diffraction.

15% Fenofibrate in 90:10 PEG 8000:PVP:

Fenofibrate (40-100 mesh) was added to the 90:10 PEG 8000:PVP control dispersion (see above) which was also sized to 40-100 mesh and mixed with spatula on a piece of weighing paper. The mixture was then processed as described above for the 15% fenofibrate dispersion in PEG 8000.

D. Griseofulvin Dispersion Preparation:

15% griseofulvin in PEG 8000:

Both griseofulvin and PEG 8000 were sized to 40-100 mesh prior to mixing on a weighing paper with a spatula. The sample was then added to an 4 ml stainless steel vessel which was sealed under a N_2 atmosphere. The vessel was then immersed into an oil bath maintained at 180°C. The sample was occasionally shaken to mix the molten contents. After 5 minutes the vessel was immersed into a

liquid N_2 bath for 30 minutes. The contents of the vessel were removed, gently ground and sized to 40-100 mesh.

15% griseofulvin in 80:20 PEG 8000:PVP:

This dispersion was prepared in a similar manner as describe above for the 15% griseofulvin in PEG 8000 dispersion using the 80:20 PEG8000:PVP control dispersion.

E. Results:

ABT-538:

Figure 1 shows the X-ray powder diffraction (XPD) pattern of ABT-538, processed PEG 8000, a physical mixture of the two components and the 30% solid dispersion. A similar plot is shown in Figure 2 with PVP incorporated into the matrix. It is apparent from these figures that ABT-538 is not crystalline within either matrix. Figure 3 shows the DSC thermograms of ABT-538, PEG8000, the 30% physical mixture and the dispersion. A similar plot is seen in Figure 4 for the PEG:PVP dispersion. The endotherm associated with drug melting can clearly be discerned from the other components. Thus, it is possible to follow the kinetics of ABT-538

crystallization via DSC measurements. Crystallization kinetics were determined by heating the samples to 85°C, holding them isothermally for predetermined times followed by heating through the melting transition temperature of ABT-538. The heats of fusion were determined and ratioed against the heat of fusion of the drug melting in the physical mixture, giving the fraction crystallized. The percent crystallized as a function of isothermal (85°C) hold time is shown in Figure 5. It is clear from this experiment that the presence of PVP within the matrix suppresses the crystallization rate of ABT-538.

The crystallization rate was also followed via the heat associated with crystallization of ABT-538 using a isothermal calorimetry. The shapes and magnitudes of the crystallization peaks in Figure 6 indicate that ABT-538 crystallizes more readily in the PEG matrix as compared to the PEG:PVP matrix. This stabilizing effect of PVP is also reflected in the times required for complete crystallization (time to reach baseline) which were <10 hours for PEG and >30 hours for PEG:PVP (95:5). These data support the previous DSC results.

An additional study was performed with a dispersion containing 15% PVP. The samples were held at 50°C (above

the T_g of ABT-538) and X-ray diffraction patterns were measured over time to monitor for the appearance of crystalline ABT-538. Figure 7 shows that in the presence of PVP, crystalline ABT-538 is not present after 272 hours, while in PEG8000 alone crystalline drug is detected at 233 hours (and before, data not shown).

Fenofibrate:

Figure 8 shows the XPD patterns of PEG 8000, fenofibrate, a 15% physical mixture and the 15% fenofibrate solid dispersion. The figure illustrates that the fenofibrate is X-ray-amorphous within the matrix. A similar plot with the XPD patterns for the 15% fenofibrate dispersion in a 90:10 PEG 8000:PVP matrix is presented in Figure 9. Again, the fenofibrate is amorphous. Upon storage at 25°C, the fenofibrate begins to crystallize in the PEG 8000 matrix within 1 hour (Figure 10). Additional crystallization follows upto 12 hours, when the experiment was terminated. In the presence of PVP (Figure 11), the fenofibrate does not crystallize in the timeframe of the experiment. This clearly demonstrates the inhibitory effects of PVP on crystallization within the PEG 8000 matrix.

75

Griseofulvin:

Similar XPD patterns for the griseofulvin dispersion in PEG 8000 and 80:20 PEG 8000:PVP matrices are shown in Figures 12 and 13, respectively. In both instances, amorphous griseofulvin is isolated within the respective matrices. The XPD rate of crystallization experiments show that after one hour at 25°C, griseofulvin begins to crystallize (Figure 14). However, in the presence of PVP (Figure 15), crystallization is not observed even after 15 hours under the same conditions. This again demonstrates the inhibitory effects of PVP amorphous drug crystallization within a PEG matrix.

E. Conclusions:

The data presented demonstrate that PVP incorporated within a hydrophilic matrix, such as PEG 8000, inhibits crystallization of drug molecules having varying physicochemical properties. Thus, the instant invention has a broad application to development of viable solid dispersion formulations where the high energy amorphous (non-crystalline) form of a drug is desired.

Example 2

Stability of Dispersion in Molten PEG 8000

The stability of the dispersion of ABT-538 in PEG 8000 in the molten state at 70 °C was examined. Individual approximately 5 mg quantities of the dispersion (aged for 6 weeks at room temperature) were placed in 4 ml glass vials. These vials, with the exception of the initial time point, were placed in a 70 °C oven which was sampled at pre-determined intervals, chilled in ice water and placed in the freezer until HPLC analysis. After all samples were collected, they were analyzed for ABT-538 content by HPLC. The HPLC system consisted of a Hitachi AS 4000 autosampler, SP 8800 ternary pump, Applied Biosystems 783 detector, and PE Nelson Data acquisition system. Other chromatographic details included a Regis Little Champ 5 cm C-18 column, a mobile phase consisting of an aqueous solution of 0.1% trifluoroacetic acid in 10 mM aqueous tetramethyl ammonium perchlorate (TMAP)/acetonitrile/methanol (55/40/5). The flow rate was 1 ml/minute, the wavelength of detection was 205 nm, and the injection volume was 100 µl. Standard curves of peak area of ABT-538 vs.

concentration in the range of interest were compared with experimentally obtained area counts.

Example 3

Protocol For Oral Bioavailability Studies

Dogs (beagle dogs, mixed sexes, weighing 7-14 kg) are fasted overnight prior to dosing, but are permitted water *ad libitum*. Each dog receives a 100 μg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. Each dog receives a single solid dosage form corresponding to a 5 mg/kg dose of the drug. The dose is followed by approximately 10 milliliters of water. Blood samples are obtained from each animal prior to dosing and at 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug administration. The plasma is separated from the red cells by centrifugation and frozen (- 30 °C) until analysis. The concentrations of parent drug is determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The parent drug area under the curve is calculated by the trapezoidal method over the time course of the study. The absolute bioavailability of each test composition is calculated by comparing the area under the curve after oral dosing to

that obtained from a single intravenous dose. Each capsule or capsule composition is evaluated in a group containing at least six dogs. The values reported are averages for each group of dogs.

5

79

WE CLAIM:

1. A pharmaceutical composition comprising a solid dispersion of a pharmaceutical compound, a water soluble carrier, and a crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone (PVP) and hydroxypropylcellulose (HPMC).

2. The composition of Claim 1 wherein said water soluble carrier is polyethylene glycol (PEG).

3. The composition of Claim 1 wherein said pharmaceutical compound is an HIV protease inhibitor dissolved in an organic solvent.

4. The composition of Claim 3 wherein said organic solvent is ethanol.

5. The composition of Claim 3 wherein said HIV protease inhibitor is 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

6. The composition of Claim 3 wherein said HIV protease inhibitor is (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane (ABT-378).

7. The composition of Claim 3 wherein said HIV protease inhibitor is a combination of 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

8. The composition of Claim 2 wherein said solid dispersion is encapsulated in a hard gelatin capsule.

9. The composition of Claim 2 wherein said solid dispersion is compressed into a tablet.

10. The composition of Claim 1 further comprising an additive or a mixture of additives independently selected

81

from the group consisting of pharmaceutically acceptable surfactants and antioxidants.

11. The composition of Claim 1 wherein said pharmaceutical compound is fenofibrate.

12. The composition of Claim 1 wherein said pharmaceutical compound is griseofulvin.

13. A method of preparing a composition of Claim 1 which comprises:

a) dissolving a pharmaceutical compound inhibitor into an organic solvent to form a solution;

b) adding a water soluble carrier to said solution to form a mixture;

c) adding PVP to said mixture of step b);

d) optionally flash evaporating said solvent;

e) optionally drying the resulting residue remaining after evaporation;

f) optionally grinding and sieving the solid dispersion to obtain a resultant product.

14. The method of Claim 13 additionally comprising encapsulating the solid dispersion in a hard gelatin capsule.

15. The method of Claim 13 additionally comprising compressing said solid dispersion into a tablet.

16. The method of Claim 13 wherein said pharmaceutical compound is an HIV protease inhibitor.

17. The method of Claim 16 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6)-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

18. The method of Claim 13 wherein said solvent is ethanol.

19. The method of Claim 13 wherein said water soluble carrier is polyethylene glycol (PEG).

20. A method of treating an HIV infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is an HIV protease inhibitor.

21. The method of Claim 20 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6)-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

22. A method of treating hyperlipidemia comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is fenofibrate.

23. A method of treating a fungal infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is griseofulvin.

85

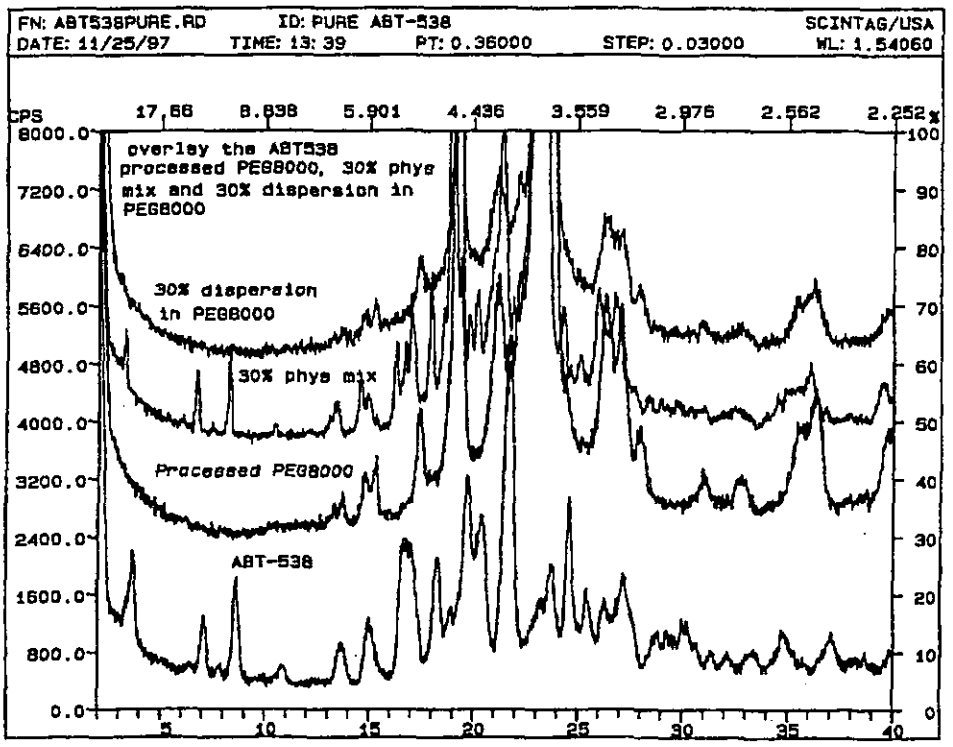

FN: ABT538PURE.RD ID: PURE ABT-538 SCINTAG/USA
DATE: 11/25/97 TIME: 13: 39 PT: 0.36000 STEP: 0.03000 WL: 1.54060
CPS
17.66 8.838 5.901 4.436 3.559 2.976 2.562 2.252 x
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
overlay the ABT538 processed PEG8000, 30% phys mix and 30% dispersion in PEG8000
30% dispersion in PEG8000
30% phys mix
Processed PEG8000
ABT-538
5 10 15 20 25 30 35 40

Figure 1

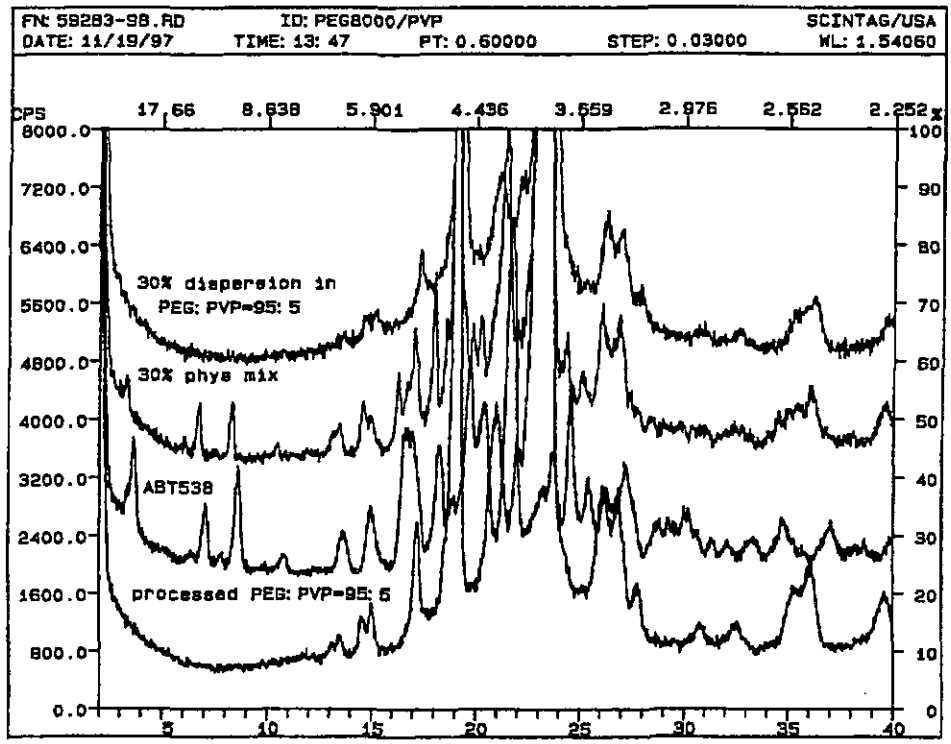


Figure 2

87

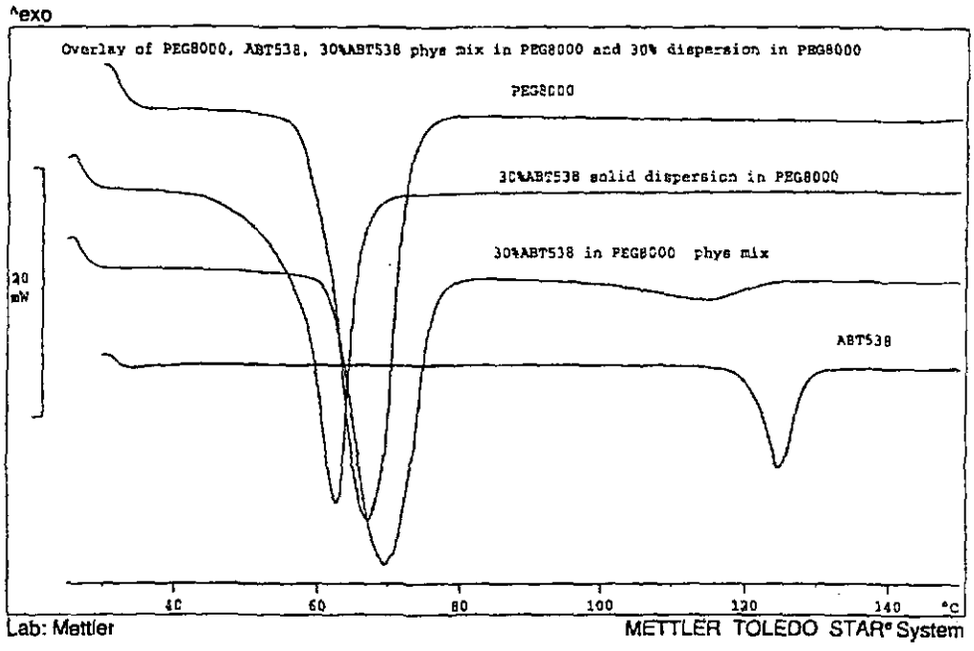

^exo
Overlay of PEG8000, ABT538, 30%ABT538 phys mix in PEG8000 and 30% dispersion in PEG8000
PEG8000
30%ABT538 solid dispersion in PEG8000
30%ABT538 in PEG8000 phys mix
ABT538
20
mW
40
60
80
100
120
140
°C
Lab: Mettler
METTLER TOLEDO STAR° System

Figure 3

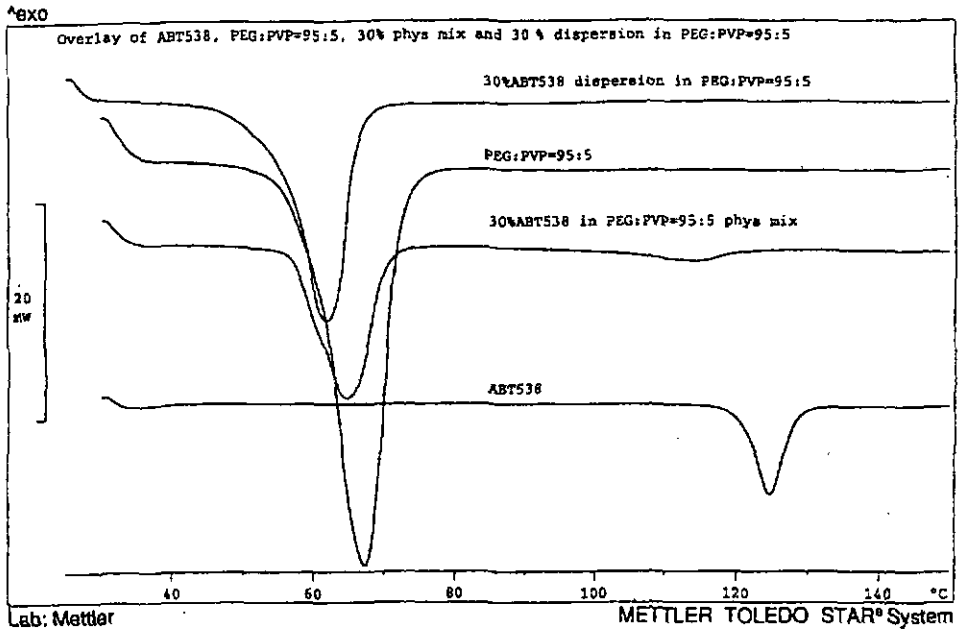


Figure 4

89

Missing at the time of publication

Figure 5

ABT-538 Isothermal Calorimetry (40°C)

Missing at the time of publication

Figure 6

91

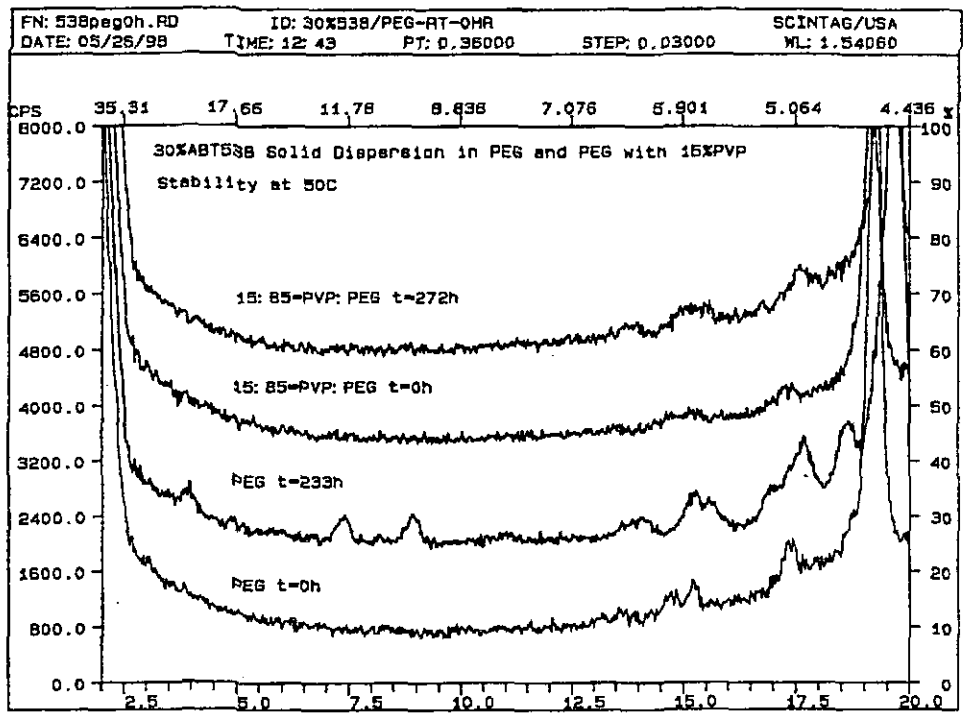

FN: 538peg0h.RD
ID: 30%538/PEG-RT-0HR
SCINTAG/USA
DATE: 05/26/98
TIME: 12: 49
PT: 0.36000
STEP: 0.03000
WL: 1.54060
CPS
35.31
17.66
11.78
8.838
7.076
5.901
5.064
4.436 X
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
30%ABT538 Solid Dispersion in PEG and PEG with 15%PVP
Stability at 50C
15: 85=PVP: PEG t=272h
15: 85=PVP: PEG t=0h
PEG t=233h
PEG t=0h
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0

Figure 7

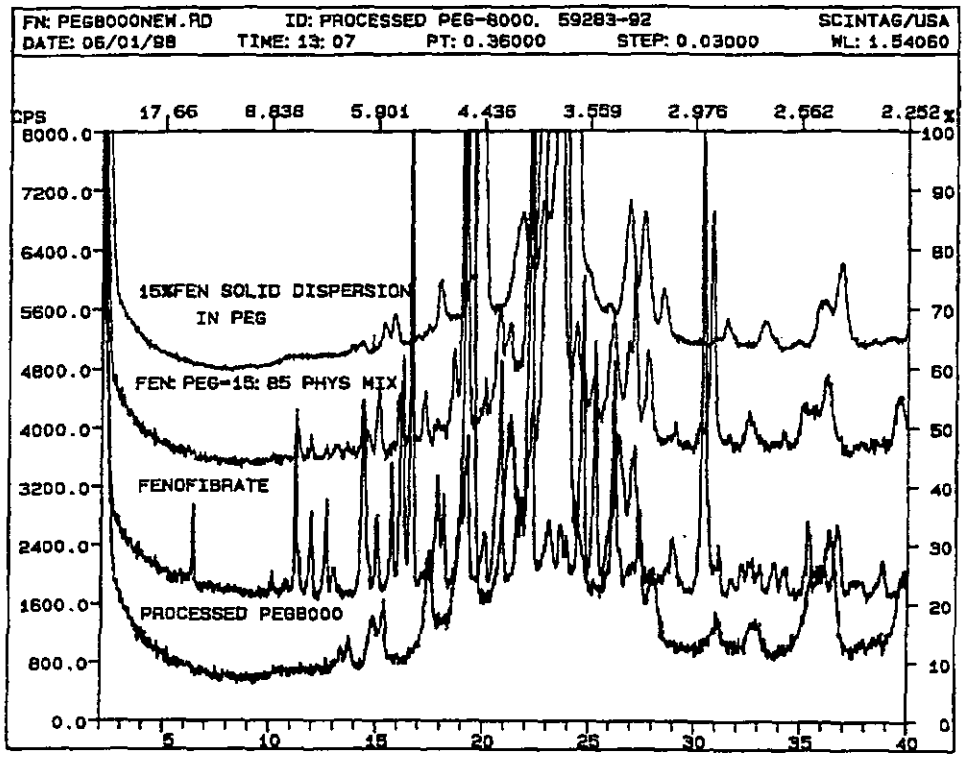


Figure 8

93

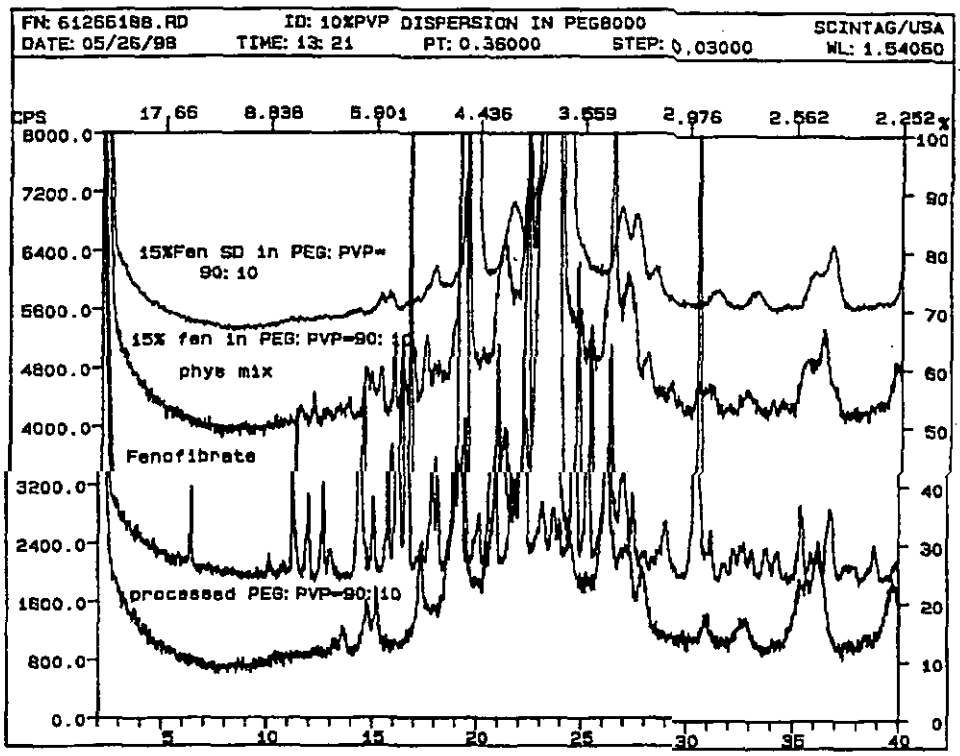

FN: 61266188.RD
ID: 10%PVP DISPERSION IN PEG8000
SCINTAG/USA
DATE: 05/26/98
TIME: 13: 21
PT: 0.36000
STEP: 0.03000
WL: 1.54060
CPS
17.66
8.838
5.901
4.436
3.559
2.976
2.562
2.252
%
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
15%Fen SD in PEG: PVP=
90: 10
15% fen in PEG: PVP=90: 10
phys mix
Fenofibrate
processed PEG: PVP=90: 10
5
10
15
20
25
30
35
40

Figure 9

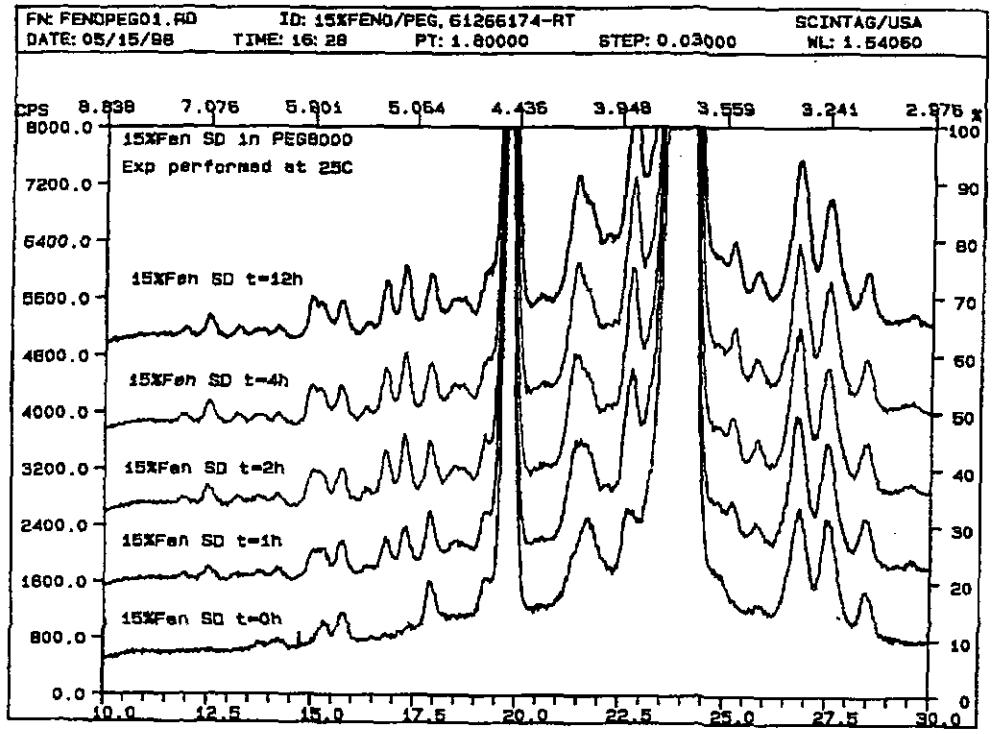


Figure 10

15

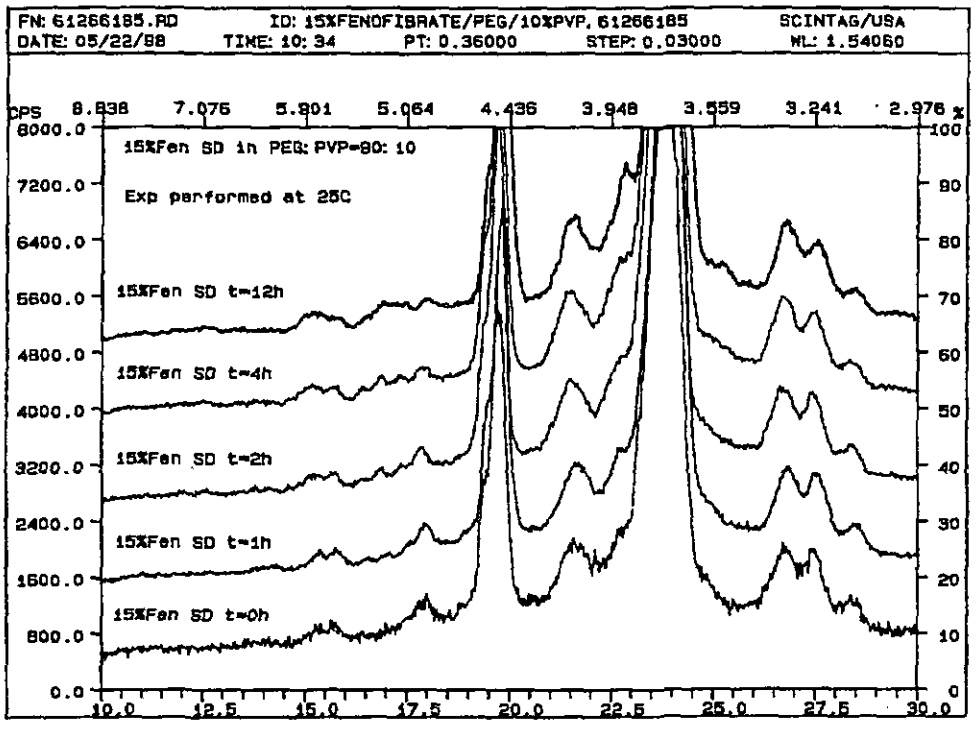

FN: 61266185.RD ID: 15%FENOFIBRATE/PEG/10%PVP, 61266185 SCINTAG/USA
DATE: 05/22/98 TIME: 10: 34 PT: 0.36000 STEP: 0.03000 WL: 1.54060
CPS 8.838 7.076 5.801 5.064 4.436 3.948 3.559 3.241 2.976 x
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
15%Fen SD in PEG: PVP=90: 10
Exp performed at 25C
15%Fen SD t=12h
15%Fen SD t=4h
15%Fen SD t=2h
15%Fen SD t=1h
15%Fen SD t=0h
10.0 12.5 15.0 17.5 20.0 22.5 25.0 27.5 30.0

Figure 11

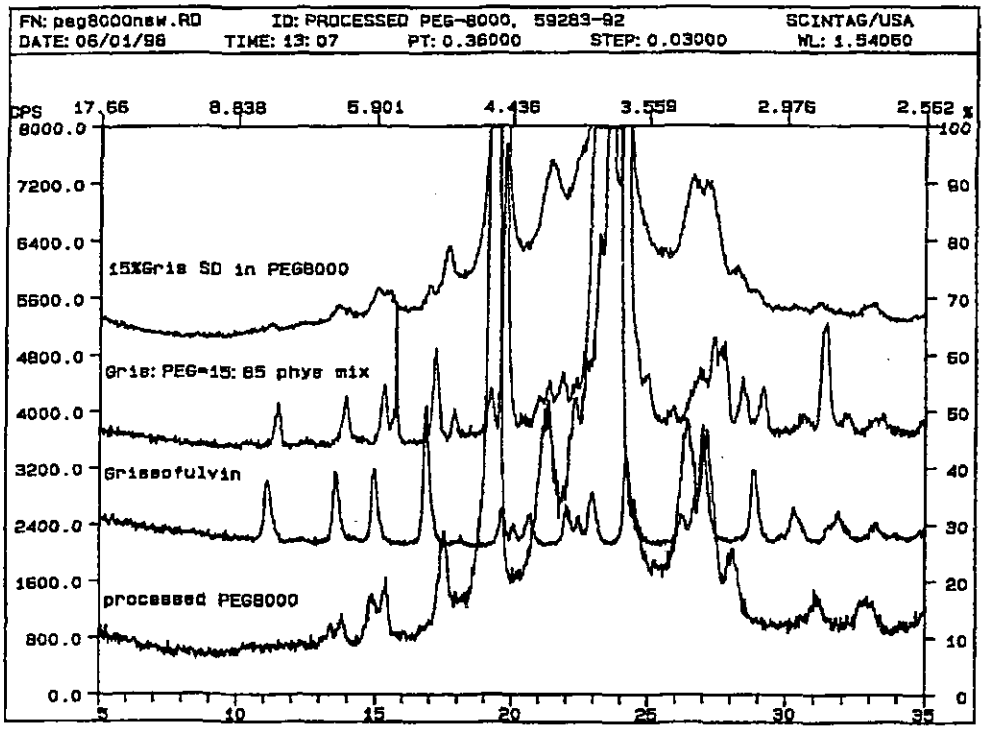


Figure 12

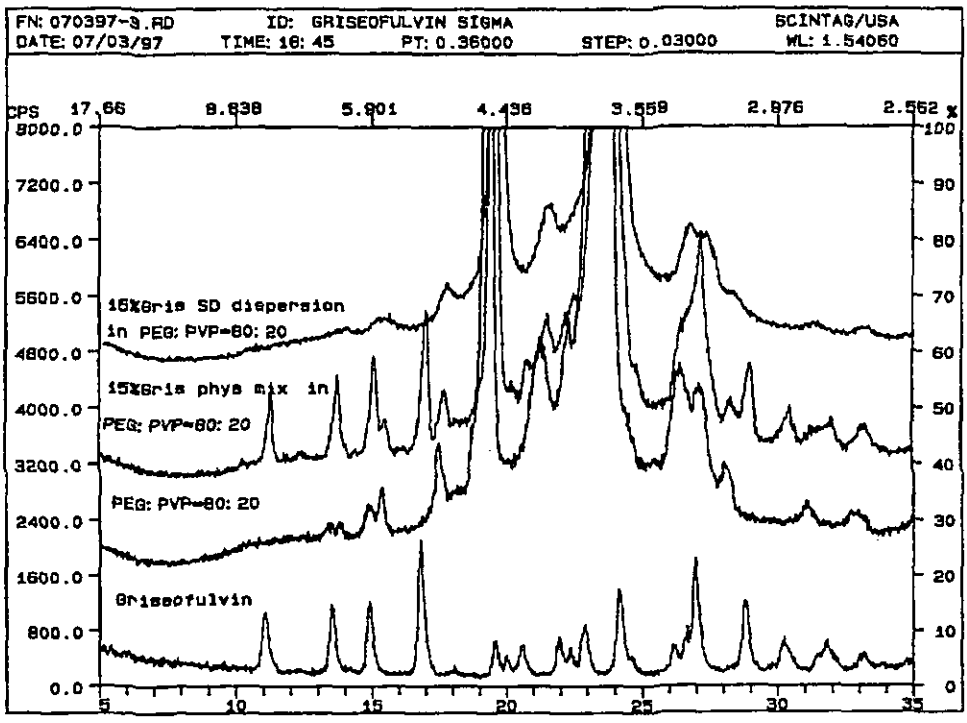

FN: 070397-3.RD ID: GRISEOFULVIN SIGMA SCINTAG/USA
DATE: 07/03/97 TIME: 16:45 PT: 0.36000 STEP: 0.03000 WL: 1.54060
CPS
17.66
8.838
5.901
4.436
3.559
2.876
2.562 X
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
15%Gris SD dispersion in PEG: PVP=80: 20
15%Gris phys mix in PEG: PVP=80: 20
PEG: PVP=80: 20
Griseofulvin
5
10
15
20
25
30
35

Figure 13

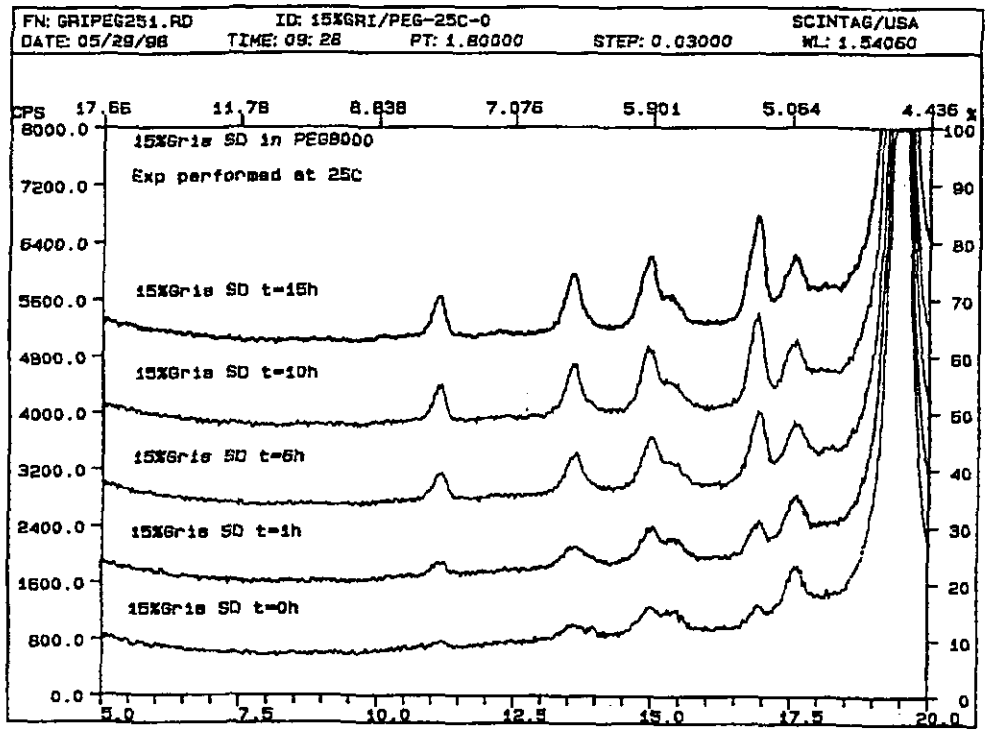


Figure 14

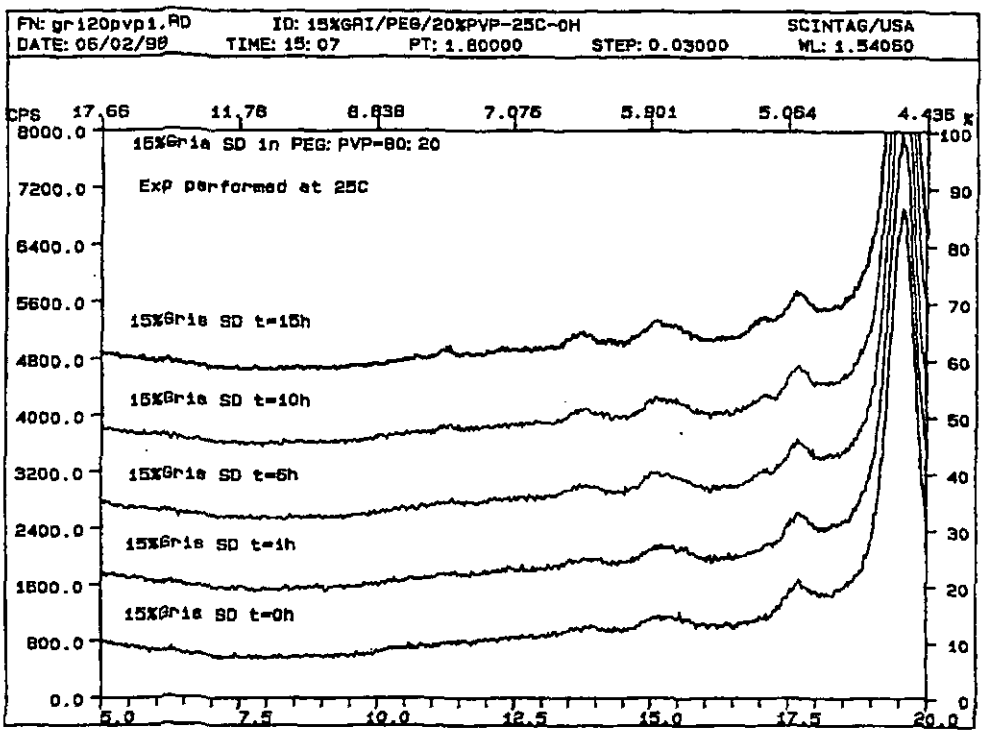

FN: gri20pvp1.RD ID: 15%GRI/PEG/20%PVP-25C-0H SCINTAG/USA
DATE: 06/02/98 TIME: 15:07 PT: 1.80000 STEP: 0.03000 WL: 1.54060
CPS
17.66
11.78
8.838
7.076
5.901
5.064
4.435
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
15%Gria SD in PEG: PVP=80: 20
Exp performed at 25C
15%Gria SD t=15h
15%Gria SD t=10h
15%Gria SD t=5h
15%Gria SD t=1h
15%Gria SD t=0h
100
90
80
70
60
50
40
30
20
10
0
5.0
7.5
10.0
12.5
15.0
17.5
20.0

Figure 15

EXHIBIT·3

100

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/74677 A2

(51) International Patent Classification[7]: A61K 31/425, 9/48, A61P 31/18

(21) International Application Number: PCT/US00/14342

(22) International Filing Date: 25 May 2000 (25.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/325,826 4 June 1999 (04.06.1999) US

(71) Applicant: ABBOTT LABORATORIES [US/US]; Dept. 377, Building AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

(72) Inventors: ALANI, Laman, A.; 3015 Gates Court, Morris Plains, NJ 07950 (US). GHOSH, Soumojeet; Apartment 2A, 219 Dittmer Lane, Lindenhurst, IL 60046 (US).

(74) Agents: STRODE, Janelle, D. et al.; Abbott Laboratories, Dept. 377, Building AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

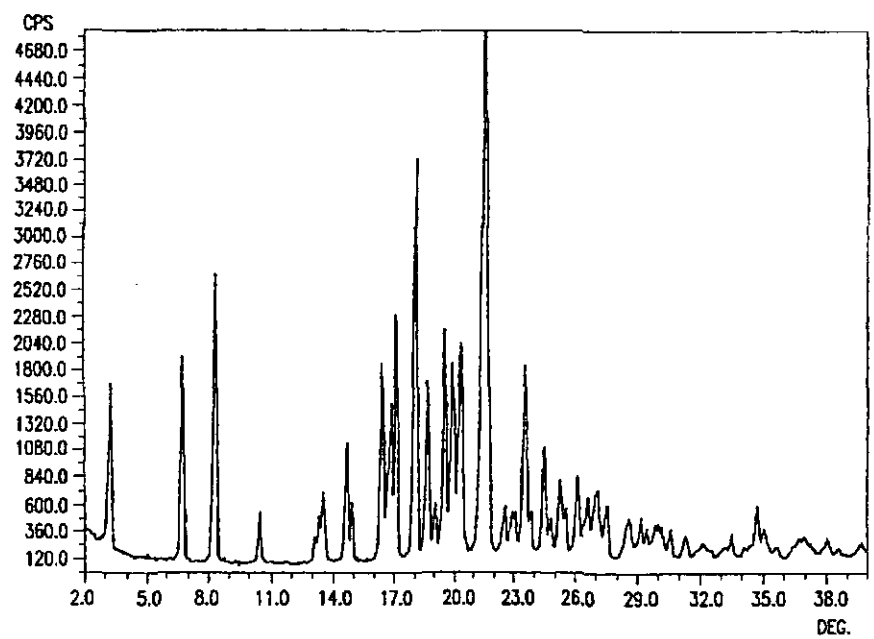
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG,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

(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).

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

[Continued on next page]

(54) Title: IMPROVED PHARMACEUTICAL FORMULATIONS



(57) Abstract: Improved pharmaceutical compositions are provided comprising one or more HIV protease inhibiting compounds having improved dissolution properties in a mixture of a fatty acid, ethanol, and water.

WO 00/74677 A2

101

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.

IMPROVED PHARMACEUTICAL FORMULATIONS

Technical Field

This invention relates to improved pharmaceutical formulations comprising at least one HIV protease inhibiting compound in a pharmaceutically acceptable solution of a long chain fatty acid, ethanol, and water, wherein said HIV protease inhibiting compound contained therein has improved solubility properties.

Background of the Invention

Inhibitors of human immunodeficiency virus (HIV) protease have been approved for use in the treatment of HIV infection for several years. A particularly effective HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir), which is marketed as NORVIR®. Ritonavir is known to have utility for the inhibition of HIV protease, the inhibition of HIV infection and the enhancement of the pharmacokinetics of compounds which are metabolized by cytochrome P450 monooxygenase. Ritonavir is particularly effective for the inhibition of HIV infection when used alone or in combination with one or more reverse transcriptase inhibitors and/or one or more other HIV protease inhibitors.

HIV protease inhibiting compounds typically are characterized by having poor oral bioavailability and there is a continuing need for the development of improved oral dosage forms for HIV protease inhibitors which have suitable oral bioavailability, stability and side effects profiles.

Ritonavir and processes for its preparation are disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996, the disclosure of which is herein incorporated by reference. This patent discloses processes for preparing ritonavir which produce a crystalline polymorph of ritonavir, known as crystalline Form I.

Another process for the preparation of ritonavir is disclosed in U.S. Patent No. 5,567,823, issued October 22, 1996, the disclosure of which is herein incorporated by reference. The process disclosed in this patent also produces ritonavir as crystalline Form I.

Pharmaceutical compositions comprising ritonavir or a pharmaceutically acceptable salt thereof are disclosed in U.S. Patent Nos. 5,541,206, issued July 30, 1996; 5,484,801, issued January 16, 1996; 5,725,878, issued March 10, 1998; and 5,559,158, issued September 24, 1996 and in International Application No. WO98/22106, published May 28, 1998 (corresponding to U.S. Serial No. 08/966,495, filed November 7, 1997), the disclosures of all of which are herein incorporated by reference.

The use of ritonavir to inhibit an HIV infection is disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996. The use of ritonavir in combination with one or more reverse

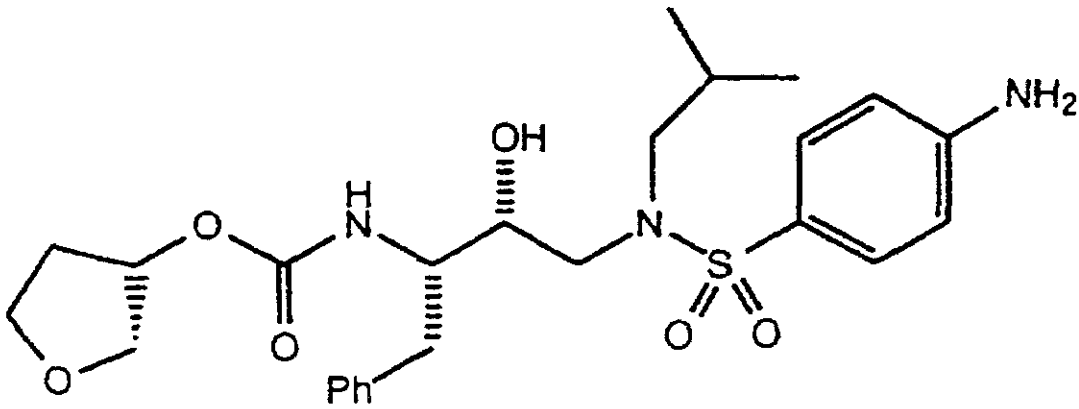
transcriptase inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,635,523, issued June 3, 1997. The use of ritonavir in combination with one or more HIV protease inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,674,882, issued October 7, 1997. The use of ritonavir to enhance the pharmacokinetics of compounds metabolized by cytochrome P450 monooxygenase is disclosed in WO 97/01349, published January 16, 1997 (corresponding to U.S. Serial No. 08/687,774, filed June 26, 1996). The disclosures of all of these patents and patent applications are herein incorporated by reference.

Examples of HIV protease inhibiting compounds include N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (for example, indinavir) and related compounds, disclosed in European Patent Application No. EP 541168, published May 12, 1993, and U.S. Patent No. 5,413,999, issued May 9, 1995, both of which are herein incorporated by reference;

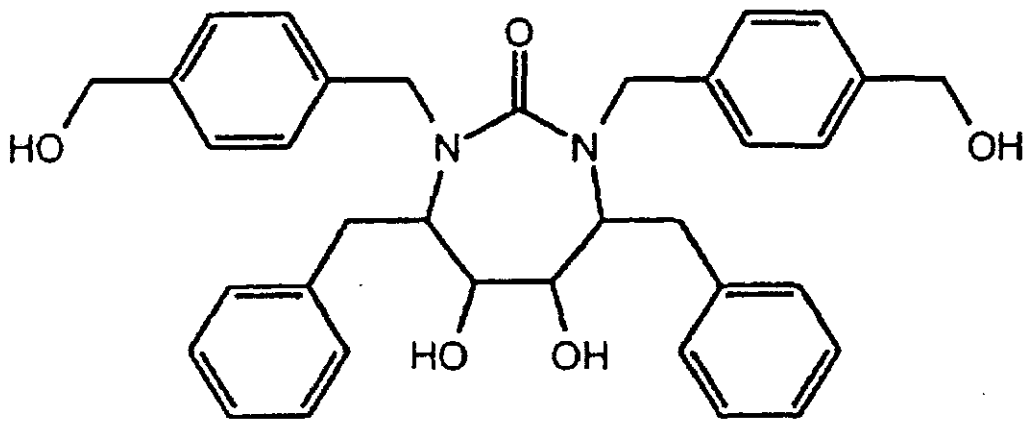
N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (for example, saquinavir) and related compounds, disclosed in U.S. Patent No. 5,196,438, issued March 23, 1993, which is incorporated herein by reference;

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide and related compounds,

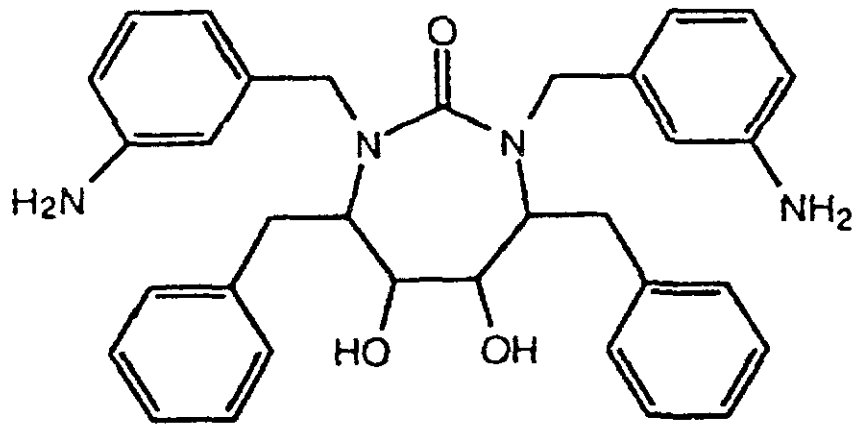
disclosed in European Patent Application No. EP532466, published March 17, 1993, which is incorporated herein by reference; 1 -Naphthoxyacetyl-beta- methylthio-Ala-(2S,3S) -3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-t-butylamide (for example, 1-Naphthoxyacetyl-Mta-(2S,3S)-AHPBA-Thz-NH-tBu), 5-isoquinolinoxyacetyl-beta-~nethylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide (for example, iQoa-Mta-Apns-Thz-NHtBu) and related compounds, disclosed in European Patent Application No. EP490667, published June 17, 1992 and Chem. Pharm. Bull. 40 (8) 2251 (1992), which are both incorporated herein by reference; [1 S-[1 R-(R-),2S*])-Nl [3-[[[(1,1 -dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1 -(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide (for example, SC-52151) and related compounds, disclosed in PCT Patent Application No. W092/08701, published May 29, 1992 and PCT Patent Application No. W093/23368, published November 25, 1993, both of which are herein incorporated by reference;



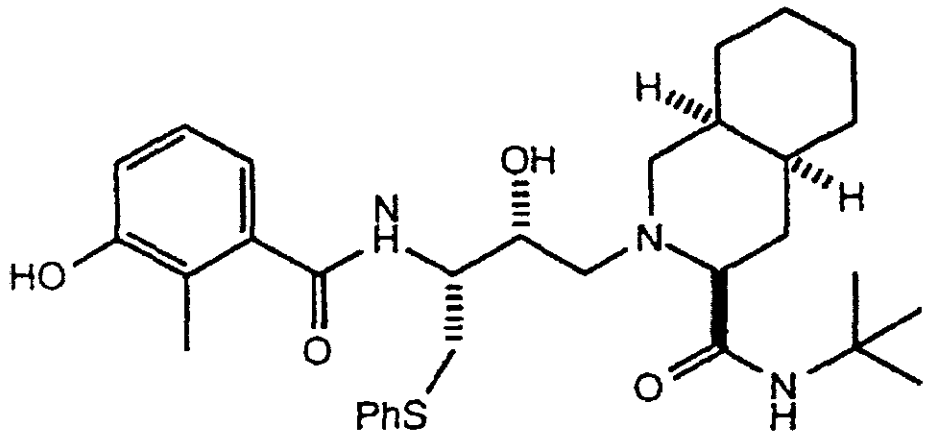
(for example, VX-478) and related compounds, disclosed in PCT Patent Application No. WO 94/05639, published March 17, 1994, which is incorporated herein by reference;



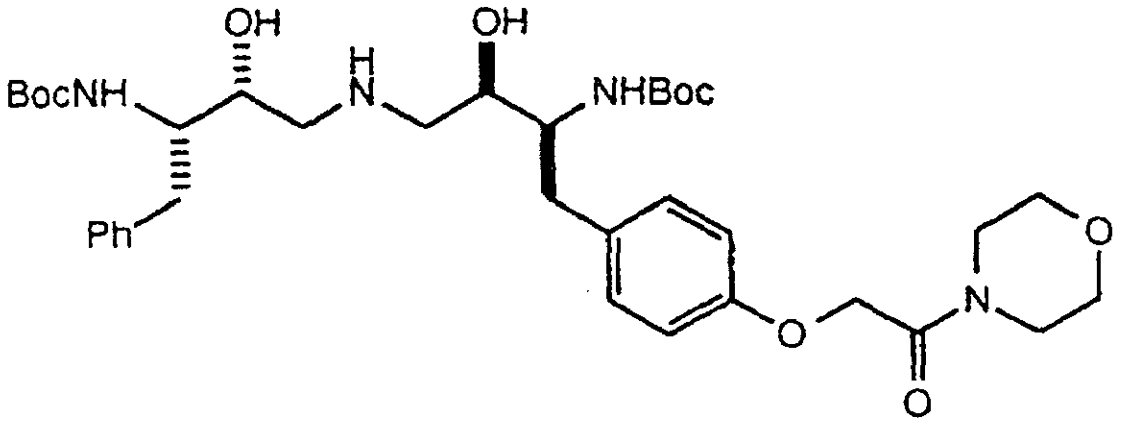
(for example, DMP-323) or



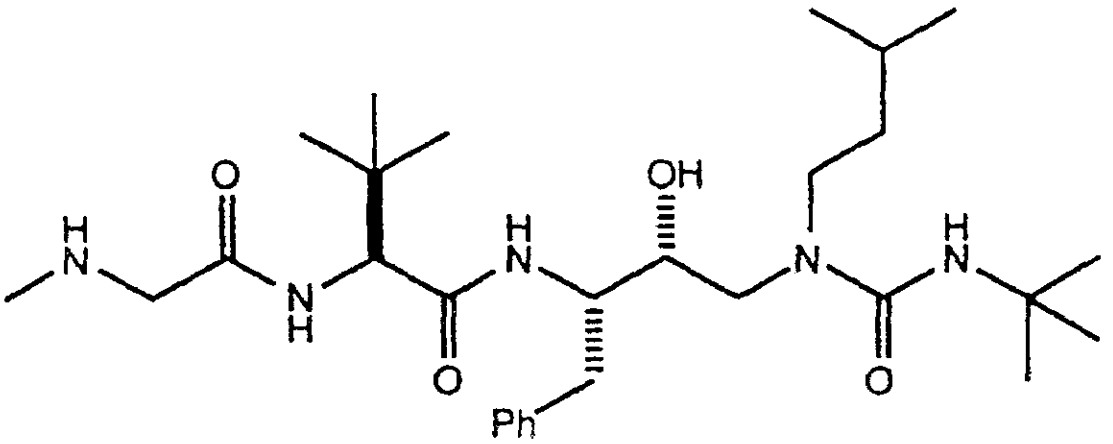
(for example, DMP-450) and related compounds, disclosed in PCT Patent Application No. WO 93/07128, published April 15, 1993, which is incorporated herein by reference;



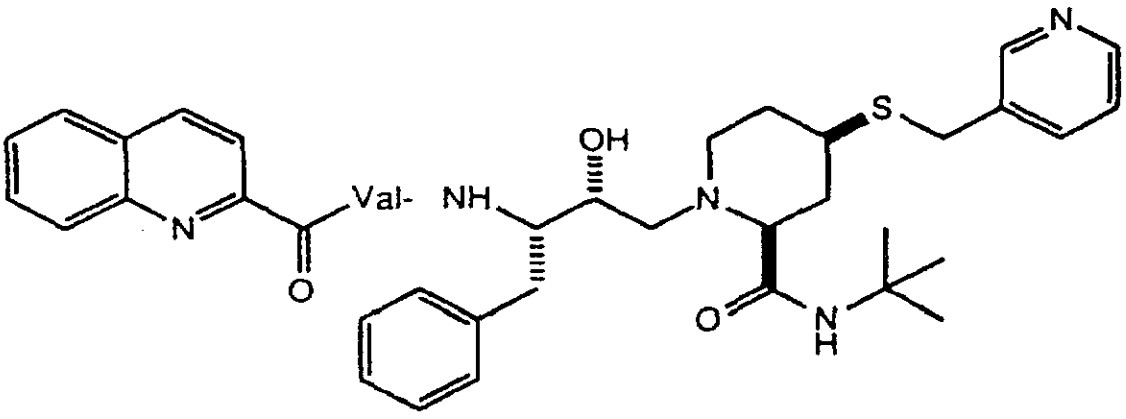
for example, AG1343, (nelfinavir)),
disclosed in PCT Patent Application No. WO 95/09843, published April 13, 1995 and U.S. Patent No. 5,484,926, issued January 16, 1996, which are both incorporated herein by reference;



(for example, BMS 186,318) disclosed in European Patent Application No. EP580402, published January 26, 1994, which is incorporated herein by reference;

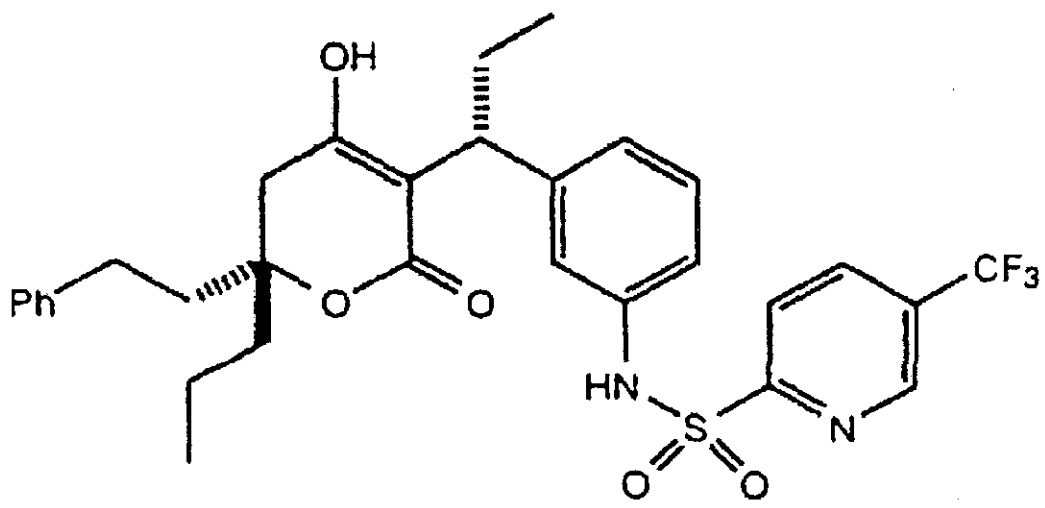


(for example, SC-55389a) and related compounds disclosed in PCT Patent Application No. WO 9506061, published March 2, 1995, which is incorporated herein by reference and at 2nd National Conference on Human Retroviruses and Related Infections, (Washington, D.C., Jan. 29 - Feb. 2, 1995), Session 88; and



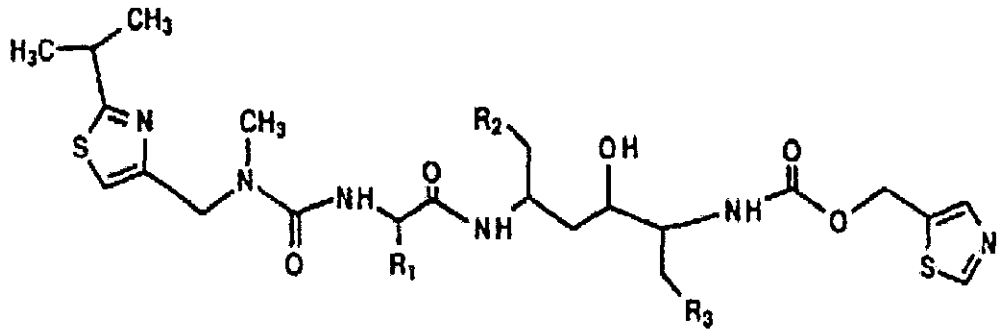
(for example, BILA 1096 BS) and related compounds disclosed in European Patent Application No. EP560268, published September 15, 1993, which is incorporated herein by reference; and

10



(for example, U-140690) and related compounds disclosed in PCT Patent Application No. WO 9530670, published November 16, 1995, which is incorporated herein by reference; or a pharmaceutically acceptable salt of any of the above.

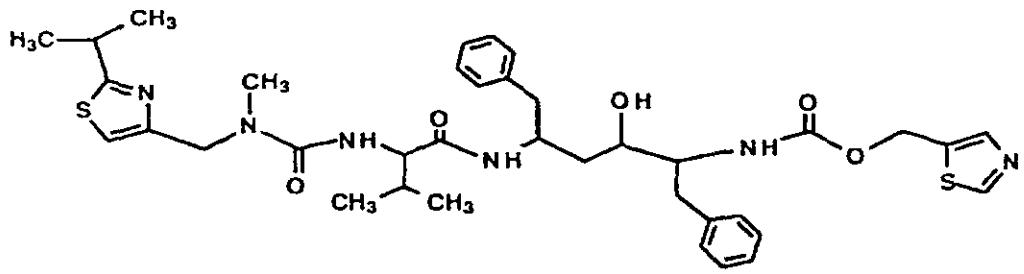
Other examples of HIV protease inhibiting compounds include compounds of formula I:



I

wherein R1 is lower alkyl and R2 and R3 are phenyl and related compounds or a pharmaceutically acceptable salt thereof, disclosed in PCT Patent Application No. WO 94/14436, published July 7, 1994 and U.S. Patent No. 5,541,206, issued July 30, 1996, both of which are incorporated herein by reference. The compounds of formula I are useful to inhibit HIV infections and, thus, are useful for the treatment of AIDS.

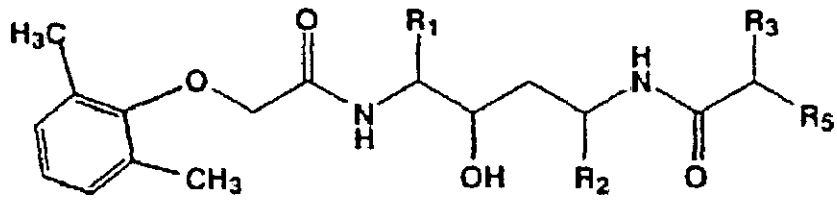
In particular, the compound of formula II, has been found to be especially effective as an inhibitor of HIV protease.



II

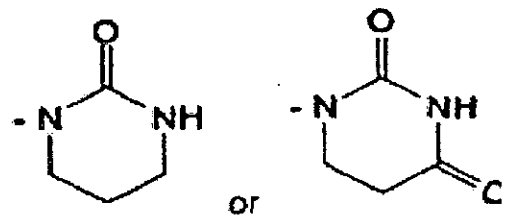
The most preferred compound of formula II is (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl methoxycarbonyl)amino)-1 6-diphenyl-3-hydroxyhexane (ritonavir; a compound of formula III) or a pharmaceutically acceptable salt thereof.

Other examples of HIV protease inhibiting compounds also include compounds of formula IV:



IV

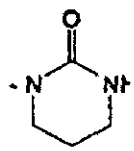
wherein R1 is benzyl, R2 is benzyl or loweralkyl, R3 is loweralkyl and R5 is



and related compounds or a pharmaceutically acceptable salt thereof, disclosed in U.S. Patent Application No. 08/572,226, filed December 13, 1996 and U.S. Patent Application No. 08/753,201, filed November 21, 1996 and International Patent

Application No. W097/21685, published June 19, 1997, all of which are incorporated herein by reference.

A preferred compound is the compound of formula IV wherein R1 and R2 are benzyl, R3 is isopropyl and R5 is



A most preferred compound of formula IV is (2S, 3S, 5S)-2-(2,6Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (a compound of formula V) or a pharmaceutically acceptable salt thereof. The preparation of a compound of formula V is disclosed in U.S. Patent Application No. 08/572,226, filed December 13, 1996 and U.S. Patent Application No. 08/753,201, filed November 21, 1996 and International Patent Application No. W0 97/21685, published June 19, 1997.

A compound of formula III has an aqueous solubility of approximately 6 micrograms per milliliter at pH >2. This is considered to be extremely poor aqueous solubility and, therefore, a compound of formula III in the free base form would be expected to provide very low oral bioavailability. In fact, the free base form of a compound of formula III,

administered as an unformulated solid in a capsule dosage form, is characterized by a bioavailability of less than 2% following a 5 mg/kg oral dose in dogs.

Acid addition salts of a compound of formula III (for example, bis-hydrochloride, bistosylate, bis-methane sulfonate and the like) have aqueous solubilities of <0.1 milligrams/milliliter. This is only a slight improvement over the solubility of the free base. This low aqueous solubility would not make practical the administration of therapeutic amounts of an acid addition salt of a compound of formula III as an aqueous solution. Furthermore, in view of this low aqueous solubility, it is not surprising that the bis-tosylate of compound III, administered as an unformulated solid in a capsule dosage form, is characterized by a bioavailability of less than 2% following a 5 mg/kg oral dose in dogs.

In order to have a suitable oral dosage form of a compound of formula III, the oral bioavailability of a compound of formula III should be at least 20%. Preferably, the oral bioavailability of a compound of formula III from the dosage form should be greater than about 40% and, more preferably, greater than about 50%.

One measure of the potential usefulness of an oral dosage form of a pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength and first pass effect. Aqueous solubility is one of

the most important of these factors. When a drug has poor aqueous solubility, attempts are often made to identify salts or other derivatives of the drug which have improved aqueous solubility. When a salt or other derivative of the drug is identified which has good aqueous solubility, it is generally accepted that an aqueous solution formulation of this salt or derivative will provide the optimum oral bioavailability. The bioavailability of the oral solution formulation of a drug is then generally used as the standard or ideal bioavailability against which other oral dosage forms are measured.

For a variety of reasons, such as patient compliance and taste masking, a solid dosage form, such as capsules, is usually preferred over a liquid dosage form. However, oral solid dosage forms, such as a tablet or a powder, and the like, of a drug generally provide a lower bioavailability than oral solutions of the drug. One goal of the development of a suitable capsule dosage form is to obtain a bioavailability of the drug that is as close as possible to the ideal bioavailability demonstrated by the oral solution formulation of the drug.

While some drugs would be expected to have good solubility in organic solvents, it would not necessarily follow that oral administration of such a solution would give good bioavailability for the drug. It has been found that a compound of formula III has good solubility in pharmaceutically acceptable organic solvents and that the solubility in such solvents is enhanced in the presence of a pharmaceutically acceptable long chain fatty acid. Administration of the

solution as an encapsulated dosage form (soft elastic capsules or hard gelatin capsules) provides an oral bioavailability of as high as about 60% or more.

Solubility is therefore an important factor in the formulation of HIV protease inhibiting compounds.

Thus, it would be an important contribution to the art to provide an improved pharmaceutical formulation comprising at least one HIV protease inhibiting compound having enhanced dissolution properties.

Brief Description of the Drawings

Figure 1 illustrates the powder X-ray diffraction pattern of the substantially pure Form I crystalline polymorph of ritonavir.

Figure 2 illustrates the powder X-ray diffraction pattern of the substantially pure Form II crystalline polymorph of ritonavir.

Figure 3 illustrates the equilibrium solubility of Ritonavir Form II.

Figure 4 illustrates the equilibrium solubility of Ritonavir Form I.

Figure 5 illustrates the effect of added water on the solubility of Ritonavir Form II.

Figure 6 illustrates the dissolution profile of Ritonavir Form II crystals.

Figure 7 illustrates the 3D plots for the solubility of Ritonavir Form I and II as a function of temperature, water, and ethanol.

Summary of the Invention

The instant invention provides a pharmaceutical composition comprising at least one HIV protease inhibiting compound in a pharmaceutically acceptable solution of a long chain fatty acid, ethanol, and water, wherein said HIV protease inhibiting compound contained therein has improved solubility properties.

Detailed Description of the Invention

The instant invention comprises a solution of an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds or pharmaceutically acceptable salts thereof in a pharmaceutically acceptable organic solvent comprising a mixture of at least one pharmaceutically acceptable long chain fatty acid, ethanol, and water.

The compositions of the instant invention provide greatly improved solubility for HIV protease inhibiting compounds contained therein when compared to analogous compositions without added water.

A preferred composition of the invention is a solution comprising (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds (preferably, a compound of the formula II or IV or saquinavir or nelfinavir or indinavir or, more preferably, a compound of formula III or V or

saquinavir or nelfinavir or indinavir, or, most preferably, a compound of the formula III or V); or a combination of a compound of the formula II or nelfinavir and another HIV protease inhibitor (preferably, the compound of the formula IV or saquinavir or indinavir or nelfinavir, or, more preferably, a combination of a compound of the formula III or nelfinavir and another HIV protease inhibitor (preferably, the compound of the formula V or saquinavir or indinavir or nelfinavir), or, most preferably, a combination of a compound of formula III and a compound of formula V) in the amount of from about 1% to about 50% (preferably, from about 1% to about 40%; more preferably, from about 10% to about 40% by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 20% to about 99% (preferably, from about 30% to about 75% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 20% to about 99% (preferably, from about 30% to about 75% by weight of the total solution; (2) ethanol in the amount of from about 1% to about 15% (preferably, from about 3% to about 12%) by weight of the total solution; (c) water in the amount of from about 0.4% to about 3.5%; and (d) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 40% (preferably, from about 2% to

about 20% and most preferably, from about 2.5% to about 15%) by weight of the total solution. In a preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

Preferably, the pharmaceutically acceptable organic solvent comprises from about 50% to about 99% by weight of the total solution. More preferably, the pharmaceutically acceptable organic solvent or mixture of pharmaceutically acceptable organic solvents comprises from about 50% to about 75% by weight of the total solution.

Preferred pharmaceutically acceptable solvents comprise (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 75% by weight of the total solution; (2) ethanol in the amount of from about 1% to about 15% by weight of the total solution; and (3) water in the amount of from about 0.4% to about 3.5% by weight of the total solution. More preferred pharmaceutically acceptable solvents comprise (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 75% by weight of the total solution and (2) ethanol in the amount of from about 3% to about 12% by weight of the total solution. Even more preferred pharmaceutically acceptable solvents comprise (1) oleic acid in the amount of from about 40% to about 75% by weight of the total solution and (2) ethanol in the

amount of from about 3% to about 12% by weight of the total solution.

In one embodiment of the invention, a more preferred composition of the invention is a solution comprising (a) ritonavir in the amount of from about 1% to about 30% (preferably, from about 5% to about 25%) by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 99% (preferably, from about 30% to about 75% by weight of the total solution or (ii) a mixture of (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 99% (preferably, from about 30% to about 75% by weight of the total solution and (2) ethanol in the amount of from about 1% to about 15% (preferably, from about 3% to about 12%) by weight of the total solution, (c) water in the amount of from about 0.4% to about 3.5% and (d) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 20% (preferably, from about 2.5% to about 10%) by weight of the total solution.

In a more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

An even more preferred composition of the invention is a solution comprising (a) ritonavir in the amount of

from about 1 % to about 30% (preferably, from about 5% to about 25%) by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 15% to about 99% (preferably, from about 30% to about 75% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 15% to about 99% (preferably, from about 30% to about 75% by weight of the total solution and (2) ethanol in the amount of from about 1% to about 15% (preferably, from about 3% to about 12%) by weight of the total solution, (c) water in the amount of from about 0.4% to about 3.5%, and (d) polyoxyl 35 castor oil in the amount of from about 0% to about 20% (preferably, from about 2.5% to about 10%) by weight of the total solution.

In an even more preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

A most preferred composition of the invention is a solution comprising (a) ritonavir in the amount of about 10% by weight of the total solution, (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of from about 70% to about 75% by weight of the total solution and (2) ethanol in the amount of from about 3% to about 12%, preferably, about 12%, by weight of the total solution, (c) water in the amount of from about

0.4% to about 1.5% and (d) polyoxyl 35 castor oil in the amount of about 6% by weight of the total solution.

In a most preferred embodiment of the invention, the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule and the solution also comprises an antioxidant (preferably, BHT (butylated hydroxytoluene)) in the amount of about 0.025% by weight of the total solution.

The term "pharmaceutically acceptable long chain fatty acid" as used herein refers to saturated, mono- or di-unsaturated C_{12} to C_{18} carboxylic acids which are liquids at room temperature. Preferred long chain fatty acids are mono-unsaturated C_{16}-C_{20} carboxylic acids which are liquids at room temperature. A most preferred long chain fatty acid is oleic acid.

The amount of water employed in the pharmaceutical composition of the instant invention comprises from about 0.4% to about 3.5% by weight of the total solution of water. Preferably, the weight of the total solution of water is from about 0.4% to about 2.0%; more preferably from about 0.4% to about 1.5%; and the most preferred being about 1%.

In addition, the solution composition of the invention can comprise antioxidants (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability.

The term "pharmaceutically acceptable acid" as used herein refers to (i) an inorganic acid such as hydrochloric acid,

hydrobromic acid, hydroiodic acid and the like, (ii) an organic mono-, di- or tri-carboxylic acid (for example, formic acid, acetic acid, adipic acid, alginic acid, citric acid, ascorbic acid, aspartic acid, benzoic acid, butyric acid, camphoric acid, gluconic acid, glucuronic acid, galactaronic acid, glutamic acid, heptanoic acid, hexanoic acid, fumaric acid, lactic acid, lactobionic acid, malonic acid, maleic acid, nicotinic acid, oxalic acid, pamoic acid, pectinic acid, 3-phenylpropionic acid, picric acid, pivalic acid, propionic acid, succinic acid, tartaric acid, undecanoic acid and the like) or (iii) a sulfonic acid (for example, benzenesulfonic acid, sodium bisulfate, sulfuric acid, camphorsulfonic acid, dodecylsulfonic acid, ethanesulfonic acid, methanesulfonic acid, isethionic acid, naphthalenesulfonic acid, p-toluenesulfonic acid and the like).

The term "pharmaceutically acceptable surfactant" as used herein refers to a pharmaceutically acceptable non-ionic surfactant for example, polyoxyethylene castor oil derivatives (for example, *polyoxyethyleneglyceroltriricinoleate or polyoxyl* 35 castor oil (Cremophor(&EL, BASF Corp.) or polyoxyethyleneglycerol oxystearate (CremophorVRH 40 (polyethyleneglycol 40 hydrogenated castor oil)) or Cremophor,&RH 60 (polyethyleneglycol 60 hydrogenated castor oil), BASF Corp. and the like) or block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylenepolypropylene glycol, such

as Poloxamer@124, Poloxamersl 88, Poloxamer8237, Poloxamer'9388, Poloxamer'9407 and the like, (BASF Wyandotte Corp.) or a mono fatty acid ester of polyoxyethylene (20) sorbitan (for example, polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monopalmitate (Tween@ 40), polyoxyethylene (20) sorbitan monolaurate (Tweens 20) and the like) and the like) or a sorbitan fatty acid ester (including sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan stearate and the like). A preferred pharmaceutically acceptable surfactant is polyoxyl 35 castor oil (Cremophor@EL, BASF Corp.), polyoxyethylene (20) sorbitan monolaurate (Tween@) 20), polyoxyethylene (20) sorbitan monooleate (Tween@ 80) or a sorbitan fatty acid ester, for example sorbitan oleate. A most preferred pharmaceutically acceptable surfactant is polyoxyl 35 castor oil (CremophorsEL, BASF Corp.).

As used herein, the term "substantially pure", when used in reference to a polymorph of ritonavir, refers to a polymorph of ritonavir, Form I or Form II, which is greater than about 90% pure. This means that the polymorph of ritonavir does not contain more than about 10% of any other compound and, in particular, does not contain more than about 10% of any other form of ritonavir. More preferably, the term "substantially pure" refers to a polymorph of ritonavir, Form I or Form II,

which is greater than about 95% pure. This means that the polymorph of ritonavir does not contain more than about 5% of any other compound and, in particular, does not contain more than about 5% of any other form of ritonavir. Even more preferably, the term "substantially pure" refers to a polymorph of ritonavir, Form I or Form II, which is greater than about 97% pure. This means that the polymorph of ritonavir does not contain more than about 3% of any other compound and, in particular, does not contain more than about 3% of any other form of ritonavir.

As used herein, the term "substantially pure", when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than about 90% pure. This means that the amorphous ritonavir does not contain more than about 10% of any other compound and, in particular, does not contain more than about 10% of any other form of ritonavir. More preferably, the term "substantially pure", when used in reference to amorphous ritonavir, refers to amorphous ritonavir, which is greater than about 95% pure. This means that the amorphous ritonavir does not contain more than about 5% of any other compound and, in particular, does not contain more than about 5% of any other form of ritonavir. Even more preferably, the term "substantially pure", when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than about 97% pure. This means that the amorphous ritonavir does not contain more than about 3% of any other compound and, in particular, does not contain more than about 3% of any other form of ritonavir.

The composition and preparation of soft elastic gelatin capsules is well known in the art. The composition of a soft elastic gelatin capsule typically comprises from about 30% to about 50% by weight of gelatin NF, from about 20% to about 30% by weight of a plasticizer and from about 25% to about 40% by weight of water. Plasticizers useful in the preparation of soft elastic gelatin capsules are glycerin, sorbitol or propylene glycol and the like; or combinations thereof. A preferred soft elastic gelatin capsule has a composition comprising gelatin NF (Type 195) (about 42.6% by weight), glycerin (USP) (about 96% active; about 13.2% by weight), purified water (USP) (about 27.4% by weight), sorbitol special (about 16% by weight) and titanium dioxide (USP) (about 0.4% by weight).

The soft elastic gelatin capsule material can also comprise additives such as preservatives, opacifiers, dyes or flavors, and the like.

Various methods can be used for manufacturing and filling the soft elastic gelatin capsules, for example, a seamless capsule method, a rotary method (developed by Scherer) or a method using a Liner machine or an Accogel machine and the like. Also various manufacturing machines can be used for manufacturing the capsules.

Hard gelatin capsules are purchased from Capsugel, Greenwood, S.C. Capsules are filled manually or by capsule filling machine. The target filling volume/weight depends on the potency of the filling solution in combination with the desired dosage strength.

In general, the compositions of this invention can be prepared in the following manner. The pharmaceutically acceptable long chain fatty acid and ethanol and water are mixed at a temperature from 15-30 °C, along with the antioxidant. The HIV protease inhibitor, or mixture of HIV protease inhibitors, is added and stirred until dissolved. The pharmaceutically acceptable surfactant is added with mixing. The appropriate volume of the resulting mixture needed to provide the desired dose of the HIV protease inhibiting compound)s) is filled into hard gelatin capsules or soft elastic gelatin capsules.

Similar increases in the solubility of HIV protease inhibitors in oral solution formulations may be obtained by the addition of water in ranges as disclosed herein. Oral solution formulations are disclosed in U.S. 5,484,801, issued January 16, 1996, the disclosure of which is herein incorporated by reference.

EXAMPLES

The following Examples will serve to further illustrate the instant invention.

Powder X-ray diffraction analysis of samples was conducted in the following manner. Samples for X-ray diffraction analysis were prepared by spreading the sample powder (with no prior grinding required) in a thin layer on the sample holder and gently flattening the sample with a microscope slide.

A Nicolet 12/V X-ray Diffraction System was used with the following parameters: X-ray source: Cu-Kα1; Range: 2.00-40.00° Two Theta; Scan Rate: 1.00 degree/minute; Step Size: 0.02 degrees; Wavelength: 1.540562 angstroms.

Characteristic powder X-ray diffraction pattern peak positions are reported for polymorphs in terms of the angular positions (two theta) with an allowable variability of ± 0.1°. This allowable variability is specified by the U.S. Pharmacopeia, pages 1843-1844 (1995). The variability of ± 0.1° is intended to be used when comparing two powder X-ray diffraction patterns. In practice, if a diffraction pattern peak from one pattern is assigned a range of angular positions (two theta) which is the measured peak position ± 0.1° and a diffraction pattern peak from the other pattern is assigned a range of angular positions (two theta) which is the measured peak position ± 0.1° and if those ranges of peak positions overlap, then the two peaks are considered to have the same angular position (two theta). For example, if a diffraction pattern peak from one pattern is determined to have a peak

position of 5.20°, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 5.10° - 5.30°. If a comparison peak from the other diffraction pattern is determined to have a peak position of 5.35°, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 5.25° - 5.45°. Because there is overlap between the two ranges of peak positions (for example, 5.10° - 5.30° and 5.25°- 5.45°) the two peaks being compared are considered to have the same angular position (two theta).

Solid state nuclear magnetic resonance analysis of samples was conducted in the following manner. A Bruker AMX-400 MHz instrument was used with the following parameters: CP- MAS (cross-polarized magic angle spinning); spectrometer frequency for 13C was 100.627952576 MHz; pulse sequence was cp2lev; contact time was 2.5 milliseconds; temperature was 27.0 °C; spin rate was 7000 Hz; relaxation delay was 6.000 sec; 1st pulse width was 3.8 microseconds; 2nd pulse width was 8.6 microseconds; acquisition time was 0.034 seconds; sweep width was 30303.0 Hz; 2000 scans.

FT near infrared analysis of samples was conducted in the following manner. Samples were analyzed as neat, undiluted powders contained in a clear glass 1 dram vial. A Nicolet Magna System 750 FT-IR spectrometer with a Nicolet SabIR near infrared fiber optic probe accessory was used with the following parameters: the source was white light; the detector was PbS; the beamsplitter was CaF2; sample spacing was 1.0000; digitizer bits was 20; mirror velocity was 0.3165; the aperture

was 50.00; sample gain was 1.0; the high pass filter was 200.0000; the low pass filter was 11000.0000; the number of sample scans was 64; the collection length was 75.9 seconds; the resolution was 8.000; the number of scan points was 8480; the number of FFT points was 8192; the laser frequency was 15798.0 cm -1; the interferogram peak position was 4096; the apodization was Happ-Genzel; the number of background scans was 64 and the background gain was 1.0.

FT mid infrared analysis of samples was conducted in the following manner. Samples were analyzed as neat, undiluted powders. A Nicolet Magna System 750 FT-IR spectrometer with a Spectra-Tech InspectIR video microanalysis accessory and a Germanium attenuated total reflectance (Ge ATR) crystal was used with the following parameters: the source was infrared; the detector was MCT/A; the beamsplitter was KBr; sample spacing was 2.0000; digitizer bits was 20; mirror velocity was 1.8988; the aperture was 100.00; sample gain was 1.0; the high pass filter was 200.0000; the low pass filter was 20000.0000; the number of sample scans was 128; the collection length was 79.9 seconds; the resolution was 4.000; the number of scan points was 8480; the number of FFT points was 8192; the laser frequency was 15798.0 cm -1; the interferogram peak position was 4096; the apodization was triangular; the number of background scans was 128 and the background gain was 1.0.

Differential scanning calorimetric analysis of samples was conducted in the following manner. A T.A. Instruments Thermal Analyzer 3100 with Differential Scanning Calorimetry module 2910 was used, along with Modulated DSC software version 1.1A.

The analysis parameters were: Sample weight: 2.28 mg, placed in a covered, uncrimped aluminum pan; Heating rate: room temperature to 150°C at 5°C/minute under a nitrogen purge.

Example 1

Preparation of Amorphous Ritonavir

Form I crystalline polymorph of ritonavir (100 g) was melted at 125°C by heating Form I. The melt was maintained at a temperature of 125°C for 3 hours. The melt was rapidly cooled by placing the container holding the melt into a Dewar flask containing liquid nitrogen. The resulting glass was ground with a mortar and pestle to provide amorphous ritonavir (100 g). Powder X-ray diffraction analysis confirmed that the product was amorphous. Differential scanning calorimetric analysis determined that the glass transition point was from about 45°C to about 49°C. (Measured onset at 45.4°C and which ends at 49.08°C, with a midpoint of 48.99°C).

Example 2

Preparation of Crystalline Ritonavir (Form II)

Amorphous ritonavir (40.0 g) was dissolved in boiling anhydrous ethanol (100 mL). Upon allowing this solution to cool to room temperature, a saturated solution was obtained. After standing overnight at room temperature, the resulting solid was isolated from the mixture by filtration and was air dried to provide Form II (approximately 24.0 g).

Example 3

Preparation of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)carbonyl)amino)-3-methylbutanamide

Example 3a

Preparation of (4S,5S)-5-((2S)-2-t-butyloxycarbonylamino-3-phenylpropyl)-4-benzyl-1,3-oxazolidin-2-one

(2S,3S,5S)-2-Amino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexane succinate salt (30 g, 63 mmol; U.S. Patent No. 5,654,466), ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate hydrochloride (22.2 g; U.S. Patent No. 5,597,926) and sodium bicarbonate (16.2 g) were mixed with 300mL of water and 300 mL of ethyl acetate and the mixture was stirred at room temperature for about 30 minutes. The organic layer was then separated and heated at about 60°C for 12 hours, and then

stirred at 20-25°C for 6 hours. 3 mL of ammonium hydroxide (29% ammonia in water) was added and the mixture stirred for 1.5 hours. The resulting mixture was washed with 4 x 200 mL of 10% aqueous potassium carbonate and the organic layer was separated and evaporated under vacuum to provide an oil. The oil was suspended in about 250 mL of heptane. The heptane was evaporated under vacuum to provide a yellow solid. The yellow solid was dissolved in 300 mL of THF and 25 mL of 10% aqueous sodium hydroxide was added. After stirring for about 3 hours, the mixture was adjusted to pH 7 by addition of 4N HCl (about 16 mL). The THF was evaporated under vacuum to leave an aqueous residue, to which was added 300 mL of distilled water. After stirring this mixture, a fine suspension of solids resulted. The solid was collected by filtration and the filtered solid was washed with water (1400 mL) in several portions, resulting in the desired product.

Example 3b

Preparation of (4S,5S)-5-((2S)-2-amino-3-phenylpropyl)-4-benzyl-1,3-oxazolidin-2-one

The crude, wet product of Example 3a was slurried in 1N HCl (192 mL) and the slurry was heated to 70°C with stirring. After 1 hour, THF (100 mL) was added and stirring at 65°C was continued for 4 hours. The mixture was then allowed to cool to 20-25°C and was stirred overnight at 20-25°C. The THF was removed by evaporation under vacuum and the resulting aqueous

solution was cooled to about 5°C, causing some precipitation to occur. The aqueous mixture was adjusted to pH 7 by addition of 50% aqueous sodium hydroxide (about 18.3 g). The resulting mixture was extracted with ethyl acetate (2 x 100 mL) at about 15°C. The combined organic extracts were washed with 100 mL of brine and the organic layer was separated and stirred with sodium sulfate (5 g) and Darco G-60 (3 g). This mixture was warmed on a hot plate for 1 hour at 45°C. The hot mixture was then filtered through a bed of diatomaceous earth and the filter pad was washed with ethyl acetate (100 mL). The filtrate was evaporated under vacuum to provide an oil. The oil was redissolved in methylene chloride (300 mL) and the solvent was evaporated under vacuum. The resulting oil was dried at room temperature under vacuum to provide the desired product (18.4 g) as a glassy syrup.

Example 3c

Preparation of (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-(((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)carbonyl)amino)-3-methylbutanamide

N-((N-Methyl-N((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (10.6 g, 33.9 mmol; U.S. Patent No. 5,539,122 and International Patent Application No. WO98/00410), the product of Example 3b (10.0 g, 32.2 mmol) and 1-hydroxybenzotriazole (5.2 g, 34 mmol) were dissolved in

THF (200 mL). 1,3-dicylcohexylcarbodiimide (DCC, 7.0 g, 34 mmol) was then added to the THF mixture and the mixture was stirred at 22°C for 4 hours. Citric acid (25 mL of 10% aqueous solution) was added and stirring continued for 30 minutes. The THF was then evaporated under vacuum. The residue was dissolved in ethyl acetate (250 mL) and washed with 10% citric acid solution (175 mL). NaCl (5 g) was added to accelerate the separation of the layers. The organic layer was sequentially washed with 10% aq. sodium carbonate (2 x 200 mL) and water (200 mL). The organic layer was then dried over sodium sulfate (20 g), filtered and evaporated under vacuum. The resulting product (20.7 g of a foam) was dissolved in hot ethyl acetate (150 mL) and then heptane (75 mL) was added. Upon cooling, another 75 mL of heptane was added and the mixture was heated to reflux. Upon cooling to room temperature, no precipitate formed. The solvents were evaporated under vacuum and the residue was redissolved in a mixture of 200 mL ethyl acetate/100 mL heptane. The small amount of undissolved solid was removed by filtration. The filtrate was evaporated under vacuum and the residue was dissolved in a mixture of 100 mL ethyl acetate/ 50 mL heptane, giving a clear solution. The solution was cooled to -10°C and a white precipitate formed. The mixture was allowed to sit at -15°C for 24 hours. The resulting solid was collected by filtration, washed with 1:1 ethyl acetate/heptane (2 x 24 mL) and dried in a vacuum oven at 55°C to provide the desired product as a beige solid (16.4 g).

Example 4

Preparation of Crystalline Ritonavir (Form II)

To a solution of 1.595 g of ritonavir Form I in 10 mL of 200 proof ethanol was added approximately 50 micrograms of the product of Example 3c. This mixture was allowed to stand at about 5°C for 24 hours. The resulting crystals were isolated by filtration through 0.45 micron nylon filter and air dried to provide ritonavir Form II.

Example 5

Alternative Preparation of Crystalline Ritonavir (Form II)

Ethyl acetate (6.0 L/kg of ritonavir) was added to ritonavir (Form I or a mixture of Form I and Form II) in a reaction vessel. The mixture was stirred and heated to 70°C until all solids were dissolved. The solution was filtered (utilizing a centrifuge pump and 5X20 inch cartridge filters having a porosity of 1.2 microns) and the filtrate was allowed to cool to 52°C at a rate of 2-10°C/hour. To this solution was added ritonavir Form II seed crystals (about 1.25 g of Form II seed crystals/kg of ritonavir) and the mixture was stirred at 52°C for not less than 1 hour at an agitation rate of 15 RPM. The mixture was then allowed to cool to 40°C at a rate of 10°C/hour. Heptane (2.8 L/kg of ritonavir) was added at a rate

of 7L/minute with mixing. The mixture was allowed to cool to 25°C at a rate of 10°C/hour with mixing. Then the mixture was stirred for not less than 12 hours at 25°C. The product was isolated by filtration using a Heinkel type centrifuge (run time approximately 16 hours). The product was dried at 55°C under vacuum (50 mm Hg) for 16-25 hours to provide ritonavir crystal Form II.

Example 6

Preparation of Amorphous Ritonavir

Ritonavir Form I (40 g) was dissolved in methylene chloride (60 mL). This solution was slowly added over 15 minutes to a round bottom flask equipped with an overhead stirrer and containing hexanes (3.5 L). The resulting slurry was allowed to stir for 10 minutes. The precipitate was filtered and dried at room temperature in a vacuum oven to provide amorphous ritonavir (40 g).

Example 7

Preparation of Amorphous Ritonavir

Ritonavir Form I (5 g) was dissolved in methanol (8 mL). This solution was slowly added to a round bottom flask equipped with an overhead stirrer and containing distilled water (2 L), while maintaining the internal temperature near 0°C. The resulting solid was filtered to give a sticky solid which was dried in a vacuum oven to give amorphous ritonavir (2.5 g).

Example 8

Comparative Solubilities

Solubility experiments were performed on the various formulations of Ritonavir Form I and Form II. Data is provided in Figures 3-7.

Table 1 provided hereinbelow illustrates the pharmaceutical composition without water. Example 9 illustrates the pharmaceutical composition containing water.

Table 1. Composition of Formulation T-1 and T-2.

Components	T-1		T-2	
	mg/g	mg/cap	mg/g	mg/cap
Ritonavir	200.0	200.0	200.0	200.0
Alcohol, dehydrated, USP	100.0	100.0	100.0	100.0
Oleic acid, NF	650.0	650.0	600.0	600.0
Polyoxyl 35 Castor Oil (Cremophor EL®)	50.0	50.0	100.0	100.0
BHT	0.01	0.01	0.01	0.01

Example 9

Preparation of Norvir® Soft Gelatin Capsules, 100 mg

The following protocol is employed in the preparation of 1000 soft gelatin capsules:

Scale (mg/capsule)	Name	Amount (g)
Q.S.	Nitrogen, N.F.	Q.S.
118.0	Ethanol, dehydrated, USP, 200 Proof	118.0
2.0	Ethanol, dehydrated, USP, 200 Proof	2.0
0.25	Butylated Hydroxytoluene, NF	0.25
704.75	Oleic Acid, NF	704.75
100.0	Ritonavir	100.0
10.0	Water, purified, USP (distilled)	10.0
60.0	Polyoxyl 35 Castor Oil, NF	60.0
5.000	Oleic Acid, NF	5.000

A mixing tank and suitable container are purged with nitrogen. 118.0 g of ethanol is weighed, blanketed with nitrogen, and held for later use. The second aliquot of ethanol (2 g) is then weighed, and mixed with 0.25 g of butylated hydroxytoluene until clear. The mixture is blanketed with nitrogen and held. The main mixing tank is heated to 28 °C (not to exceed 30 °C). 704.75 g of oleic acid is then charged into the mixing tank. 100.0 g of ritonavir is then

added to the oleic acid with mixing. The ethanol/butylated hydroxytoluene is then added to the mixing tank, followed by the 118.0 g of ethanol measured previously, and mixed for at least 10 minutes. 10 g of water is then charged into the tank and mixed until the solution is clear (for not less than 30 minutes). The sides of the vessel are scraped for ritonavir, and mixed for not less than an additional 30 minutes. 60.0 g of Polyoxyl 35 castor oil is charged into the tank and mixed until uniform. The solution is stored at 2-8 °C until encapsulation. 1.0 g of the solution is filled into each soft gelatin capsule (die: 18 oblong [18BE]; gel: 005L2DDXHB-EP; gel dyes: white 920P). The soft gelatin capsules are then dried, and stored at 2-8 °C.

Example 10

Protocol for Oral Bioavailability

Dogs (beagle dogs, mixed sexes, weighing 7-14 kg) were fasted overnight prior to dosing, but were permitted water ad libitum. Each dog received a 100 µg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. Each dog received a single dosage form corresponding to a 5 mg/kg dose of the drug. The dose was followed by approximately 10 milliliters of water. Blood samples were obtained from each animal prior to dosing and 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after drug administration. The plasma was separated from the red cells by centrifugation and frozen (-30

°C) until analysis. Concentrations of parent drug were determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The parent drug area under the curve was calculated by the trapezoidal method over the time course of the study. The absolute bioavailability of each test composition as calculated by comparing the area under the curve after oral dosing to that obtained from a single intravenous dose. Each capsule or capsule composition was evaluated in a group containing at least six dogs; the values reported are averages for each group of dogs.

145

CLAIMS

We Claim:

1. A pharmaceutical composition which is a solution comprising:
   (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds, or pharmaceutically acceptable salts thereof;
   (b) a pharmaceutically acceptable organic solvent which comprises a long chain fatty acid or a mixture of long chain fatty acids and ethanol;
   (c) water; and
   (d) optionally a pharmaceutically acceptable surfactant.

2. The composition according to Claim 1 wherein said HIV protease inhibiting compound is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

3. The composition according to Claim 1 wherein said combination of HIV protease inhibiting compounds is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane.

4. The composition according to Claim 1 wherein said HIV protease inhibiting compound or combination of HIV protease inhibiting compounds is selected from the group consisting of:
2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);
2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)
amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane;
N-(2(R)-hydroxy-1
(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);
N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);
5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;
1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-t-butylamide;
5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;
[1S-[1R-(R-),2S*])-N^1 [3-[[[(1,1 -dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-

147

hydroxy-1 -(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;
VX-478;
DMP-323;
DMP-450;
AG1343 (nelfinavir);
BMS 186,318;
SC-55389a;
BILA 1096 BS; and
U-140690,
or a pharmaceutically acceptable salt thereof.

5. The composition according to Claim 1 wherein said long chain fatty acid is oleic acid.

6. The composition according to Claim 1 wherein said surfactant is Polyoxyl 35 castor oil (Cremophor EL®).

7. The composition according to Claim 1 wherein the solution is encapsulated into a hard gelatin capsule or a soft gelatin capsule.

8. The composition of Claim 1 wherein the solvent comprises (1) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 75% by weight of the total solution; (2) ethanol in the amount of from about 3% to about 12% by weight of the

total solution; and (3) water in the amount of from about 0.4% to about 1.5% by weight of the total solution.

9. The composition of Claim 1 wherein the solvent comprises (1) oleic acid in the amount of from about 40% to about 75% by weight of the total solution; (2) ethanol in the amount of from about 3% to about 12% by weight of the total solution; and (3) water in the amount of from about 0.4% to about 1.5% by weight of the total solution.

10. The composition of Claim 9 wherein the HIV protease inhibiting compound is selected from the group consisting of:
2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);
2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)
amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane;
N-(2(R)-hydroxy-1
(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);

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

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

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

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

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

VX-478;

DMP-323;

DMP-450;

AG1343 (nelfinavir);

BMS 186,318;

SC-55389a;

BILA 1096 BS; and

U-140690,

or a pharmaceutically acceptable salt thereof.

11. The composition of Claim 9 wherein the HIV protease inhibiting compound is ritonavir, (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyI

butanoyl) amino-1,6diphenylhexane, indinavir, saquinavir, nelfinavir, or VX-478.

12. The composition of Claim 1 wherein the HIV protease inhibiting compound is ritonavir or a combination of ritonavir and another HIV protease inhibiting compound.

13. The composition of Claim 12 wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC).

14. The composition of Claim 1 which comprises:

(a) ritonavir in the amount of from about 1% to about 30% by weight of the total solution;

(b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 15% to about 99% by weight of the total solution and (2) ethanol in the amount of from about 3% to about 12% by weight of the total solution; and

(c) water in the amount of from about 0.4% to about 1.5% by weight of the total solution; and

(d) polyoxyl 35 castor oil in the amount of from about 0% to about 20% by weight of the total solution.

15. The composition of Claim 14 which comprises:

(a) ritonavir in the amount of from about 5% to about 10% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises (1) oleic acid in the amount of from about 70% to about 75% by weight of the total solution; and (2) ethanol in the amount of from about 3% about 12% by weight of the total solution;

(c) water in the amount of from about 0.4% to about 1.5% by weight of the total solution; and

(d) polyoxyl 35 castor oil in the amount of about 6% by weight of the total solution.

16. The composition of Claim 15 wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC).

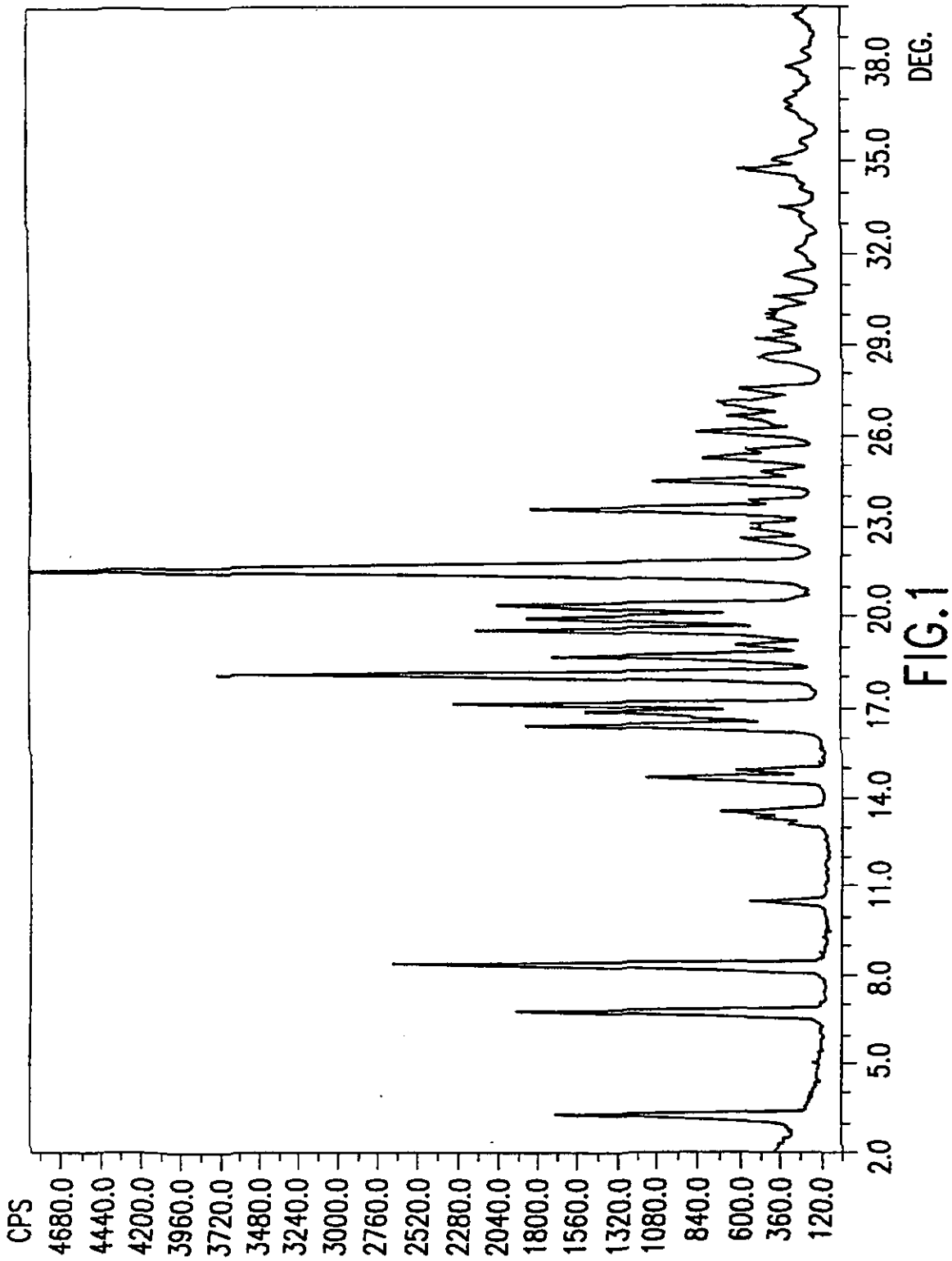


FIG. 1

153

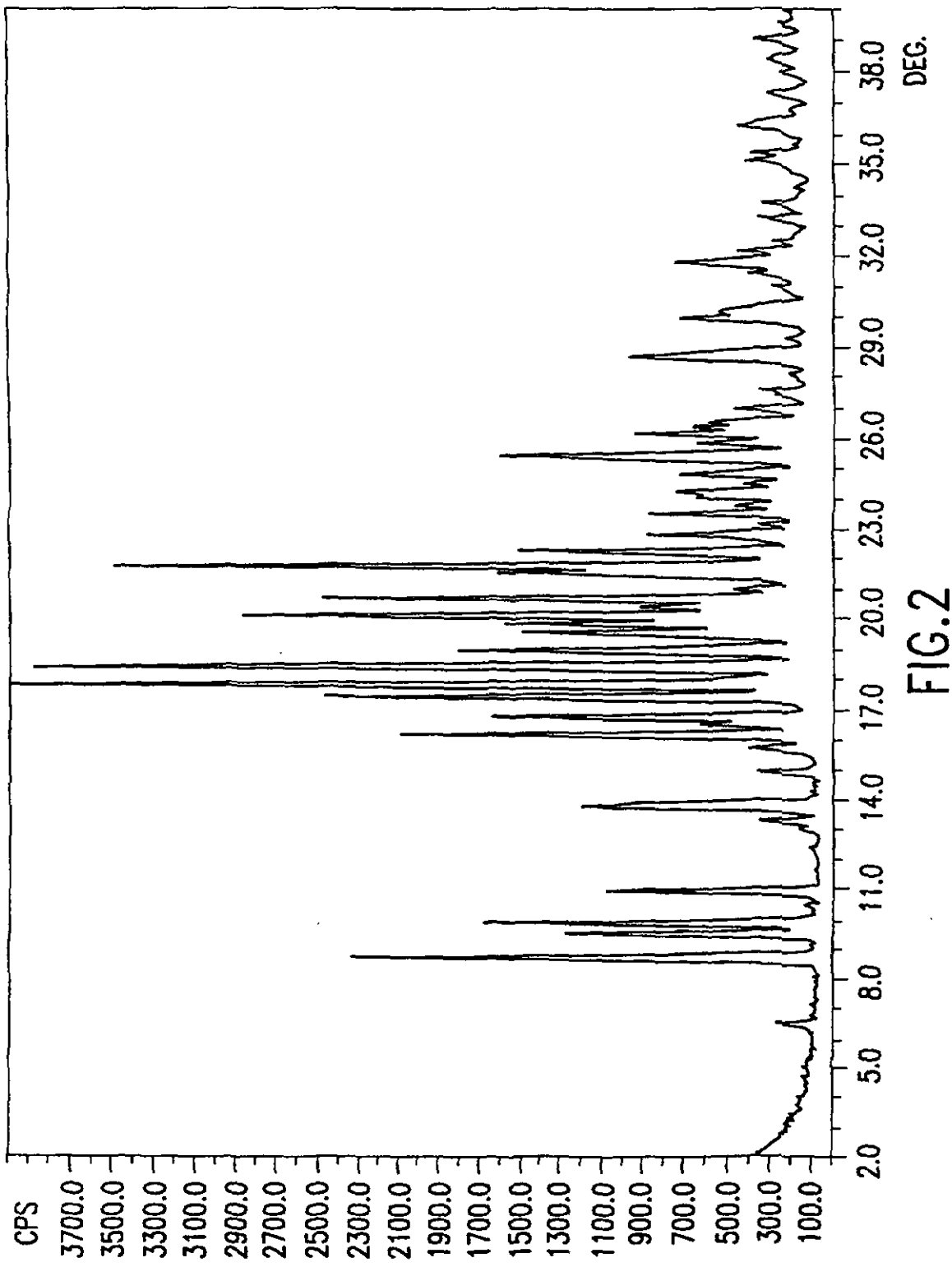

CPS
3700.0
3500.0
3300.0
3100.0
2900.0
2700.0
2500.0
2300.0
2100.0
1900.0
1700.0
1500.0
1300.0
1100.0
900.0
700.0
500.0
300.0
100.0
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
DEG.

FIG.2

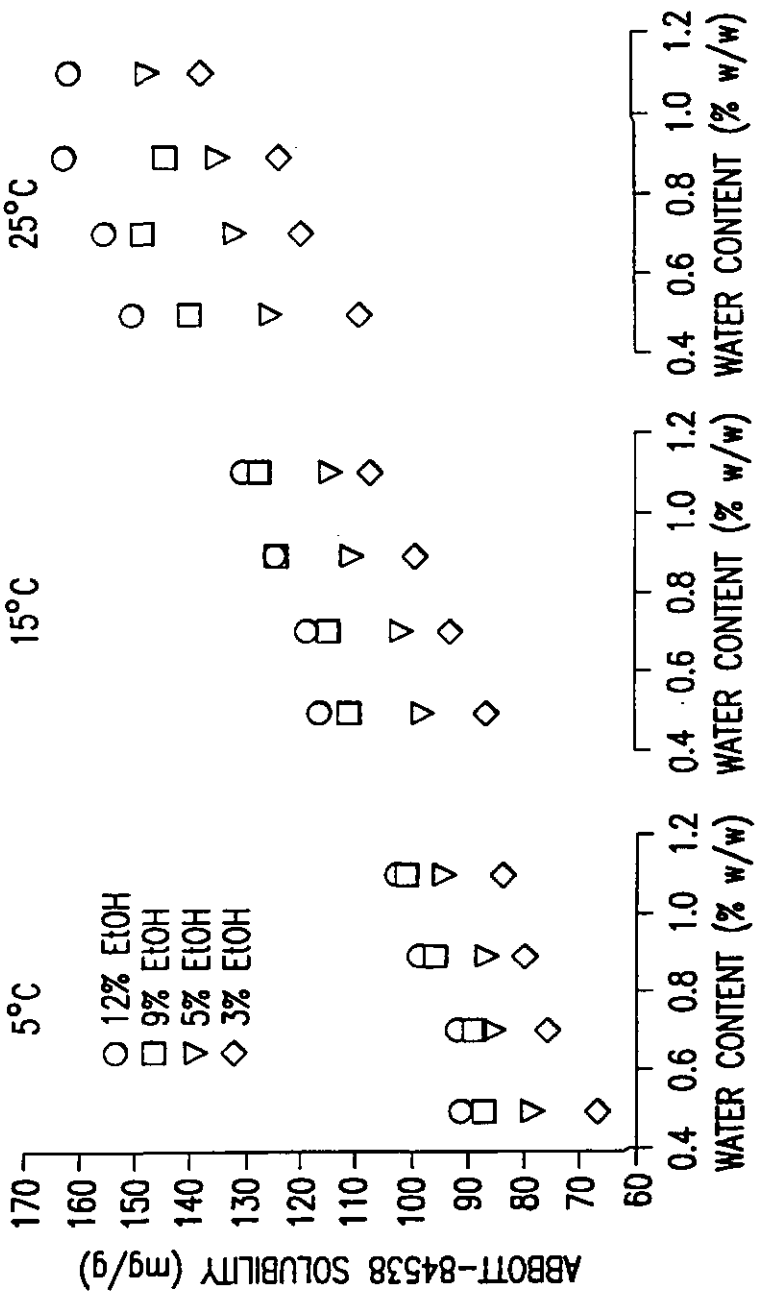


FIG. 3A FIG. 3B FIG. 3C

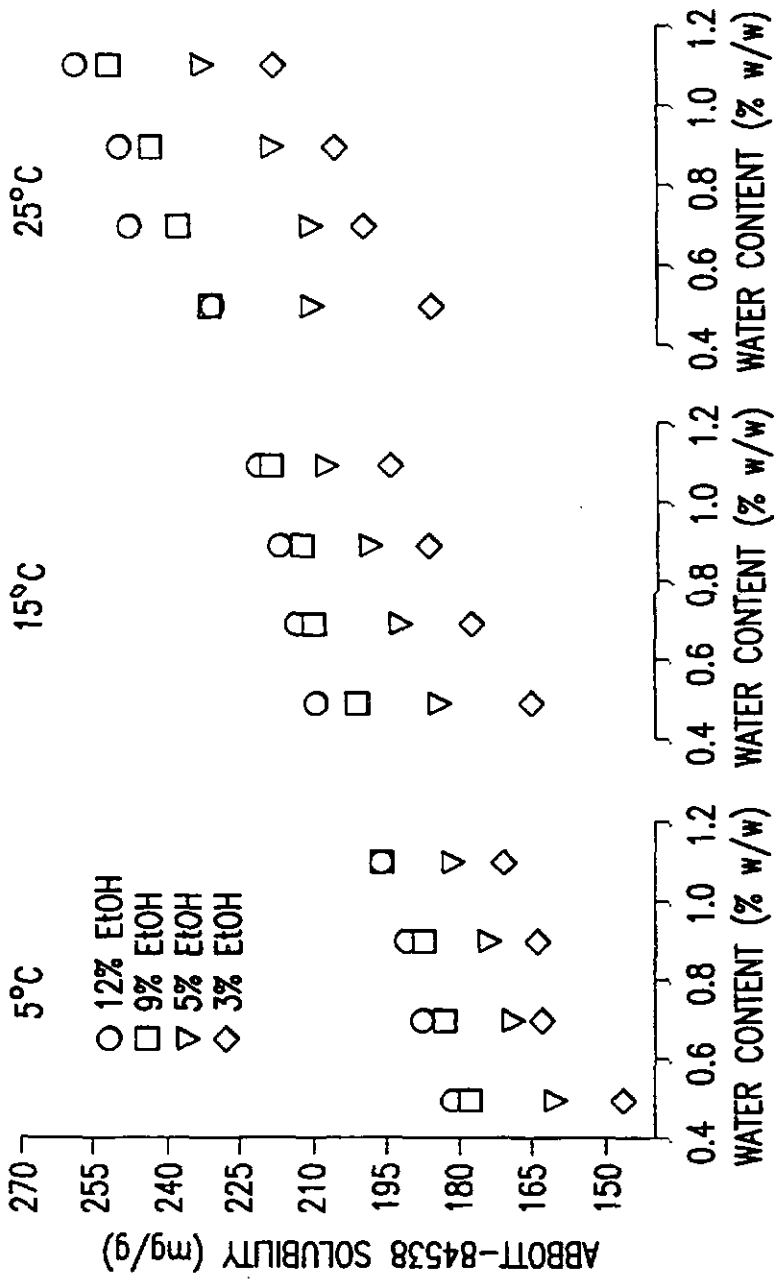


FIG. 4A FIG. 4B FIG. 4C

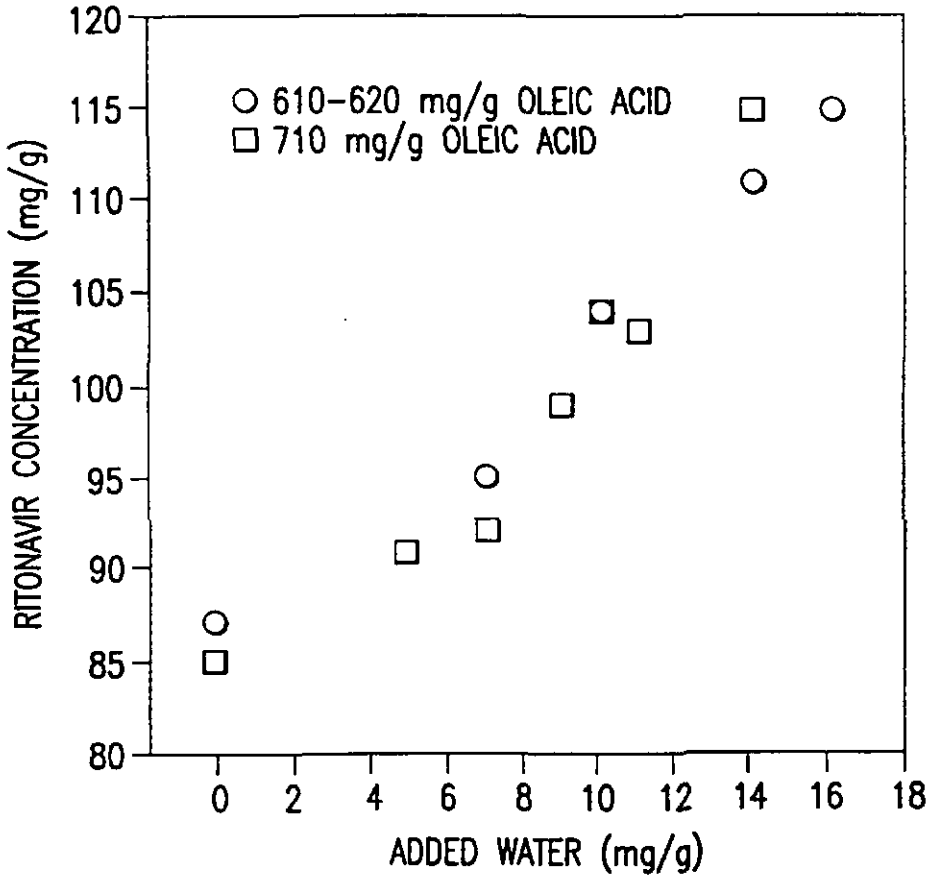


FIG.5

157

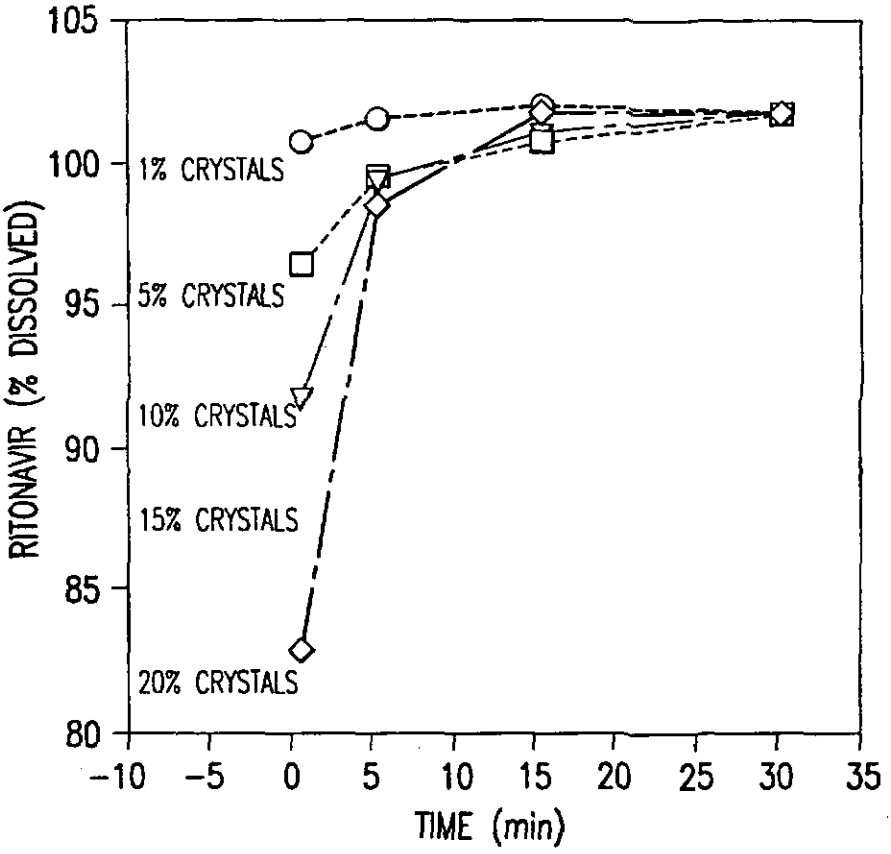

105
100
95
90
85
80
RITONAVIR (% DISSOLVED)
1% CRYSTALS
5% CRYSTALS
10% CRYSTALS
15% CRYSTALS
20% CRYSTALS
−10
−5
0
5
10
15
20
25
30
35
TIME (min)

FIG.6

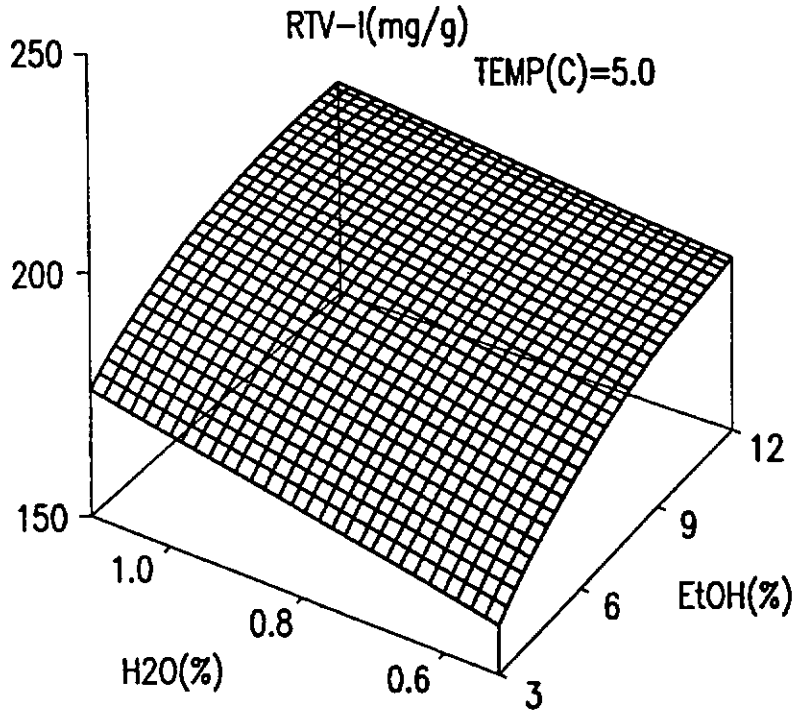

RTV-I(mg/g)
TEMP(C)=5.0
250
200
150
1.0
0.8
0.6
H2O(%)
3
6
9
12
EtOH(%)

FIG. 7A

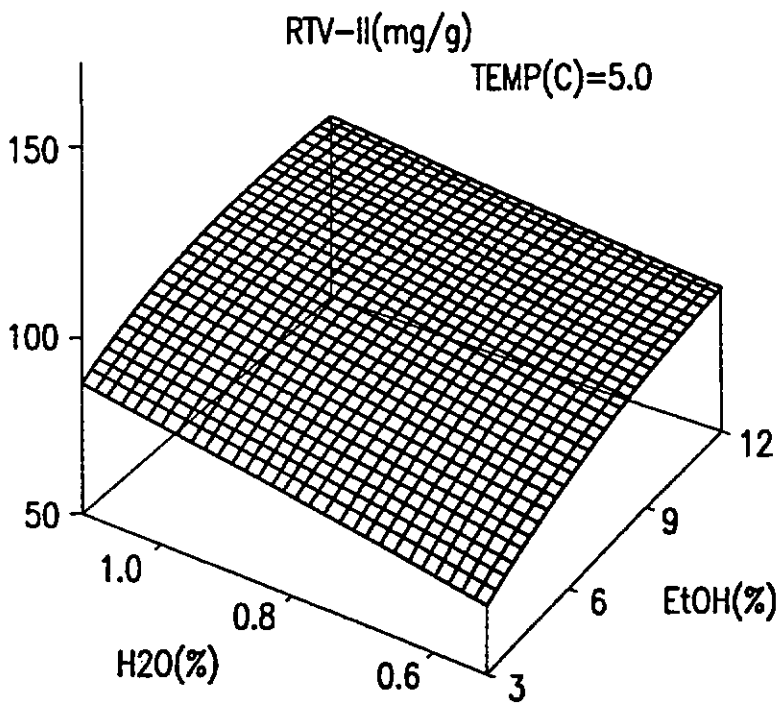

RTV-II(mg/g)
TEMP(C)=5.0
150
100
50
1.0
0.8
0.6
H2O(%)
3
6
9
12
EtOH(%)

FIG. 7B

159

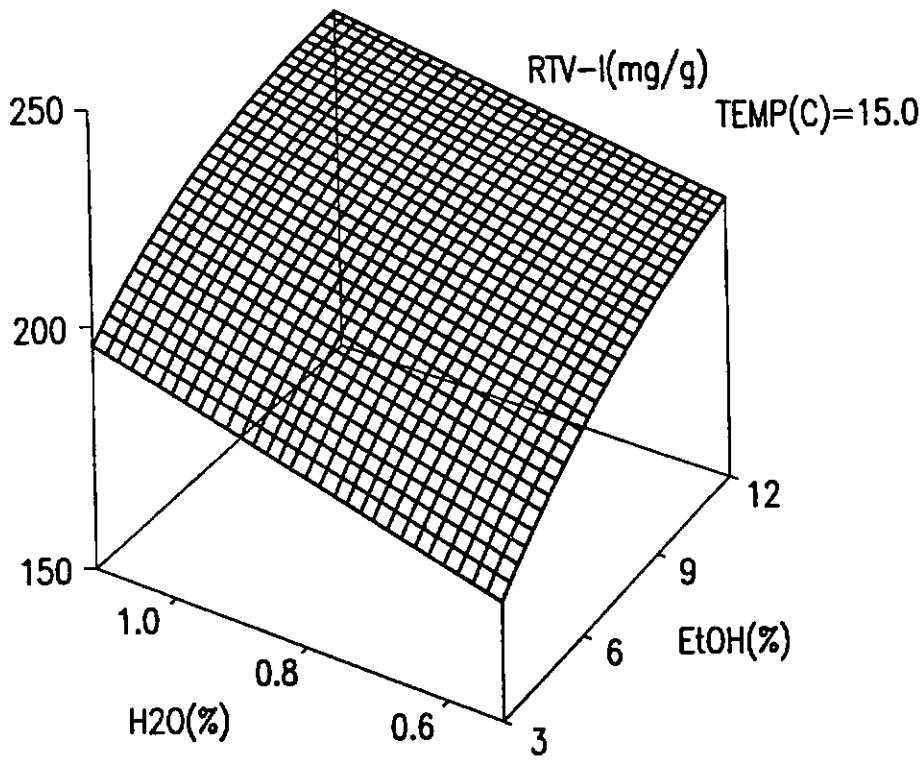


FIG. 7C

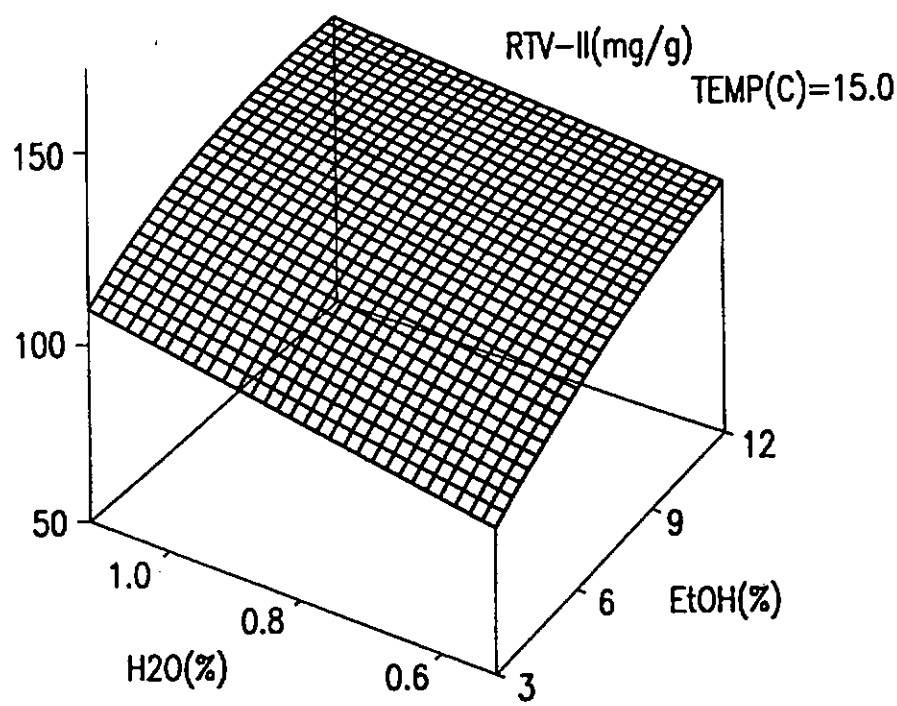


FIG. 7D

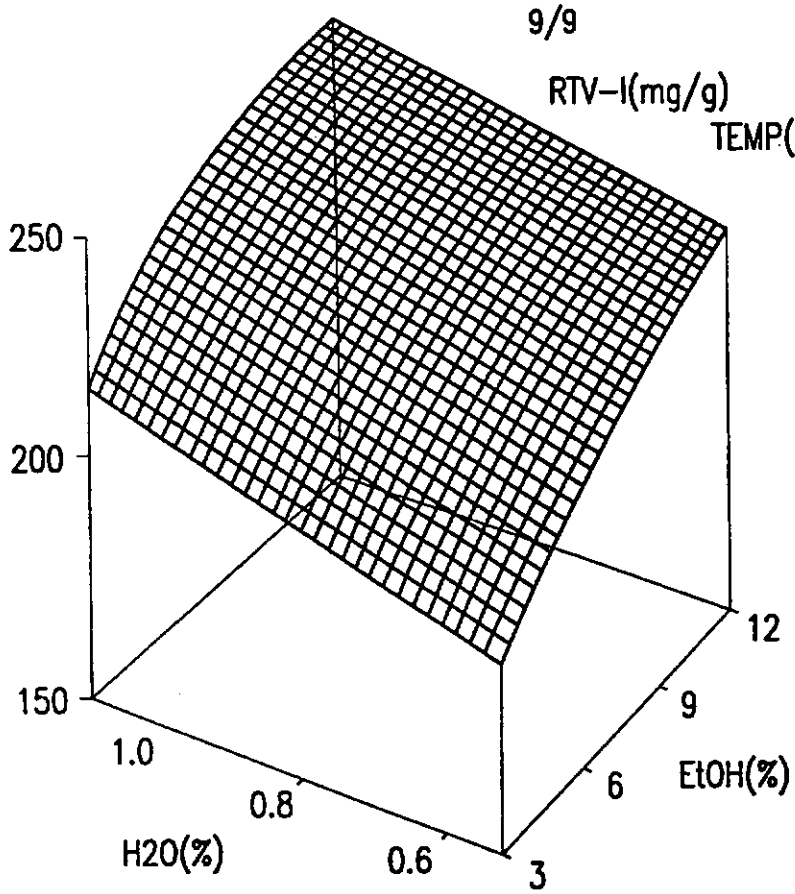

RTV-I(mg/g)
TEMP(C)=25.0
250
200
150
1.0
0.8
H2O(%)
0.6
3
6
9
12
EtOH(%)

FIG. 7E

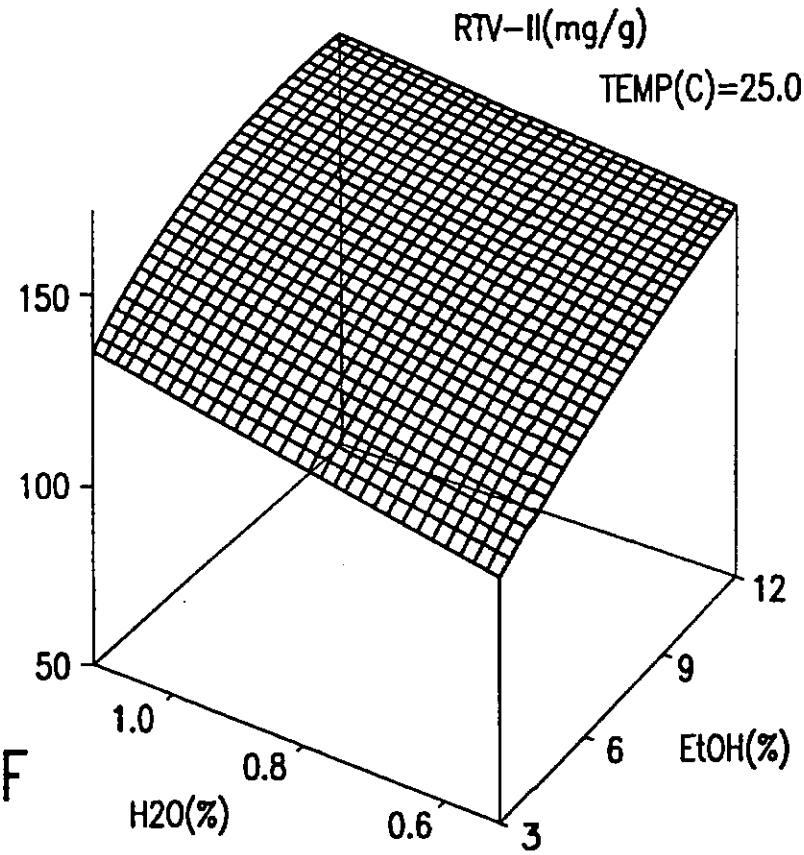

RTV-II(mg/g)
TEMP(C)=25.0
150
100
50
1.0
0.8
H2O(%)
0.6
3
6
9
12
EtOH(%)

FIG. 7F

EXHIBIT. 4. 161

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/14, 31/495

A1

(11) International Publication Number: WO 97/44014

(43) International Publication Date: 27 November 1997 (27.11.97)

(21) International Application Number: PCT/EP97/02507

(22) International Filing Date: 12 May 1997 (12.05.97)

(30) Priority Data:
96201430.4 20 May 1996 (20.05.96) EP
(34) Countries for which the regional or international application was filed: DE et al.
97200698.5 7 March 1997 (07.03.97) EP
(34) Countries for which the regional or international application was filed: DE et al.

(71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and
(75) Inventors/Applicants (for US only): BAERT, Lieven, Elvire, Colette [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). VERRECK, Geert [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). THONE, Dany [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

(74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States: AL, AM, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ANTIFUNGAL COMPOSITIONS WITH IMPROVED BIOAVAILABILITY

(57) Abstract

The present invention is concerned with novel pharmaceutical compositions of itraconazole which can be administered to a mammal suffering from a fungal infection, whereby a single such dosage form can be administered once daily, and in addition at any time of the day independently of the food taken in by said mammal. These novel compositions comprise particles obtainable by melt-extruding a mixture comprising itraconazole and an appropriate water-soluble polymer and subsequently milling said melt-extruded mixture.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

ANTIFUNGAL COMPOSITIONS WITH IMPROVED BIOAVAILABILITY

The present invention is concerned with novel pharmaceutical compositions of itraconazole which can be administered to a mammal suffering from a fungal infection, whereby a single such dosage form can be administered once daily, and in addition at any time of the day independently of the food taken in by said mammal. These novel compositions comprise innovative particles obtainable by melt-extruding a mixture comprising itraconazole and an appropriate water-soluble polymer and subsequently milling said melt-extruded mixture.

The development of pharmaceutical compositions having good bioavailability of itraconazole, a compound that is practically insoluble in aqueous media, remains one of the main challenges of pharmaceutical development of this compound.

The term "practically insoluble" or "insoluble" is to be understood as defined in the United States Pharmacopeia, i.e. a "very slightly soluble" compound requiring from 1000 to 10,000 parts of solvent for 1 part of solute; a "practically insoluble" or "insoluble" compound requiring more than 10,000 parts of solvent for 1 part of solute. The solvent referred to herein is water.

Itraconazole or (±)-*cis*-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one, is a broadspectrum antifungal compound developed for oral, parenteral and topical use and is disclosed in US-4,267,179. Its difluoro analog, saperconazole or (±)-*cis*-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methoxypropyl)-3*H*-1,2,4-triazol-3-one, has improved activity against *Aspergillus* spp. and is disclosed in US-4,916,134. Both itraconazole and saperconazole consist of a mixture of four diastereoisomers, the preparation and utility of which is disclosed in WO 93/19061 : the diastereoisomers of itraconazole and saperconazole are designated [2R-[2α,4α,4(R*)]], [2R-[2α,4α,4(S*)]], [2S-[2α,4α,4(S*)]] and [2S-[2α,4α,4(R*)]]. The term "itraconazole" as used hereinafter is to be interpreted broadly and comprises the free base form and the pharmaceutically acceptable addition salts of itraconazole, or of one of its stereoisomers, or of a mixture of two or three or four of its stereoisomers. The preferred itraconazole compound is the (±)-(2R*, 4S*) or (cis) forms of the free base form, having the Chemical Abstracts Registry Number

[84625-61-6]. The acid addition forms may be obtained by reaction of the base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-butenedioic, (E)-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

In WO 94/05263, published on March 17, 1994, there are disclosed beads or pellets having a 25 -30 mesh sugar core (600 - 710 µm) coated with an antifungal, more particularly itraconazole (or saperconazole) and a hydrophilic polymer, more particularly, hydroxypropyl methylcellulose. Finished with a sealing film coat, such cores are referred to as beads or pellets. The beads are filled into capsules suitable for oral administration. The itraconazole is present in the drug-coating and is released readily from the surface of said coated beads, which leads to improved bioavailability of itraconazole (or saperconazole) over the then known oral dosage forms of itraconazole.

The preparation of coated beads as described in WO 94/05263 requires special techniques and special equipment in a purpose-built plant. Indeed, the beads described in the prior art are prepared in a quite complex manner requiring a lot of manipulation steps. First, a drug coating solution is prepared by dissolving into a suitable solvent system appropriate amounts of the antifungal agent and a hydrophilic polymer, preferably hydroxypropyl methylcellulose (HPMC). A suitable solvent system comprises a mixture of methylene chloride and an alcohol. Said mixture should comprise at least 50% by weight of methylene chloride acting as a solvent for the drug substance. As hydroxypropyl methylcellulose does not dissolve completely in methylene chloride, at least 10% alcohol has to be added. Subsequently, the 25-30 mesh sugar cores are drug-coated in a fluidized bed granulator equipped with a bottom spray insert. Not only should the spraying rate be regulated carefully, but also temperature control in the fluidized bed granulator is crucial. Hence, this process requires a lot of control in order to obtain a good quality product reproducibly. Moreover, this technique adequately, but still only partially solves the issue of residual organic solvents, such as methylene chloride and methanol or ethanol, being present in the coating. In order to remove any solvents which might remain in the drug-coated intermediate product, an extra drying step is required. Subsequently, a seal coating is applied and this adds yet another two steps to the production process as it involves another drying step, too.

About 460 mg beads, equivalent to about 100 mg itraconazole, are filled into a hard-gelatin capsule (size 0) and two of these capsules are administered once daily to a patient suffering from a fungal infection. The capsules are commercially available in many countries under the Trademark Sporanox™. In order to achieve the desired antifungal effect, it is essential that the two capsules are ingested at the end of a meal. This may seriously limit how easily the patients can comply with their prescribed therapy; for example, some patients are not able to eat normally or swallow medica-ments easily because of illness, nausea or because of fungal infection of the esophagus. It would therefore be highly desirable to have pharmaceutical dosage forms which can be administered to a patient - or for that matter, to any mammal - at any time of the day independently of food taken in, i.e. dosage forms which can be administered to patients (mammals) in a fasted state. Dosage forms with a high drug content, one unit of which contains the required daily dose of the active ingredient instead of two such units, are another desirable goal in the pharmaceutical development of itraconazole.

At this stage, it may be remarked that therapeutically effective plasma levels of itraconazole can be maintained easily for at least 24 hours as its half-life is sufficiently long. The condition is that the itraconazole must reach the plasma. The absorption of dissolved itraconazole from the stomach is in itself not a problem. Thus, there is no need for a sustained release dosage form of itraconazole, an immediate release form will do just as well. In other words, the main problem with the administration of itraconazole in therapeutically effective amounts is in the first place concerned with ensuring that a sufficient amount of itraconazole remains in solution sufficiently long enough to allow it to get into the circulation, and that it does not convert into a form that is not readily bioavailable, in particular into crystalline itraconazole (which forms, for example, when itraconazole precipitates in an aqueous medium).

The present invention provides pharmaceutical compositions of itraconazole and a water-soluble polymer which can be administered to a mammal, in particular a human, suffering from a fungal infection, whereby a single such dosage form can be administered once daily, and in addition at any time of the day independently of the food taken in by said mammal. The bioavailability of the drug from these dosage forms in fasted and in fed mammals is comparable. The dosage forms can be prepared easily, for example by conventional tabletting techniques. The dosage forms comprise a therapeutically effective amount of novel particles as described in detail hereunder.

Said novel particles consist of a solid dispersion comprising

(a) itraconazole, or one of its stereoisomers, or a mixture of two or three or four of its stereoisomers, and

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

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 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 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.

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 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. Domains of (a) typically have a size of up to about 25 μm, preferably up to 20 μm.

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,

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 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.

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 120°C and about 300°C. At temperatures lower than 120°C, itraconazole will not dissolve completely in most water-soluble polymers and the extrudate will not have the required bioavailability. In addition, the process is difficult because of the high viscosity of the mixture. At temperatures of more than 300°C the water-soluble polymer may decompose to an unacceptable level. It may be noted that there is no need to fear decomposition of itraconazole at temperatures up to 300°C, since this active ingredient is thermally very stable.

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 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.

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

168

solid dispersion. Yet another possible preparation consists of preparing a solution 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 600 µm, preferably less than 400 µm and most preferably less than 125 µm. The particle size proves to be an important factor determining the speed with which tablets having sufficient hardness can be manufactured on a large scale ; the smaller the particles, the faster the tabletting speed can be without detrimental effects on their quality. The particle size distribution is such that more than 70% of the particles (measured by weight) have a diameter ranging from about 50 µm to about 500 µm, in particular from about 50 µm to about 200 µm 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 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 mm and to the corresponding Sieve No. in the ASTM E11-70 standard.

Preferred are particles wherein the itraconazole is in a non-crystalline phase as these have an intrinsically faster dissolution rate than those wherein part or all of the itraconazole is in a microcrystalline or crystalline form.

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

The water-soluble polymer in the particles according to the present invention is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. 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.
- 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 derivates such as chitosan,
- polysaccharides such as 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 and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing particles according to the present invention.

Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. 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-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 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 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 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 form about 3 to about 15 mPa.s, preferably about 5 mPa.s The most preferred type of HPMC having a 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 itraconazole can be prepared as will be discussed hereunder and in the experimental part.

The weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 17, preferably 1 : 1 to 1 : 5. In the case of (itraconazole) : (HPMC 2910 5 mPa.s), said ratio may range from about 1 : 1 to about 1 : 2, and optimally is about 1 : 1.5 (or 2 : 3). The weight by weight ratio of itraconazole to other water-soluble polymers 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 itraconazole (from about 50 mg to about 300 mg, preferably about 200 mg per day), 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 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 itraconazole over hydroxypropyl methyl cellulose will be about 1 : 17 (50 mg itraconazole + 850 mg water-soluble polymer).

On the other hand, if the ratio is too high, this means the amount of itraconazole is relatively high compared to the amount of water-soluble polymer, then there is the risk that the itraconazole will not dissolve sufficiently in the water-soluble polymer, and thus the required 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. The 1 : 1 upper limit is determined by the fact that above said ratio it was observed that the extrudate resulting from extruding itraconazole with HPMC 2910 5 mPa.s is not "clear", presumably due to the fact that not all of the itraconazole has dissolved in the HPMC. It will be appreciated that the upper limit of 1 : 1 may be underestimated for particular 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.

Preferred particles are those obtainable by melt-extrusion of the components and grinding, and optionally sieving. More in particular, the present invention concerns particles consisting of a solid solution comprising two parts by weight of itraconazole 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 120°C - 300°C, grinding the extrudate, and optionally sieving the thus obtained particles. The preparation is easy to perform and yields itraconazole particles that are free of organic solvent.

The particle as described hereinabove may further comprise one or more 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.

In the current itraconazole : HPMC 2910 5 mPa.s formulations, 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 is formed, and this lowering of the melting point is advantagous where the polymeer 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 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 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 is milled and sieved and used as a "normal" ingredient to make pharmaceutical dosage forms.

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 forms are those adapted for oral administration shaped as a tablet. They can be produced by conventional tabletting techniques with conventional ingredients or excipients and with conventional tabletting machines. In addition, they can be produced at substantially lower cost than the coated cores. As mentioned above, an effective antifungal daily dose of itraconazole ranges from about 50 mg to about 300 mg o.d., and preferably is about 200 mg o.d. 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 400 mg. 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. 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.

Tablets that give an immediate release of itraconazole 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 itraconazole 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.

Suitable disintegrants are those that have a large coefficient of expansion. Examples thereof are hydrophilic, insoluble or poorly water-soluble crosslinked polymers such as crospovidone (crosslinked polyvinylpyrrolidone) and croscarmellose (crosslinked sodium carboxymethylcellulose). The amount of disintegrant in immediate release tablets according to the present invention may conveniently range from about 3 to about 15 % (w/w) and preferably is about 7 to 9 %, in particular about 8.5 % (w/w). This amount tends to be larger than usual in tablets in order to ensure that the particles are spread over a large volume of the stomach contents upon ingestion. Because

disintegrants by their nature yield sustained release formulations when employed in bulk, it is advantageous to dilute them with an inert substance called a diluent or filler.

A variety of materials may be used as diluents or fillers. Examples are spray-dried or anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (e.g. microcrystalline cellulose Avicel™), dihydrated or anhydrous dibasic calcium phosphate, and others known in the art, and mixtures thereof. Preferred is a commercial spray-dried mixture of lactose monohydrate (75 %) with microcrystalline cellulose (25 %) which is commercially availble as Microcelac™. The amount of diluent or filler in the tablets may conveniently range from about 20 % to about 40 % (w/w) and preferably ranges from about 25 % to about 32 % (w/w).

The tablet may include a variety of one or more other conventional excipients such as binders, buffering agents, lubricants, glidants, thickening agents, sweetening agents, flavors, and colors. Some excipients can serve multiple purposes.

Lubricants and glidants can be employed in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants and glidants are hydrogenated vegetable oils, e.g hydrogenated Cottonseed oil, magnesium stearate, stearic acid, sodium lauryl sulfate, magnesium lauryl sulfate, colloidal silica, talc, mixtures thereof, and others known in the art. Interesting lubricants and glidants are magnesium stearate, and mixtures of magnesium stearate with colloidal silica. A preferred lubricant is hydrogenated vegetable oil type I, most preferably hydrogenated, deodorized Cottonseed oil (commercially available from Karlshamns as Akofine NF ™ (formerly called Sterotex™)). Lubricants and glidants generally comprise 0.2 to 7.0 % of the total tablet weight.

Other excipients such as coloring agents and pigments may also be added to the tablets of the present invention. Coloring agents and pigments include titanium dioxide and dyes suitable for food. A coloring agent is an optional ingredient in the tablet of the present invention, but when used the coloring agent can be present in an amount up to 3.5 % based on the total tablet weight.

Flavors are optional in the composition and may be chosen from synthetic flavor oils and flavoring aromatics or natural oils, extracts from plants leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, bay oil, anise oil, eucalyptus, thyme oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences,

including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. The amount of flavor may depend on a number of factors including the organoleptic effect desired. Generally the flavor will be present in an amount from about 0 % to about 3 % (w/w).

As known in the art, tablet blends may be dry-granulated or wet-granulated before tabletting. The tabletting process itself is otherwise standard and readily practised by forming a tablet from desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press.

Tablets of the present invention may further be film-coated to improve taste, to provide ease of swallowing and an elegant appearance. Many suitable polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropyl methylcellulose HPMC, especially HPMC 2910 5 mPa.s. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylate-methacrylate copolymers. Besides a film-forming polymer, the film coat may further comprise a plasticizer (e.g. propylene glycol) and optionally a pigment (e.g. titanium dioxide). The film-coating suspension also may contain talc as an anti-adhesive. In immediate release tablets according to the invention, the film coat is small and in terms of weight accounts for less than about 3 % (w/w) of the total tablet weight.

Preferred dosage forms are those wherein the weight of the particles is at least 40 % of the total weight of the total dosage form, that of the diluent ranges from 20 to 40 %, and that of the disintegrant ranges from 3 to 10 %, the remainder being accounted for by one or more of the excipients described hereinabove. As an example of a preferred oral dosage form comprising 200 mg of itraconazole, the following formula may be given :

21.65 %	itraconazole (200 mg)
32.48 %	HPMC 2910 5 mPa.s (300 mg)
30.57 %	spray-dried lactose monohydrate : microcrystalline cellulose (75 : 25) mixture (282.4 mg)
8.49 %	crospolyvidone (78.4 mg)
2.79 %	talc (25.8 mg)
0.93 %	hydrogenated vegetable oil Type I (8.6 mg)
0.28 %	colloidal anhydrous silica (2.6 mg)
0.24 %	magnesium stearate (2.2 mg), yielding
97.43 %	tablet core, and

1.47 %	HPMC 2910 5 mPa.s (13.57)

0.37 % propyleneglycol (3.39 mg)
0.29 % talc (2.71 mg)
0.44 % titanium dioxide (4.07 mg). yielding
2.57 % film-coat.

Preferred dosage forms according to the present invention are those from which at least 85 % of the available itraconazole dissolves within 60 minutes when a dosage form equivalent to 200 mg itraconazole is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following : 900 ml phosphate buffer, pH 6.0, 37°C with paddles turning at 100 rpm. Tablets complying with the preceding definition can be said to have Q > 85 % (60'). Preferably, tablets according to the present invention will dissolve faster and have Q > 85 % (15'), more preferably Q > 85 % (5').

The present invention further concerns a process of preparing particles as described hereinbefore, characterized by blending the components, extruding said blend at a temperature in the range of 120 - 300 °C, grinding the extrudate, and optionally sieving the particles.

The invention also concerns solid dispersions obtainable by melt-extrusion of
(a) itraconazole or one of its stereoisomers or a mixture of two or three or four of its stereoisomers, and
(b) one or more pharmaceutically acceptable water-soluble polymers.

It is another object of the invention to provide a process of preparing a pharmaceutical dosage form as described hereinbefore, characterized by blending a therapeutically effective amount of particles as described hereinbefore, with pharmaceutically acceptable excipients and compressing said blend into tablets.

Further, this invention concerns particles as described hereinbefore, for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from a fungal infection, wherein a single such dosage form can be administered once daily to said mammal.

The invention also relates to particles as described hereinbefore, for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from a fungal infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

The present invention also concerns the use of particles according to as described hereinbefore, for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from a fungal infection, wherein a single such dosage form can be administered once daily to said mammal.

The present invention also concerns the use of particles as described hereinbefore, for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from a fungal infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

The invention also relates to a method of treating a fungal infection in a mammal which comprises administering to said mammal an effective antifungal amount of itraconazole in a single oral dosage form which can be administered once daily.

The invention also relates to a method of treating a fungal infection in a mammal which comprises administering to said mammal an effective antifungal amount of itraconazole in a single oral dosage form which can be administered at any time of the day independently of the food taken in by said mammal.

The invention also relates to a pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of itraconazole as described hereinbefore, and associated with said package written matter non-limited as to whether the dosage form can be taken with or without food.

It has been observed that the tablets of the present invention showed a remarkably lower food-effect than the prior art Sporanox™ capsules. This means that the difference between taking the medication after a meal or in fasted state is significantly less when the tablet of the present invention is administered than when Sporanox™ capsules are administered. This is of course a huge advantage because the medication can be taken in at any time during the day and is no longer dependent upon the intake of a meal. Moreover, patients. who are feeling nauseous or who are not able to eat can still take the tablets of the present invention.

Example 1

a) preparation of Triaset®

A 40/60 (w/w) mixture of itraconazole (21.74 kg) and hydroxypropyl methylcellulose 2910 5 mPa.s(1) or HPMC 2910 5 mPa.s (32.11 kg) were both sieved and mixed in a

planetary mixer until the mixture was homogenous. This physical mixture of itraconazole and HPMC is also known as Triaset®.

b) preparing the melt extrudate

1500 g of Triaset® was fed into a twin screw melt extruder of the type APV-Baker MP19 L/D 15having the following operating parameters : temperature of the first compartment was 245°C, temperature of the second compartment was 265°C, the twin screw had a rate of 20 - 300 revolutions/min and was extruded during 120 minutes. The extrudate was brought in a hammer mill of type Fitzmill, the mesh of the sieve was 0.125 inch (= 0.32 cm) and revolving speed was 1640 revolutions per minute. The milled extrudate was again brought in a hammer mill, this time with a sieve of mesh 0.063 inch (= 0.16 cm) and a revolving speed of 1640 revolutions per minute. Yield was 1169 g (78 %).

c) preparation of a tabletting mixture

Microcrystalline cellulose (351 g, 21 % (w/w)), Crospovidone (117 g, 7 % (w/w)) , Aerosil (colloidal silicon dioxide) (5 g, 0.3 % (w/w)) and Sterotex (8 g, 0.5 % (w/w)) were sieved and mixed together with the milled extrudate (1169 g, 71 % (w/w)) using a planetary mixer until a homogenous mixture was obtained (15 minutes).

d) Tabletting

Using the mixture obtained in c) 1450 oval biconvex half-scored tablets of 706 mg (die length = 17.6 mm, breadth = 8.4 mm) were prepared on an Excenterpress Courtoy 27.

Example 2

The process as described in example 1 was repeated, but the extrusion step was carried out as follows :

1000 g of Triaset® was inserted into a meltextruder of the type APV-Baker MP19 L/D 15 having the following operating parameters : temperature of the first compartment was 170°C, temperature of the second compartment was 170°C, the twin screw had a rate of 450 revolutions/min. The extrudate was brought in a hammer mill of type Fitzmill, the mesh of the sieve was 0.125 inch (= 0.32 cm) and revolving speed was 1640 revolutions per minute. The milled extrudate was again brought in a hammer mill, this time with a sieve of mesh 0.063 inch (= 0.16 cm) and a revolving speed of 1640 revolutions per minute.

The tablets were prepared in the same manner as described in Example 1 and had the following characteristics :

- nominal weight : 706 mg
- disintegation time : < 15 minutes
- hardness : > 6 daN (deca Newton)
- height : 6.7 ± 0.1 mm

Example 3

Itraconazole plasma levels in healthy volunteers after single oral administration of 200 mg in two different formulations in fasting conditions.

Treatment with the available prior art itraconazole capsules

200 mg as two 100 mg coated cores-capsules (Sporanox®) in fasting conditions

five volunteers

time (h)	plasma level (ng/ml) mean value (S.D.)
0	ND(1)
1	26.8 (27.1)
2	125 (111)
3	128 (101)
4	110 (84.3)
5	84.5 (68.9)
6	71.1 (55.2)
8	54.5 (44.3)
24	25.6 (20.3)

Treatment with tablets of the present invention as prepared in example 1, i.e one 200 mg "melt extrusion tablet" in fasting conditions

time (h)	plasma level (ng/ml) mean value (S.D.)
0	ND(1)
1	54.4 (51.3)
2	143 (97.8)
3	191 (111)
4	208 (124)
5	198 (136)
6	153 (107)
8	124 (79)
24	44.5 (24.2)

This limited study in volunteers (n=5) shows that in fasted state the melt extrusion tablet gives a AUC of itraconazole (which is a measure for the bioavailability of itraconazole) that is 2.3 times the AUC of itraconazole when administered as 2 times a 100 mg capsule of Sporanox™. When using the non-parametric test (WILCOXON) this difference appears to be significant at a confidence level of 90 %.

Example 4

a) preparation of a tabletting mixture

A spray-dried mixture of lactose monohydrate (75 %) and microcrystalline cellulose (25 %) (2.824 kg, 30.57 % (w/w)), Crospovidone (784 g, 8.49 % (w/w)) ,Talc (258 g, 2.79 % (w/w)), Aerosil (26 g, 0.28 % (w/w)), magnesium stearate (22 g, 0.24 % (w/w)) and Sterotex (86 g, 0.093 % (w/w)) were sieved and mixed together with the milled extrudate (5 kg, 54.13 % (w/w)) using a planetary mixer until a homogenous mixture was obtained (15 minutes). All % (w/w) are based on the total weight of a film-coated tablet.

b) Tabletting

Using the mixture obtained in a) 3,000 oval biconvex tablets of 900 mg were prepared on an Excenterpress Courtoy 27.

c) Film-coating

The tablets obtained in b) were film-coated using a suspension comprising by weight : HPMC 2910 5 mPa.s (8.5 %), propylene glycol (2.1 %), talc (1.7 %), and titanium dioxide (2.6 %) in demineralised water (85 %). HPMC 2910 5 mPa.s was added to the purified water and mixed until completely dispersed. The solution was left to stand until clear. Propylene glycol was added and mixed until uniform. Talc and titanium dioxide were added to the solution and mixed until uniform. The tablets obtained in d) were placed in a coating pan and the pigmented coating solution was sprayed onto the cores. Average tablet weight was 924.7 mg.

d) Packing

The coated tablets were packed into polyvinyl/aluminium foil blister packs, which in turn were packed into cardboard cartons.

e) Dissolution Properties

In-vitro dissolutions studies were performed on the 200 mg tablet formulation. The medium was 900 ml of 0.1 N HCl at 37°C in Apparatus 2 (USP 23, <711> Dissolution, pp. 1791-1793) (paddle, 100 rpm). The concentration of the active ingredient itraconazole dissolved in the test medium was determined by removing a 3 ml sample at the indicated time, measuring its absorbance at 254 nm and calculating the concentration therefrom.

The following results were obtained :

Time (min)	Calculated concentration (% w/w) of the active dose						
	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	83.70	85.10	79.56	87.39	86.04	89.73	85.25
15	97.65	97.79	97.34	97.20	97.29	100.62	97.98
30	97.43	98.78	98.82	100.71	98.82	99.59	99.02
45	98.42	98.55	98.69	100.49	98.87	99.18	99.03
60	99.27	99.54	99.36	100.44	98.91	99.23	99.46

Example 5

a) preparation of particles < 125 µm.

1500 g of Triaset® was melt extruded as as described in example 1 and milled in Fitzmill hammer mill at 4736 rpm and a sieve of 0.51 mm. The particle fraction with a size < 125 µm was isolated by further sieving through a sieve No 120 (ASTM E 11-70) ; yield < 10 %.

b) tabletting

A tabletting mixture having a composition as described in Example 4, but comprising particles having a size < 125 µm was prepared and compressed on a Korsch tabletting machine operating at a speed of 10,800 tablets/hour, a compression pressure of 1500 to 1950 kg /cm^2 (147 - 191.1 MPa). The length of the die was 19 mm, breadth 9.5 mm, and the radius of curvature 9.57 mm. The tablets had the following characteristics :

- nominal weight : 906.9 mg
- maximum height : 5.88 mm
- hardness : 11 daN
- disintegration time : 2'15''
- friability : 0 %

182

Claims

1. A particle consisting of a solid dispersion comprising
(a) itraconazole, or one of its stereoisomers, or a mixture of two or three or four of its stereoisomers, and
(b) one or more pharmaceutically acceptable water-soluble polymers.

2. A particle according to claim 1 having a particle size of less than 600 µm.

3. A particle according to claim 1 or 2 wherein the itraconazole is in a non-crystalline phase.

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 water-soluble polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.

6. A particle according to claim 5 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 derivates such as chitosan,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof,

carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,

- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

7. A particle according to claim 6 wherein the water-soluble polymer is hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.

8. A particle according to claim 7 wherein the weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 17.

9. A particle according to any one of the preceding claims obtainable by melt-extrusion of the components and grinding, and optionally sieving.

10. A particle according to any one of the previous claims consisting of a solid solution comprising two parts by weight of itraconazole 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 120°C - 300°C, grinding the extrudate, and optionally sieving the thus obtained particles.

11. A particle according to the preceding claims further comprising one or more pharmaceutically acceptable excipients.

12. A pharmaceutical dosage form comprising a therapeutically effective amount of particles as claimed in any one of the preceding claims.

13. A dosage form according to claim 12 adapted for oral administration shaped as a tablet.

14. A dosage form according to claim 12 for immediate release of itraconazole upon oral ingestion wherein said particles are homogeneously distributed throughout a mixture of a diluent and a disintegrant.

15. A dosage form according to claim 13 or 14 surrounded by a film-coat comprising a film-forming polymer, a plasticizer and optionally a pigment.

16. A dosage form according to claim 14 wherein the diluent is a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75 : 25), and the disintegrant is crospovidone or croscarmellose.

17. A dosage form according to any one of claims 12 to 16 wherein the weight of said particles is at least 40 % of the total weight of the dosage form.

18. A dosage form according to claim 12 comprising by weight based on the total weight of the dosage form :
21.65 % itraconazole (200 mg)
32.48 % HPMC 2910 5 mPa.s (300 mg)
30.57 % spray-dried lactose monohydrate : microcrystalline cellulose (75 : 25) mixture (282.4 mg)
8.49 % crospovidone (78.4 mg)
2.79 % talc (25.8 mg)
0.93 % hydrogenated vegetable oil Type I (8.6 mg)
0.28 % colloidal anhydrous silica (2.6 mg)
0.24 % magnesium stearate (2.2 mg), yielding
97.43 % tablet core, and

1.47 % HPMC 2910 5 mPa.s (13.57)
0.37 % propyleneglycol (3.39 mg)
0.29 % talc (2.71 mg)
0.44 % titanium dioxide (4.07 mg), yielding
2.57 % film-coat.

19. A dosage form according to any one of claims 12 to 18 from which at least 85 % of the available itraconazole dissolves within 60 minutes when a dosage form equivalent to 200 mg itraconazole is tested as set forth in USP test <711> in a USP-2 dissolution apparatusunder conditions at least as stringent as the following : 900 ml phosphate buffer, pH 6.0, 37°C with paddles turning at 100 rpm.

20. A process of preparing particles as claimed in any one of claims 1 to 11 characterized by blending the components, extruding said blend at a temperature in the range of 120 - 300 °C, grinding the extrudate, and optionally sieving the particles.

21. A solid dispersion obtainable by melt-extrusion of
(a) itraconazole or one of its stereoisomers or a mixture of two or three of its stereoisomers, and
(b) one or more pharmaceutically acceptable water-soluble polymers.

22. A process of preparing a pharmaceutical dosage form as claimed in any one of claims 12 to 19 characterized by blending a therapeutically effective amount of particles as claimed in any one of claims 1 to 11 with pharmaceutically acceptable excipients and compressing said blend into tablets.

23. Particles according to any one of claims 1 to 11 for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from a fungal infection, wherein a single such dosage form can be administered once daily to said mammal.

24. Particles according to any one of claims 1 to 11 for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from a fungal infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

25. Use of particles according to any one of claims 1 to 11 for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from a fungal infection, wherein a single such dosage form can be administered once daily to said mammal.

26. Use of particles according to any one of claims 1 to 11 for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from a fungal infection, wherein said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

27. A pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of itraconazole as claimed in any one of claims 12 to 19, and associated with said package written matter non-limited as to whether the dosage form can be taken with or without food.

186

INTERNATIONAL SEARCH REPORT

Intern. ..al Application No
PCT/EP 97/02507

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/14 A61K31/495

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 05263 A (JANSSEN PHARMACEUTICA N.V.) 17 March 1994 cited in the application see page 1, line 9 - page 2, line 2 see page 6, line 25 - line 32 see page 7, line 1 - line 15 ---	1-27
Y	EP 0 012 523 A (AMERICAN HOME PRODUCTS CORPORATION) 25 June 1980 see page 6, line 1 - page 7, line 8 see page 9, line 26 - line 30 see page 17, line 10 - line 16 see page 27; example 17 --- -/--	1-8, 11-19, 23-27

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 1997	09.09.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Benz, K

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/EP 97/02507

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 44, no. 3, March 1996, TOKYO (JP), pages 568-571, XP000582694 T. KAI ET AL.: "ORAL ABSORPTION IMPROVEMENT OF POORLY SOLUBLE DRUG USING SOLID DISPERSION TECHNIQUE" see the whole document ---	1-8
Y	DATABASE WPI Week 8325 Derwent Publications Ltd., London, GB; AN 83-59971K XP002016409 & JP 58 079 915 A (NIPPON SODA KK) , 13 May 1983 see abstract ---	9,10, 20-22
Y	DE 42 26 753 A (BASF AG) 17 February 1994 see the whole document see page 5; example 6 -----	9,10, 20-22

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interm al Application No
PCT/EP 97/02507

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9405263 A	17-03-94	AP 444 A	19-01-96
		AT 145327 T	15-12-96
		AU 665867 B	18-01-96
		AU 4954693 A	29-03-94
		CA 2142848 A	17-03-94
		CN 1088432 A	29-06-94
		CZ 9500542 A	13-09-95
		DE 69306119 D	02-01-97
		DE 69306119 T	13-03-97
		EP 0658103 A	21-06-95
		ES 2097536 T	01-04-97
		FI 950975 A	02-03-95
		HR 931158 A	30-06-95
		HU 70419 A	30-10-95
		JP 8501092 T	06-02-96
		NO 950829 A	02-05-95
		NZ 255379 A	25-06-96
		PL 307791 A	26-06-95
		SI 9300461 A	31-03-94
		US 5633015 A	27-05-97
		ZA 9306493 A	02-03-95
EP 12523 A	25-06-80	AT 5852 T	15-02-84
		US 4344934 A	17-08-82
DE 4226753 A	17-02-94	AU 4457293 A	17-02-94
		CA 2103961 A	14-02-94
		EP 0596203 A	11-05-94
		JP 6172160 A	21-06-94
		NO 932875 A	14-02-94
		US 5641516 A	24-06-97

EXHIBIT 5

189

Pharmaceutical Research, Vol. 16, No. 11, 1999

Research Paper

Physical Properties of Solid Molecular Dispersions of Indomethacin with Poly(vinylpyrrolidone) and Poly(vinylpyrrolidone-co-vinylacetate) in Relation to Indomethacin Crystallization

Takahiro Matsumoto[1,2] and George Zografi[1,3]

Received April 30, 1999; accepted July 24, 1999

Purpose. To measure solid-state features of amorphous molecular dispersions of indomethacin and various molecular weight grades of poly(vinylpyrrolidone), PVP, and poly(vinylpyrrolidone-co-vinylacetate), PVP/VA, in relation to isothermal crystallization of indomethacin at 30°C.

Methods. The glass transition temperatures (Tg) of molecular dispersions were measured using differential scanning calorimetry (DSC). FT-IR spectroscopy was used to investigate possible differences in interactions between indomethacin and polymer in the various dispersions. The enthalpy relaxation of 5%w/w and 30%w/w polymer dispersions was determined following various aging times. Quantitative isothermal crystallization studies were carried out with pure indomethacin and 5%w/w polymers in drug as physical mixtures and molecular dispersions.

Results. All coprecipitated mixtures exhibited a single glass transition temperature. All polymers interacted with indomethacin in the solid state through hydrogen bonding and in the process eliminated the hydrogen bonding associated with the carboxylic acid dimers of indomethacin. Molecular mobility at 16.5°C below Tg was reduced relative to indomethacin alone, at the 5%w/w and 30%w/w polymer level. No crystallization of indomethacin at 30°C was observed in any of the 5%w/w polymer molecular dispersions over a period of 20 weeks. Indomethacin alone and in physical mixtures with various polymers completely crystallized to the γ form at this level within 2 weeks.

Conclusions. The major basis for crystal inhibition of indomethacin at 30°C at the 5%w/w polymer level in molecular dispersions is not related to polymer molecular weight and to the glass transition temperature, and is more likely related to the ability to hydrogen bond with indomethacin and to inhibit the formation of carboxylic acid dimers that are required for nucleation and growth to the γ crystal form of indomethacin.

KEY WORDS: indomethacin; molecular dispersion; polymer; crystallization; molecular mobility; glass transition.

INTRODUCTION

It is well recognized that crystalline drugs exhibiting very poor water solubility often have inadequate bioavailability when administered in solid dosage forms. Converting such a material to the high-energy amorphous state offers a strategy for improving dissolution rates and hence bioavailability (1,2). Such amorphous states, however, are metastable relative to the crystalline state and under certain conditions of temperature and relative humidity during storage and use they can spontaneously crystallize (3–5). From a pharmaceutical perspective, therefore, it is necessary to add excipients that might be able to retard any tendencies for such instability over meaningful timescales.

Co-lyophilization or co-precipitation of a drug with a second component having a higher glass transition temperature, Tg, to form a miscible molecular dispersion has been suggested as a way to meet this objective (6,7). The basic premise is that the molecular dispersion will have a Tg greater than that of the drug alone, and hence that the molecular mobility of the drug will be reduced, therefore reducing tendencies for crystallization. In particular, polymeric excipients with high Tg values would appear to provide the basis for accomplishing these objectives; and, indeed, there have been a number of reports of enhanced physical stability of amorphous drugs using polymers such as poly(vinylpyrrolidone), PVP (8,9).

In this laboratory we have carried out a series of studies using indomethacin and PVP90 as a model system. Having characterized the amorphous properties of indomethacin (5,10,11) and PVP90 (12,13) individually, we have examined the glass transition temperature, intermolecular hydrogen bonding and inhibition of crystallization of indomethacin as function of PVP90 concentration (14,15). We have shown significant inhibition of crystallization at low levels of PVP90, where the Tg values of the mixtures were very close to that of indomethacin alone due to nonidealities of mixing. Using FTIR spectroscopy we were able to observe significant hydrogen bonding between indomethacin and PVP90 and the elimination of FTIR spectral peaks associated with the dimerization of indomethacin (15). A possible relationship of such hydrogen bonding to crystallization inhibition by PVP was suggested (15).

Amorphous indomethacin presents an interesting challenge with regard to crystallization because it can form one of two polymorphs depending on the storage temperature relative to its Tg of 42°C; the more thermodynamically stable γ form crystallizes well below Tg and the less stable α form preferentially crystallizes above Tg (10). Whereas many amorphous systems tend to exhibit optimal conditions for nucleation and crystal growth above Tg, where molecular mobility is greater, the γ form of indomethacin exhibits an optimal rate of both nucleation and growth near its Tg of 42°C (16). Thus, it is this crystal form that must be inhibited during storage at or below Tg to maintain the amorphous form of indomethacin. In this study we have focused our attention on storage at 30°C because we are interested in the crystallization behavior of a drug like indomethacin when it is stored under room temperature conditions. It has been shown that storage of amorphous indomethacin at temperatures about 40–50°C below Tg, near refrigerator temperatures, can and does prevent crystallization over very long time periods (10). For most solid dosage forms, such as capsules or tablets, however, such low temperature storage is not practical, and room temperature storage is more desirable. We also have focused our attention on using low levels of polymer so that we can produce the smallest total weight (small

[1] School of Pharmacy, University of Wisconsin-Madison, 425 N. Charter St., Madison, Wisconsin 53706.

[2] Present address: Daiichi Pharmaceutical Co., Ltd., Pharmaceutical Research Laboratory, Tokyo R&D Center, 16-13, Kita-Kasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan.

[3] To whom correspondence should be addressed. (e-mail: gzografi@facstaff.wisc.edu)

0724-8741/99/1100-1722$16.00/0

capsule or tablet size) needed to provide the necessary dose of drug, while still maintaining long term stability.

MATERIALS AND METHODS

Materials

Indomethacin 1-(p-chlorobenzoyl)-5-methoxy-2-methlyl-indole-3-acetic acid, was obtained in its γ crystal form from Sigma Chemical Co. Poly(vinylpyrrolidone) (PVPK90, K30, 17PF, 12PF) and Poly(vinylpyrrolidone-co-vinylacetate) (PVP/VA64) were obtained from the BASF corporation. The weight-average molecular weight of each PVP was reported by the supplier to be 1,000,000 ~ 1,500,000, 44,000 ~ 54,000, 7,000 ~ 11,000 and 2,000 ~ 3,000 respectively (17). PVP/VA64 is a random copolymer containing vinyl pyrrolidone and vinyl acetate at a molar ratio of 60:40 with a reported molecular weight range of 45,000 ~ 70,000 (17). PVP and PVP/VA were dried at 105°C for 12 hours under vacuum before use.

Methods

Preparation of Molecular Dispersions

Molecular dispersions were prepared using a solvent evaporation technique, wherein 2 g of the appropriate ratios of the two components were dissolved in 20 ml of anhydrous methanol at 65°C. The solvent was removed under vacuum at 50°C using a rotary evaporator. Any residual solvent was removed by drying under vacuum at room temperature for 24 hours. Amorphous indomethacin was prepared by quench-cooling of the melt of the γ crystal form. The melt was held at 165°C for 5 min and then quench-cooled by immersion into liquid nitrogen (5). The samples were ground gently in a mortar, passed through a 60 mesh sieve, and stored at −20°C over phosphorous pentoxide.

X-ray Powder Diffraction

A scanning X-ray powder diffractometer (PadV, Scintag Inc., Santa Clara, CA) controlled by a computer (Model #B10610, Tektronix Inc., Wilsonville, OR) was used to quantify the presence of any crystalline indomethacin in the various samples. The radiation used was generated by a copper Kα filter, with a wavelength of 1.5418Å at 35 kV and 40 mA. Samples were scanned over a range of 2θ values from 5° to 50° at a scan rate of 2.5°/min.

Density Determination

The densities of the various samples used in this study were determined by helium pycnometry (Quantachrome Corp.) at ambient temperature. The densities of the PVP90, PVP30, PVP17, PVP12 and PVP/VA were determined to be 1.21, 1.20, 1.16, 1.17 and 1.18 gcm^{-3}, respectively. The density of amorphous indomethacin was previously determined to be 1.31 gcm^{-3} (10).

Differential Scanning Calorimetry

DSC measurements were performed using a Seiko SSC5200 DSC (Seiko Instruments, Horsham, PA) fitted with an automated liquid nitrogen cooling accessory. Samples (7–15 mg) were carefully weighed out into aluminum pans that allow removal of any residual water with a pinhole in the lid. Dry nitrogen was used as the purge gas and liquid nitrogen as the coolant. Unless otherwise noted, heating and cooling rates of 10°C/min were used. Temperatures and enthalpy values were calibrated with pure indium and gallium. Glass transition temperatures (Tg) were determined by first heating the samples to at least 20°C above Tg to erase the previous thermal history of the samples and then cooling them to 100°C below Tg at a cooling rate of 40°C/min. The samples were subsequently heated a second time to 220°C during which the onset Tg and the change in heat capacity at Tg (ΔCp) were determined. Enthalpy relaxation for pure amorphous indomethacin and the various molecular dispersions containing 5%w/w and 30%w/w polymers was determined by first heating the samples to at least 20°C above Tg and then cooling to 100°C below Tg to form a glass with a standardized thermal history. The samples were heated to 16.5°C below Tg and held isothermally from 0 to 16 hours. The samples were subsequently cooled to −40°C and then reheated through Tg to 220°C. The pronounced endothermic recovery peak reflecting enthalpy relaxation was analyzed. The area of the endotherm (ΔH) was determined by constructing a tangent to the curve in the region above Tg and extrapolating to lower temperatures as reported previously (18,19). The ΔH of pure indomethacin was corrected for dilution with polymer to allow comparison with that of the dispersions with polymer.

IR Spectroscopy

IR absorbance spectra were measured by the KBr disk method using a Mattson Galaxy 5020FTIR spectrometer equipped with a DTGS detector. 64 scans were collected for each sample at a resolution of 2 cm^{-1} over the wave number region 4000 ~ 400 cm^{-1}.

Isothermal Crystallization Studies

Mixtures of indomethacin containing 5%w/w of the various PVP samples and PVP/VA, as physical mixtures and molecular dispersions, and amorphous indomethacin itself were used to estimate the extent of any crystallization from the amorphous state. Samples (250 mg) were placed in sealed glass vials and stored in desiccators containing P_2O_5 at a constant temperature below Tg for up to 20 weeks. The presence of either α or γ crystals as a possible crystalline form was monitored by removing vials at appropriate time intervals, mixing with 20%w/w of LiF and measuring the X-ray peak height ratios. The ratios of peak height at 2θ = 8.5° for the α form and 11.6° for the γ form to that of LiF at 2θ = 38.7° were used for the determination of the crystalline indomethacin fraction based on calibration curves as previously reported (3,4,14).

RESULTS AND DISCUSSION

Glass Transition Temperatures

The onset Tg values and ΔCp values at Tg for indomethacin, PVP and PVP/VA used in this study are given in Table I, where it can be seen that the Tg values of PVP increase as the molecular weight of the sample increases, consistent with the expected molecular weight dependence of Tg (20). The Tg

Table I. Glass Transition Temperature, Tg, and Change in Heat Capacity at Tg, ΔCp, for Single Components Measured using DSC with a Heating Rate of 10°C/min

Material	Onset Tg (°C)	ΔCp(Tg) (J/g K)
indomethacin	42	0.55
PVP90	172	0.30
PVP30	156	0.26
PVP17	136	0.33
PVP12	99	0.34
PVP/VA	102	0.39

Note: The standard deviations in the measurement of Tg and ΔCp are within ± 1°C, 0.02 J/g, respectively.

value of PVP/VA is lower than that of PVP30, both having about the same molecular weight, and very similar to that of PVP12. Figure 1 shows plots of the onset Tg values versus the weight fraction of PVP and PVP/VA for the various dispersions. The amorphous nature of all samples was verified by X-ray powder diffraction analysis. A single Tg between the Tg values of the pure components is observed over the entire composition range, indicating a single miscible amorphous phase for all dispersions. At the lower concentration range of PVP and PVP/VA (5–30%w/w), the Tg values of all dispersions are not significantly different for a particular weight %w/w of polymer as given in Table II.

The extent to which these dispersions might exhibit deviations from ideal mixing was evaluated by comparison of the experimental Tg values with those predicted using Eq. 1.

$$Tg = \frac{w_1 Tg_1 + K w_2 Tg_2}{w_1 + K w_2} \quad (1)$$

where w_1 and w_2 are the weight-fractions of each component, and Tg_1 and Tg_2 are the corresponding Tg values of each component. Using free volume theory, the constant K can be estimated with a knowledge of the density (ρ_1, ρ_2) of both components using the Simha-Boyer rule (21). In this form equation 1 is the Gordon-Taylor equation (22), and

$$K \approx \frac{\rho_1 Tg_1}{\rho_2 Tg_2} \quad (2)$$

Using a thermodynamic model, equation (1) is known as the Couchman-Karasz equation, where K now is defined as in Eq. 3 (23).

$$K = \frac{\Delta Cp_2}{\Delta Cp_1} \quad (3)$$

where ΔCp is the change in heat capacity at Tg.

The lines in Fig. 1 show the values of Tg that would be predicted from Eq. 1 using both the free volume and thermodynamic models. As has been shown before (24), the two theoretical models generally produce small but, in some cases, significant differences in predicted values. In all of the molecular dispersions evaluated in this study the experimental values of Tg fall well within reasonable agreement with either predicted values, indicating fairly ideal mixing. However, in the case of PVP90, up to about 20%w/w PVP, there appears to be no significant change in Tg, a clear indication of non-ideal mixing in this range of concentration for the highest molecular weight form of PVP (10).

FTIR Studies

Figure 2 shows the IR spectra of the carbonyl region of the various dispersions at different polymer concentrations for only PVP90, PVP12 and PVP/VA, since the spectra for PVP17 and PVP30 were identical to other PVP samples. In this figure we focus on three major regions associated with: 1) the dimerization of the carboxylic acid groups of indomethacin at 1710 cm^{-1}; 2) the non-hydrogen bonded carbonyl group of PVP at 1680 cm^{-1} (and vinyl acetate in the case of PVP/VA at 1745 cm^{-1}; and 3) the hydrogen bonding between polymer and indomethacin at 1726 cm^{-1}, as described in great detail earlier (15). The patterns observed with PVP90 are in excellent agreement with our earlier study using this polymer and, as observed earlier also, no changes in spectra for indomethacin are observed when amorphous indomethacin and polymers are physically *mixed, rather than being formed as coprecipitates (15).*

Up to the 5%w/w polymer level, in all cases, we could detect no significant changes in spectra relative to that of pure amorphous indomethacin. However, above this composition the absorbance at 1710 cm^{-1}, assigned to the asymmetric stretch of the carboxylic acid in a dimer structure, significantly decreases in intensity until somewhere between 20%w/w and 30%w/w polymer it reaches a minimum value. At this point absorbance at 1726 cm^{-1}, attributed to the hydrogen bonding between the indomethacin carboxyl and the PVP carbonyl group (15), becomes significant. It is important to note that such changes are essentially the same for all PVP samples and PVP/VA. The PVP free carbonyl dominates the spectra as the concentration of polymer increases beyond 30%w/w, as does the vinyl acetate peak at 1745 cm^{-1} for PVP/VA.

Enthalpy Relaxation Studies

To gain some measure of the effects of low polymer concentration on the molecular mobility of indomethacin when formed as molecular dispersions, structural relaxation for the 5%w/w and 30%w/w polymer systems below Tg was assessed by comparison of the rates of enthalpy change required to approach a supercooled liquid from the glassy state (18,19,25). In previous studies with pure indomethacin, PVP90, and sucrose, this approach was used to estimate the relaxation time (τ) as a function of temperature below Tg (18). Recent studies with sucrose-polymer molecular dispersions showed effects of polymers on molecular mobility, relative to sucrose alone, but no effects in physical mixtures (19).

The dispersions containing 5%w/w polymer were selected for evaluation, since the Tg values were essentially the same for all polymers used and for pure amorphous indomethacin. The dispersions containing 30%w/w polymer were also selected to evaluate the effect of the polymer concentration on the molecular mobility of indomethacin, since hydrogen bonding associated with carboxylic acid dimers was completely eliminated at this polymer level as indicated above and because all systems exhibited a higher Tg than that of indomethacin alone. Samples stored for 16 hours at 16.5°C below Tg showed no crystallization, but did exhibit a distinctly increasing enthalpy relaxation with time, reflecting greater structural relaxation of the glass towards the equilibrium supercooled liquid state.

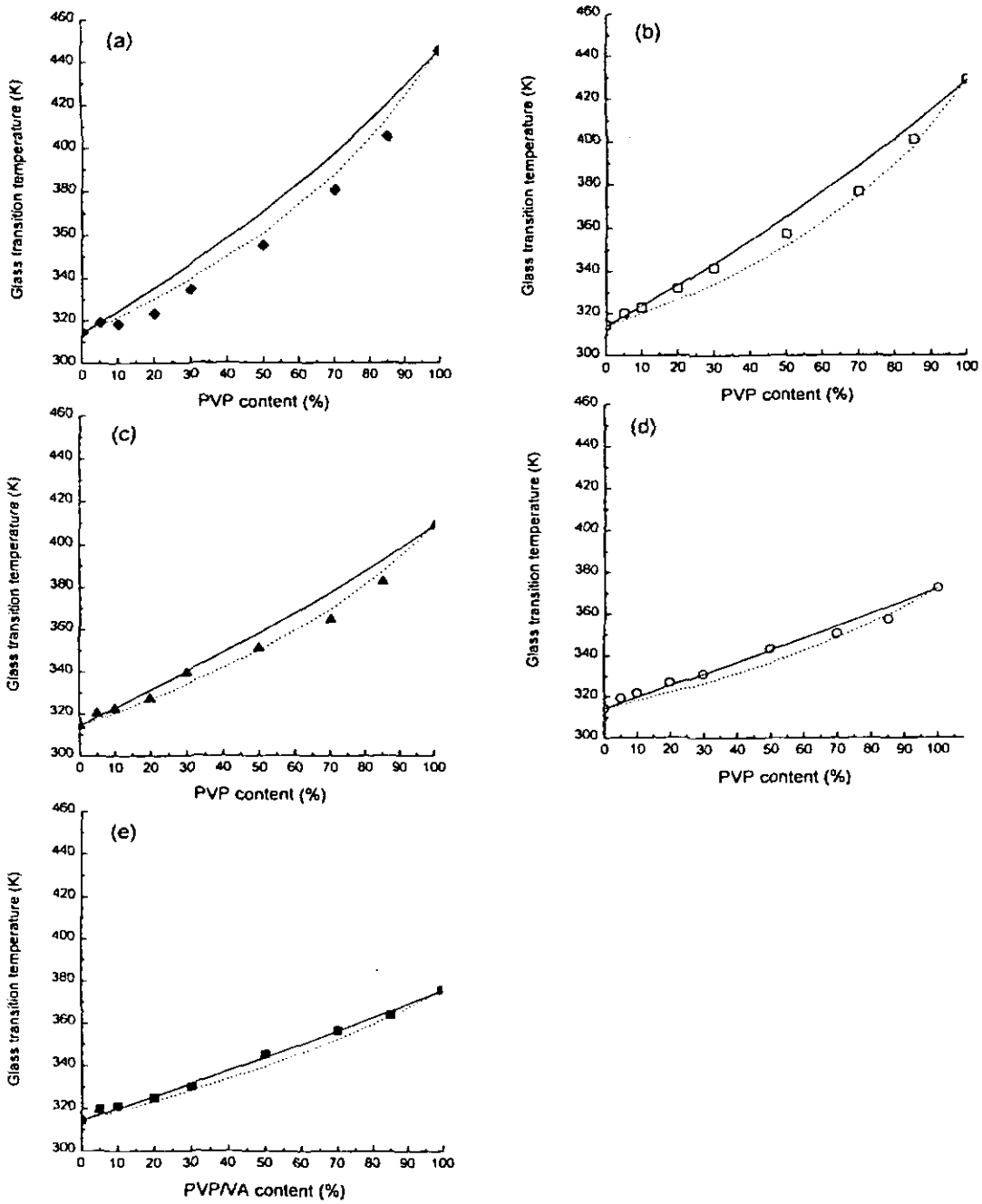


Fig. 1. Tg values of molecular dispersions of indomethacin with (a) PVP90, (b) PVP30, (c) PVP17, (d) PVP12, and (e) PVP/VA as a function of composition. The symbols represent the measured onset Tg values at a heating rate of 10°C min^{-1}. The solid lines represent the prediction of the Gordon-Taylor equation, and the dotted lines represent the prediction of the Couchman-Karasz equation. (eq.1, 2, 3 in text).

To compare the relative effects of the different molecular weights of PVP and of PVP/VA on the mobility of the dispersions, the extent of relaxation of the dispersions was calculated with respect to the total enthalpy change that was required for the glass to relax to a supercooled liquid. First the maximum enthalpy recovery for the dispersions (ΔH_∞) was calculated from the following Eq. 4 (26), where ΔH_∞ is assumed to be constant from the storage temperature to Tg.

$$\Delta H_\infty = (Tg - T) \cdot \Delta Cp \quad (4)$$

where Tg is the glass transition temperature, T is the experiment temperature, and ΔCp is the change in heat capacity at Tg. Equation 4 for estimating ΔH_∞ was validated using the 5%w/w dispersions and measuring ΔH after an extensive period of storage, i.e., 2,880 hours at 16.5°C below Tg. Values of ΔH after 2880 hours ranging from 7.2 to 7.4 J/g were obtained for

Table II. Glass Transition Temperature, Tg, for Molecular Dispersions of Indomethacin Containing 5%w/w and 30%w/w Polymers

Polymer	5%w/w dispersion(°C)	30%w/w dispersion(°C)
PVP90	47	61
PVP30	47	68
PVP17	46	66
PVP12	46	59
PVP/VA	46	57

Note: The Tg for pure indomethacin is 42°C.

all PVP and PVP/VA samples, while the ΔH_∞ values estimated from eq. 4 for these samples ranged from 7.1 to 7.6 J/g.

From this maximum enthalpy recovery a measure of the extent to which a material relaxes, $\varphi(t)$, under any given time (t) was calculated using equation 5 (25)

$$\varphi(t) = 1 - (\Delta H/\Delta H_\infty), \quad (5)$$

the greater value of $\varphi(t)$, the less the extent of relaxation.

To estimate the overall average relaxation time, τ, we use the KWW equation (18,25,28).

$$\varphi(t) = \exp(-(t/\tau)^\beta) \quad (6)$$

where τ is the mean relaxation constant and β is a relaxation time distribution parameter with an expected value of between 0 and 1. Typical relaxation processes in disordered systems are non-exponential, thus β generally is less than one. An iterative non-linear regression analysis procedure based on the Marquart-Levenberg algorithm was used to find the best fit to the data. The initial parameters provided were τ = 100s and β = 0.5 for all samples. Figure 3 shows the extent of relaxation of the dispersions containing 5%w/w and 30%w/w polymer, respectively, in terms of $\varphi(t)$ versus time. Here we may note that whereas indomethacin alone exhibits a value of $\varphi(t)$ after 16 hours of about 0.3, 5% and 30% polymer compositions produce significantly less change. In the case of the 5% samples, the value is in the range of 0.4 to 0.5; while at the 30% level, the changes with molecular weight of PVP, for example, range from 0.5 to 0.8. Thus, at least with the higher molecular weight PVP samples, at 30% polymer where Tg is higher, there is a significant reduction in the extent of relaxation (higher $\varphi(\tau)$) relative to lower molecular weight samples; much less differences are noted with the 5% samples where Tg values are relatively unchanged. Values of τ and β are listed in Table III where we can see that at the 5%w/w polymer level each sample produces roughly double the average relaxation time, τ, of indomethacin alone, with no significant differences in β, reflective of the distribution of relaxation times. However, there do not appear to be any systematic differences between the various molecular weight grades of PVP or PVP/VA. At the 30% w/w polymer level the values of τ appear to be consistently larger than those of the corresponding 5% polymer mixtures, while the β terms again, are relatively unchanged. Given the larger standard deviations for τ at the 30% level, it is difficult to determine whether τ values for the various polymer samples are significantly different.

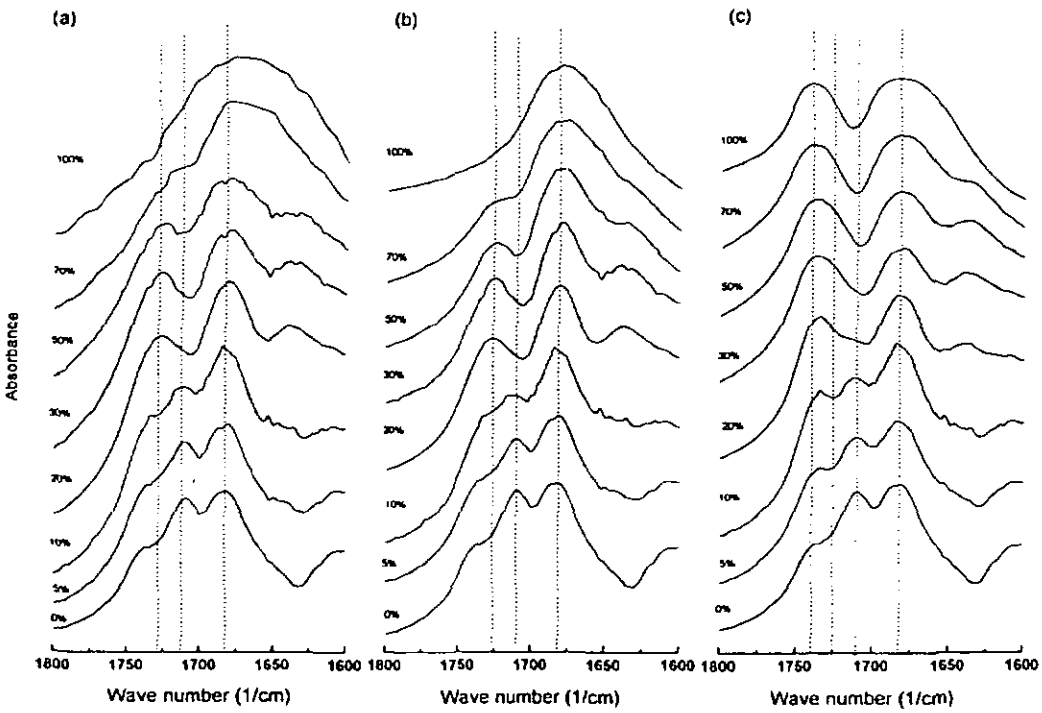


Fig. 2. IR spectra of the carbonyl stretching region of molecular dispersions of indomethacin with (a) PVP90, (b) PVP12, and (c) PVP/VA. The percentages refer to the amount of PVP90, PVP12, and PVP/VA, respectively. Vertical lines depict wave numbers monitored with different systems (see text)

194

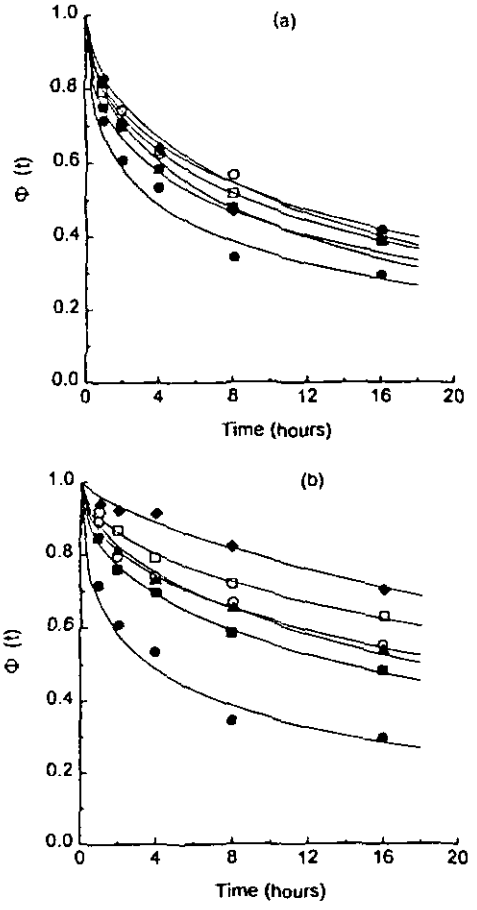


Fig. 3. Proportion of glass that has relaxed with aging time for molecular dispersions of indomethacin containing (a) 5%w/w polymers, (b) 30%w/w polymers. Key:(♦) PVP90; (□) PVP30; (▲) PVP17; (○) PVP12; (□) PVP/VA; (●) Indomethacin alone. The lines represent non linear fits to the Kohlrausch-Williams-Watta equation (eq. 6 in text).

Crystallization Studies

Previously, Yoshioka *et al.* reported that a molecular dispersion of 5%w/w PVP90 and indomethacin stored at 30°C exhibited no crystallization after 20 days of storage (14). In this study all samples evaluated for possible crystallization were stored for 20 weeks (140 days) at 30°C to allow more time for any crystallization. Such studies were carried out with pure *amorphous indomethacin, the physical mixture and the molecular dispersion.* Figure 4 shows the results for pure indomethacin and the 5%w/w PVP90 mixture, as representative of all results at the 5%w/w polymer level. Whereas pure indomethacin and the physical mixture are completely crystallized to the γ polymorphic form within 14 days, the molecular dispersion remains uncrystallized for the entire 20-week period. This is also true for the other 5%w/w molecular dispersions. Thus, over this time period all polymer samples at a 5%w/w level are equally effective inhibitors of crystallization.

Table III. The Parameters of the Kohlrausch-Williams-Watts Equation *Calculated by Nonlinear Regression Analysis for Molecular Dispersions* of Indomethacin Containing 5%w/w and 30%w/w Polymer

	5%w/w dispersion		30%w/w dispersion	
Polymer	τ (days)	β	τ (days)	β
PVP90	17.9 ± 4.3	0.52 ± 0.09	62.5 ± 21.0	0.78 ± 0.14
PVP30	18.8 ± 3.2	0.59 ± 0.06	60.6 ± 16.9	0.56 ± 0.07
PVP17	13.9 ± 2.2	0.55 ± 0.07	34.1 ± 7.1	0.59 ± 0.07
PVP12	21.3 ± 3.5	0.51 ± 0.06	41.5 ± 15.2	0.52 ± 0.10
PVP/VA	14.9 ± 3.3	0.45 ± 0.07	28.8 ± 10.0	0.52 ± 0.10

Note: The τ and β values for pure indomethacin are 9.1 ± 1.7 days, 0.48 ± 0.08, respectively.

CONCLUSIONS

From the results of the crystallization studies reported above, we can reach two fundamental conclusions. First, these studies reveal that molecular dispersions of PVP and PVP/VA, made with indomethacin by coprecipitation, are all capable of inhibiting crystallization at 30°C over a period of at least 20 weeks, at levels of polymer as low as 5%w/w, whereas indomethacin alone and in 5%w/w physical mixtures, exhibits complete crystallization within 14 days. A second important observation is that up to 20 weeks storage at 30°C there appear to be no differences in the ability of PVP, ranging in molecular weight from about 10^3 to 10^6 gmole^{-1} and in Tg values from 99°C to 172°C, to inhibit crystallization at a 5%w/w polymer level. Also, there appears to be no difference when about 40% of the vinylpyrrolidone monomers are replaced by vinyl acetate groups, as in PVP/VA. Thus, a minimum number of monomer units available to the indomethacin molecule appears to be a critical factor, as opposed to some property more reflective of molecular size of the polymer chain, or as in the case of PVP/VA, any differences in the hydrogen bonding capability of the vinyl pyrrolidone versus vinyl acetate carbonyl groups (24).

Since the Tg values of all dispersions at the 5%w/w polymer level are essentially the same as that of indomethacin alone, any antiplasticizing effects of polymers at the 5% level, based directly on mobility associated with the glass transition temperature, would not appear to be significant. From the enthalpy

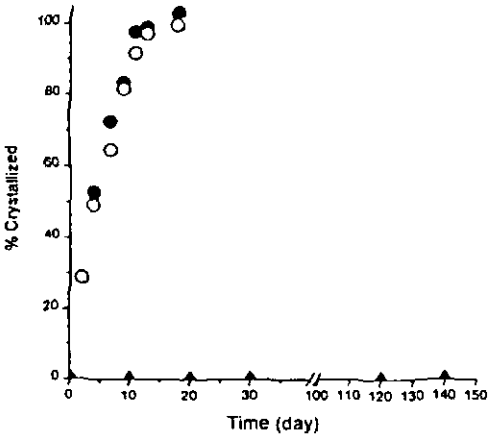


Fig. 4. Isothermal crystallization of amorphous indomethacin stored at 30°C as a function of time. Key(▲) Molecular dispersion containing 5%w/w PVP90; (○) Physical mixture with 5%w/w PVP90; (●) Indomethacin alone.

relaxation data in Table III, we can see that the 5%w/w polymer samples produce relaxation times, τ, at about 30°C (Tg − T = 16.5°C) that are somewhat longer than that for the pure indomethacin. However, we believe that they may not be long enough to totally account for the extensive increase in stability of indomethacin with this level of polymer.

The most compelling evidence for identifying possible factors giving rise to such efficient inhibition of crystallization would appear to come from the FTIR studies shown in Fig. 2. Here, with all polymer samples, we see a distinct loss of the peak associated with the carboxylic acid dimerization of amorphous indomethacin over the range of 5–30%w/w polymer, and the development of a new peak related to the formation of the polymer-indomethacin hydrogen bond (15). This ability to inhibit dimerization would seem to be important since such dimerization is required in the formation of the γ crystal nucleus, as shown from its crystal structure (29). It is interesting to note in this regard that the dimer peak is completely eliminated by all polymer samples, presumably due to indomethacin-polymer hydrogen bonding, in the range of 20–30%w/w, where we have shown previously that the molar ratio of indomethacin to monomer unit of the polymer is close to 1:1, or close to enough monomer units, if accessible, to interact with most of the indomethacin molecules present (15). Since changes in IR spectra at very low levels of polymer, $\leq$ 5% could not be detected in these systems, it will be important to probe these very dilute systems with more sensitive techniques to ascertain more definitely whether or not such hydrogen bonding at these low polymer levels actually is the critical factor in the inhibition of indomethacin crystallization.

ACKNOWLEDGMENTS

The authors wish to thank the sponsors of the Purdue/Wisconsin Joint Program on Molecular Mobility and Solid-State Properties for financial support of this project. We are grateful to Dr. James Dumesic of the Chemical Engineering Department, University of Madison-Wisconsin for access to the FTIR instrument. Takahiro Matsumoto expresses his appreciation to Daiichi Pharmaceutical Company for granting him a one-year leave of absence to pursue these studies.

REFERENCES

1. K. Yamamoto, M. Nakano, T. Arita, Y. Takayama, and Y. Nakai. Dissolution behavior and bioavailability of phenytoin from a ground mixture with microcrystalline cellulose. *J. Pharm. Sci.* **65**:1484–1488 (1970).
2. W. L. Chiou and S. T. Reigelman. Oral absorption of griseofulvin in dogs. Increased absorption via solid dispersion in polyethylene glycol 6000. *J. Pharm. Sci.* **59**:937–942 (1970).
3. H. Imaizumi, N. Nambu, and T. Nagai. Stability and several physical properties of amorphous and crystalline forms of indomethacin. *Chem. Pharm. Bull.* **28**:2565–2569 (1980).
4. M. Otsuka and N. Kaneniwa. A kinetic study of the crystallization process of noncrystalline indomethacin under isothermal conditions. *Chem. Pharm. Bull.* **36**:4026–4032 (1988).
5. V. Andronis, M. Yoshioka, and G. Zografi. Effect of sorbed water on the crystallization of indomethacin from the amorphous state. *J. Pharm. Sci.* **86**:346–351 (1997).
6. W. L. Chiou and S. T. Reigelman. Pharmaceutical application of solid dispersion systems. *J. Pharm. Sci.* **60**:1281–1302 (1971).
7. A. P. Simonelli, S. C. Mehta, and W. I. Higuchi. Dissolution rates of higher energy sulfathiazole-povidone coprecipitates 2: Characterization of form of drug controlling its dissolution rate via solubility studies. *J. Pharm. Sci.* **65**:355–361 (1976).
8. H. Imaizumi, N. Nambu, and T. Nagai. Stabilization of amorphous state of indomethacin by solid dispersion in polyvinylpyrrolidone. *Chem. Pharm. Bull.* **31**:2510–2512 (1983).
9. H. Sekizaki, K. Danjo, H. Eguchi, Y. Yonezawa, H. Sunada, and A. Otsuka. Solid-state interaction of ibuprofen with polyvinylpyrrolidone. *Chem. Pharm. Bull.* **43**:988–993 (1995).
10. M. Yoshioka, B. C. Hancock, and G. Zografi. Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. *J. Pharm. Sci.* **83**:1700–1705 (1994).
11. V. Andronis and G. Zografi. The molecular mobility of supercooled amorphous indomethacin as a function of temperature and relative humidity. *Pharm. Res.* **15**:835–842 (1998).
12. C. A. Okasanen and G. Zografi. The relationship between the glass transition temperature and water vapor absorption by poly(-vinylpyrrolidone). *Pharm. Res.* **7**:654–657 (1990).
13. C. A. Okasanen and G. Zografi. Molecular mobility in mixtures of absorbed water and solid poly(vinylpyrrolidone). *Pharm. Res.* **10**:791–799 (1993).
14. M. Yoshioka, B. C. Hancock, and G. Zografi. Inhibition of indomethacin crystallization in poly(vinylpyrrolidone) coprecipitates. *J. Pharm. Sci.* **84**:983–986 (1995).
15. L. S. Taylor and G. Zografi. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.* **14**:1691–1698 (1997).
16. V. Andronis. Crystallization of amorphous indomethacin. *Ph. D. Thesis.* University of Wisconsin-Madison (1997).
17. V. Buhler. *Kollidone, Second ed.*, BASF Akiengesellschaft, Ludwigshafen, 1993.
18. B. C. Hancock, S. L. Shamblin, and G. Zografi. The molecular mobility of amorphous pharmaceutical solids below their glass transition temperature. *Pharm. Res.* **12**:799–806 (1995).
19. S. L. Shamblin and G. Zografi. Enthalpy relaxation in binary amorphous mixtures containing sucrose. *Pharm. Res.* **15**:1828–1834 (1998).
20. B. C. Hancock, C. R. Dalton, M. J. Pikal, and S. L. Shamblin. A pragmatic test of a simple calorimetric method for determining the fragility of some amorphous pharmaceutical materials. *Pharm. Res.* **15**:762–767 (1998).
21. R. Simha and R. F. Boyer. On a general relation involving the glass temperature and coefficients of expansion of polymers. *J. Chem. Phys.* **37**:1003–1007 (1962).
22. M. Gordon and J. S. Taylor. Ideal copolymers and the second-order transition of synthetic rubbers 1. Non-crystalline co-polymers. *J. Appl. Chem.* **2**:493–500 (1952).
23. P. R. Couchman and F. E. Karasz. A classical thermodynamic discussion on the effect of composition on glass-transition temperatures. *Macromol.* **11**:117–119 (1978).
24. S. L. Shamblin, L. S. Taylor, and G. Zografi. Mixing behavior of colyophilized binary systems. *J. Pharm. Sci.* **87**:694–701 (1998).
25. J. Cowie and R. Ferguson. Physical aging studies in poly(vinyl methyl ether). 1. Enthalpy relaxation as a function of aging temperature. *Macromol.* **22**:2307–2312 (1989).
26. I. M. Hodge. Enthalpy relaxation and recovery in amorphous materials. *J. Non-Cryst. Solids* **169**:211–266 (1994).
27. A. Brunacci, J. Cowie, R. Ferguson, and I. McEwen. Enthalpy relaxation in glassy polystyrenes: 1. *Polymer* **38**:865–870 (1997).
28. M. D. Ediger, C. A. Angell, and S. R. Nagel. Supercooled liquids and glasses. *J. Phys. Chem.* **100**:13200–13212 (1996).
29. T. J. Kistenmacher and R. E. March. Crystal and molecular structure of an antiinflammatory agent, Indomethacin. *J. Amer. Chem. Soc.* **94**:1340–1345 (1972).

ANNEXURE-C 196

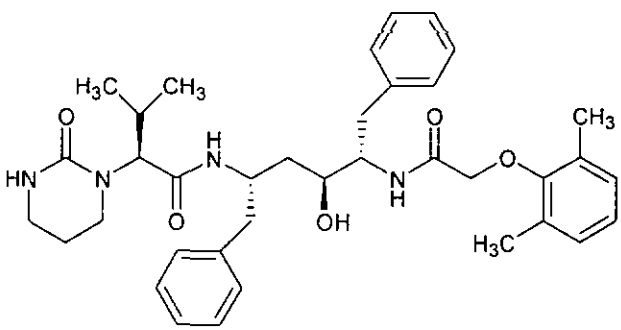
(Nos. 3956 and 3959)
NEW

KALETRA™
(lopinavir/ritonavir) capsules
(lopinavir/ritonavir) oral solution

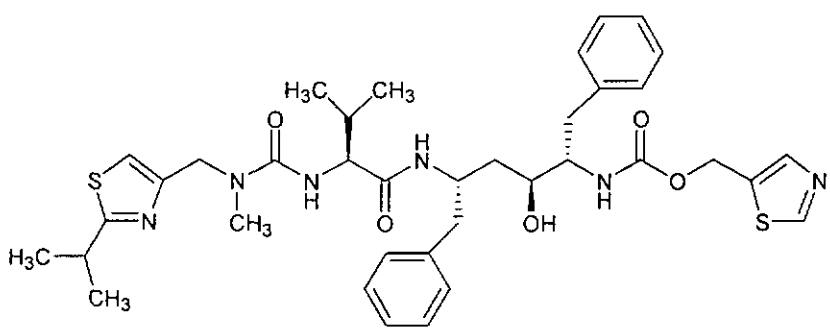
R_x only

DESCRIPTION
KALETRA (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in KALETRA, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Lopinavir is chemically designated as [1S-[1R*,(R*), 3R*, 4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir has the following structural formula:



Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

KALETRA capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

KALETRA oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: Acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural & artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

KALETRA oral solution contains 42.4% alcohol (v/v).

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of action: Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Antiviral activity in vitro: The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10-27 nM (0.006 – 0.017 µg/mL, 1 µg/mL = 1.6 µM) and ranged from 4-11 nM (0.003 – 0.007 µg/mL) against several HIV-1 clinical isolates (n=6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65 – 289 nM (0.04 – 0.18 µg/mL), representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance: HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in vitro*.

The selection of resistance to KALETRA in antiretroviral treatment naive patients has not yet been characterized. In Phase II studies of 227 antiretroviral treatment naive and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (>400 copies/mL) viral RNA following treatment with KALETRA for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least 4 mutations associated with protease inhibitor resistance immediately prior to KALETRA therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. The assessment of these mutational patterns is under study.

Cross-resistance - Preclinical Studies: Varying degrees of cross-resistance have been observed among protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during KALETRA therapy.

The *in vitro* activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed >4-fold reduced susceptibility to nelfinavir (n=13) and saquinavir (n=4), displayed <4-fold reduced susceptibility to lopinavir. Isolates with >4-fold reduced susceptibility to indinavir (n=16) and ritonavir (n=3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.

Clinical Studies - Antiviral activity of KALETRA in patients with previous protease inhibitor therapy. The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to KALETRA therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naive patients with HIV RNA >1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir and ritonavir (Study 957). The EC_{50} of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC_{50} against wild type HIV. Fifty-five percent of these baseline isolates displayed a >4-fold reduced susceptibility to lopinavir with a mean reduction in lopinavir susceptibility of 27.9-fold.

After 24 weeks of treatment with KALETRA, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA ≤400 copies/mL was observed in 93% (27/29) and 65% (15/23) of patients with <10-fold and ≥10-fold reduced susceptibility to lopinavir at baseline, respectively.

In addition, virologic response was observed in 96% (24/25) of patients whose baseline viral isolates contained up to 5 mutations recognized to be associated with protease inhibitor resistance. Fourteen of those 25 isolates contained mutations at positions 82, 84 and/or 90. Virologic response was observed in 67% (18/27) of patients whose baseline viral isolates contained 6 or more mutations, including those at positions 82, 84 and/or 90 plus multiple other mutations. There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

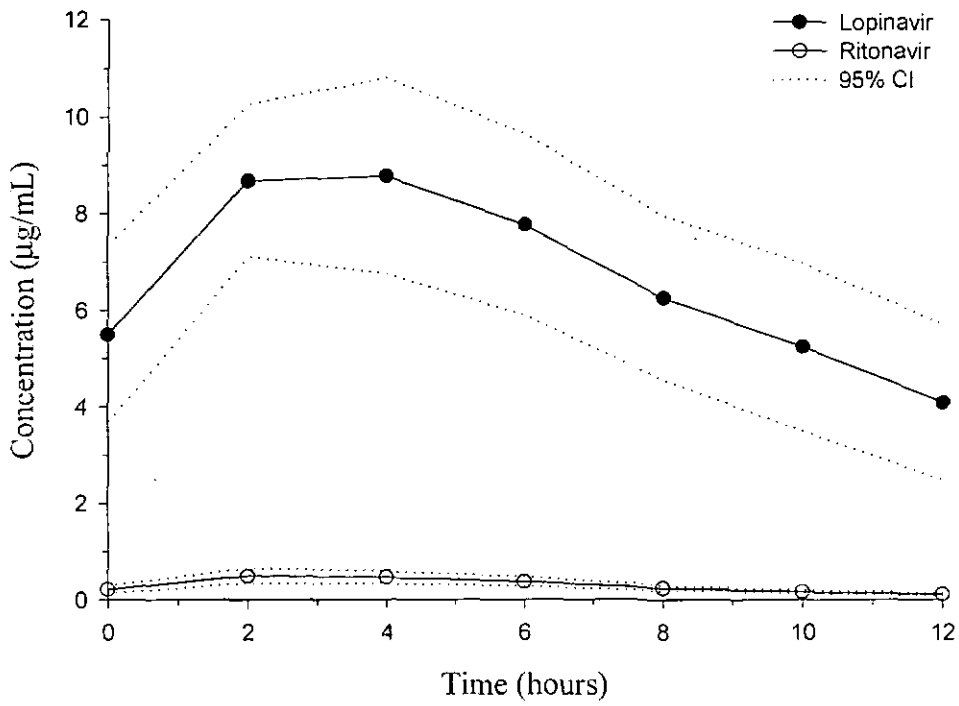
Pharmacokinetics

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of KALETRA 400/100 mg BID yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg BID. The *in vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of KALETRA is due to lopinavir.

199

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after KALETRA 400/100 mg BID for 3-4 weeks from a pharmacokinetic study in HIV-infected adult subjects (n=21).

Figure 1
Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (N = 21)



Absorption: In a pharmacokinetic study in HIV-positive subjects (n=21) without meal restrictions, multiple dosing with 400/100 mg KALETRA BID for 3 to 4 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.6 ± 4.4 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA co-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA liquid relative to the capsule formulation.

Effects of Food on Oral Absorption: Administration of a single 400/100 mg dose of KALETRA capsules with a moderate fat meal (500-682 Kcal, 23 to 25% calories from fat) was associated with a mean increase of 48 and 23% in lopinavir AUC and C_{max}, respectively, relative to fasting. For KALETRA oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 and 54%, respectively. Relative to fasting, administration of KALETRA with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC and C_{max} by 97 and 43%, respectively, for capsules, and 130 and 56%, respectively, for oral solution. To enhance bioavailability and minimize pharmacokinetic variability KALETRA should be taken with food.

Distribution: At steady state, lopinavir is approximately 98-99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg KALETRA BID, and is similar between healthy volunteers and HIV-positive patients.

Metabolism: *In vitro* experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg KALETRA dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination: Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after 8 days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The half-life of lopinavir over a 12 hour dosing interval averaged 5-6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 L/h.

Special Populations:

Gender, Race and Age: Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Pediatric Patients: The pharmacokinetics of KALETRA 300/75 mg/m^2 BID and 230/57.5 mg/m^2 BID have been studied in a total of 53 pediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1 μg•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 μg/mL, respectively after KALETRA 230/57.5 mg/m^2 BID without nevirapine (n=12), and were 85.8 ± 36.9 μg•h/mL, 10.0 ± 3.3 and 3.6 ± 3.5

201

µg/mL, respectively after 300/75 mg/m^2 BID with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BID (3 months to 8 years) or 4 mg/kg BID (>8 years).
Renal Insufficiency: Lopinavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.
Hepatic Impairment: Lopinavir is principally metabolized and eliminated by the liver. Although KALETRA has not been studied in patients with hepatic impairment, lopinavir concentrations may be increased in these patients (see **PRECAUTIONS**).
Drug-Drug Interactions: See also **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS: Drug Interactions**.

KALETRA is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in *increased plasma concentrations of the other drug, which could increase or prolong its* therapeutic and adverse effects (see **CONTRAINDICATIONS**).

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with KALETRA and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} *are summarized in Table 1 (effect of other drugs on lopinavir) and Table 2 (effect of* KALETRA on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see Table 6 in **PRECAUTIONS**.

Table 1: Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug
(See Precautions, Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered *Drug*	Dose of Co-*administered Drug* (mg)	Dose of *KALETRA* (mg)	n	Ratio (with/without co-administered drug) of *Lopinavir Pharmacokinetic Parameters* (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir[1]	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	0.89 (0.83, 0.95)	0.85 (0.81, 0.90)	0.81 (0.74, 0.89)
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz[2]	600 QHS, 9 d	400/100 BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
Ketoconazole	200 single dose	400/100 BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nevirapine	200 QD, 14 days; BID, 6 days	400/100 BID, 20 d	5, 9*	0.95 (0.73, 1.25)	0.99 (0.74, 1.32)	1.02 (0.68, 1.53)
	7 mg/kg or 4 mg/kg QD, 2 wk; BID 1 wk[3]	300/75 mg/m^2 BID, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 QD, 10 d	400/100 BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampin	600 QD, 10 d	400/100 BID, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
Ritonavir[4]	100 BID, 3-4 wk	400/100 BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

[1] Composite effect of amprenavir 450 and 750 mg Q12h regimens on lopinavir pharmacokinetics.

[2] The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

[3] Study conducted in HIV-positive pediatric subjects ranging in age from 6 months to 12 years.

[4] Study conducted in HIV-positive adult subjects.

* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.

Table 2: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA
(See Precautions, Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (with/without KALETRA) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	See text below for discussion of interaction.		
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Efavirenz	600 QHS, 9 d	400/100 BID, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 µg QD, 21 d (Ortho Novum®)	400/100 BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Indinavir	600 single dose	400/100 BID, 10 d	11	See text below for discussion of interaction.		
Ketoconazole	200 single dose	400/100 BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Methadone	5 single dose	400/100 BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nevirapine	200 QD, 14 d; BID, 6 d	400/100 BID, 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 QD, 21 d (Ortho Novum®)	400/100 BID, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin	300 QD, 10 d; 150 QD, 10 d	400/100 BID, 10 d	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25-0-desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25-O-desacetyl rifabutin[1]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Saquinavir	800 single dose	400/100 BID, 10 d	11	See text below for discussion of interaction.		

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.
* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.
N/A =not available.

Effect of KALETRA on other Protease Inhibitors (PIs): The pharmacokinetics of single-dose indinavir and saquinavir, and multiple-dose amprenavir obtained in healthy subjects after at least 10 days of KALETRA 400/100 mg BID were compared to historical data in HIV-infected subjects (refer to Table 2 for information on study design and doses). Because of the limitations in the study design and the use of comparisons between healthy and HIV infected subjects, it is not possible to recommend definitive dosing recommendations. However, based on these comparisons, amprenavir 750 mg BID and indinavir 600 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC, lower C_{max}, and higher C_{min} compared to their respective established clinical dosing regimens. Saquinavir 800 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC and higher C_{min} to its respective established clinical dosing regimen (no comparative information regarding C_{max}). The clinical significance of the lower C_{max} and higher C_{min} is unknown. Appropriate doses of amprenavir, indinavir and saquinavir in combination with KALETRA with respect to safety and efficacy have not been established (see **PRECAUTIONS** – Table 6).

INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in a controlled study of KALETRA of 24 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 72 weeks duration. At present, there are no results from controlled trials evaluating the effect of KALETRA on clinical progression of HIV.

Description of Clinical Studies

Patients Without Prior Antiretroviral Therapy

Study 863: KALETRA BID + stavudine + lamivudine compared to nelfinavir TID + stavudine + lamivudine

Study 863 is an ongoing, randomized, double-blind, multicenter trial comparing treatment with KALETRA (400/100 mg BID) plus stavudine and lamivudine versus nelfinavir (750 mg TID) plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4 cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies/mL (range: 2.6 to 6.8 log_{10} copies/mL).

The percent of patients with HIV RNA <400 copies/mL and outcomes of patients through 24 weeks are summarized in Figure 2 and Table 3, respectively.

205

Figure 2: Virologic Response Through 24 Weeks (Study 863)

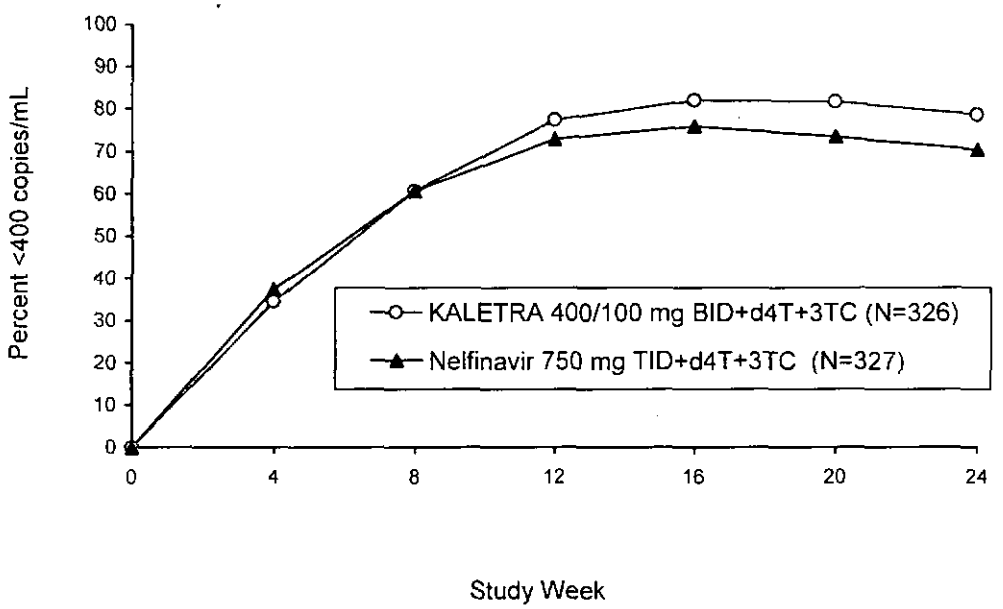


Table 3: Outcomes of Randomized Treatment Through Week 24 - (Study 863)

Outcome	KALETRA (400/100mg BID) + d4T + 3TC N=326	NELFINAVIR (750mg TID) + d4T + 3TC N=327
HIV RNA <400 copies/mL	79%	70%
HIV RNA >400 copies/mL	8%	16%
Discontinued due to KALETRA or nelfinavir adverse event*	2%	2%
Discontinued due to other adverse event*	2%	1%
Other**	8%	7%
Missing HIV RNA Level	2%	2%

*Includes laboratory abnormalities leading to discontinuation
**Lost to follow up, noncompliance, or consent withdrawn

In the KALETRA arm, the proportion <400 copies/mL for patients with baseline HIV RNA >100,000 copies/mL (78%) was similar to that for patients with baseline HIV RNA <100,000 copies/mL (81%).

Through 24 weeks of therapy, the proportion of patients with HIV RNA <50 copies/mL was 65% in the KALETRA arm and 60% in the nelfinavir arm.

Through 24 weeks of therapy, the mean increase from baseline in CD4 cell count was 154 cells/mm^3 for the KALETRA arm and 150 cells/mm^3 for the nelfinavir arm.

Four patients in the KALETRA arm and 6 patients in the nelfinavir arm experienced a new CDC Class C event following at least one week of treatment, including 3 patients in each arm who achieved HIV RNA <400 copies/mL at 24 weeks.

Study 720: KALETRA BID + stavudine + lamivudine

Study 720 is an ongoing, randomized, blinded, multicenter trial evaluating treatment with KALETRA at three dose levels (Group I: 200/100 mg BID and 400/100 mg BID; Group II: 400/100 mg BID and 400/200 mg BID) plus lamivudine (150 mg BID) and stavudine (40 mg BID) in 100 patients. All patients were converted to open-label KALETRA at the 400/100 mg BID dose between weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59), 70% were Caucasian, and 96% were male. Mean baseline CD4 cell count was 338 cells/mm^3 (range: 3 to 918 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies/mL (range: 3.3 to 6.3 log_{10} copies/mL).

Through 72 weeks of treatment, the proportion of patients with HIV RNA < 400 (<50) copies/mL was 80% (78%) and the mean increase from baseline in CD4 cell count was 256 cells/mm^3 for the 51 patients originally randomized to the 400/100 mg dose of KALETRA. At 72 weeks, 13 patients (13%) had discontinued the study for any reason. Four discontinuations (4%) were secondary to adverse events or laboratory abnormalities, and one of these discontinuations (1%) was attributed to a KALETRA adverse event.

Patients with Prior Antiretroviral Therapy

Study 765: KALETRA BID + nevirapine + NRTIs

Study 765 is an ongoing, randomized, blinded, multicenter trial evaluating treatment with KALETRA at two dose levels (400/100 mg BID and 400/200 mg BID) plus nevirapine (200 mg BID) and two NRTIs in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI) naive patients. Patients had a mean age of 40 years (range 22-66), were 73% Caucasian, and were 90% male. Mean baseline CD4 cell count was 372 cells/mm^3 (range 72 to 807 cells/μL) and mean baseline plasma HIV-1 RNA was 4.0 log_{10} copies/mL (range 2.9 to 5.8 log_{10} copies/mL).

Through 72 weeks of treatment, the proportion of patients with HIV RNA < 400 (<50) copies/mL was 75% (58%) and the mean increase from baseline in CD4 cell count was 174 cells/mm^3 for the 36 patients receiving the 400/100 mg dose of KALETRA. At 72 weeks, 13 patients (19%) had discontinued the study for any reason. Six discontinuations (9%) were secondary to adverse events or laboratory abnormalities, and three of these discontinuations (4%) were attributed to KALETRA adverse events.

CONTRAINDICATIONS

KALETRA is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir.

Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 4.

207

Table 4: Drugs That Are Contraindicated With KALETRA

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA
Antiarrhythmics	Flecainide, Propafenone
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, Triazolam

WARNINGS

ALERT: Find out about drugs that should not be taken with KALETRA. This statement is included on the product's bottle label.

Drug Interactions

KALETRA is an inhibitor of the P450 isoform CYP3A. Co-administration of KALETRA and drugs primarily metabolized by CYP3A or CYP2D6 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **Pharmacokinetics: Drug-Drug Interactions, CONTRAINDICATIONS – Table 4: Drugs That Are Contraindicated With KALETRA, PRECAUTIONS - Table 5: Drugs That Should Not Be Co-administered With KALETRA** and **Table 6: Established and Other Potentially Significant Drug Interactions**).

Particular caution should be used when prescribing sildenafil in patients receiving KALETRA. Co-administration of KALETRA with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, syncope, visual changes and prolonged erection (see **PRECAUTIONS: Drug Interactions** and the complete prescribing information for *sildenafil.*)

Concomitant use of KALETRA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including KALETRA, are used in combination with these drugs.

Concomitant use of KALETRA and St. John's wort (hypericum perforatum), or products containing St. John's wort, is not recommended. Co-administration of protease inhibitors, including KALETRA, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to loss of virologic response and possible resistance to lopinavir or to the class of protease inhibitors.

Pancreatitis

Pancreatitis has been observed in patients receiving KALETRA therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see **PRECAUTIONS – Lipid Elevations**). Patients with advanced HIV disease may be at

increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during KALETRA therapy.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

Hepatic Impairment and Toxicity

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations.

Resistance/Cross-resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of KALETRA therapy on the efficacy of subsequently administered protease inhibitors is under investigation (see **MICROBIOLOGY**).

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations

Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS** – Table 8). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at

periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **PRECAUTIONS Table 6: Established and Other Potentially Significant Drug Interactions** for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

Information for Patients

A statement to patients and health care providers is included on the product's bottle label: "**ALERT: Find out about drugs that should NOT be taken with KALETRA.**" A Patient Package Insert (PPI) for KALETRA is available for patient information.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of KALETRA is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that KALETRA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of KALETRA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with KALETRA can reduce the risk of transmitting HIV to others through sexual contact.

KALETRA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients taking didanosine should take didanosine one hour before or two hours after KALETRA.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with KALETRA.

KALETRA should be taken with food to enhance absorption.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see **Table 6: Established and Other Potentially Significant Drug Interactions**). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the

most susceptible to large increases in AUC (>3-fold) when co-administered with KALETRA.

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see **Table 6: Established and Other Potentially Significant Drug Interactions**). Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drugs that are contraindicated and not recommended for co-administration with KALETRA are included in **Table 5: Drugs That Should Not Be Co-administered With KALETRA**. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 5: Drugs That Should Not Be Co-administered With KALETRA

Drug Class: Drug Name	***Clinical Comment***
Antiarrhythmics: flecainide, propafenone	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 6: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction
(See CLINICAL PHARMACOLOGY for Magnitude of Interaction, Tables 1 and 2)

Concomitant Drug Class: Drug Name	Effect on Concentration of lopinavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ Lopinavir	A dose increase of KALETRA to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **DOSAGE AND ADMINISTRATION**). NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with KALETRA.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ Lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA (given with food).
HIV-Protease Inhibitors: amprenavir*, indinavir*, saquinavir*	↑ Amprenavir (Similar AUC, ↓ C_{max}, ↑ C_{min}) ↑ Indinavir (Similar AUC, ↓ C_{max}, ↑ C_{min}) ↑ Saquinavir (Similar AUC, ↑ C_{min})	Appropriate doses of the combination with respect to safety and efficacy have not been established (see **CLINICAL PHARMACOLOGY**: Table 2 and Effect of KALETRA on other Protease Inhibitors (PIs)).
HIV-Protease Inhibitor: ritonavir*	↑ Lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), and quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with KALETRA, if available.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Anti-infective: clarithromycin	↑ Clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered:

		• For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole	↑ Ketoconazole ↑ Itraconazole	High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.
Antimycobacterial: rifabutin*	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is *recommended (i.e., a maximum dose of 150* mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
Antiparasitic: atovaquone	↓ Atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Calcium Channel Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ Dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Disulfiram/metronidazole		KALETRA oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
Erectile Dysfunction Agent: sildenafil	↑ Sildenafil	Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: atorvastatin*, cerivastatin	↑ Atorvastatin ↑ Cerivastatin	Use lowest possible dose of atorvastatin or cerivastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
Immunosuppresants: cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Narcotic Analgesic: Methadone*	↓ Methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.
Oral Contraceptive: ethinyl estradiol*	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and KALETRA are co-administered.

213

* See **CLINICAL PHARMACOLGY** for Magnitude of Interaction, Tables 1 and 2

Other Drugs:
Drug interaction studies reveal no clinically significant interaction between KALETRA and pravastatin, stavudine or lamivudine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

Zidovudine and Abacavir: KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies of KALETRA in animal systems have not been completed.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA BID). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA BID regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg BID).

Pregnancy
Pregnancy Category C: No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving KALETRA.**

Geriatric Use

Clinical studies of KALETRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of KALETRA in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use

The safety and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 6 months have not been established. In HIV-infected patients age 6 months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of KALETRA in pediatric patients in clinical trials is ongoing.

Study 940 is an ongoing open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naive (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naive. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naive patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m^2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL.

Through 24 weeks of therapy, the proportion of patients with HIV RNA < 400 copies/mL was 82% for antiretroviral naive patients and 66% for antiretroviral experienced patients. The mean increase from baseline in CD4 cell count was 328

215

cells/mm^3 for antiretroviral naive and 335 cells/mm^3 for antiretroviral experienced patients treated through 24 weeks. At 24 weeks, one patient (1%) had prematurely discontinued the study. This discontinuation was secondary to an HIV-related event in an antiretroviral experienced patient that was not attributed to a KALETRA adverse event.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

ADVERSE REACTIONS

Adults:

Treatment-Emergent Adverse Events: KALETRA has been studied in 612 patients as combination therapy in Phase I/II and Phase III clinical trials. The most common adverse event associated with KALETRA therapy was diarrhea, which was generally of mild to moderate severity. Rates of discontinuation of randomized therapy due to adverse events were 2.8% in KALETRA and 3.1% in nelfinavir treated patients in Study 863.

Drug related clinical adverse events of moderate or severe intensity in ≥ 2% of patients treated with combination therapy including KALETRA for up to 24 weeks (Phase III) and for up to 72 weeks (Phase I/II) are presented in Table 7. For other information regarding observed or potentially serious adverse events, please see **WARNINGS** and **PRECAUTIONS**.

Table 7: Percentage of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Patients

	Antiretroviral Naive Patients			Protease Inhibitor Experienced Patients
	Study 863 (24 Weeks)		Study 720 (72 Weeks)	Phase I/II and Phase III
	KALETRA 400/100 mg TID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA BID[2] + d4T + 3TC (N= 84)	KALETRA BID[3] + nevirapine + NRTIs (N= 186)
Body as a Whole				
Abdominal Pain	3.1%	2.4%	4.8%	1.1%
Asthenia	3.4%	2.8%	7.1%	5.4%
Headache	2.5%	1.8%	7.1%	1.6%
Pain	0.3%	0.0%	2.4%	1.6%
Digestive System				
Abnormal Stools	0.0%	0.3%	6.0%	1.6%
Diarrhea	13.8%	14.4%	23.8%	15.1%
Nausea	6.4%	4.0%	15.5%	2.2%
Vomiting	2.1%	2.4%	4.8%	1.6%
Nervous System				
Insomnia	1.5%	1.2%	2.4%	1.1%
Skin and Appendages				
Rash	0.6%	1.2%	3.6%	2.0%

[1] Includes adverse events of possible, probable or unknown relationship to study drug.

[2] Includes adverse event data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35]) and 400/200 mg BID [N=36]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.

[3] Includes adverse event data from patients receiving 400/100 mg BID, 400/200 mg BID, and 533/133 mg BID for 16-72 weeks. All 186 patients received KALETRA in combination with NRTIs and either nevirapine or efavirenz.

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving KALETRA in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment with KALETRA and of at least moderate intensity are listed below by body system.

Body as a Whole: Back pain, chest pain, chest pain substernal, chills, drug interaction, drug level increased, face edema, fever, flu syndrome, malaise, and viral infection.

Cardiovascular System: Deep vein thrombosis, hypertension, palpitation, thrombophlebitis, and vasculitis.

Digestive System: Anorexia, cholecystitis, constipation, dry mouth, dyspepsia, dysphagia, enterocolitis, eructation, esophagitis, fecal incontinence, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, hemorrhagic colitis, increased appetite, pancreatitis, sialadenitis, stomatitis, and ulcerative stomatitis.

Endocrine System: Cushing's syndrome and hypothyroidism.

Hemic and Lymphatic System: Anemia, leukopenia, and lymphadenopathy.

Metabolic and Nutritional Disorders: Avitaminosis, dehydration, edema, glucose tolerance decreased, lactic acidosis, obesity, peripheral edema, and weight loss.

Musculoskeletal System: Arthralgia, arthrosis and myalgia.

Nervous System: Abnormal dreams, agitation, amnesia, anxiety, ataxia, confusion, depression, dizziness, dyskinesia, emotional lability, encephalopathy, hypertonia, libido decreased, nervousness, neuropathy, paresthesia, peripheral neuritis, somnolence, thinking abnormal, and tremor.

Respiratory System: Bronchitis, dyspnea, lung edema, and sinusitis.

Skin and Appendages: Acne, alopecia, dry skin, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritis, skin benign neoplasm, skin discoloration, and sweating.

Special Senses: Abnormal vision, eye disorder, otitis media, taste perversion, and tinnitus.

Urogenital System: Abnormal ejaculation, gynecomastia, hypogonadism male, kidney calculus, and urine abnormality.

Laboratory Abnormalities: The percentages of adult patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 8.

Table 8: Grade 3-4 Laboratory Abnormalities Reported in > 2% of Adult Patients

Variable	Limit[1]	Antiretroviral Naive Patients			Antiretroviral Experienced Patients
		Study 863 (24 Weeks)		Study 720 (72 Weeks)	Phase I/II and Phase III
		KALETRA 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA BID[2] + d4T + 3TC (N=84)	KALETRA BID[3] + NNRTI + NRTIs (N=186)
Chemistry	High				
Glucose	>250 mg/dL	1.6%	0.6%	2.4%	4.4%
Uric Acid	>12 mg/dL	1.3%	0.3%	3.6%	0.5%
SGOT/AST	>180 U/L	0.3%	2.2%	9.5%	4.4%
SGPT/ALT	>215 U/L	1.0%	2.2%	8.3%	6.6%
GGT	>300 U/L	N/A	N/A	3.6%	24.6%[4]
Total Cholesterol	>300 mg/dL	6.7%	2.8%	14.3%	25.7%
Triglycerides	>750 mg/dL	5.1%	0.9%	10.7%	26.2%
Amylase	>2 x ULN	1.9%	1.9%	4.8%	3.3%

217

Chemistry	Low				
Inorganic Phosphorus	<1.5 mg/dL	0.0%	0.0%	0.0%	2.2%
Hematology	*Low*				
Neutrophils	0.75 x 10^9/L	0.6%	1.6%	2.4%	2.7%

[1] ULN = upper limit of the normal range; N/A = Not Applicable.
[2] Includes clinical laboratory data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35] and 400/200 mg BID [N=36]).
[3] Includes clinical laboratory data from patients receiving 400/100 mg BID, 400/200 mg BID, and 533/133 mg BID for 16-72 weeks. All 186 patients received KALETRA in combination with NRTIs and either nevirapine or efavirenz.
[4] GGT was only measured in 69 patients receiving 400/100 mg BID or 400/200 mg BID in combination with nevirapine.

Pediatrics:

Treatment-Emergent Adverse Events: KALETRA has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Rash (2%) was the only drug-related clinical adverse event of moderate or severe intensity in ≥ 2% of pediatric patients treated with combination therapy including KALETRA (300/75 mg/m^2) for up to 24 weeks (Study 940). This includes adverse events of at least possible, probable or unknown relationship to study drug.

Laboratory Abnormalities: The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 9.

Table 9: Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients

Variable	Limit[1]	KALETRA BID[2]+ RTIs (N=100)
Chemistry	High	
Total bilirubin	> 2.9 x ULN	3.0%
SGOT/AST	> 180 U/L	7.0%
SGPT/ALT	>215 U/L	4.0%
Total cholesterol	> 300 mg/dL	2.0%
Amylase	> 2.5 x ULN	4.0%
Chemistry	Low	
Sodium	< 130 mEq/L	3.0%
Hematology	Low	
Platelet Count	< 50 x 10^9/L	4.0%
Neutrophils	< 0.40 x 10^9/L	2.0%

[1] ULN = upper limit of the normal range.
[2] Includes clinical laboratory data from the 230/57.5 mg per m^2 (N=49) and 300/75 mg per m^2 (N=51) dose arms.

OVERDOSAGE

KALETRA oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

Human experience of acute overdosage with KALETRA is limited. Treatment of overdose with KALETRA should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with KALETRA. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since KALETRA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

DOSAGE AND ADMINISTRATION

Adults

The recommended dosage of KALETRA is 400/100 mg (3 capsules or 5.0 mL) twice daily taken with food.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS** – Table 6).

Pediatric Patients

In children 6 months to 12 years of age, the recommended dosage of KALETRA oral solution is 12/3 mg/kg for those 7 to <15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2) twice daily taken with food, up to a maximum dose of 400/100 mg in children >40 kg (5.0 mL or 3 capsules) twice daily. The following table contains dosing guidelines for KALETRA oral solution based on body weight.

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
Without nevirapine or efavirenz		
7 to <15kg	12 mg/kg BID	
7 to 10 kg		1.25 mL
>10 to <15 kg		1.75 mL
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
>20 to 25 kg		2.5 mL
>25 to 30 kg		3.0 mL
>30 to 40 kg		3.5 mL
>40 kg	Adult dose	5 mL (or 3 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA oral solution to 13/3.25 mg/kg for those 7 to <15 kg and 11/2.75 mg/kg for those 15 to 50 kg (approximately equivalent to 300/75 mg/m^2) twice daily taken with food, up to a maximum dose of 533/133 mg in children >50 kg twice daily should be considered when used in combination with efavirenz or nevirapine in treatment experienced children 6 months to 12 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz or nevirapine in children (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS** – Table 6).

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)

219

With nevirapine or efavirenz		
7 to <15 kg	13 mg/kg BID	
7 to 10 kg		1.5 mL
>10 to <15 kg		2.0 mL
15 to 50 kg	11 mg/kg BID	
15 to 20 kg		2.5 mL
>20 to 25 kg		3.25 mL
>25 to 30 kg		4.0 mL
>30 to 40 kg		4.5 mL
>40 to 50 kg		5.0 mL (or 3 capsules)
>50 kg	Adult dose	6.5 mL (or 4 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

HOW SUPPLIED

KALETRA (lopinavir/ritonavir) capsules are orange soft gelatin capsules imprinted with the corporate logo ⓐ and the Abbo-Code PK. KALETRA is available as 133.3 mg lopinavir/33.3 mg ritonavir capsules in the following package sizes:
Bottles of 180 capsules each..... (**NDC** 0074-3959-77)
Packages of 120 unit dose blisters.....(**NDC** 0074-3959-11)

Recommended storage: Store KALETRA soft gelatin capsules at 36°F - 46°F (2°C - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA capsules remain stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), capsules should be used within 2 months.

KALETRA (lopinavir/ritonavir) oral solution is a light yellow to orange colored liquid supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL (80 mg lopinavir/20 mg ritonavir per mL) packaged with a marked dosing cup in the following size:
160 mL bottle.....(**NDC** 0074-3956-46)

Recommended storage: Store KALETRA oral solution at 36°F - 46°F (2°C - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), oral solution should be used within 2 months.

Revised: NEW

ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.A.

----------(Perforation)----------

KALETRA™
(lopinavir/ritonavir) capsules

भारतीय गैर न्यायिक

सौ रुपये Rs. 100

ONE HUNDRED RUPEES

सत्यमेव जयते

भारत INDIA

INDIA NON JUDICIAL

RAMESH CHANDRA TIWARI NOTARY MAROL ANDHERI (E) MUMBAI MAHARASHTRA REGN NO 3361 GOVT OF INDIA

General Stamp Office, Mumbai

L.S.V.No. 207

महाराष्ट्र MAHARASHTRA

25 FEB 2010

Proper Officer

- 3 MAR 2010

CU 529256

परवानाधारक मुद्रांक विक्रेता

परवाना क्रमांक नं. २०७

क्रमांक 1321 दिनांक

Mr/Mrs/Mr

मुद्रांक पेपर विकला

CIPLA LTD MUMBAI 400 008 INDIA MUMBAI CENTRAL

SHRI. M. D. KADAM

BEFORE THE CONTROLLER OF PATENTS

PATENT OFFICE, MUMBAI

In the matter of The Patents Act, 1970 *as amended by* The Patents (Amendment) Act 2005,

And

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

And

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

MSD

In the matter of Patent Application 726/MUMNP/2009 dated April 15, 2009 by Abbott Laboratories, DEPT. 377 Bldg AP6A-1, 100 Abbott Park Road, Abbott Park, IL 60064-6008. U.S.A.

..... Applicant

And

IN THE MATTER of opposition of the grant of a patent thereto by, Cipla Limited, Mumbai Central, Mumbai-400 008. India.

..... Opponent

EVIDENCE IN SUPPORT OF OPPOSITION

I, Dr. (Mrs.) M. S. Nagarsenker aged about 52 years residing at A - 401, Vikas Palms, Dr. Ambedkar Road, Thane (W) - 400601 solemnly affirm and declare as under:

1. I am working as a Technical consultant to many Pharmaceutical industries in India. My educational qualifications and experience are as under

Degree	University	Field	Year
Ph.D. (Tech)	Bombay College of Pharmacy, Kalina	Biopharmaceutics and Pharmacokinetics	1989
M. Pharm.	The University Department of Chemical Technology	Pharmaceutics	1981
B.Pharm.	The University Department of Chemical Technology	Pharmacy	1978

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

Professional Experience:

- Lecturer in Pharmaceutics : 9 years
- Asst. Professor of Pharmaceutics: 6 years.
- Professor of Pharmaceutics: 12 years.

(i) **Professor** For 12 years, From August, '97 till date.

(ii) **Assistant Professor in pharmaceutics** For 6 years, from July '91 till August, '97

(iii) **Lecturer in pharmaceutics** For 9 years, from Aug. '82 to July '91.

Research Experience: 31 years. (1978-till date)

Research Students:

Present:	M.Pharm. – 4
	Ph.D (Tech) – 6
Completed:	M.Pharm. – 26
	Ph.D (Tech) - 13

Industrial Projects:

Chemicircle Pharmaceuticals (1992)	Novartis (India) Ltd. (2001)
Opthalmics (India) Ltd. (1992)	Novartis (India) Ltd. (2002)
Bombay Drug House (1994)	Macleods India (2003)
Bayer (India) Ltd. (1995)	SASMA (2003)
Khandelwal Laboratories (1995-96)	IPCA Laboratories(2004)
Bharat Serum (1996)	Macleods India (2004)
Dynamix (I) Ltd. (1997)	Jiggisha Enterprises(2004)
La Pharma (1998)	Atlantic Pharma(2005)
Parke Davis Ind (Ltd) (1998)	Galaxy Surfactants(2005)
Lubrichem (1999)	Marico Industries (2006)
Bayer (India) Ltd (2000)	Centaur Pharmaceuticals (2006)
Pharmaceuttical Coatings (2000)	Macleods India (2007)
	Gattefosse(2009)

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

Projects:

Sr. No	Name of Agency and title of project.	Year Started	Year of Completion	Total Budget (in Rs.)
1	ICMR: Pharmacokinetics of rifampicin in presence of other drugs	1986	1988	72,000/-
2	ICMR: Pharmacokinetics of atenolol in presence of other drugs to study effectiveness in treatment of hypertension.	1994	1996	74,800/-
3	AMRF: Film coating and evaluation of film coating polymer.	1994	1996	70,800/-
4	CSIR: Cyclodextrin based drug delivery .	1995	1998	2,50,000/-
5.	Amrut Mody Research Foundation (AMRF): Colonic targeting of therapeutic agents	1996	1997	70,400/-
6	AICTE (R & D) : Design, optimisation and evaluation of liposomal dispersion.	1996	1999	5,00,000/-
7	CSIR : Cyclodextrins for improved drug delivery	1998	2001	4,00,000/-
8	CSIR: Novel drug delivery systems	1997	2001	2,00,000/-
9	UGC: Transdermal Drug delivery	1999	2003	3,20,000/-
10	AICTE (TAPTEC): Novel liposomal drug delivery systems.	2000	2003	13,70,000/-
11	UGC: Controlled release systems for oral delivery of drugs having pH dependent solubility	2000	2003	4,25,000/-
12	AMRF: Novel drug delivery	2001	2004	70,800/-
13	AICTE (MODROB): Modernization of pharmaceutical technology laboratory for stability-testing.	2002	2004	12,00,000/-
14	CSIR: Design and evaluation of improved delivery system of drugs having poor solubility.	2000	2004	4,14,400/-

NOTARY RAMESHCHANDRA TIWARI State of Maharashtra Regn. 3361

5 AUG 2010

15	CSIR: Improved delivery systems for diuretic agents.	2000	2004	Rs. 4,14,400/-
16	ICMR: Novel drug delivery systems of some antimalarial drugs.	2003	2006	3,64,500/-
17	BRNS: Drug Delivery To Colon: Novel Approach Of Pressure Sensitive System and Gamma Scintigraphic Validation	2005	2008	9,99,800/-
18	ICMR: Novel Systems for Improved Delivery of Antidiabetic Drugs	2006	2009	5,80,000/-
19	DBT: Development of an antidiabetic formulation from leaf extract of *Annona squamosa'*	2006	2009	14,34,000/-
20	CSIR: Biopharmaceutical modification of lipid based particulate carriers for improved delivery of chemotherapeutic agents	2008	2011	7,44,600/-
21	DBT: Development and evaluation of liposomal drug delivery systems	2008	2011	39,80,000/-
22	AICTE: Novel Lipid Based Carrier Systems of drugs with poor oral bioavailability	2008	2010	12,00,000/-
23	UGC: Biopharmaceutical modifications of lipid particulate carriers for delivery of antileishmanial agents	2009	2012	4,52,300/-

Patents granted:

1. Indian Patent No. 206316.
2. Indian Patent No. 234801.

Patent Applications filed: 3

2. I have published more than 50 papers in reviewed National and International Journals and details of a few of such publications are set out hereunder –

1. Number of Research Papers published in National/International Journals : 33 (International Journals) + 23 (National Journals) = **56**

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA 5 AUG 2010

2. Number of Research Papers presented in National/International conference/conference proceedings : **75**

Research Papers:

International

1. M.S. Nagarsenkar, D. D. Hegde. Optimization of mechanical properties and water vapour transmission properties of free films of hydroxy propyl methyl cellulose. Drug Dev. Ind. Pharm. 1996, 22: 95-98.
2. M.S. Nagarsenkar, H. Shenai. Influence of hydroxypropyl β-cyclodextrin on solubility and dissolution profiles of ketoprofen in its solid dispersions. Drug Dev. Ind. Pharm. 1996, 22: 987-992.
3. M.S. Nagarsenker, A. Joshi. Preparation, characterisation and evaluation of liposomal lidocaine dispersion for dermal delivery. Drug Dev.Ind. Pharm. 1997, 23: 1159-1165.
4. *M.S. Nagarsenkar, J.S. Tantry, H. Shenai. Influence of hydroxypropyl* β-cyclodextrin on the dissolution of ketoprofen and on the irritation to gastric mucosa after oral administration in rats. J. Pharm. Sci. 1997, 3: 443-445.
5. M.S. Nagarsenkar, S.D. Garad. Physical characterization optimisation of dissolution properties of Prochlorperazine maleate coevaporates. Int. J. Pharm. 1998, 160: 251-255.
6. M S. Nagarsenker, R. Govindarajan. Solid dispersion for extended release of Verapamil HCl. Pharm. Pharmacol. Comm. 1998, 4: 331-334.
7. M.S. Nagarsenker, V.M. Bhave. Kneaded solid dispersion of hydroxypropyl β-cyclodextrin and carbamazepine: Study of complexation and in-vitro dissolution profile. Pharm. Pharmacol. Comm. 1998, 4: 335-338.
8. M.S. Nagarsenker, V.Y. Londhe, G.D. Nadkarni. Preparation and evaluation of liposomal formulations of tropicamide for ocular delivery. Int. J. Pharm. 1999, 190: 63-71.
9. M.S. Nagarsenkar, S.D. Garad, R. Govindarajan. Design, optimization and evaluation of Domperidone coevaporates. J. Control. Rel. 2000, 63: 31-39.
10. M.S. Nagarsenker, R.N. Meshram, R. Govindarajan. Solid dispersions of hydroxypropyl β-cyclodextrin and ketorolac: enhancement of in vitro

NOTARY RAMESHCHANDRA TIWARI Area Dist. Mumbai Andheri Maharashtra State of Maharashtra Regn. 3361 5 AUG 2010 INDIA

dissolution rates, improvement in anti-inflammatory activity and reduction in ulcerogenicity in rats. J. Pharm. Pharmcol. 2000, 52: 949-956.

11. V.P. Sant, M.S. Nagarsenker, S.G.A. Rao, R.P. Gude. Enhancement of antimetastatic activity of pentoxifylline by encapsulation in conventional liposomes and sterically stabilized liposomes in murine experimental B16F10 melanoma model. J. Pharm. Pharmacol. 2000, 52: 1461-1466.
12. M.S. Chavan, V.P. Sant, M.S. Nagarsenker. Azo Containing urethane analog: Synthesis, characterization and evaluation in colonic drug delivery. J. Pharm. Pharmacol. 2001, 53: 895-900.
13. M.S. Nagarsenker, V.Y. Londhe. Preparation and evaluation of a liposomal formulation of sodium cromoglycate. Int. J. Pharm. 2003, 251: 49-56.
14. V.P. Sant, M.S. Nagarsenker, S.G.A. Rao, R.P. Gude. Sterically stabilized etoposide liposomes: evaluation of antimetastatic activity and its potentiation by combination with sterically stabilized pentoxifylline liposomes in mice. Cancer Biother. Radiopharm. 2003, 18: 811-817.
15. A. Mukne, M.S. Nagarsenker. Triamterene-β-cyclodextrin systems: Preparation, characterization and in vivo evaluation. AAPS PharmSciTech 2004, 5: article 19.
16. R. Govindarajan, M.S. Nagarsenker. Influence of preparation methodology on solid state of flurbiprofen in cyclodextrin based systems, effect of formulation variables on drug release. J. Pharm. Pharmacol. 2004, 56: 725-733.
17. R. Govindarajan, M.S. Nagarsenker. Basic drug-enterosoluble polymer coevaporates: Development of oral controlled release systems. Drug Dev. Ind. Pharm. 2004, 30: 847-858.
18. R. Govindarajan, M.S. Nagarsenker. Formulation studies and in vivo evaluation of flurbiprofen-hydroxypropyl β-cyclodextrin systems. Pharm. Dev. Tech., 2005, 10: 105-114.
19. M.S. Nagarsenker, M.S. Joshi. Celecoxib-cyclodextrin systems: characterization and evaluation of in-vitro and in-vivo advantage. Drug Dev. Ind. Pharm. 2005, 31: 169-178.
20. N.G. Tayade, M.S. Nagarsenker. Validated HPTLC method of analysis for artemether and its formulations. J. Pharm. Biomed. Anal. 2007, 43: 839-844.

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

21. A.A. Date, M.S. Nagarsenker. Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. Int. J. Pharm. 2007, 329: 166-172.
22. R.P. Dixit, M.S. Nagarsenker, Dry adsorbed emulsion of simvastatin: optimization and in vivo advantage. Pharm. Dev. Tech. 2007, 12: 495-504.
23. A.A. Date, M.S. Nagarsenker. Novel delivery systems of atorvastatin should be evaluated for pharmacodynamics instead of pharmacokinetics. J. Pharm. Pharmacol. 2007, 59: 1583-1584.
24. A.A. Date, M.S. Nagarsenker. HPTLC determination of cefpodoxime proxetil in formulations. Chromatographia, 2007, 66: 905-908.
25. A.A. Date, M.S. Nagarsenker. Design and evaluation of microemulsions for improved parenteral delivery of propofol. AAPS PharmSciTech, 2008, 9: 138-145.
26. R.P. Dixit, C.R. Barhate, M.S. Nagarsenker. Stability-indicating HPTLC method for simultaneous determination of ezetimibe and simvastatin. Chromatographia, 2008, 67: 101-107.
27. A. Dinge, M.S. Nagarsenker. Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity. AAPS PharmSciTech 2008, 9: 349-356.
28. R.P. Dixit, M.S. Nagarsenker. Self nanoemulsifying granules of ezetimibe: design, optimization and evaluation. Eur. J. Pharm. Sci. 2008, 35: 183-192.
29. M.S. Nagarsenker, L. Amin, A.A. Date. Potential of cyclodextrin complexation and liposomes in topical delivery of ketorolac: in vitro and in vivo evaluation. AAPS PharmSciTech 2008, 9 (4), 1165-1170.
30. R.P. Dixit, M.S. Nagarsenker. Formulation and in vivo evaluation of self nanoemulsifying granules for oral delivery of a combination of ezetimibe and simvastatin. Drug Dev. Ind. Pharm. 2009, 35
31. P. O. Pathak, M. S. Nagarsenker. Formulation and evaluation of Lidocaine lipid nanosystems for dermal delivery, AAPS PharmSci Tech., 2009, 10(3), 985-992.

NOTARY
RAMESHCHANDRA TIWARI
Area-Mazgaon Pradhe
Andheri, Mumbai
State of Maharashtra
Regn 3361
GOVT. OF INDIA

MSN

5 AUG 2010

National

1. S.K. Unadket, M.S. Nagarsenker, H.P. Tipnis. Bioavailability of rifampicin on oral administration. Indian Drugs 1988, 25: 413-417.
2. S.K. Unadket, M.S. Nagarsenker, H.P. Tipnis. Bioavailability and pharmacokinetic study of rifampicin in tuberculosis patients. Indian Drugs 1989, 26: 688-690.
3. S.K. Unadket, M.S. Nagarsenker, H.P. Tipnis. Kinetics of rifampicin and isoniazid, administered alone and in combination. Indian Drugs 1989, 26: 679-683.
4. M.S. Nagarsenker, H.P. Tipnis. Effect of dapsone on rifampicin pharmacokinetics in healthy volunteers and leprosy patients. Indian Drugs 1990, 27: 40-42.
5. M.S. Nagarsenker, H.P. Tipnis. Pharmacokinetics of trimethoprim and rifampicin in healthy volunteers. Indian Drugs 1990, 27: 44-48.
6. M.S. Nagarsenker, S.G. Deshpande. Pan coating of paracetamol granules using tamarind seed polysaccharides. Indian Drugs 1990, 27: 48-54.
7. H. Shenai, M.S. Nagarsenker. Intra-ocular irrigation solutions. Eastern Pharmacist, 1994, 41-46.
8. S. Vanarase, M.S. Nagarsenker, In vitro dissolution studies on prochlorperazine pellets coated with ethyl cellulose. Indian Drugs 1995, 32: 134-138.
9. A. Upadhyaya, M.S. Nagarsenker. Evaluation of film coating polymer. Indian Drugs 1996, 33: 219-229.
10. D. Hegde, H.P. Tipnis, M.S. Nagarsenker. Application of differential scanning calorimetry to preformulation compatibility studies between chloroquine phosphate and tablet excipients. Ind.J. Pharm. Sci. 1996, 58: 71-75.
11. S. Garad, J. Tantry, R. Patki, M.S. Nagarsenker. Application of DSC to preformulation compatibility studies between sparfloxacin and tablet excipients. Indian Drugs 1997, 34: 109-111.
12. J. Musale, M.S. Nagarsenker. Influence of hydroxypropyl β-cyclodextrin on solubility of piroxicam and on irritation to stomach of rats upon oral administration. Ind. J. Pharm. Sci. 1997, 59: 174-180.

13. H.P. Tipnis, M.S. Nagarsenker, S.D. Garad, R.V. Patki. Bioequivalance studies on metoclopramide controlled release formulation in healthy human volunteers. Indian Drugs 1997, 34: 630-633.

14. M.S. Nagarsenker, S.D. Garad, J.S. Tantry. Differential Scanning Calorimetry (DSC) as a quick scanning technique for solid state stability studies, Eastern Pharmacist, 1998, XLI: 125-128.

15. V. Y. Londhe, M. S. Nagarsenker. Solid dispersions of hydroxypropyl β-cyclodextrin and carbamazepine: study of complexation and in-vitro dissolution profile. Indian Drugs 1999, 36: 15-20.

16. V. Y. Londhe, M.S. Nagarsenker. Comparison between hydroxypropyl β-cyclodextrin and polyvinylpyrrolidone as carriers for carbamazepine solid dispersions. Ind. J. Pharm. Sci. 1999, 61: 237-240.

17. D.D. Hegde, M.S. Nagarsenker, S.D. Garad. Design and evaluation of extended release tablets of prochlorperazine maleate. Indian Drugs 2001, 38: 69-74.

18. J.S. Tantry, M.S. Nagarsenker. Rheological study of guar gum. Ind. J. Pharm. Sci. 2001, 63: 74-76.

19. V.Y. Londhe, M.S. Nagarsenker. Optimization of liposomes containing sodium chromoglycate using factorial design: study of encapsulation efficiency and particle size. Indian Drugs 2001, 38: 363-367.

20. V.P. Sant, A.R. Paradkar, M.S. Nagarsenker. Obtimization of pentoxifylline liposomes using 2^4 factorial design. Ind. J. Pharm. Sci. 2002, 64: 459-464.

21. R.P. Dixit, M.S. Nagarsenker. In vitro and in vivo advantage of celecoxib surface solid dispersion and dosage form development. Ind. J. Pharm. Sci. 2007, 69: 370-377.

22. M. Kulkarni, M.S. Nagarsenker. A study on improvement of solubility of rofecoxib and its effect on permeation of drug from topical formulations. Ind. J. Pharm. Sci. 2008, 70 (4), 466-471.

23. U. A. Shinde, M.S. Nagarsenker. Ind. J. Pharm. Sci. In Press.

NOTARY RAMESHCHANDRA TIVARI Advocate Bombay State of Maharashtra Regn. 3361 GOVT. OF INDIA

MSD

5 AUG 2010

Review Articles

1. A.A. Date, B. Naik, M.S. Nagarsenker. Novel drug delivery systems: potential in improving topical delivery of anti acne agent. Skin Pharmacol. Physiol. 2006, 19: 2-16.
2. A.A. Date, M.S. Nagarsenker. Parenteral microemulsions: an overview, Int. J. Pharm., 2008, 355, 19-30.

Papers Presented In The Conferences / Seminars / Workshops:

1. Preformulation compatibility studies on ciprofloxacin HCl and tablet excipients using differential scanning calorimetry., 47th IPC, Vishakapatnam, 95
2. Preformulation compatibility studies on chloroquine phosphote and tablet excipients using DSC., 47th IPC, Vishakapatnam, 95
3. Influence of HPB on dissolution of ketoprofen and piroxicam on the irritation to gastric mucosa of rats upon their oral administration., 48th IPC,1996
4. Modified release systems of prochlorperazine maleate: optimization of in-vitro dissolution parameters. 1st International symposium CRS, Ind. Local Chapter Feb 98 Mumbai.
5. Verapamil HCl coevaporates using enterosoluble polymers: Development of oral controlled release systems, 50th IPC at Mumbai 1998.
6. Liposome dispersion containing tropicamide for ocular delivery: characterization and γ-scintigraphic evaluation, Workshop on basics in clinical pharmacology, 1998.
7. Preparation and evaluation of ophthalmic liposomal formulation containing Tropicamide. 50th IPC Mumbai 98.
8. Design, optimization and evaluation of domperidone coevaporates 50th IPC Mumbai 98.
9. Application of factorial design to study the effect of different variables on encapsulation of pentoxyphylline in liposomes, 2nd International Symposium on Advances in technology and business potential of new drug delivery systems organised by Controlled Release Society Indian local chapter in Feb 99, Goa.

NOTARY RAMESHCHANDRA TIWARI Area-Mazgaon Dockline Andheri Mumbai State-of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

10. Preparation and evaluation of liposomal formulation of sodium chromoglycate for pulmonary delivery, at 51st IPC, Indore 1999.
11. Solid dispersions of flurbiprofen with hydroxylpropyl-β-cyclodextrin. 4th International Symposium, B.V. Patel Education trust, Feb 2000.
12. Optimization of liposomes containing sodium chromoglycate using factorial design: Study of encapsulation efficiency and particle size, B.V. Patel Education trust, Feb 2000.
13. Solid dispersion of hydroxypropyl ß-cyclodextrin and ketorolac: enhancement of dissolution rates, improvement in anti-inflammatory activity and reduction in ulcerogenicity, *10th International Cyclodextrin Symposium, Ann Arbor, Michigan*, May 2000.
14. Role of hydroxypropyl ß-cyclodextrin in improving dissolution and reducing ulcerogenicity of flurbiprofen: effect of l-tyrosine on bioavailability from coevaporates, *10th International Cyclodextrin Symposium, Ann Arbor, Michigan, May 2000.*
15. Development of oral controlled release systems for pH independent release of a weak base, *3rd International Symposium on Advances in Technology and business potential of new drug delivery systems, Ootacamund, India,* October 2000.
16. Evaluation of antimetastatic activity of conventional and sterically stabilized liposomes of pentoxifylline in murine experimental metastasis model, *3rd International Symposium on Advances in Technology and business potential of new drug delivery systems, Ootacamund, India,* October 2000.
17. pH Independant Oral Controlled Release Of Verapamil Hcl: Solubilisation In The Microenvironment Using Enterosoluble Polymer Or Organic Acid *Controlled Release Society 28th Annual Symposium, San Diego, USA, June* 2001, was accepted for presentation.
18. Characterization and evaluation of liposomal and cyclodextrin based systems for dermal and transdermal delivery of ketorolac, Controlled Release Society 28th Annual Symposium, San Diego, USA, June 2001, was accepted for presentation.
19. Effect of succinic acid on the release of verapamil hydrochloride from hydrophilic matrix, at *53rd IPC, Delhi, December 2001.*

NOTARY RAMESHCHANDRA TIWARI Area-Mazgaon Pune Address Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

20. Proliposomal systems of clotrimazole: optimization of entrapment efficiency and size distribution using factorial design, at *53rd IPC*, Delhi, December 2001.
21. Design And Evaluation Of Solid Dispersions Of Weakly Basic Drug For Controlled Release. 4th *International Symposium on Advances in Technology and business potential of new drug delivery systems*, Mumbai, *India*, Feb 2002.
22. Preparation and Characterization of Triamterene-ß-Cyclodextrin Systems. 4th *International Symposium on Advances in Technology and business potential of new drug delivery systems*, Mumbai, *India*, Feb 2002.
23. Sodium Alginate - Gelatin Complex Coacervation: Characterization By Viscosity, Turbidity, Coacervate Yield And Chemical Analysis. 4th *International Symposium on Advances in Technology and business potential of new drug delivery systems*, Mumbai, *India*, March 2002.
24. Proliposomal System of Clotrimazole: Design and Evaluation 4th *International Symposium on Advances in Technology and business potential of new drug delivery systems*, Mumbai, *India*, March 2002.
25. Preparation and Evaluation of Solid Dispersion Systems of Celecoxib, at *54th IPC, Pune, December 2002.*
26. Preparation, characterization and evaluation of HPβCD inclusion complex of an antimalarial drug, at *54th IPC, Pune, December 2002.*
27. Formulation, Evaluation and optimization of ophthalmic mucoadhesive drug delivery systems, at *54th IPC, Pune, December 2002.*
28. pH-Independent Controlled Release of a Drug Having pH-Dependent Solubility, at *54th IPC, Pune, December 2002.*
29. Design, Optimization and Evaluation of Transdermal Drug Delivery System, at *54th IPC, Pune, December 2002.*
30. Triamterene - B-Cyclodextrin Systems: Characterization, *Invivo* Evaluation and Formulation Studies, at *54th IPC, Pune, December 2002.*
31. Role of organic acid in programming the release of weakly basic drug having pH-dependent solubility, at B V PERD's 5th International Symposium, Feb.'2003.

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

32. Microencapsulation of Eugenol by sodium alginate gelatin complex coacervation, at B V PERD's 5th International Symposium, Feb.'2003.
33. Controlled release system for a weakly basic drug: Preparation, Optimization and Evaluation, at B V PERD's 5th International Symposium, Feb.'2003.
34. Interaction between celecoxib and cyclodextrin: differential scanning calorimetry, X-ray diffraction studies and in-vitro dissolution studies, at B V PERD's 5th International Symposium, Feb.'2003.
35. Binary systems of furosemide and cyclodextrins: preparation, characterization and in-vivo evaluation, at B V PERD's 5th International Symposium, Feb.'2003.
36. Mucoadhesive microemulsion systems: a novel approach to optimize ophthalmic drug delivery, at B V PERD's 5th International Symposium, Feb.'2003.
37. Development and validation of HPLC method of analysis, stability evaluation and anti-inflammatory studies of Transdermal Drug Delivery System of Ketorolac. 55th IPC, Chennai, Dec'2003.
38. M. S. Rane and M. S. Nagarsenker, pH-independent controlled release oral formulation of weakly basic drug – pharmacokinetic evaluation and IVIVC, to be held at 5th International CRS symposium, Indian chapter, Feb'2004.
39. S. Phadke and M. S. Nagarsenker, gastroretentive systems for cinnarizine, to be held at 5th International CRS symposium, Indian chapter, Feb'2004.
40. U. A. Shinde and M. S. Nagarsenker, sodium alginate-gelatin complex coacervation: microencapsulation of nitrofurantoin, to be held at 5th International CRS symposium, Indian chapter, Feb'2004.
41. M. C. Kulkarni and M. S. Nagarsenker, development of dermal delivery systems for a COX-2 selective NSAID's using various permeation enhancers, to be held at 5th International CRS symposium, Indian chapter, Feb'2004.
42. A. P. Mukne and M. S. Nagarsenker, formulation studies of poorly soluble diuretic agents, to be held at 5th International CRS symposium, Indian chapter, Feb'2004.

NOTARY RAMESHCHANDRA TIWARI Area-Mazgaon Bombay State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

43. A. L. Kulkarni and M. S. Nagarsenker, liposomal system of 5-fluorouracil: optimization of entrapment efficiency and size distribution using 2^2 factorial design, to be held at 5th International CRS symposium, Indian chapter, Feb'2004.
44. Aditya Dinge, R. P. Dixit and M. S. Nagarsenker, fast dissolving films for delivery of poorly water soluble drug, 6th International CRS symposium, Indian chapter, Feb'2005.
45. Design, optimization and evaluation of submicronemulsions systems for poorly water soluble drugs, 1st Indojapanese International conference, November 2005.
46. *Studies on cyclodextrin association of a poorly soluble lipid lowering drug*, 1st Indojapanese International conference, November 2005.
47. Design of Self-Microemulsifying Systems for Cefpodoxime proxetil delivery, 32nd Annual Meeting and Exposition of the CRS International conference, June 2005.
48. Gelatin- sodium alginate complex coacervation: microencapsulation of Nitrofurantoin, 15th International Symposium on microencapsulation held at Parma, Italy, September 2005
49. Solubilization of Triameterene by use of cosolvent, 2005 AAPS Annual Meeting & Exposition held at Tennessee.
50. Preparation, characterization and formulation studies of Triameterene-β-cyclodextrin systems, 2005 AAPS Annual Meeting & Exposition held at Tennessee.
51. Optimization of methotrexate liposomes using 24 factorial design, 58th Indian Pharmaceutical Congress, 2006, Mumbai.
52. Studies on cyclodextrin-glipizide binary systems and in vivo advantages, 58th Indian Pharmaceutical Congress, 2006,Mumbai
53. Preparation, optimization and characterization of dry emulsions of anti-hypercholesterolemic agent, 58th Indian Pharmaceutical Congress, 2006,Mumbai
54. Antibody guided targeted drug delivery systems for effective control of malaria: Evaluation in *P.berghei* infected mice, 7th International Symposium

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

on Advances in Technology and business potential of New Drug Delivery Systems, 2007, Mumbai

55. Dry adsorbed microemulsifying systems of Simvastatin: Design, optimization and in vivo advantage, 7th International Symposium on Advances in Technology and business potential of New Drug Delivery Systems, 2007, Mumbai.
56. Simple method for rapid screening of excipients used in spontaneously emulsifying systems, 7th International Symposium on Advances in Technology and business potential of New Drug Delivery Systems, 2007, Mumbai.
57. Formulation and Evaluation of Solid Lipid Nanoparticle System Containing Lidocaine for Dermal Drug Delivery, 60th Indian Pharmaceutical Congress, 2008, Lucknow.
58. Design and Evaluation of Lidocaine Lipid Nanoparticulate Systems for Dermal Drug Delivery, 8th International Symposium on Advances in Technology and business potential of New Drug Delivery Systems, 2008, Ahmedabad.
59. Preparation and Characterization of Thermosensitive Liposomes of Fluorouracil, 8th International Symposium on Advances in Technology and business potential of New Drug Delivery Systems, 2008, Ahmedabad.
60. Preparation and characterization of binary mixtures of Repaglinide with beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin at 1st International conference on Drug discovery and Development-South Asian perspective organized by South Asian chapter of American College of Clinical Pharmacology
61. Phospholipid based cationic nanocomplexes for improved drug delivery at 2nd International conference on Drug discovery and Development-South Asian perspective organized by South Asian chapter of American College of Clinical Pharmacology
62. Validated HPTLC method for quantification of rutin in leaf extract of *Annona squamosa* and its formulation at 2nd International conference on Drug discovery and Development-South Asian perspective organized by South

NOTARY RAMESHCHANDRA TIWARI Area-Mumbai Suburban State of Maharashtra Regn. 5361 GOVT. OF INDIA

5 AUG 2010

Asian chapter of American College of Clinical Pharmacology held at Mumbai 2008.

63. Single step fabrication of pharmaceutical nanocarriers using novel biocompatible solvents at Inter University research festival-Avishkar 2008-09.
64. Single Step Fabrication of Eudragit RLPO Nanoparticles and Nanocapsules Using Biocompatible Solvents and Their Applications in Drug Delivery at 9th International Symposium of controlled release society, Indian Chapter held at Mumbai 2009.
65. Single step fabrication of pharmaceutical nanocarriers from novel biocompatible solvents and their application in dermal and oral delivery at 36th Annual exposition and meeting of controlled release society held at Copenhagen, Denmark in 2009.
66. Ethanolic extract of leaves of *Vitex Negundo*: Evaluation and feasibility of formulation development at 9th International Symposium of controlled release society, Indian Chapter held at Mumbai 2009.
67. Formulation, optimization and evaluation of SLNs of a hydrophilic drug for oral delivery at 9th International Symposium of controlled release society, Indian Chapter held at Mumbai 2009.
68. Formulation and evaluation of long circulating liposomes for Amphotericin B, tracer kinetic study using TC ^{99m} in healthy Balb/c mice at 9th International Symposium of controlled release society, Indian Chapter held at Mumbai 2009.
69. Formulation, optimization and characterization of meloxicam nanosuspension at 9th International Symposium of controlled release society, Indian Chapter held at Mumbai 2009.
70. Formulation of carbamazepine nanosuspensions by nanoprecipitation method at 9th International Symposium of controlled release society, Indian Chapter held at Mumbai 2009.
71. Fluticasone Propionate Liposomes for Pulmonary Delivery at IPA symposium on Nasal and Pulmonary Drug Delivery held at Mumbai 2009.
72. Formulation, optimization and evaluation of solid lipid nanoparticles of simvastatin for oral delivery at 3rd International conference on Drug

discovery and Development-South Asian perspective organized by South Asian chapter of American College of Clinical Pharmacology held at Mumbai 2009.

73. Liposomal dry powder inhalation for pulmonary delivery of Beclomethasone dipropionate at 3rd International conference on Drug discovery and Development-South Asian perspective organized by South Asian chapter of American College of Clinical Pharmacology held at Mumbai 2009.
74. *Preparation and in-vivo evaluation of self-microemulsifying drug delivery* system (smedds) of repaglinide at 3rd International conference on Drug discovery and Development-South Asian perspective organized by South Asian chapter of American College of Clinical Pharmacology held at Mumbai 2009.
75. Validated HPTLC method for quantification of isoquercitrin in leaf extract of *Annona squamosa* and its formulation at 3rd International conference on Drug discovery and Development-South Asian perspective organized by South Asian chapter of American College of Clinical Pharmacology held at Mumbai 2009.
76. Positively charged polymeric nanoparticles of poorly water soluble drug Meloxicam at 10th International Symposium of controlled release society, Indian Chapter held at Mumbai 2010.
77. Targeted drug delivery system for colon using soy polysaccharide at 10th International Symposium of controlled release society, Indian Chapter held at Mumbai 2010.
78. Bio-engineered drug delivery system for active targeting at 10th International Symposium of controlled release society, Indian Chapter held at Mumbai 2010.
79. Solid lipid nanoparticles of acid labile hydrophilic drug: Enhanced chemical stability and bioavailability at 10th International Symposium of controlled release society, Indian Chapter held at Mumbai 2010.
80. Templating of polymeric and lipid nanocarriers using biocompatible solvents at 1st AAPS-NUS-BCP regional conference held at Mumbai 2010.

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn. 3361 GOVT. OF INDIA

5 AUG 2010

81. Formulation of silver sulfadiazine nanosuspension based gels for treatment of burn wounds solvents at 1st AAPS-NUS-BCP regional conference held at Mumbai 2010.
82. Fractionated aqueous extract of DBT/DM/06: Characterization, invivo evaluation and formulation development at 1st AAPS-NUS-BCP regional conference held at Mumbai 2010.
83. Colon specific drug delivery and its validation by gamma scintigraphy at 1st AAPS-NUS-BCP regional conference held at Mumbai 2010.

Lectures Delivered

1. "Stability Studies guidelines" in Drug Inspectors' Training Programme in K. M. K. College of pharmacy, Mumbai, 1998.
2. "Optimisation techniques" in Faculty Development Programme in Bombay College of Pharmacy, Mumbai, 1998.
3. "Dosage Forms for intra ocular use" in Faculty Development Programme in Bombay college of Pharmacy, Mumbai, 1999.
4. "Liposomes as drug delivery systems" organized by IPA-MSB, Mumbai, Sept. 2001.
5. "Liposomes as drug delivery systems" organized by CRS Indian Local Chapter, at *4th International Symposium on Advances in Technology and business potential of new drug delivery systems*, Mumbai, *India,* March 2002.
6. "Oral controlled release drug delivery systems of weakly basic drugs" organized by IIPC, at a seminar on *R & D in drug delivery systems*, held on 28th February 2003 in Bombay College of Pharmacy, Mumbai.
7. "Changing needs in pharma curriculum in India", at *55th Indian Pharmaceutical Congress, Chennai, Dec. 2003*
8. Liposomes as drug delivery systems" organized by IPCA, Kandivli, Mumbai April 2004.
9. Oral specialized drug delivery systems" organized by Macleods, Mumbai, March 2004.
10. Influence of excipients and manufacturing on physical stability of drug, Oct 2005.

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

11. 'Optimization in design of liposomes' in *Teachers training programme at* Pune, July 2005.
12. Liposomal drug delivery at UICT
13. Lipid based carriers at PCT college of Pharmacy, Thane
14. Delivered a lecture on drug delivery systems in course of post grad diploma in Pharm Management, Garaware Institute and G. S. Medical college collaboration on Sept 7, 2006
15. Delivered a lecture on "Cyclodextrin based drug delivery systems " at NMIMS, Mumbai on 18 Nov 2006
16. 'Drug Delivery Systems' at Garware Institute, Mumbai
17. *Lectures delivered in Hyderabad Sindh College of Pharmacy, Ulhasnagar* on "Stability Studies" for Sem VI in March 2007.
18. Lipid nanocarriers for improved drug delivery at 1st AAPS-NUS-BCP regional conference held at Mumbai, 2010.

Awards / Prizes / Certificates/ fellowship etc.:

- G.P. Nair IDMA Gold Medal for securing First Rank in Final Year B.Pharm. examination (1978) in the University of Bombay.
- *Prof. (Mrs.) M. R. Baichwal Visiting fellow in Pharm Sci. and Technology for* UICT, year 2005-2006.

Paper and Poster Awards:

- Dixit RP, Nagarsenker MS, Prof M. L. Khorana Memorial award for Best research paper entitled "In vitro and in vivo advantage of celecoxib surface solid dispersion and dosage form development", in Indian Journal of Pharmaceutical Sciences (Section: Pharmaceutics) for the year 2007.
- Dixit RP, Barhate CR, Nagarsenker MS, Certificate of merit awarded to the research paper entitled "Stability indicating HPTLC method for simultaneous determination of ezetimibe and simvastatin" in 4th P. D. Sethi Annual award 2008 for best research paper in the field of Pharmaceutical Analysis.
- Dixit RP, Barhate CR, Nagarsenker MS, Certificate of merit awarded to the research paper entitled "Stability indicating HPTLC method for simultaneous

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn. 3361 GOVT OF INDIA

5 AUG 2010

determination of ezetimibe and simvastatin" in P. D. Sethi Annual award 2008 for best research paper on applications of TLC and HPTLC in Pharma, Herbal and Miscellaneous Analysis.

- Desai NS, Nagarsenker MS, Best poster presentation entitled Preparation and characterization of binary systems of repaglinide with BCD and HPBCD.
- Desai NS, Biyani S, Kulkarni SR, Nagarsenker MS, Best poster presentation entitled Validated HPTLC method for quantification of rutin in leaf extract of Annona squamosa and its formulation.
- Nagarsenker KS, Kulkarni SR, Nagarsenker MS, Best poster presentation entitled Composition and antilipid peroxidation activity of ethanolic extract and supercritical fluid extract of leaves of *Vitex Negundo linn.*
- Date AA, Nagarsenker MS, Best oral presentation entitled Phospholipid based cationic nanocomplexes for improved drug delivery.
- Nirale N.M., Vidhate R.D. Nagarsenker M. S., Best poster presentation entitled Fluticasone Propionate Liposomes for Pulmonary Delivery.
- Nirale N.M., Nagarsenker M. S., Best poster presentation entitled Liposomal dry powder inhalation for pulmonary delivery of Beclomethasone dipropionate
- Desai NS, Nagarsenker MS, Best poster presentation entitled Preparation and in-vivo evaluation of self-microemulsifying drug delivery system (smedds) of repaglinide
- Date AA, Nagarsenker MS Best poster presentation entitled Templating of polymeric and lipid nanocarriers using biocompatible solvents
- Desai NS, Biyani S, Kulkarni SR, Nagarsenker MS, Best oral presentation entitled Fractionated aqueous extract of DBT/DM/06: Characterization, invivo evaluation and formulation development

Professional affiliations:

1. Member of the Indian Pharmaceutical Association.
2. Member of the Controlled Release Society (Indian Local Chapter).

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

3. Member of Association of Pharmaceutical Teachers of India.
4. Member of editorial board of Indian Journal of Pharmaceutical Sciences.
5. Referee for reviewing papers in Indian Journal of Pharmaceutical Sciences, Indian Drugs, Indian Journal of Pharmacology, International Journal of Pharmaceutics, PDA's Journal of Pharm Technology and Current Drug Delivery. 1274360

In view of my position, qualifications, experience and knowledge in the field of pharmaceuticals, I am competent to depose this affidavit.

3. I am informed that the opponent is in the process of opposing the Patent Application no. 726/MUMNP/2009 dated April 15, 2009 and the opponent has given me copies of the documents relating to the pre-grant proceedings, namely complete specification of Indian Patent Application no. 726/MUMNP/2009 (specification), the draft representation including copies of the following publications:

Sr. No.	Document	Publication Date
Exhibit 1	US6599528	July 29, 2003
Exhibit 2	WO0134119	May 17, 2001.
Exhibit 3	WO0074677	December 14, 2001
Exhibit 4	WO199744014	November 27, 1997

4. I have been asked to consider the invention disclosed and claimed in the specification and Exhibit-1 to Exhibit-4 with Annexures to give my opinion on whether the invention claimed in the patent specification is obvious and lacking inventive step.

5. I have carefully gone through the documents being filed in the present proceedings including the complete specification of the applicant. I have understood the invention claimed by the applicant and have also understood the opponent's case made out in the written statement of opposition.

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

6. The invention is directed to solid pharmaceutical dosage form comprising at least an HIV protease inhibitor and process for preparation. In paragraph 4 of the specification the applicant has highlighted poor aqueous solubility as one for the factors affecting drug bioavailability. In other words HIV protease inhibitors due to poor aqueous solubility are less bio-available. Accordingly, the invention is directed at developing an improved oral solid dosage forms for HIV protease inhibitors that have suitable oral bioavailability and stability that does not necessitate high vehicle volume. The aforesaid objective is achieved by formulating a solid pharmaceutical dosage form comprising solid dispersion of at least one HIV formulation in at least one pharmaceutically acceptable water soluble polymer and at least one pharmaceutically acceptable surfactant.

7. The applicant has provided a list of HIV protease inhibitors suitable for use in the invention on pages 3 and 4 of the specification. The specification and the claims recite various HIV protease inhibitors that can be incorporated in the invention disclosed therein. Further, pages 6 and 7 of the patent application lists out the non-ionic surfactants that may be used and states that surfactant with HLB 4 to 10 are suitable. Water soluble polymers being an essential feature of the applicant's invention are listed on page 8 and 9 of the specification. Additionally the applicant states that such water soluble polymers with Tg from about 80°C to about 180 °C allow preparation of mechanically stable solid dispersion. Further, the applicant states that various methods can be used for manufacturing the said solid dosage forms. The methods include melt-extrusion, spray drying and solution evaporation, where melt extrusion is being preferred by the applicant. It may be noted that all the said methods comprises the preparation of solid solution of the active ingredient in a matrix of the water soluble polymer and the surfactant and converting the solution into the desired dosage form.

8. The applicant in its specification has provided various exemplary compositions for ritonavir/lopinavir in combination and ritonavir alone.

NOTARY RAMESHCHANDRA TIWARI Area-Mazgaon Mumbai State of Maharashtra Regd. 3361 GOVT. OF INDIA

MSD

5 AUG 2010

9. The applicant's claims are directed to a solid pharmaceutical dosage form comprising a solid dispersion of at least one HIV protease inhibitor in water soluble polymer with Tg at least about 50° C and surfactant.

10. I have studied the documents from Exhibit-1 to Exhibit-4 and now proceed to highlight certain key aspects in the opponent's representation and the documents relied upon in the said representation.

11. I say that Exhibit-1 teaches a mechanically stable pharmaceutical presentation for oral administration of one or more active ingredient, melt processable matrix forming excipient and a surface active substance with HLB 2 to 18, (abstract). As apparent from column 1 last paragraph, I say that Exhibit 1 is specifically directed to formulation of active ingredient with low solubility and low bioavailability. This is brought about in Exhibit 1 by solid dispersion; wherein in the active ingredient is in the form of a molecular dispersion in an excipient matrix. Exhibit-1 further states that "The addition of surface active substance to formulations of low solubility is "**generally known per se**"; column 2, line 9. With respect to the active ingredients suitable for use in Exhibit 1 includes protease inhibitors in addition to immunosuppressants, reverse transcriptase inhibitors, cytostatics, antimycotics, CNS active substances. Exhibit 1 also recites examples of surface active agents in column 3, lines 1-17 and the ones that require special mention are sorbitan fatty acid esters, polyoxyethylene 20 sorbitan monopalmitate and the said surfactant have HLB value from 2 to 18. It further enlists examples of polymers (Column 3, lines 30-38) like homo- and copolymers of N-vinylpyrrolidone, copolymers, for example copovidone among others. Moreover, the dosage forms disclosed in exhibit 1 are produced by a melt process (Column 3, lines 62-63). I say that essential attributes of the invention are present in Exhibit 1. I further say the Exhibit 1 does not explicitly mention specific HIV protease inhibitors like lopinavir and / or ritonavir as its 'one or more active ingredient' but indeed HIV protease inhibitor as a class of drug. I therefore say that in my opinion the objective of the invention as stated in paragraph 9 is wholly addressed by Exhibit 1.

NOTARY RAMESHCHANDRA TIWARI Area-Marol Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2016

12. I say that Exhibit 1 teaches about mechanically stable preparations comprising actives having low solubility. I say that the object of the present invention being the preparation of solid pharmaceutical dosage of HIV protease inhibitors, which have low aqueous solubility, having a suitable bioavailability and stability, the inventors of the impugned application would be led by Exhibit 1 for reasons mentioned hereinabove. The applicant has only applied the teachings of Exhibit 1 to provide stable formulations of HIV protease inhibitors and therefore the claimed features are not the applicant's contribution to the state of art.

13. I state that Exhibit-2 teaches a solid dispersion of a pharmaceutical compound in a water soluble carrier, such as polyethylene glycol (PEG), and a crystallization inhibitor, such as polyvinylpyrrolidone or hydroxypropylmethylcellulose. It may be noted that the pharmaceutical formulation taught in Exhibit-2 comprises HIV protease inhibitors, in particularly, Ritonavir, Lopinavir (mentioned as ABT-378) and their combination as active ingredients similar to the invention claimed by the applicant in its application under opposition. I further state that Exhibit-2 has also attempted to solve the problem of low bioavailability of HIV protease inhibitors and recrystallization of the said active ingredient. According to Exhibit-2, Polyvinylpyrrolidone (PVP) is known to inhibit crystallization of drugs as some drugs tend to form crystals when placed in solution, which can be problematic during formulation and also deteriorates the physical stability of the formulation. Exhibit 2 teaches dispersion of the pharmaceutical active in a matrix to improve the dissolution profile of actives having poor aqueous solubility. It also teaches the use of PVP which as already mentioned inhibits crystallization thereby increasing the stability of the formulation. The solution derived to overcome the aforesaid problem is to improve the aqueous dissolution properties and physical stability and ultimately achieve improved bioavailability and also enhances the physical stability of the formulation. Exhibit-2 clearly teaches that PVP has the added advantage of having a high Tg, which imparts stabilization of amorphous regions by reducing mobility (page 11, lines 16-18). Therefore, in view of this teaching, I say that it would have been obvious to use PVP as a water-soluble polymer for use with the melt-extrusion process. It may be further noted that

NOTARY RAMESHCHANDRA TIWARI Area-Worli Pipeline Andheri Mumbai State of Maharashtra Regn 3361 GOVT. OF INDIA

5 AUG 2010

the process for preparation of the dosage formulation as claimed in the impugned application is same as the process taught in Exhibit-2.

14. I have been informed that the Patent Application No. 726/MUMNP/2009 is divisional to Patent Application No. 339/MUMNP/2006, the grant of which is also under opposition. I am made to understand that the hearing in respect of 339/MUMNP/2006 is already concluded and during the hearing the applicant made reference to Biopharmaceutics Classification System (BCS) and it was argued that ritonavir falls under class IV and that no prior art discusses solid dispersion of class IV drugs. I say that as per BCS classification drugs are classified into four classes based on decreasing order of solubility and permeability; i.e., Class I drugs have High Solubility – High Permeability and Class IV drugs have Low Solubility – Low Permeability. I say that HIV protease inhibitor Nelfinavir mesylate is classified as a Class IV drug per BCS. I am aware of WO2002089835 (annexed herewith as Exhibit EA) that pertains to Class IV drug formulation. Interestingly Exhibit EA relates to solid unit oral pharmaceutical dosage form of amorphous nelfinavir mesylate. The process used is hot melt granulation. The formulation comprises nonionic block polymer of ethylene oxide and propylene oxide (as surfactant and a water soluble polymer) having melting point about 45°C and HLB of 18-29 at 25 °C. I say that pharmaceutical formulation embodiments of Exhibit- EA are illustrated by example-II through example-X with crospovidone and Poloxamer. Also the formulations of the aforesaid examples may be prepared by hot melt extrusion, fluid bed process or equipped with or without rotor processor, and jacketed centrifugal granulator or spheronizer (column 5, lines 15-18). Exhibit EA on page 2, lines 25-27 states that solid dispersion of homogenous melt mixture results from cooling the mixture followed by solidification and that inclusion of the surfactant is to enhance solubilization of the highly insoluble drug. I further say that claim 19 of the impugned patent application claims a process comprising preparing a homogenous melt of HIV protease inhibitor, water soluble polymer and surfactant, followed by solidification of the melt. I say the solid dispersion is indeed taught in Exhibit EA. The general process followed by Exhibit EA is melting the blend and processing the melt to form solid unit oral dosage form of the drug. Use of excipients such as stabilizers, wetting agent, binders, disintegrant, solubilizers is taught on page 6 line

NOTARY RAMESHCHANDRA TIWARI Area-Market Complex Andheri Mumbai State of Maharashtra Regn. 3351 GOVT. OF INDIA

5 AUG 2010

20-23 of Exhibit EA. It also refers to use of povidone, polyethylene glycol, polyoxyethylene sorbitan fatty acid esters as additives. Given that impugned patent application claims solid pharmaceutical dosage form comprising solid dispersion of HIV protease inhibitor of BCS Class IV, water soluble polymer and surfactant, I say that basic principles are found in teachings of Exhibit EA. I say that choosing a water soluble polymer and / or a surfactant is part of standardization a formulator is bound to go through. I further say that Class IV drugs of BCS may be difficult to formulate, but such formulations have been well described in prior art. I say that Exhibit EA indeed teaches a solid dispersion of a class IV compound with satisfactory dissolution and bioavailability with solubilization enhancement brought *about by inclusion of a surfactant.*

15. I am further aware of an article entitled "Physicochemical considerations in the preparation of amorphous ritonavir-PEG 8000 solid dispersions"; published in Journal of Pharmaceutical Sciences, 2001, Vol. 90, Issue 8, pg 1015-1025 (annexed herewith as Exhibit EB). Exhibit EB relates to solid dispersions of Ritonavir with PEG as the water-soluble polymer having improved dissolution profile and long-term stability. It also mentions that PVP and PEG are commonly used polymers when attempting to prepare a dispersion of an amorphous drug in hydrophilic polymer (page 1016, column 1, 1st paragraph). Further, Exhibit EB mentions that the ability of PVP to stabilize amorphous phase has been well documented. In my opinion therefore the class IV category of the product under challenge does not show any unexpected or unpredictable advantages vis-à-vis bioavailability and physical stability.

16. I further say that surface active agents at low concentrations, adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial tension. *Surface active agents have a characteristic structure, possessing both polar* (hydrophilic) and nonpolar (hydrophobic) regions in the same molecule which makes them amphiphilic in nature. Because of their unique functional properties, surfactants find a wide range of uses in pharmaceutical preparations which include improving the solubility or stability of the drug in a liquid preparation, stabilizing and modifying the texture of a semisolid preparation, etc. Surfactants enhance

NOTARY RAMESHCHANDRA TIWARI Area-Mazgaon Dist-Mumbai State of Maharashtra Regn. 3361 GOVT. OF INDIA

5 AUG 2010

solubilization of the active thereby improving efficacy of the product. It is well known to a person skilled in the field of pharmaceutical formulations that use of surfactants can alter the thermodynamic activity, solubility, diffusion, disintegration and dissolution rate of the drug and each of these parameters in turn influence the rate and extent of drug absorption which is directly proportional to pharmacological response.

17. I am aware of an article entitled "Solid Dispersion of poorly water soluble drugs: Early promises, subsequent problems and recent breakthroughs" by Abu T. M. Serajuddin published in Journal of Pharmaceutical Sciences Vol. 88, No.10 October 1999 (annexed herewith as Exhibit EC). Exhibit EC elaborates on the development of process of solid dispersion for poorly water soluble drugs in order to enhance the bioavailability of the dosage form and its advantages and disadvantages. It suggests that use surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs (page 5, column 2). It also suggests that the use of surface-active carrier in solid dispersion for increasing the dissolution of drugs. It specifically states that the bioavailability of ritonavir (Norvir, Abbott), a poorly soluble HIV protease inhibitor, was enhanced by formulation as a solid dispersion in a mixture of such surface-active carriers as Gelucire 50/13, polysorbate 80, polyoxyl 35 castor oil.

18. I say that surfactants are more often employed in pharmaceutical formulation as solubility enhancing agents for active ingredients with low aqueous solubility. The increased solubilization of active ingredient results in enhanced absorption of the drug in digestive tract thereby increasing the bioavailability of drug. Thus addition of surfactant to formulate active ingredient of low solubility in a solid dispersion prepared by hot melt extrusion technique is generally known per se. I say that the preparation of solid dispersions by melt or solvent method is an alternative way to enhance the solubility of a sparingly or poorly water soluble drug. I say that extent of experiments and research in the field of melt extrusion technique employing polymers, surfactants and additives to prepare solid dispersions in order to enhance the drug dissolution rate of poorly soluble drugs is very vast and exhaustive and thereby provides enough knowledge to a formulator to design a

NOTARY RAMESHCHANDRA TIWARI Area-Mazgaon Mumbai Andheri Maharashtra State of Maharashtra Regn. 3361 GOVT. OF INDIA

5 AUG 2010

formulation on the said principles. The chosen combination of polymers, surfactants and additives can contribute to a more desirable dissolution rate profile and the potential of a development of a superior dosage form.

19. It is therefore evident that the pharmaceutical formulation comprising active ingredient, water soluble binder and/or polymer, lipid component and/or surfactant, excipient formulated by homogenous melt extrusion process was well known in prior art and with reasonable expectation a person skilled in the art would try the prior art.

20. The pharmaceutical formulation claimed in the subject application in my opinion is a result of a combination of routine work, optimization and experimentation, which is a part of any formulation lab. For a given product one has to try different options so as to come out with the best formulation and such trials are very routine in nature and does not really require any inventive contribution nor involve any technical advancement. Thus the subject-matter claimed in the Patent Application No. 726/MUMNP/2009 is obvious having regard to the literature discussed about coupled with the general state of art.

21. The statements made in 1-20 herein are true to my knowledge.

Declared at Mumbai this 4th day of August 2010,

Dr. (Mrs.) M. S. Nagarsenker

Identified by me.

04/08/2010.

ASHOK KUMAR TIWARI
ADVOCATE HIGH COURT, MUMBAI

NOTARY
RAMESHCHANDRA TIWARI
Area-Marol Pipeline
Andheri Mumbai
State of Maharashtra
Regn 3361
29
GOVT. OF INDIA

04/08/10

RAMESH CHANDRA TIWARI
ADVOCATE & NOTARY
GOVT. OF INDIA
Res. 129, A-Wing, Appli Ekta Hsg. Soc.
Nav Pada, Marol Naka, A. K. Road,
Andheri (E), Mumbai-400 059.
Mob. 9820846083

5 AUG 2010

EXHIBIT. EA

249

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 November 2002 (14.11.2002)

PCT

(10) International Publication Number
WO 02/089835 A2

(51) International Patent Classification[7]: A61K 38/55, 9/20, A61P 31/12, 31/18

(21) International Application Number: PCT/EP02/04711

(22) International Filing Date: 29 April 2002 (29.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/288,410 3 May 2001 (03.05.2001) US

(71) Applicant: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; 124 Grenzacharstrasse, CH-4070 Basel (CH).

(72) Inventors: **INFELD, Martin, Howard**; 6 Tuers Place, Upper Montclair, NJ 07043 (US). **PHUAPRADIT, Wantanee**; 42 Robinson Terrace, Clifton, NJ 07013 (US). **SHAH, Navnit, Hargovindas**; 203 Beverly Hill Road, Clifton, NJ 07012 (US). **ZHANG, Lin**; 900 Davidson Road, Apartment 56, Piscataway, NJ 08854 (US).

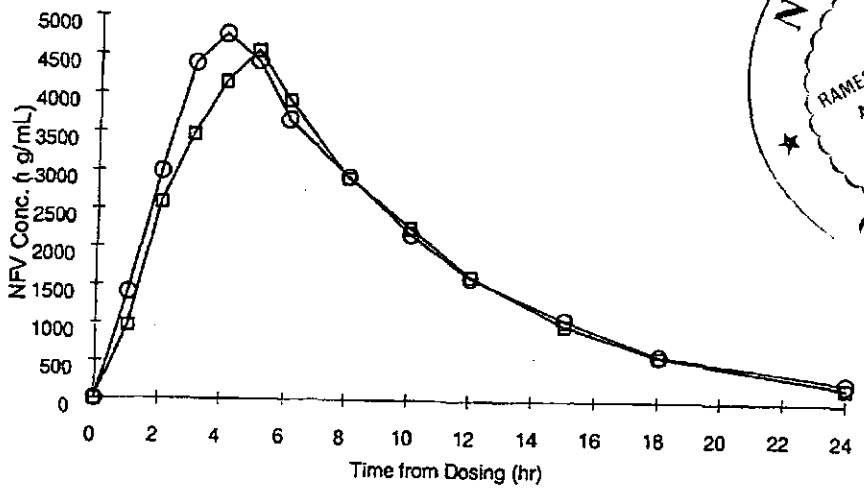
(74) Agent: **RAUBER, Beat**; 124 Grenzacherstrasse, CH-4070 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, 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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: PHARMACEUTICAL DOSAGE FORM OF AMORPHOUS NELFINAVIR MESYLATE



(57) Abstract: A solid unit oral pharmaceutical dosage form of amorphous nelfinavir mesylate is provided comprising amorphous nelfinavir mesylate, and a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, said copolymer having a melting point of at least 40°C. A hot melt granulation process for making the dosage form is provided.

WO 02/089835 A2

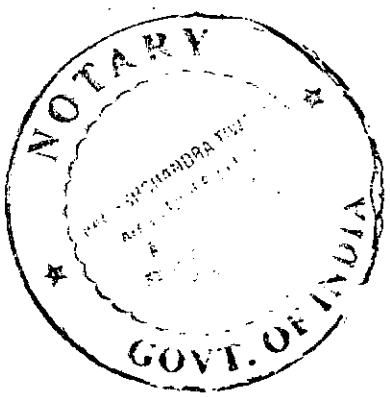
MSD

5 AUG 2010

250

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



Pharmaceutical Dosage Form of Amorphous Nelfinavir Mesylate

Nelfinavir mesylate is one of several protease inhibitors used to limit viral replication and improve immune function in HIV-infected individuals. Information regarding nelfinavir mesylate is reported in "Viracept (Nelfinavir Mesylate, AG1343): A Potent, Orally Bioavailable Inhibitor of HIV-1 Protease", Kaldor et al., J. Med. Chem., 40, 3979-85 (1997), and its use in the treatment of HIV is reported in "Nelfinavir: An Update on its Use in HIV Infection", Bardsley-Elliot et al., Drugs, 59(3), 581-620 (2000).

Nelfinavir mesylate is a white to off-white amorphous powder that is slightly soluble in water at pH less than or equal to 4. Nelfinavir mesylate has a molecular weight of 663.90 (567.79 as the free base).

Nelfinavir mesylate is commercially available as a 250 mg tablet (as nelfinavir free base). It is sold under the name Viracept® by Agouron Pharmaceuticals, Inc., a Pfizer company. Viracept® tablets are known to additionally contain calcium silicate, crospovidone, magnesium stearate, FD&C blue #2 powder, hydroxypropyl methylcellulose and triacetin. U.S. Patent No. 6,001,851 to Albizati et al., assigned to Agouron Pharmaceuticals, Inc., reports a tablet composition (formulation 9) containing 292 mg of an HIV inhibitor which can be nelfinavir mesylate. The patent does not specify the market formulation, Viracept®, although the reported composition contains calcium silicate, crospovidone and magnesium stearate. Calcium silicate and crospovidone each constitute 25% of the composition reported in the patent.

For adult patients, the recommended oral dosage of nelfinavir mesylate (calculated as nelfinavir free base) is 750 mg (3 x 250 mg tablets) 3 times daily or an alternative regimen of 1250 mg (5 x 250 mg tablets) twice daily. Whether a two- or three-times per day dosage program is followed, the tablet burden remains significant over the course of a day. Patient compliance is therefore a real concern.

Block copolymers of ethylene oxide and propylene oxide that are listed as poloxamers in the NF Monograph "Poloxamer" are available in a wide range of molecular weights and melting points. They are marketed under the name Lutrol® or Pluronic® by BASF Corporation. Poloxamers have been extensively used as pharmaceutical wetting and solubilizing agents, typically in small amounts.

It has also been noted that poloxamers can be used in pharmaceutical formulations to enhance the bioavailability of a drug. U.S. Patent No. 5,834,472 to Sangekar et al., for example, reports that including a non-ionic surfactant that is a block copolymer of ethylene oxide and propylene oxide in a composition of an antifungal compound having extremely low water solubility can enhance the bioavailability of the compound. U.S. Patent No. 5,281,420 to Kelm et al. addresses formulation of the drug tebufelone, an anti-inflammatory, analgesic and/or antipyretic agent that is essentially water-insoluble. Absorption of tebufelone is quite low from the gastrointestinal tract. Kelm et al. report a solid dispersion of tebufelone, produced by melting together poloxamer and tebufelone (melting point of 70°C) to form a homogeneous melt mixture. Solid dispersions of the homogeneous melt mixture result from cooling the mixture and allowing it to solidify. The poloxamer surfactant is included to provide the necessary solubilization of the highly insoluble drug in forming the melt mixture.

A high dosage strength solid unit oral dosage form, e.g., a tablet, of nelfinavir mesylate having satisfactory dissolution and bioavailability has apparently not been successfully developed prior to the present invention. This may be due in part to the hydrophobic nature of the drug, which accounts for its low aqueous solubility. In addition, nelfinavir mesylate in high dose solid unit dosage forms gels upon exposure to physiological fluid. The gel retards dissolution and bioavailability of the drug. The problem of gelling worsens with increased drug loading.

SUMMARY OF THE INVENTION

The present invention provides a solid unit oral pharmaceutical dosage form of amorphous nelfinavir mesylate comprising amorphous nelfinavir mesylate and a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, the copolymer having a melting point of at least 40°C. The high dose nelfinavir mesylate pharmaceutical dosage form of the invention exhibits satisfactory dissolution and bioavailability.

The present invention also provides a process for preparing a solid unit oral pharmaceutical dosage form of amorphous nelfinavir mesylate, comprising: (a) heating a blend of amorphous nelfinavir mesylate and a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, the copolymer having a melting point of at least 40°C at a temperature of from the melting point temperature of the copolymer to below the decomposition temperature of nelfinavir mesylate, (b) mixing the blend to form a melt granulation, and (c) processing the melt granulation into the solid unit oral dosage form of amorphous nelfinavir mesylate.

MSD

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 presents dissolution profiles of 625 mg tablets of nelfinavir mesylate (Examples II and III) compared to that of the 250 mg market (tablet) formulation (Example I).

Figure 2 presents dissolution profiles of 625 mg nelfinavir mesylate tablets in accordance with the invention (Examples IV and V) compared to other 625 mg nelfinavir mesylate tablets (Examples II and III).

Figure 3 shows the effect of Poloxamer 188 concentration on the dissolution profiles of 625 mg tablets of nelfinavir mesylate (Examples VI, VII, VIII and IX).

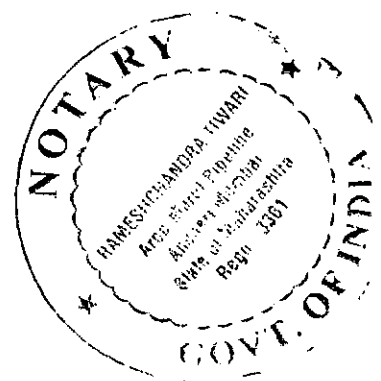
Figure 4 shows mean plasma concentration versus time profiles after administration of 2 x 625 mg nelfinavir mesylate tablets of the invention (Example IV) compared to administration of 5 x 250 mg tablets of the market formulation (Example I).

DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that when amorphous nelfinavir mesylate is melt granulated with a pharmaceutically acceptable, water-soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide in accordance with the invention, a significant improvement in the dissolution rate of the drug is shown with resulting satisfactory bioavailability. The nelfinavir mesylate used for the solid unit dosage form of the invention is amorphous. Dosage amounts are calculated as nelfinavir free base, unless specified otherwise. The pharmaceutical dosage form of the invention is a high per unit dosage of the nelfinavir mesylate as compared to the 250 mg market formulation, and is amenable to oral administration. For patient compliance and acceptability, the maximum weight of a

solid unit oral pharmaceutical dosage form is typically from 1.0 g to 1.5 g. The present invention encompasses solid unit oral dosage forms having the nelfinavir mesylate in a dose from 400 mg, the dose at which the gelling potential of the nelfinavir mesylate begins to be problematic when formulated using conventional pharmaceutical excipients and processes, to 700 mg. The dosage form comprises nelfinavir mesylate in an amount of from 400 mg to 700 mg, preferably from 500mg to 700 mg. A preferable dosage amount is, for example, 625 mg.

The pharmaceutically acceptable, water-soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide in accordance with the present invention as a rule has a molecular weight of from 6,000 D to 18,000 D, preferably from 6800 D to 17500 D and a melting point of preferably 40°C to 60°C, more preferably from 49°C to 57°C. The hydrophil/lipophil balance ("HLB") value at 25°C expediently is at least 14, preferably 14 to 29, more preferably 22 to 29. The copolymer is readily water soluble. Typically, the copolymer of the present invention has an ethylene oxide content (percentage of oxyethylene-groups) of at least 70% by weight, preferably 70% to 85% by weight. Suitable pharmaceutically acceptable water-soluble, non-ionic synthetic block copolymers of ethylene oxide and propylene oxide are listed in the NF Monograph "Poloxamer". Preferred copolymers in accordance with the invention include Lutrol® or Pluronic® F68, F87, F108 and F127 (BASF Corporation). Very good results have been achieved with Pluronic® F68. The coplymers have the following characteristics:



Lutrol®	Poloxamer, NF	% Weight Oxyethylene	Molecular Weight (D)	Melting Point (°C)	HLB Value at 25°C
F68	188	81.8 ± 1.9	7680-9510	52	29
F87	237	72.4 ± 1.9	6840-8830	49	24
F108	338	83.1± 1.7	12700-17400	57	27
F127	407	73.2± 1.7	9840-14600	56	22

The pharmaceutical dosage form of the invention expediently contains the block copolymer in an amount of from 40% to 65% by weight of the nelfinavir mesylate, preferably from 45% to 60%, and more preferably from 50% to 55% by weight of the nelfinavir mesylate.

The nelfinavir mesylate dosage form of the present invention is advantageously produced by a hot melt granulation process. The hot melt granulation process of the present invention comprises blending the nelfinavir mesylate and the copolymer, and heating the blend to a temperature of from the copolymer melting point temperature to below the decomposition temperature of nelfinavir mesylate. The hot melt granulation process results in a melt granulation which comprises granules of the drug embedded in the copolymer. The heated blend is mixed until such melt granules are obtained. Preferably, the blend is heated to a temperature at which the nelfinavir mesylate remains in solid form in the nelfinavir mesylate-copolymer mixture. A jacketed mixer or a hot melt extruder can be used to prepare a melt granulation.

One or more excipients can be included in the mixture of nelfinavir mesylate and copolymer. The excipient can be selected from the group of stabilizers, wetting agents, binders, disintegrants, diluents and solubilizers. Examples of additives for inclusion in the nelfinavir mesylate-copolymer mixture are povidone, polyethylene glycol, and polyoxyethylene sorbitan esters of C_8-C_{18} fatty acids, (e.g., Tween® 20, Tween® 60, and Tween® 80), etc. The heated blend is mixed

and melt granules are formed, thus resulting in a melt granulation that includes one or more pharmaceutically acceptable excipients. The melt granulation can then be milled and mixed with one or more pharmaceutical excipients. The excipient added to the milled granulation can be selected from the group of lubricants, disintegrants and diluents. The pharmaceutical excipient may be, for example, microcrystalline cellulose, corn starch, magnesium stearate, etc.

The hot melt granulation process of the present invention comprises hot melt granulating the nelfinavir with a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, the copolymer having a melting point of at least 40°C , at a temperature of from the melting point temperature of the copolymer to below the decomposition temperature of nelfinavir mesylate. Preferably, the temperature is from 50ºC to 85ºC, with the proviso that the temperature be at least at the melting point temperature of the copolymer. The melt granulation, prepared with or without any additional pharmaceutical excipients, is then processed into a solid unit oral dosage form.

For preparing tablets, the melt granulation can be processed into a solid unit oral dosage form by milling, lubricating, compressing (tabletting), and, typically, aqueous film coating.

In an embodiment of the present invention, tablets are prepared as follows:

a) blend amorphous nelfinavir mesylate in an amount of from 400 mg to 700 mg (calculated as free base) per unit dosage with the copolymer of the invention in an amount from 40% to 65% by weight of the nelfinavir mesylate;

b) mix the powder blend from step (a) in a jacketed high shear granulator at 60°±10°C with the proviso that the temperature be at least at

the melting point temperature of the copolymer, or in a jacketed hot melt extruder at 80°±5°C, until melt granules are obtained;

cool the melt granulation to room temperature;

c) mill the granulation from step (b) into a fine powder;

d) blend the milled granulation from step (c) with other suitable tablet diluents, such as corn starch and microcrystalline cellulose;

e) lubricate the granulation from step (d) with a suitable lubricant, such as magnesium stearate;

f) compress the final blend from step (e) on a tablet press;

g) aqueous film coat the tablet from step (f).

A pharmaceutical dosage form of the invention, can alternatively be prepared by hot melt extrusion. Hot melt extrusion can be used to make molded tablets.

The solid oral unit dosage form can be a tablet, capsule or caplet. The pharmaceutical composition can include one or more pharmaceutically acceptable excipients selected from the group of stabilizers, wetting agents, binders, disintegrants, diluents, solubilizers and lubricants. For example, the excipient can be microcrystalline cellulose, corn starch, magnesium stearate, povidone, polyethylene glycol, and polyoxyethylene sorbitan esters of C_8-C_{18} fatty acids (e.g., Tween® 20, Tween® 60 and Tween® 80), etc.

EXAMPLES

Example I: 250 mg Nelfinavir Mesylate Tablet (Market Formulation)

Commercial Viracept® tablets were used in the present Example.

Example II: 625 mg Nelfinavir Mesylate Tablet

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Crospovidone	240.000
Calcium Silicate	217.375
Purified Water	q.s.**
Magnesium Stearate	12.000
Tablet Weight	1200.000

* Equivalent to 625 mg of Nelfinavir free base
** Removed during processing

The tablet formulation of Example II was produced by a conventional aqueous wet granulation process.

Example III: 625 mg Nelfinavir Mesylate Tablet

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Crospovidone	100.000
Dibasic Calcium Phosphate, Anhydrous	169.375
Purified Water	q.s.**
Magnesium Stearate	10.000
Tablet Weight	1010.000

* Equivalent to 625 mg of Nelfinavir free base
** Removed during processing

260

The tablet formulation of Example III was produced by a conventional aqueous-wet granulation process.

Example IV: 625 mg Nelfinavir Mesylate Tablet of the Invention

Composition	mg/tablet
Kernel:	
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	394.375**
Corn Starch	60.000
Magnesium Stearate	7.000
Kernel Weight	1192.000
Film Coat:	
HPMC 2910 – 6 cps	7.341
Pharmacoat 603	10.500
Talcum	5.969
Titanium Dioxide	5.682
Red Iron Oxide	0.048
Yellow Iron Oxide	0.048
Aquacoat ECD-30	5.987***
Triacetin	2.425
Purified Water	138.030****
Total Weight	1230.000

* Equivalent to 625 mg of Nelfinavir free base
** Approximately 54% w/w of Nelfinavir Mesylate
*** Based on dry basis-solids content of a 30% suspension
**** Removed during processing; this amount of water does not include the amount of water present in Aquacoat ECD-30

The tablet formulation of Example IV was produced using a hot melt granulation process, as follows:

Step 1) Nelfinavir mesylate and Lutrol® F68 were mixed in a jacketed high shear granulator with a temperature setting at 25°±5°C for 5 minutes using impeller at low speed and chopper at low speed.

Step 2) The jacketed temperature was raised to 60°±10°C with the proviso that the temperature was at least at the melting point temperature of the Lutrol® F68, while mixing of the powder blend (step 1) in the high shear granulator was continued using impeller at low speed and chopper at low speed until a suitable granulation was obtained, at which time the impeller and chopper were turned off.

Step 3) The heat to the jacket was turned off. The product was cooled to room temperature by passing tap water (25°±5°C) into the jacketed vessel, with intermittent jogging of both impeller and chopper at low speed.

Step 4) The granulation from step 3 was passed through a mill.

Step 5) Approximately 50% of the milled granulation from Step 4 was placed into a twin shell blender. Corn starch and magnesium stearate (passed through a #30 mesh stainless steel screen) were added into the blender. The remainder of the milled granulation from step 4 was added to the blender and mixed for 8 minutes.

Step 6) The granulation from step 5 was compressed into a tablet containing nelfinavir mesylate, 625 mg (as free base).

Step 7) The coating suspension was prepared as follows: In a stainless steel container, triacetin and Aquacoat ECD-30 were dispersed in purified water using a propeller mixer, mixing for 45 minutes. HPMC 2910-6 cps, Pharmacoat 603, talcum, titanium dioxide, yellow iron oxide and red iron oxide were added and

slowly dispersed, while mixing gently to avoid air entrapment. Mixing was continued for another 60 minutes or until a uniform suspension was obtained.

Step 8) The kernels from step 6 were placed into a perforated coating pan. They were heated with warm inlet air of 50°±3°C with intermittent jogging until the outlet air temperature reached 38°±3°C.

Step 9) The inlet air temperature was increased to 60°±3°C. The kernels from step 8 were sprayed with the coating suspension from step 7, stirred continuously, using an air spray system and maintaining the outlet air temperature at 38°±3°C. The film coat, 38 mg per tablet, was applied (range 35-41 mg on a dry basis).

Step 10) The inlet air temperature was reduced to 40°±3°C and the coated tablets were dried by jogging until the loss on drying of the tablets at 90°C was less than 1.8%. The heat was turned off and the tablets were cooled to room temperature by occasional jogging.

Example V: 625 mg Nelfinavir Mesylate Tablet of the Invention

Composition	mg/tablet
Kernel:	
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	394.375**
Microcrystalline Cellulose	40.000
Corn Starch	20.000
Magnesium Stearate	7.000
Kernel Weight	1192.000
Film Coat:	
HPMC 2910 – 6 cps	13.140
Talcum	4.085
Titanium Dioxide	4.084

FD&C Blue #2	0.591
Aquacoat ECD-30	4.400***
Triacetin	1.700
Purified Water	117.290****
Total Weight	1220.000

* Equivalent to 625 mg of Nelfinavir free base
** Approximately 54% w/w of Nelfinavir Mesylate
*** Based on dry basis-solids content of a 30% suspension
**** Removed during processing; this amount of water does not include the amount of water present in Aquacoat ECD-30

The melt granulation method set forth in Example IV was used with the composition amounts set forth in the table above for the present example. *Differences in the tablet coating are reflected in the following steps numbered 7* and 9 that here replace steps 7 and 9 of Example IV.

The coating suspension was prepared as follows: In a stainless steel container, triacetin and Aquacoat ECD-30 were dispersed in purified water using a propeller mixer, mixing for 45 minutes. HPMC 2910-6 cps, talcum, titanium dioxide and FD&C Blue #2 were added and slowly dispersed, while mixing gently to avoid air entrapment. Mixing was continued for another 60 minutes or until a uniform suspension was obtained.

The inlet air temperature was increased to 60°±3°C. The kernels from step 8 were sprayed with the coating suspension from step 7, then stirred continuously, using an air spray system and maintaining the outlet air temperature at 38°±3°C. The film coat, 28 mg per tablet, was applied (range 25-31 mg on a dry basis).

Example VI: 625 mg Nelfinavir Mesylate Tablet

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	182.656**
Corn Starch	102.616
Magnesium Stearate	10.262
Tablet Weight	1026.159

* Equivalent to 625 mg of Nelfinavir free base
** Approximately 25% w/w of Nelfinavir Mesylate

The tablet formulation of Example VI was produced by hot melt granulation, as follows:

Nelfinavir mesylate and Lutrol® F68 were blended in a mixer for 10 minutes.

The powder mixture from step 1 was added to a jacketed hot melt extruder set at 80º±5ºC while thorough mixing was continued until a uniform melt mixture was obtained.

Steps 3 to 6 under Example IV were then followed as steps 3 to 6 of the present example.

Example VII: 625 mg Nelfinavir Mesylate Tablet

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	243.542**
Corn Starch	109.457
Magnesium Stearate	10.946
Tablet Weight	1094.570

* Equivalent to 625 mg of Nelfinavir free base

** Approximately 33% w/w of Nelfinavir Mesylate

The same hot melt granulation procedure was followed as described in Example VI.

Example VIII: 625 mg Nelfinavir Mesylate Tablet of the Invention

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	343.824**
Corn Starch	120.725
Magnesium Stearate	12.073
Tablet Weight	1207.247

* Equivalent to 625 mg of Nelfinavir free base

** Approximately 47% w/w of Nelfinavir Mesylate

The same hot melt granulation procedure was followed as described in Example VI.

Example IX: 625 mg Nelfinavir Mesylate Tablet of the Invention

Composition	mg/tablet
Nelfinavir Mesylate	*730.625**
Poloxamer 188 (Lutrol® F68)	443.215**
Corn Starch	131.892
Magnesium Stearate	13.189
Tablet Weight	1318.921

* Equivalent to 625 mg of Nelfinavir free base

** *Approximately 61% w/w of Nelfinavir Mesylate*

The same hot melt granulation procedure was followed as described in Example VI.

Example X: Dissolution Testing

Tablet formulations containing nelfinavir mesylate (Examples I-IX) were evaluated for dissolution in 900 mL of 0.1N hydrochloric acid solution equilibrated at 37°±0.5°C using a paddle method (USP Apparatus 2) at 50 rpm. Sample aliquots were taken at different time intervals and analyzed by UV spectrophotometry.

Figure 1 presents dissolution profiles of 625 mg tablet formulations of nelfinavir mesylate which do not contain the block copolymer of the present invention (Examples II and III) compared to that of the 250 mg market (tablet) formulation (Example I). The dissolution profiles of 625 mg nelfinavir mesylate tablets without block copolymer (Examples II and III) were significantly slower and less complete than that of the 250 mg market (tablet) formulation (Example I). The tablet formulations of Examples II and III contain conventional excipients and were produced by a conventional aqueous wet granulation process.

As shown in Figure 2, the results of the dissolution evaluation indicate that the dissolution profiles of 625 mg nelfinavir mesylate tablets in accordance with the invention (Examples IV and V) were significantly faster and essentially complete compared to the dissolution profiles of the 625 mg nelfinavir mesylate tablets which were prepared using conventional pharmaceutical excipients and a conventional aqueous wet granulation process (Examples II and III).

The dissolution profiles of tablets of Examples VI through IX are shown in Figure 3. The results indicate that the concentration of block copolymer plays a significant role with respect to the rate and completeness of dissolution of nelfinavir mesylate. Examples VI and VII contain Poloxamer 188 in an amount of 25% and 33% by weight of nelfinavir mesylate, respectively. Examples VIII and IX, which contain Poloxamer 188 in an amount of 47%, and 61% by weight of nelfinavir mesylate, respectively, show faster and more complete release.

Example XI: Pharmacokinetic Testing

Nelfinavir mesylate 250 mg tablets of the market formulation (Example I) and nelfinavir mesylate 625 mg tablets of the invention (Example IV) were evaluated for bioavailability in man. Each subject was administered a number of tablets of the given formulation totaling 1250 mg of nelfinavir mesylate (calculated as free base). In this study, 13 blood samples were drawn for each pharmacokinetic profile, i.e. at pre-dose, and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 24 hours after administration of the drug. Venous blood samples of approximately 5 ml were collected into heparinized tubes. Plasma was separated by centrifugation at 1500 g and 4°C for 10 minutes, within 60 minutes of drawing the blood. Plasma samples were subsequently stored at -20°C until analysis. Nelfinavir content in the plasma samples was determined by liquid chromatography – tandem mass spectrometry (LC-MS/MS). The limit of quantification was set to 4 ng/ml.

The plasma concentration versus time profiles were used for the estimation of pharmacokinetic parameters. Standard non-compartmental methods were applied using the software WinNonlin 3.1. The pre-dose sampling time of a profile was set to zero and the post-dose sampling times were used as actual times. The following parameters were estimated:

C_{max}, maximum observed plasma concentration

t_{max}, time of maximum observed plasma concentration

AUC_{0-24h}, calculated using WinNonlin computational rules for partial AUCs and the linear trapezoidal rule

AUC_{0-Inf}, calculated by $AUC_{last} + (C_{last})/k)$, where an assessment of k (terminal elimination rate constant) was feasible

$t_{1/2}$, terminal half-life, calculated by Ln (2) / k, where an assessment of k was feasible

The results of this bioavailability evaluation are given in Table I below.

Table I: Summary of pharmacokinetic parameters after administration of 1250 mg of nelfinavir mesylate (as free base)*: 2 x 625 mg tablets of the invention (Example IV) compared to 5 x 250 mg tablets of the market formulation (Example I)

Parameter (Unit)	Nelfinavir 1250 mg (based on the free base)	
	Example I	Example IV
	N = 12	N = 12
AUC_{0-24} (x 10^3 hr ng/mL)		
Median (Min - Max)	43.5 (21.1 - 89.7)	37.0 (27.5 - 73.2)
Mean	44.4	42.3
Geometric Mean	41.8	40.0
CV%	38.6	37.4
C_{max} (ng/mL)		
Median (Min - Max)	5275 (2520 - 9590)	4585 (3680 - 8450)
Mean	5248	5200
Geometric Mean	4971	5042
CV%	34.9	27.7
t_{max} (hr)		
Median (Min - Max)	4.0 (3.0 - 6.0)	4.0 (2.0 - 6.0)
Mean	4.1	4.0
CV%	26.5%	35.4%
AUC_{0-inf} (x 10^3 hr ng/mL)		
Median (Min - Max)	45.3 (21.7 - 98.2)	37.8 (28.5 - 77.7)
Mean	46.5	43.7
Geometric Mean	43.5	41.1
CV%	41.2%	39.7%
$t_{1/2}$ (hr)		
Median (Min - Max)	4.4 (3.3 - 6.8)	3.9 (3.0 - 5.7)
Mean	4.5	3.9
Harmonic Mean	4.3	3.8
CV%	24.9%	22.0%

*With food

The data reported in Table I and plotted in Figure 4 indicate that the bioavailability in man of 2 x 625 mg nelfinavir mesylate tablets of the invention (Example IV) was comparable to that of 5 x 250 mg tablets of the market formulation (Example I) when administered with food. The present invention advantageously provides high dosage solid unit oral pharmaceutical compositions of nelfinavir mesylate having satisfactory dissolution and bioavailability.

Claims

1. A solid unit oral pharmaceutical dosage form of amorphous nelfinavir mesylate comprising amorphous nelfinavir mesylate , and a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, said copolymer having a melting point of at least 40°C.

2. The dosage form according to claim 1, wherein said copolymer is present from 40% to 65% by weight of the nelfinavir mesylate.

3. The dosage form according to claims 1 or 2, wherein said copolymer has a melting point of 40°C to 60°C.

4. The dosage form according to claims 1 to 3, wherein said copolymer has a HLB value at 25°C of at least 14 .

5. The dosage form according to claim 4, wherein said copolymer has a HLB value at 25°C of 14 to 29 .

6. The dosage form according to claims 1 to 5, wherein said copolymer has an ethylene oxide content of at least 70 % by weight.

7. The dosage form according to claims 1 to 6, having a content of nelfinavir mesylate, calculated as nelfinavir base of 400 mg to 700 mg.

8. The dosage form according to claims 1 to 7, further comprising a pharmaceutically acceptable excipient selected from the group consisting of stabilizers, wetting agents, binders, disintegrants, diluents, solubilizers, and lubricants.

9. The dosage form according to claims 1 to 8, which is a tablet, a capsule or a caplet.

10. A process for making a solid unit oral pharmaceutical dosage form according to claims 1 to 9, comprising the steps of:

(a) heating a blend comprising amorphous nelfinavir mesylate and the pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, said copolymer having a melting point of at least 40°C, at a temperature of from the melting point temperature of the copolymer to below the decomposition temperature of nelfinavir mesylate,

(b) mixing the blend to form a melt granulation, and

(c) processing the melt granulation into said dosage form of amorphous nelfinavir mesylate.

11. Solid unit oral pharmaceutical dosage form according to claims 1 to 9 for use in therapy.

12. Solid unit oral pharmaceutical dosage form according to claim 10 for use in the treatment of HIV mediated diseases.

***

FIGURE 1

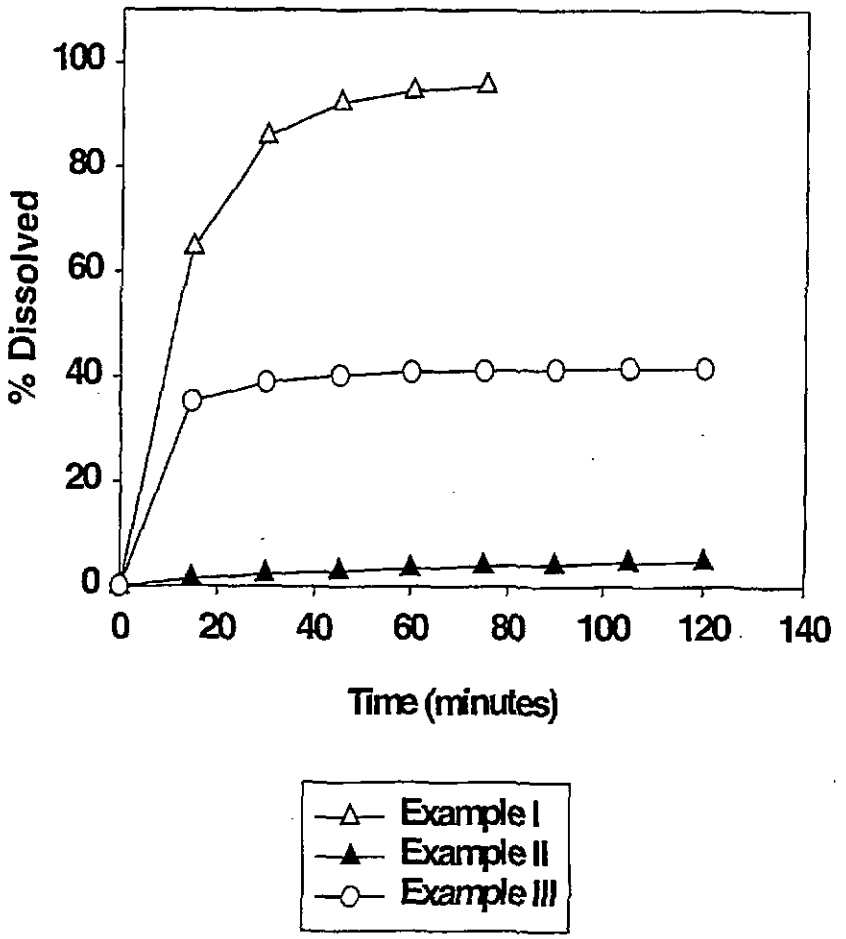

100
80
60
40
20
0
% Dissolved
0
20
40
60
80
100
120
140
Time (minutes)
Example I
Example II
Example III

FIGURE 2

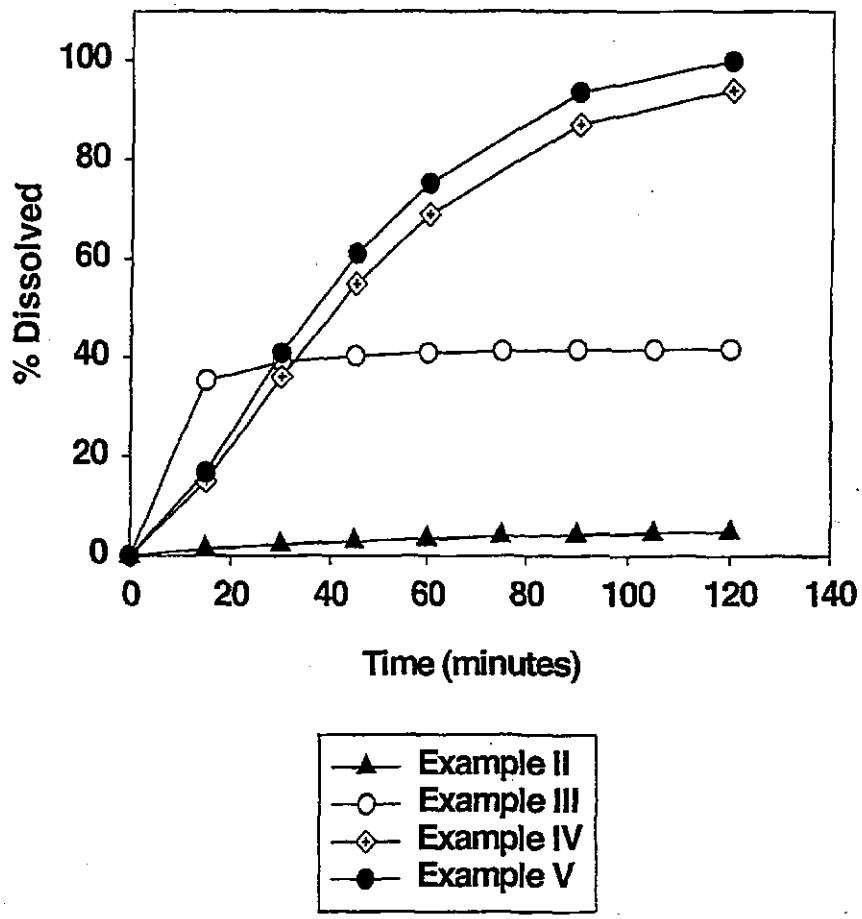


FIGURE 3

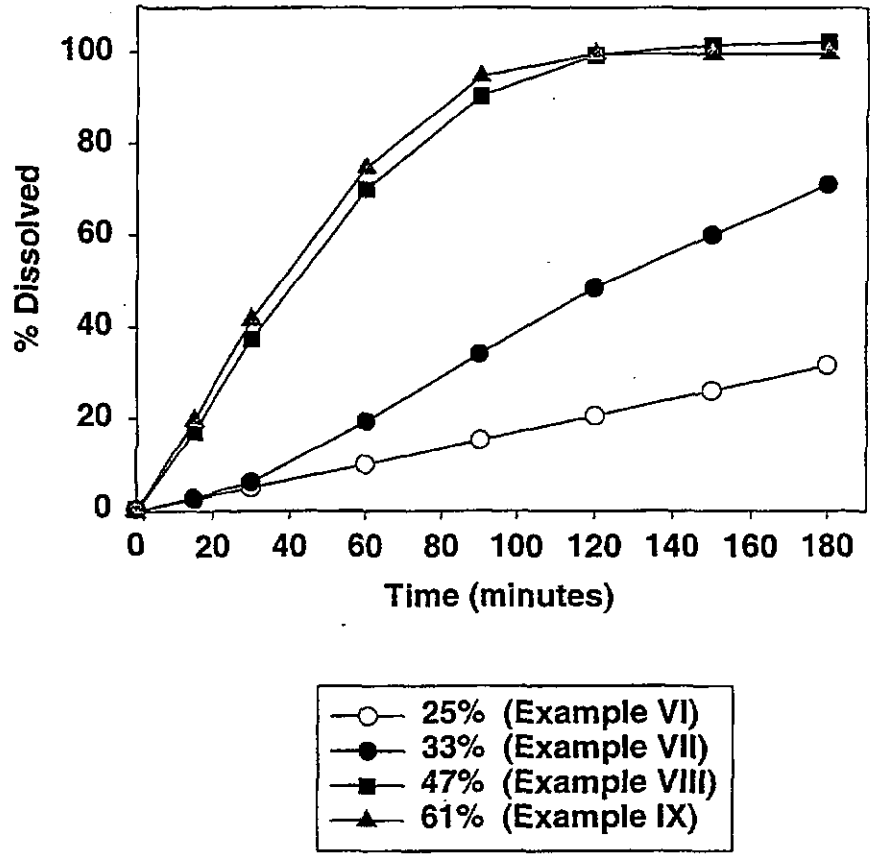
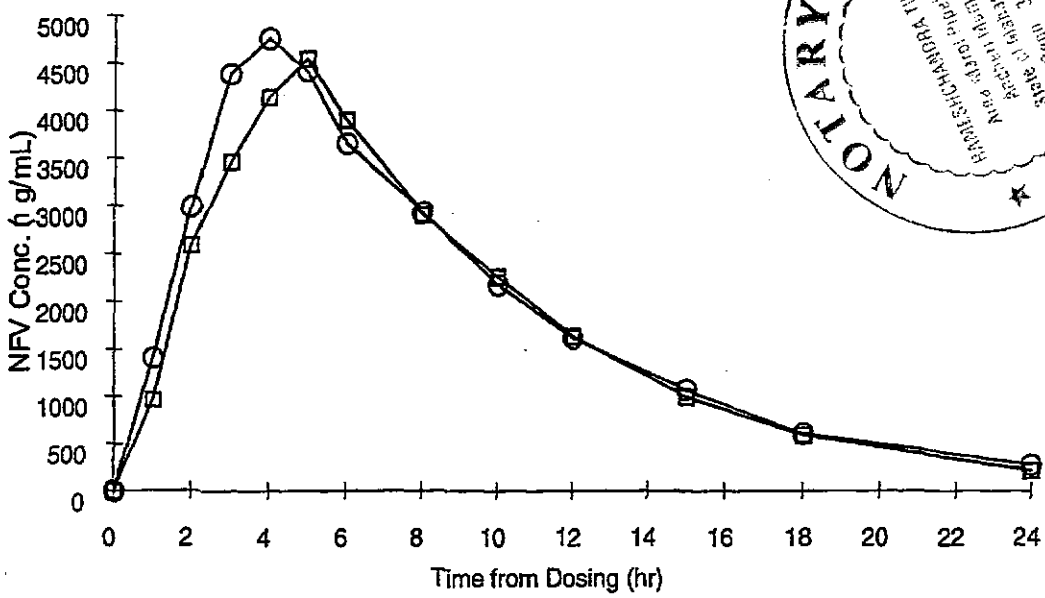


FIGURE 4



○ **Example I**

□ **Example IV**

EXHIBIT. EB

Physicochemical Considerations in the Preparation of Amorphous Ritonavir–Poly(ethylene glycol) 8000 Solid Dispersions

DEVALINA LAW,[1] STEVEN L. KRILL,[2] ERIC A. SCHMITT,[1] JAMES J. FORT,[3] YIHONG QIU,[1] WEILI WANG,[1] WILLIAM R. PORTER[1]

[1]Pharmaceutical and Analytical Research and Development, Pharmaceutical Products Division, Abbott Laboratories, D4P3, AP9, 100 Abbott Park Road, Abbott Park, Illinois 60064

[2]Novartis Pharmaceutical Corporation, East Hanover, New Jersey 07936

[3]Pharmaceutical Research and Development, Whitehall-Robins Healthcare, Richmond, Virginia 23261

Received 18 July 2000; revised 8 November 2000; accepted 13 December 2000

ABSTRACT: A systematic study of the properties of ritonavir and the influence of polyethylene glycol 8000 (PEG) on ritonavir revealed that amorphous ritonavir dispersions in PEG would have an improved dissolution profile and could exhibit long-term stability. Ritonavir, a human immunodeficiency virus (HIV) protease inhibitor, is highly lipophilic [distribution coefficient ($\log D$)= 4.3, 25°C, pH 6.8], poorly water soluble (400 μg/mL in 0.1 N HCl, 1 μg/mL at pH 6.8, 37°C), and exhibits an exceedingly slow dissolution rate (*0.03 mg/cm²-min in 0.1 N HCl at 37°C*). These properties indicated that a solid dispersion containing ritonavir might be useful for overcoming problems associated with slow dissolution. In addition, ritonavir is a good glass former [glass-transition temperature (T_g)/melting point (T_m) > 0.7]. Amorphous ritonavir has an apparent solubility of 4 mg/mL in *0.1 N HCl at 37°C* and shows reasonable stability at 25°C. Amorphous ritonavir, therefore, has properties desirable for preparing a solid dispersion containing this phase. Since PEG, a commonly used polymer, improved the aqueous solubility of crystalline ritonavir, it was expected to have a positive influence on the dissolution rate of ritonavir. Moreover, PEG was found to have negligible plasticizing effect on amorphous ritonavir, which was beneficial for the stability of the dispersion. Finally, solid dispersions of amorphous ritonavir in PEG were prepared, and these dispersions had improved *in vitro* dissolution rate and were physically stable for > 1.5 years at 25°C when protected from moisture. The performance of this solid dispersion has been attributed to the physicochemical properties of amorphous ritonavir. © 2001 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 90:1015–1025, 2001

Keywords: solid dispersion; ritonavir; PEG; amorphous; physical stability

INTRODUCTION

Ritonavir, (5*S*-(5*R**,8*R**,10*R**,11*R**))10-hydroxy-2-methyl- 5-(1-methylethyl)-1-(2-(1-methylethyl)-4-thiazolyl)-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, is a human immunodeficiency virus (HIV) protease inhibitor indicated for the treatment of autoimmune deficiency syndrome (AIDS). Ritanovir is practically insoluble in water[1] and could potentially exhibit dissolution rate limited absorption.

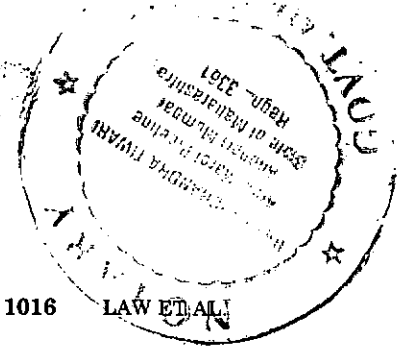
There have been numerous publications citing dissolution rate improvement of poorly soluble drugs through the production of solid dispersions.[2,3] Since the 1960s, there have been >400 publications investigating various aspects of solid dispersions, however, there are very few marketed products utilizing this technology. This poor success rate has often been attributed to processing difficulties or to physical instability.[4] When

Correspondence to: D. Law (Telephone: 847-937-7231; Fax: 847-938-4434; E-mail: devalina.law@abbott.com)

Journal of Pharmaceutical Sciences, Vol. 90, 1015–1025 (2001)

MSD

5 AUG 2010



attempting to prepare a dispersion of an amorphous drug in a hydrophilic polymer, poly(vinylpyrrolidone) (PVP) and poly(ethylene glycol) (PEG) are most commonly used.[5–7] The PVP polymers are more difficult to process, but their ability to stabilize the amorphous phase has been well documented.[8] On the other hand PEG polymers are easier to process, but amorphous drugs are often unstable in this polymer.[3,9,10] There are very few examples of PEG–amorphous drug solid dispersion systems,[11,12] and long-term stability data on these systems have not been reported.

In this study, the physicochemical properties of ritonavir were investigated to assess the feasibility of amorphous solid dispersion in PEG. Then, the dispersions were prepared and characterized to test the validity of the assessment.

EXPERIMENTAL SECTION

Materials

Ritonavir was manufactured by the Speciality Products Division of Abbott Laboratories. PEG 8000 (Carbowax, Union Carbide, Danbury, CT), absolute ethanol (McCormick Distilling Company, Weston, MO), and purified and deionized water (Millipore, Bedford, MA) were utilized in this study. All HPLC solvents were HPLC grade and all other chemicals were of analytical reagent grade.

High-Performance Liquid Chromatography (HPLC)

The HPLC system was comprised of a ternary pump (SP 8800-010, Spectra-Physics, San Jose, CA), an autosampler (AS4000, Hitachi Instruments, Danbury, CT), a programmable ultraviolet (UV) detector (783A, Applied Biosystems, Foster City, CA), a data acquisition system (PeakPro version 8.3.1, Beckman Instruments, Fullerton, CA), and a 3 μm, 4.6 × 500 mm column (Little Champ II, Regis, Morton Grove, IL). The mobile phase was 0.1% trifluoroacetic acid, 10 mM tetramethylammonium perchlorate (TMAP)/acetonitrile/methanol (55:40:5) pumped at a flow rate of 1 mL/min, and the effluent was monitored at 205 nm.

Ionization Constant (pK_a)

The pK_a values were determined spectrophotometrically in methanol/buffer solutions with linear extrapolation to aqueous pH values. The buffer solution was comprised of 0.05 M ε-amino-*n*-caproic acid and 0.05 M phosphoric acid, adjusted to the appropriate pH, with hydrochloric acid or potassium hydroxide, and to 0.15 M ionic strength (μ) with potassium chloride. Details of the method have been previously reported.[13]

Distribution Coefficient (Log *D*)

The *n*-octanol–pH 6.8 buffer (0.05 M phosphate, $\mu = 0.15$ adjusted with NaCl) distribution coefficient was determined by a shake flask method at 25°C. The phosphate buffer was equilibrated with *n*-octanol. The two phases were separated, and ritonavir (~2 mg/mL) was dissolved in the organic phase. To 1 mL of this solution, 2 mL of buffer was added, and the two phases were equilibrated overnight with mild agitation in a water bath maintained at 25°C. The two phases were physically separated, and both the buffer and the *n*-octanol phases were analyzed by HPLC.

Intrinsic Dissolution Studies (IDR)

Ritonavir (~65 mg) was compressed at 1000 lbf in a hydraulic press (model C, Carver Laboratory Press, Menomonee Falls, WI) using a 30-ls dwell time. The method and the apparatus have been described previously.[14] The dissolution studies were performed in 0.1 N HCl maintained at 37°C. Samples were withdrawn at predetermined intervals, replaced with dissolution medium, and analyzed by HPLC.

Preparation of Amorphous Ritonavir

Amorphous ritonavir was prepared by heating the drug to 135°C in an oil bath, followed by rapid cooling using liquid nitrogen or cold water. The resulting sample was amorphous as determined by powder X-ray diffraction, and HPLC analysis confirmed that no degradation had occurred during the procedure.

Solid Dispersion Preparation

Two types of dispersions were prepared: PEG in ritonavir and ritonavir in PEG. Dispersions of 5–25% PEG in ritonavir were prepared by rapidly evaporating ethanolic solutions of ritonavir and PEG, and the glass transition temperatures (T_gs) were measured to investigate the miscibility of PEG in ritonavir.

Solid dispersions containing 10, 20, and 30% ritonavir in PEG were prepared by the solvent *evaporation–fusion technique.*[15] An ethanolic solution of ritonavir (~0.13 mg/mL) in a round-bottomed flask was warmed in a water bath (75°C) until a clear solution was obtained. The required amount of PEG was then added, and the mixture was warmed for 30 s in the water bath and vigorously mixed. The flask containing the drug–polymer–solution was then attached to a rotary evaporator (Model R114, Buchi, Switzerland). Ethanol was removed under vacuum at 75°C. After 15 min, the hot-water bath was replaced with an ice-water bath to congeal the mixture. After another 15 min, the ice-water bath was removed but the vacuum was maintained for 6 h. The resulting white solid was removed from the round-bottomed flask, transferred to a crystallization dish, and placed in a vacuum oven at room temperature for ~10 h to remove any residual ethanol. The dispersions were then ground with a mortar and pestle and sifted. Particles between 149 and 420 μm were used for further studies. Placebo solid dispersion was prepared by the same method.

Powder X-ray Diffraction (PXRD)

The diffractometer (XDS 2000, Scintag, Sunnyvale, CA) consisted of a 4 kW generator (voltage 45 kV and current 40 mA) with a Cu anode tube. A liquid-nitrogen-cooled Ge detector (GLP-10195/07-S, EG&G ORTEC, Oak Ridge, TN) and data analyzer (DMSNT Data Analysis version 1.27, Scintag) were used. The samples were placed on a quartz plate and scanned at a rate of 10°2θ per minute.

Differential Scanning Calorimetry (DSC)

Thermal transitions were determined by DSC (DSC30 using STAR^e software, Mettler Instrument, Hightstown, NJ). The samples (~8 mg) were sealed in 40-μL aluminum pans (Mettler Instrument) with a single hole punched in the lid. The reference and the sample pans were identical. The sample was scanned at 10°C/min with a 50-mL/min nitrogen purge. A trimetal standard (indium/lead/zinc) was used for temperature calibration. The time constant and the heat flow calibrations were performed using indium.

The DSC experiments were also performed with a DSC 2920 (TA Instruments, New Castle, DE) equipped with a data analyzer (Universal Analysis version 2.5H, TA Instruments) and refrigerated cooling accessory (RCS). The DSC cell and the RCS were purged with dry nitrogen. Baseline calibration was performed by heating the empty cell from −20 to 300°C at 10°C/min. Heat flow calibration with indium and a three-point temperature calibration with indium tin and biphenyl were performed at a heating rate of 10°C/min. The temperature-modulated DSC (TMDSC) runs were calibrated by scanning ~22 mg of sapphire at 1°C/min with a modulation amplitude of ±1°C and a period of 60 s. The samples (~5–9 mg) were prepared in 20-μL pans (Perkin-Elmer, Norwalk, CT) with a pin hole and scanned using the same modulated temperature program that was used for calibration. The modulated heat flow and the modulated temperature curves were checked for the absence of sine wave distortion. The presence of > 6 cycles through the glass transition was insured. The T_gs of dispersions containing 5–25% PEG in ritonavir were determined by TMDSC.

Hot Stage Microscopy (HSM)

Thermal transitions were also observed using a polarizing microscope (Optiphot, Nikon, Melville, NJ) equipped with a hot stage (FP82HT stage and FP90 processor, Mettler Instruments, Hightstown, NJ). The samples were placed on an appropriate microscope slide, heated from 30 to 70°C at 10°C/min, and then held isothermally at 70°C to observe crystal growth.

Moisture Sorption

Moisture sorption isotherms were determined at 25°C using a vacuum microbalance (MB-300G, VTI Corporation, Hialeah, FL). Sample sizes ranged from 50 to 100 mg. The balance was calibrated prior to each experiment, and the accuracy of the percent relative humidity (RH) was periodically examined by determining the amount of moisture absorbed by Povidone K90 at 80% RH and 25°C. Typical operating parameters for the moisture balance included drying the sample at 25–50°C and ~0.3 mmHg before determining the moisture sorption isotherms in 5 or 10% RH intervals.

Solubility Studies

Solutions containing 0–65% (w/v) PEG in 0.05 M phosphate buffer (pH 6.8) and 0.1 N HCl were

prepared. Excess ritonavir was added to each of these solutions, and the samples were rotated at 20 rpm in a water bath maintained at 37°C for 48 h. The samples were filtered through a 0.45-μm syringe filter, diluted, and analyzed by HPLC.

The apparent solubility of amorphous ritonavir was determined by adding excess solid to 0.1 N HCl. The sample was rotated at 25 rpm in a water bath maintained at 37°C. At predetermined intervals, an aliquot was withdrawn, filtered through a 0.45-μm syringe filter, diluted, and analyzed by HPLC. At the end of the experiment, the excess solid phase was analyzed by PXRD.

Physical Stability Studies

The physical stability of the 30% drug load dispersion was monitored for > 1.5 years at 25°C. The samples were stored in desiccators over either anhydrous calcium sulfate (Drierite, W.A. Hammond, Xenia, Ohio) and a saturated NaBr solution (57.5%RH). Periodically samples were removed and examined for ritonavir crystals by DSC and HSM.

Potency and United States Pharmacopoeia (USP) Dissolution Studies

The potency of the dispersions was determined by HPLC. The dissolution experiments of ritonavir dispersions, physical mixtures, and crystalline or amorphous ritonavir were performed in 900 mL of 0.1 N HCl at 37±0.5°C using USP apparatus I, basket method at 50 rpm. An equivalent to 100 mg of ritonavir was used in each dissolution bath. Samples were withdrawn at predetermined intervals and filtered through a 0.45-μm syringe filter. The first few milliliters of the sample were discarded and the remainder was assayed by HPLC.

RESULTS AND DISCUSSION

Properties of Ritonavir

The chemical structure in Figure 1 shows that ritonavir is a large, peptide-like molecule (MW 721 g/mol). The neutral form is extremely lipophilic, as illustrated by the log D value of 4.3 at pH 6.8. The pK_a values for the two weakly basic thiazole moieties are 1.8 and 2.6. The amide and the alcohol moieties are expected to ionize at a highly alkaline pH and, therefore, are not considered to be physiologically relevant. Ritonavir would exist as a dicationic species in the stomach. However, in the intestine where the pH is 5.4–7.5,[16] the molecule would be primarily un-ionized. The solubility of ritonavir at 37°C drops from 400±10 μg/mL in 0.1 N HCl to 1±0.02 μg/mL at pH 6.8 buffer, which is consistent with the ionization of the molecule. Although the solubility in 0.1 N HCl is 400 μg/mL, the IDR value is only 0.03±0.001 mg/cm^2-min. Compounds with IDR < 0.1 mg/min/cm^2 usually exhibit dissolution-rate-limited absorption,[17] and dissolution rates may be improved through the preparation of solid dispersion;[2,3] therefore, ritonavir is a classic candidate for solid dispersion systems.

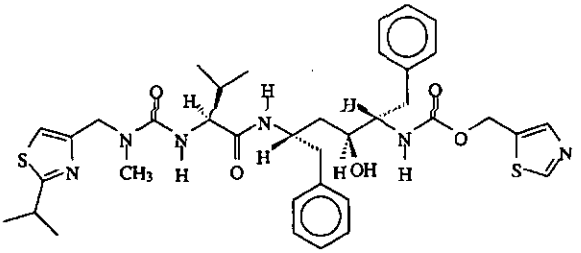


Figure 1. Chemical structure of ritonavir.

The apparent solubility of amorphous ritonavir in 0.1 N HCl reaches a maximum of ~4 mg/mL, which is 10 times higher than the crystalline phase (Figure 2). This improvement in apparent solubility, though not surprising, suggested that the preparation of solid dispersions containing the amorphous phase would be advantageous. Because physical stability is a major concern with *any amorphous system, investigation of additional* properties of amorphous ritonavir was necessary.

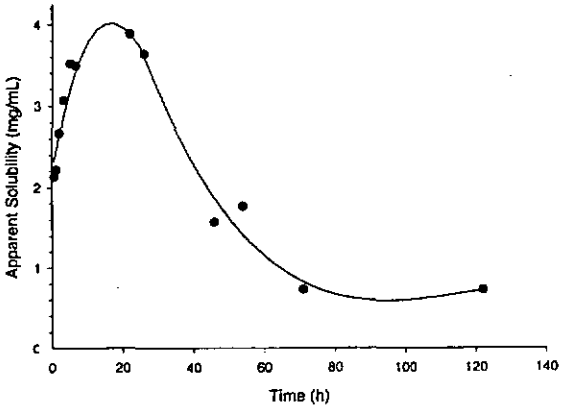


Figure 2. Apparent solubility of amorphous ritonavir. The line has no significance.

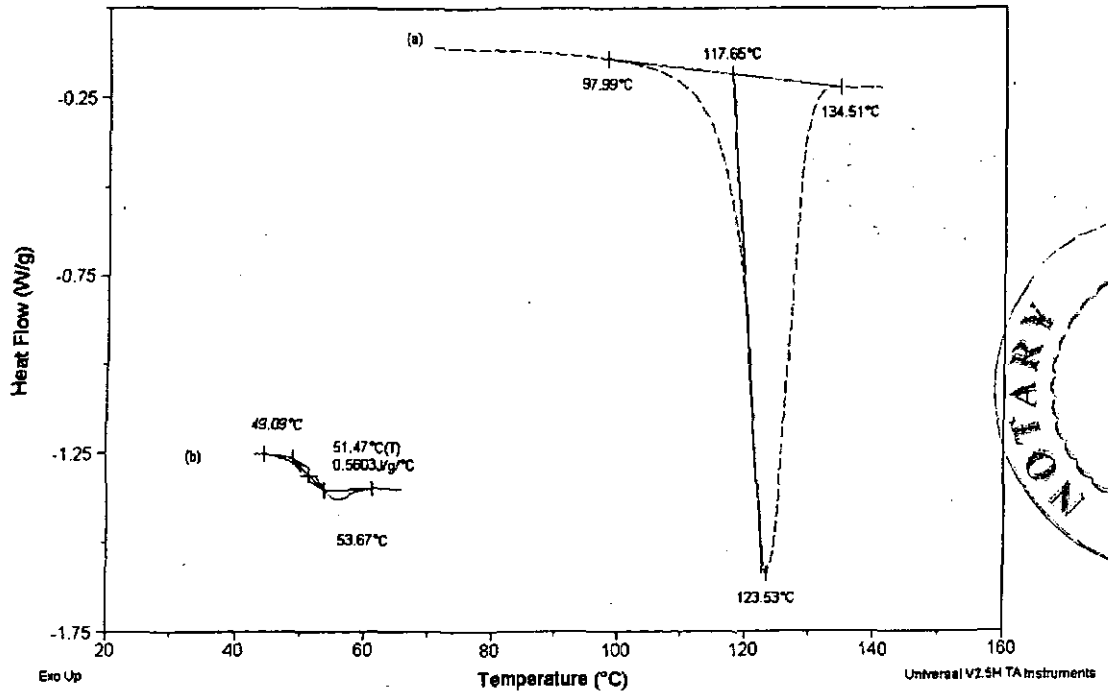


Figure 3. DSC of (a) crystalline and (b) amorphous ritonavir.

Figure 3 shows that the melting point (T_m) of ritonavir is 118°C, and the T_g is 51.5°C. When amorphous ritonavir is heated above T_g at a rate as low as 1°C/min, amorphous ritonavir does not crystallize spontaneously. In comparison, griseofulvin, which has been used as a model compound for > 60 publications involving solid dispersions, readily crystallizes when heated at ≤ 10°C/min.[18] This observation suggests that amorphous ritonavir is more difficult to crystallize than griseofulvin.

The glass-forming tendency is related to the ease with which the glassy state can be obtained. A measure of glass forming tendency is given by the ratio T_g/T_m, and for an "excellent glass former", $T_g/T_m > 0.7$.[19] Therefore, ritonavir, with $T_g/T_m = 0.82$, is expected to be an excellent glass former. The following properties of amorphous ritonavir are amenable for the preparation of solid dispersions containing amorphous ritonavir: high apparent aqueous solubility, glass forming tendency, and reasonable physical stability. Next, the potential influence of the polymer on the drug properties was evaluated.

PEG–Ritonavir Interactions

Because PEG can be easily processed, it is a common solid dispersion carrier. The properties of PEGs have been extensively discussed elsewhere and will not be reported here.[20–22] Briefly, PEG 8000 is a primarily crystalline polymer with a melting point of ~60°C. It is highly water soluble and has a rapid dissolution rate. PEG contains ~10% amorphous phase, and the T_g of this phase is ~−100°C.[21]

Figure 4 shows the solubility of crystalline ritonavir is markedly improved by PEG. The results demonstrate the presence of ritonavir–PEG interactions in aqueous solutions. Such

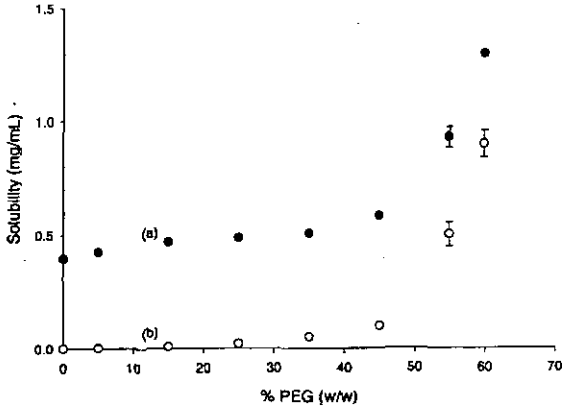


Figure 4. The effect of PEG on the solubility of crystalline ritonavir in (a) 0.1 N HCl and (b) pH 6.8 buffer.

drug–PEG interactions in aqueous solutions have been reported previously.[23,24] These solution phase interactions suggest that PEG may improve the dissolution rate of ritonavir.

In the solid state, PEG–drug interactions resulting in the formation of solid solutions have also been reported.[6,25,26] The formation of a solid solution leads to the destruction of the crystal lattice of the drug and a partial disruption of the lattice of the carrier. Solid solutions, therefore, exhibit markedly improved release profiles.[24] Solid solutions are formed when the strength of interaction between unlike components is stronger than like components.[27] This drug–carrier interaction leads to a stable dispersion. However, the reported solubility limit for these drugs in solid PEG has been < 10%(w/w);[24] therefore, ritonavir–PEG solid solution formation would impose a serious limitation on drug load.

In the absence of a solid solution, either a two-phase crystalline system (eutectic mixture) or a dispersion of amorphous ritonavir in crystalline PEG matrix is possible. In the former case, the presence of crystalline ritonavir in the dispersion would eliminate concerns regarding physical stability and the eutectic point would define the drug load. In the latter case, although drug loads higher than that achieved through the formation of solid solution may be possible, the residual amorphous regions in PEG could plasticize ritonavir if miscible. Therefore, the potential for this miscibility was investigated.

The T_g of freshly prepared amorphous PEG–ritonavir samples (*cf.* Figure 5) decreased from 51 to 13°C as the amount of PEG increased from 0 to 25% (w/w). It was difficult to prepare a one-phase system containing 30% PEG in ritonavir. This decrease in T_g clearly establishes the potential for PEG to act as a plasticizer. However, in < 7 days, the 15–25% dispersions underwent phase separation. The TMDSC of the phase-separated samples showed a PEG melting endotherm, but the ritonavir melting endotherm was absent. HSM confirmed that although PEG had crystallized, ritonavir was still amorphous. Efforts at determining the T_g of the 15–25% phase-separated samples were unsuccessful because PEG melting begins at ~40°C; therefore, the overlapping T_g and T_m of the two phases could not be separated. Figure 6 shows TMDSC thermograms of amorphous ritonavir and the 15% phase-separated dispersion of PEG in ritonavir. These data suggest that amorphous PEG and amorphous ritonavir are miscible; however, at PEG fractions

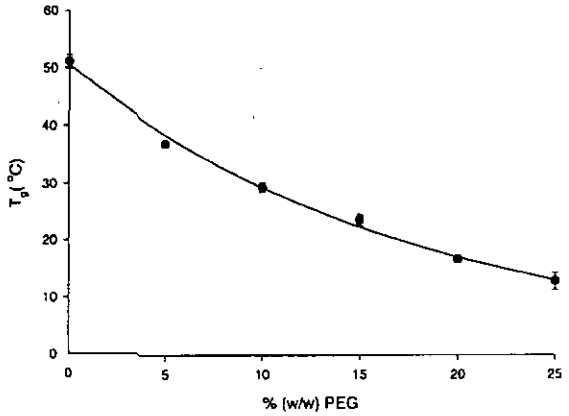


Figure 5. Plasticization of ritonavir by PEG.

≥ 15%, there is phase separation. This phase separation inhibits plasticization by PEG and is expected to be beneficial for the stability of the dispersion. Moreover, the amorphous phase in the phase-separated dispersions would have a T_g closer to that of pure ritonavir.

Solid Dispersion Properties

Figure 7 shows a DSC thermogram of a physical mixture containing 10:90 crystalline ritonavir–placebo dispersion. This thermogram exhibits two endotherms, one for the melting of PEG and a second very shallow endotherm indicating the presence of crystalline ritonavir. The DSC thermograms of solid dispersions containing 10, 20, or 30% ritonavir show a single melting endotherm for PEG (data not shown). When the dispersions were heated just above the melting point of PEG and observed under the microscope, no crystalline ritonavir was detected. However, when the melt was held at 70°C for > 3 min, crystal growth occurred.

A comparison of the PXRD pattern (Figure 8) of a physical mixture with that of the 10% dispersion shows the presence of ritonavir peaks in the physical mixture. The 10, 20, and 30% solid dispersions and the ritonavir sample prepared by the melt–quench method were all X-ray amorphous with respect to ritonavir.

The DSC, HSM, and PXRD observations suggested that the dispersions consisted of amorphous ritonavir and crystalline PEG. Hot-stage microscopy was found to be the most sensitive technique for detecting crystalline ritonavir in the dispersions. The presence of amorphous ritonavir in the PEG matrix established that the system

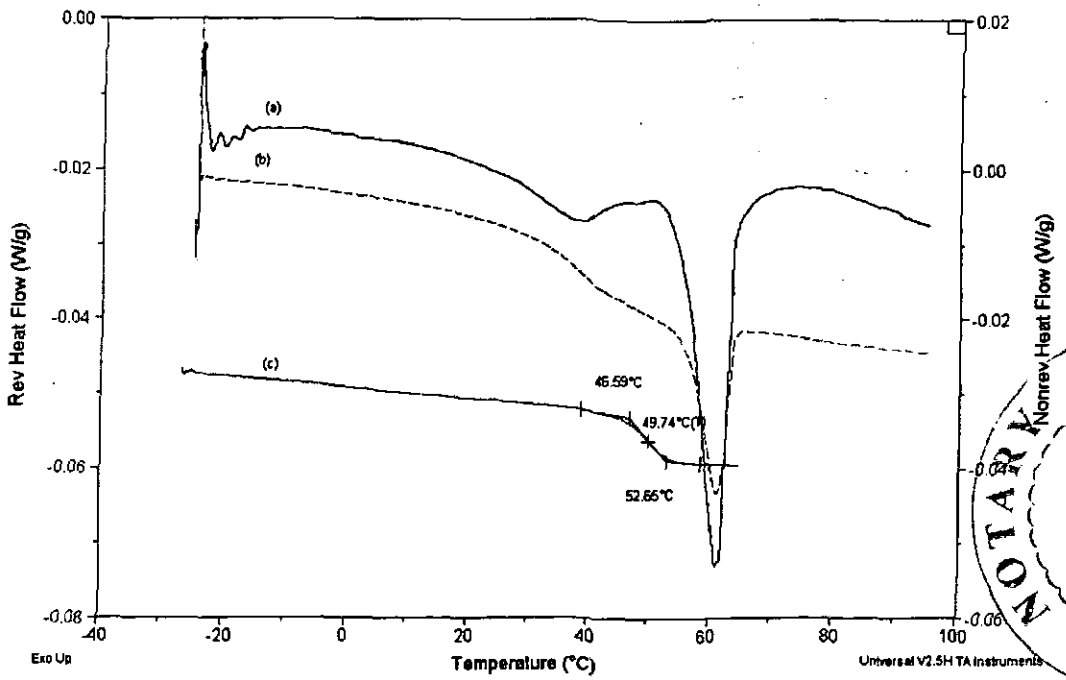


Figure 6. A representative TMDSC thermogram showing that the melting of PEG overlaps with the glass transition of ritonavir: (a) 15% PEG in ritonavir, nonreversing heat flow, (b) 15% PEG in ritonavir, reversing heat flow, and (c) amorphous ritonavir reversing heat flow.

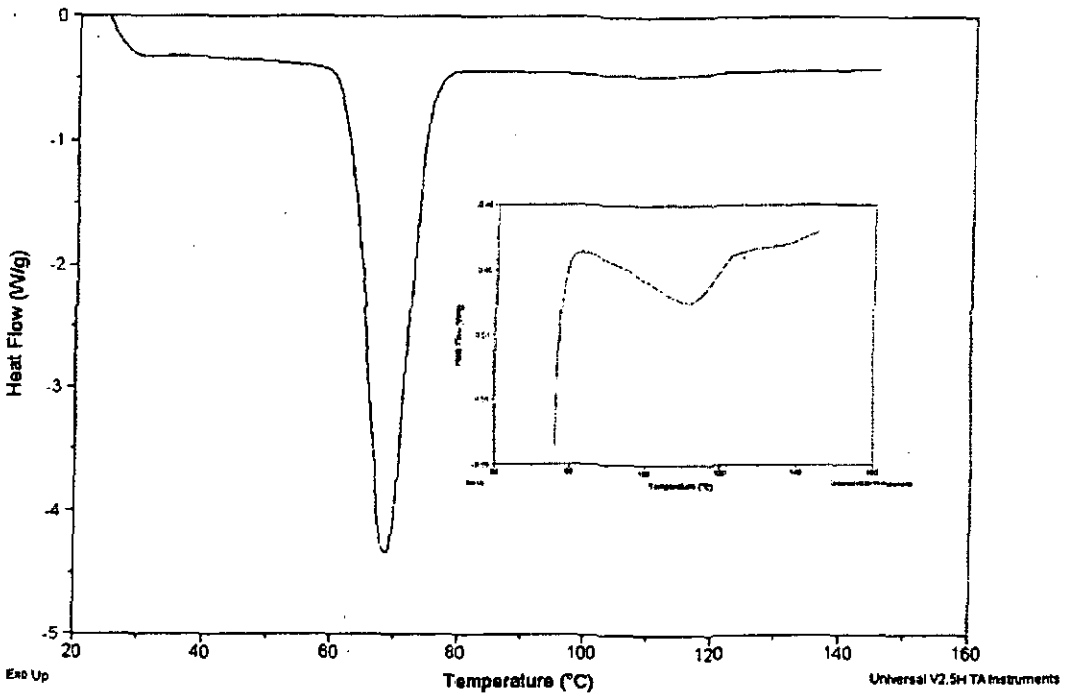


Figure 7. A representative DSC thermogram of 10% physical mixture. The inset shows the ritonavir melting endotherm.

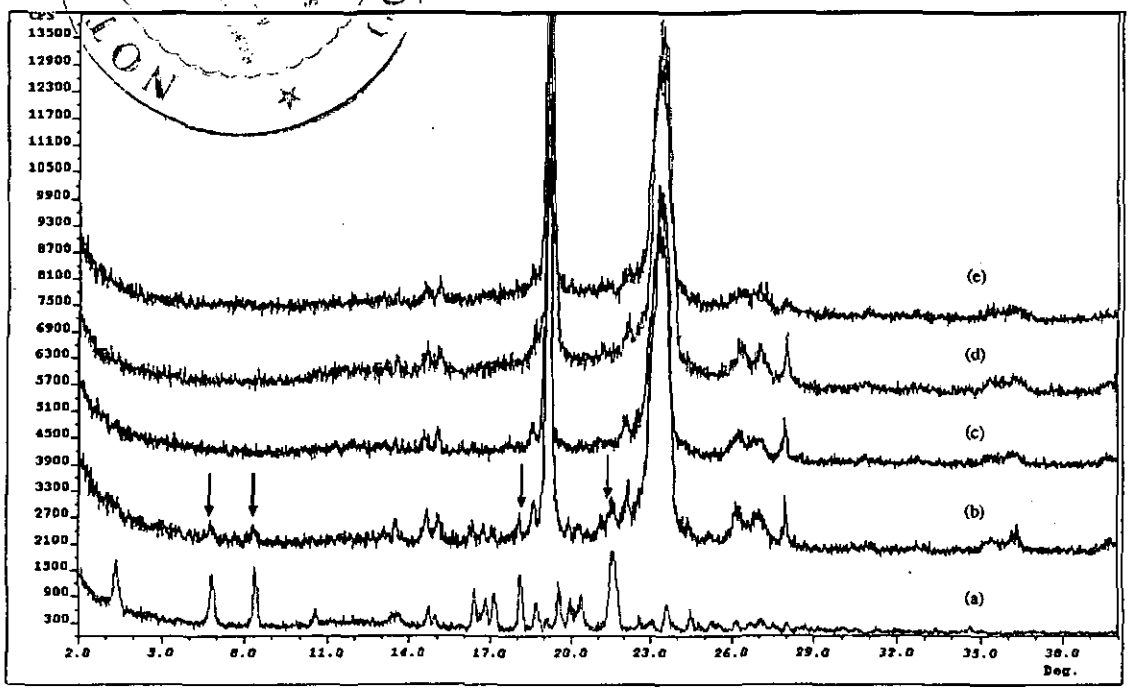


Figure 8. PXRD of (a) crystalline ritonavir; (b) a physical mixture containing 10:90 ritonavir–placebo, with arrows indicating the presence of crystalline ritonavir; and solid dispersions containing (c) 10% (d) 20% and (e) 30% ritonavir.

was not a eutectic mixture. Dispersions containing the amorphous drug would be expected to have improved dissolution profiles.

The data in Figure 9 compares the dissolution profiles of the dispersions with the physical mixture. The dispersions markedly improved the dissolution rate of ritonavir; however, the 20 and 30% dispersions showed incomplete release. The most common cause of incomplete release would be recrystallization of the amorphous phase. At the conclusion of these dissolution studies, the residual material isolated from the dissolution bath appeared as a gelatinous mass. After drying, the material did not exhibit birefringence when viewed under a polarizing microscope at room temperature or at 70°C, indicating the absence of crystalline ritonavir. Therefore, it was concluded that the incomplete release of ritonavir was not due to recrystallization of the amorphous phase.

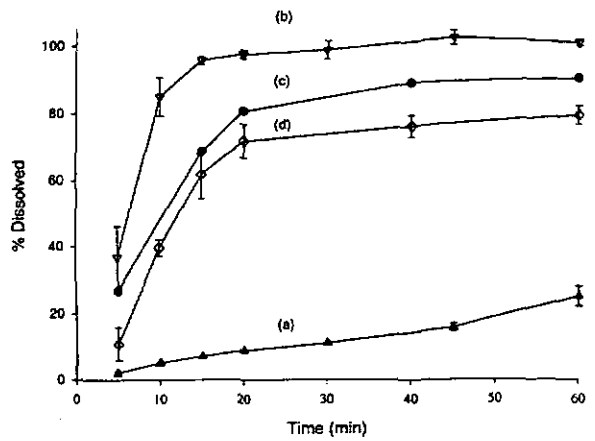


Figure 9. *In vitro* dissolution in 0.1 N HCl of (a) physical mixture containing 10:90 ritonavir–PEG, and solid dispersions of (b)10%, (c) 20%, and (d) 30% ritonavir. The data for 20% dispersion is an average of two runs, whereas the others are average of three runs.

Dissolution studies for the crystalline and amorphous ritonavir in the presence and absence PEG are shown in Figure 10. Contrary to expectation, the dissolution rate of the amorphous phase was significantly slower than the crystalline counterpart under these conditions. Again, the amorphous material formed a gelatinous mass whereas the crystalline did not. Therefore, it was established that the reason for the incomplete dissolution was not recrystallization of ritonavir. The physical mixtures show improved dissolution profiles; therefore, the gel formation was not due to adverse interaction with PEG. The reasons for gel formation and properties of the gel are beyond the scope of this paper. However, a comparison of

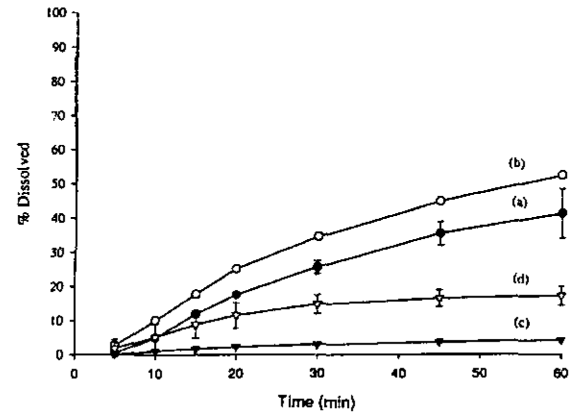


Figure 10. *In vitro* dissolution in 0.1 N HCl of (a) crystalline ritonavir, (b) a physical mixture containing 30:70 crystalline ritonavir–PEG, (c) amorphous ritonavir, and (d) a physical mixture containing 30:70 amorphous ritonavir–PEG. The data represents mean ± SD ($n = 3$).

Figures 9 and 10 reveal that the dissolution rate of ritonavir was improved through the preparation an amorphous dispersion in PEG.

Physical stability of amorphous dispersions is crucial for success. It has been shown that chemical degradation kinetics differ significantly in the glassy and the rubbery states, making stability testing at temperatures above T_g or under accelerated conditions for amorphous samples difficult to interpret.[28] Moreover, there are no guidelines for accelerated physical stability studies. Therefore, physical stability testing for the 30% dispersion was conducted at 25°C.

Samples stored under dry conditions for > 1.5 years did not contain crystalline ritonavir following the melting of PEG, as observed by HSM. Thermoanalytical methods failed to differentiate between the freshly prepared dispersion and these stability samples. At the end of the stability study, the dissolution profile of the sample was checked, and this profile remained unaltered.

There have been numerous reports citing poor physical stability of amorphous drugs in PEG matrices.[3,9,29] However, there are very few compounds[11,12] that form amorphous dispersions in PEG. Clearly, ritonavir belongs to that rare class. Therefore, understanding the properties of this model system would be beneficial for developing amorphous drug–PEG systems. Because ritonavir is amorphous in the dispersion, the dispersion could be either a solid solution or a system in

Table 1. Enthalpy of Fusion of PEG

Sample	ΔH^f (J/g)[a]
Placebo PEG	182±0.65
Physical mixture (30:70, ritonavir–placebo PEG)	180±2.8
Solid dispersion containing 30% drug load	180±1.1
Solid dispersion containing 20% drug load	180±1.4

[a]Mean±SD ($n = 3$).

which the crystalline regions of PEG remain unaffected.

Solid solutions are molecular dispersions that are expected to have long-term stability; therefore, ritonavir stability might indicate the formation of a solid solution. The formation of a solid solution leads to the production of considerable lattice distortion for the carrier. This lattice distortion would cause a decrease in internal energy, enthalpy, entropy of fusion of the host,[30,31] or, in this case, PEG. The total heat of fusion (ΔH^f) of PEG did not change with the incorporation of ritonavir (*cf.* Table 1). The ΔH^f results indicate that in these dispersions, the crystalline regions of PEG are unaltered or a solid solution was not formed. Furthermore, given the structural dissimilarity between PEG and ritonavir, formation of solid solutions with 30% amorphous ritonavir seemed highly improbable. Therefore, the amorphous ritonavir and amorphous PEG constitute a second phase. The T_g of this amorphous phase could not be determined, probably because it overlaps with the melting transition of PEG. The stability of the dispersion can thus be attributed to the physicochemical properties of amorphous ritonavir and the negligible influence of PEG on this amorphous phase.

The samples exposed to 57.5%RH, showed crystalline ritonavir after 10 months. Water, a known plasticizer, probably decreases the physical stability of amorphous ritonavir.[32,33] The extent of destabilization by water depends on the moisture sorption profiles of the amorphous phase and the water activity of the environment. The moisture sorption profile of crystalline ritonavir, PEG, 30% solid dispersion, and amorphous ritonavir in Figure 11 show that at 60% RH, amorphous ritonavir is relatively more hygroscopic than either crystalline ritonavir or PEG. Therefore, it is not surprising that the solid dispersions containing amorphous drug would

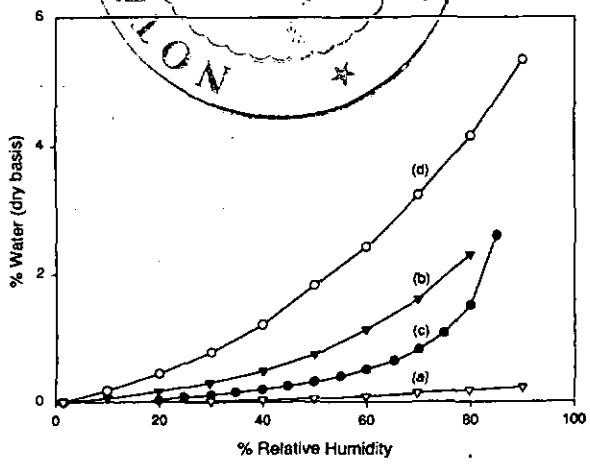


Figure 11. Moisture sorption profile of (a) crystalline ritonavir, (b) 30% dispersion of ritonavir in PEG, (c) PEG, and (d) amorphous ritonavir.

be more stable if stored under low humidity conditions.

CONCLUSIONS

Traditionally PEG–amorphous drug solid dispersions have been prepared and then tested for improved dissolution rate and stability. Because there are no guidelines for physical stability testing, this approach is time consuming. A survey of the literature shows that there are only a few compounds that form amorphous dispersion with PEG.[11,12] A successful preparation of a solid dispersion containing amorphous drug in PEG with reasonable physical stability may be evaluated from the physicochemical properties of the drug. Ritonavir, a large lipophilic molecule with low aqueous solubility and exceedingly slow IDR, was chosen as a model compound. The properties of amorphous ritonavir, such as its 10-fold higher apparent solubility, T_g higher than room temperature, excellent glass forming tendency, and an extremely slow crystallization rate, indicated that preparation of amorphous dispersions was feasible. Moreover, PEG not only improved the aqueous solubility of ritonavir, it had negligible plasticizing effect on amorphous ritonavir in the dispersions containing $\geq 15\%$ PEG. Therefore, through a systematic study of the properties of this drug and influence of the carrier on the drug properties, it was expected that an amorphous ritonavir dispersion in PEG would exhibit improved dissolution rate and may exhibit long-term stability. Finally, the dispersions were prepared and was shown to have improved *in vitro* release profile and be physically stable for > 1.5 years at 25°C when protected from moisture. The observed stability of the dispersion has been attributed to the properties of amorphous ritonavir and to the negligible plasticizing effect of PEG on the amorphous phase of the drug. Other compounds exhibiting these characteristics would be expected to form amorphous solid dispersions in PEG with acceptable shelf-lives.

ACKNOWLEDGMENTS

The authors thank the Pharmaceutical Analysis and Stability Center of Abbott Laboratories for providing the HPLC method, Mr. Yuerong Hu for his technical support, and Dr. Geoff Zhang for stimulating discussions.

REFERENCES

1. Martin D, Al-Razak L, Dias L, Eiden E, Gao R, Kaul D, Lechuga-Ballestros D, Marsh K, Poska R. 1996. Method of preparing an orally bioavailable solid formulation of an insoluble protease inhibitor, as a coprecipitate with PVP and other excipients. Pharm Res 13:S–351.
2. Sekiguchi K, Obi N. 1961. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull 9:866–872.
3. Ford JL. 1986. The current ststus of solid dispersions. Pharm Acta Helv 61:69–88.
4. Serajuddin ATM. 1999. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J Pharm Sci 88:1058–1066.
5. Guyot M, Fawaz F, Bildet J, Bonini F, Lagueny AM. 1995. Physicochemical characterization and dissolution of norfloxacin/cyclodextrin inclusion compounds and PEG solid dispersions. Int J Pharm 123:53–63.
6. Anguiano-Igea S, Otero-Espinar FJ, Vila-Jato JL, Blanco-Mendez J. 1995. The properties of solid dispersions of clofibrate in polyethylene glycols. Pharm Acta Helv 70:57–66.
7. Tantishaiyakul V, Kaewnopparat N, Ingkataworn-wong S. 1996. Properties of solid dispersion of piroxicam in polyvinylpyrrolidone K-30. Int J Pharm 143:59–66.
8. Yoshioka M, Hancock B, Zografi G. 1995. Inhibition of indomethacin crystallization in poly(vinylpyrrolidone) coprecipitates. J Pharm Sci 84:983–986.

9. Allen DJ, Kwan KC. 1969. Determination of the degree of crystallinity in solid-solid equilibria. J Pharm Sci 58:1190–1193.
10. Etman MA. 2000. Praziquantel solid dispersions with polyethylene glycol and urea: Preparation, Characterization and in vitro dissolution. Alex J Pharm Sci 14:79–84.
11. Doshi DH, Ravis WR, Betageri GV. 1997. Carbamazepine and polyethylene glycol solid dispersions: Preparation, in vitro dissolution, and characterization. Drug Dev Ind Pharm 23:1167–1176.
12. Badwan AA, Abu-Malooh A, Owais L, Salem MS, Alkaysi HN, Arafat TA. 1991. Some formulation aspects of terfenadine solid dispersions. Eur J Pharm Biopharm 37:166–170.
13. Cannon JB, Krill SL, Porter WR. 1995. Physicochemical properties of A-75998, an antagonist of luteinizing hormone releasing hormone. J Pharm Sci 84:953–958.
14. Simonelli AP, Mehta SC, Higuchi WI. 1969. Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. J Pharm Sci 58:538–549.
15. Chiou WL, Riegelman S. 1971. Pharmaceutical applications of solid dispersion systems. 60:1281–1302.
16. Davies B, Morris T. 1993. Physiological parameters in laboratory animals and humans. Pharm Res 10:1093–1095.
17. Kaplan SA. 1972. Biopharmaceutical considerations in drug formulation design and evaluation. Drug Metab Revs 1:15–34.
18. Law D, Schmitt EA, Qiu Y, Wang W, Fort JJ, Krill S. 1999. The impact of drug properties on solid dispersion systems. AAPS Pharm Sci 1:S–81.
19. Zallen R. 1983. The Formation of Amorphous Solids. In: The Physics of Amorphous Solids. New York: John Wiley & Sons. pp 1–22.
20. Lang MC, Noel C. 1977. Solid-state relaxations in poly (ethylene oxide). II. Study using the spin-labeling technique. J Polym Sci 15:1329–1338.
21. Buckley CP, Kovacs AJ. 1976. Melting behavior of low molecular weight poly (ethylene–oxide) fractions. 2. Folded chain crystals. Colloid and Polymer Sci 254:695–715.
22. Delahye N, Duclos R, Saiter JM. 1997. Characterization of PEG6000 phase transitions. Influence of kinetic conditions. Int J Pharm 157:27–34.
23. Palmieri GF, Antonini I, Martelli S. 1996. Characterization and dissolution studies of PEG 4000/fenofibrate solid dispersions. STP Pharma Sci 6:188–194.
24. Ford JL, Rubinstein MH. 1978. Phase equilibria and dissolution rates of indomethacin-polyethylene glycol 6000 solid dispersions. Pharm Acta Helv 53:93–98.
25. Suzuki H, Sunada H. 1997. Comparison of nicotinamide, ethylurea and polyethylene glycol as carriers for nifedipine solid dispersion systems. Chem Pharm Bull 45:1688–1693.
26. Craig DQM. 1990. Polyethylene glycols and drug release. Drug Dev Ind Pharm 16:2501–2526.
27. Vasil'ev ME. 1964. Classification of the phase diagrams of binary metallic systems according to atomic interaction forces. Russ J Phys Chem 38: 473–476.
28. Duddu SP, Weller K. 1996. Importance of glass transition temperature in accelerated stability testing of amorphous solids: Case study using a lyophilizea asprin formulation. J Pharm Sci 85: 345–347.
29. Dordunoo SK, Ford JL, Rubinstein MH. 1997. Physical stability of solid dispersions containing triameterene or temazepam in polyethylene glycols. J Pharm Pharmacol 49:390–396.
30. Chow KY, Go J, Mehdizadeh M, Grant DJW. 1984. Modification of adipic acid cyrstals: Influence of growth in the presence of fatty acid additives on crystal properties. Int J Pharm 20:3–24.
31. Li ZJ, Grant DJW. 1996. Effects of excess enantiomer on the crystal properties of a racemic compound: Ephedrinium 2-naphthalenesulfonate. Int J Pharm 137:21–31.
32. Shalaev EY, Zografi G. 1996. How does residual water affect the solid-state degradation of drugs in the amorphous state? J Pharm Sci 85:1137–1141.
33. Schmitt E, Davis CW, Long ST. 1996. Moisture-dependent crystallization of amorphous lamotrigine mesylate. J Pharm Sci 85:1215–1219.

287

EXHIBIT EC

Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs

ABU T. M. SERAJUDDIN†

Contribution from *Pharmaceutics R & D Department, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, New Jersey 08903-0191.*

Received October 7, 1998. Accepted for publication July 15, 1999.

Abstract □ Although there was a great interest in solid dispersion systems during the past four decades to increase dissolution rate and bioavailability of poorly water-soluble drugs, their commercial use has been very limited, primarily because of manufacturing difficulties and stability problems. Solid dispersions of drugs were generally produced by melt or solvent evaporation methods. The materials, which were usually semisolid and waxy in nature, were hardened by cooling to very low temperatures. They were then pulverized, sieved, mixed with relatively large amounts of excipients, and encapsulated into hard gelatin capsules or compressed into tablets. These operations were difficult to scale up for the manufacture of dosage forms. The situation has, however, been changing in recent years because of the availability of surface-active and self-emulsifying carriers and the development of technologies to encapsulate solid dispersions directly into hard gelatin capsules as melts. Solid plugs are formed inside the capsules when the melts are cooled to room temperature. Because of surface activity of carriers used, complete dissolution of drug from such solid dispersions can be obtained without the need for pulverization, sieving, mixing with excipients, etc. Equipment is available for large-scale manufacturing of such capsules. Some practical limitations of dosage form development might be the inadequate solubility of drugs in carriers and the instability of drugs and carriers at elevated temperatures necessary to manufacture capsules.

Introduction

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs,[1] there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability.

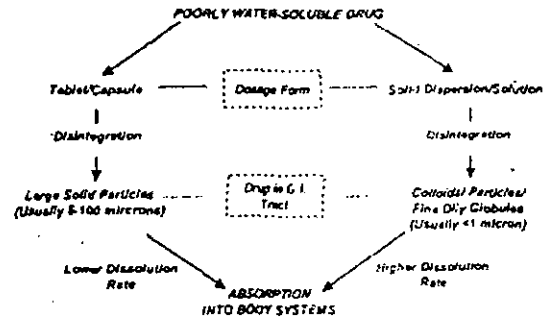


Figure 1—A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

In 1961, Sekiguchi and Obi[2] developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome. This method, which was later termed solid dispersion,[3] involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures. Sekiguchi and Obi[2] suggested that the drug was present in a eutectic mixture in a microcrystalline state. Later, Goldberg et al.[4,5] demonstrated that all the drug in a solid dispersion might not necessarily be present in a microcrystalline state, a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high.

The advantage of solid dispersion, compared with conventional capsule and tablet formulations, is shown schematically in Figure 1.[6] From conventional capsules and tablets, the dissolution rate is limited by the size of the primary particles formed after the disintegration of dosage forms. In this case, an average particle size of 5 μm is usually the lower limit, although higher particle sizes are preferred for ease of handling, formulation, and manufacturing. On the other hand, if a solid dispersion or a solid solution is used, a portion of the drug dissolves immediately to saturate the gastrointestinal fluid, and the excess drug precipitates out as fine colloidal particles or oily globules of submicron size.

Because of such early promises in the bioavailability enhancement of poorly water-soluble drugs, solid dispersion has become one of the most active areas of research in the pharmaceutical field. Numerous papers on various aspects

† Present address: Novartis, 59 Route 10, Building 401, East Hanover, New Jersey 07936.

10.1021/js980403l CCC: $18.00
Published on Web 08/27/1999

MSD

5 AUG 2010

288

of solid dispersion were published since 1961; Chiou and Riegelman[3] and Ford[4] reviewed the early research in this area. Despite an active research interest, the commercial application of solid dispersion in dosage form design has been very limited. Only two products, a griseofulvin-in-poly(ethylene glycol) solid dispersion (Gris-PEG, Novartis) and a nabilone-in-povidone solid dispersion (Cesamet, Lilly) were marketed during three decades following the initial work of Sekiguchi and Obi in 1961. The objectives of the present article are to critically review some of the limitations of solid dispersion that prevented its wider commercial application and to discuss how the situation is now changing because of the availability of new types of vehicles and the development of new manufacturing technologies.

Limitations of Solid Dispersion Systems

Problems limiting the commercial application of solid dispersion involve (a) its method of preparation, (b) reproducibility of its physicochemical properties, (c) its formulation into dosage forms, (d) the scale up of manufacturing processes, and (e) the physical and chemical stability of drug and vehicle. Some of the issues are discussed next.

Method of Preparation—In their pioneering study, Sekiguchi and Obi[2] prepared solid dispersions of sulfathiazole in such carriers as ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide, and urea by melting various drug–carrier mixtures. To minimize melting temperatures, eutectic mixtures of the drug with carriers were used. Yet, in all cases, except acetamide, the melting temperatures were >110 °C, which could chemically decompose drugs and carriers.[3] High temperatures (>100 °C) were also utilized by Goldberg et al. in preparing acetaminophen–urea,[1] griseofulvin–succinic acid,[4] and chloramphenicol–urea[5] solid dispersions. After melting, the next difficult step in the preparation of solid dispersions was the hardening of melts so that they could be pulverized for subsequent formulation into powder-filled capsules or compressed tablets. Sekiguchi and Obi[2] cooled the sulfathiazole–urea melt rapidly in an ice bath with vigorous stirring until it solidified. Chiou and Riegelman[3] facilitated hardening of the griseofulvin–PEG 6000 solid dispersion by blowing cold air after spreading it on a stainless steel plate and then storing the material in a desiccator for several days. In preparing primidone–citric acid solid dispersions, Summers and Enever[10] spread the melt on Petri dishes, cooled it by storing the Petri dishes in a desiccator, and finally placed the desiccator at 60 °C for several days. Allen et al.[11] prepared solid dispersions of corticosteroids in galactose, dextrose, and sucrose at 169, 185, and 200 °C, respectively, and then placed them on aluminum boats over dry ice. Timko and Lordi[12] also used blocks of dry ice to cool and solidify phenobarbital–citric acid mixtures that had previously been melted on a frying pan at 170 °C. The fusion method of preparing solid dispersion remained essentially similar over the period of time. More recently, Lin and Cham[13] prepared nifedipine–PEG 6000 solid dispersions by blending physical mixtures of the drug and the carrier in a V-shaped blender and then heating the mixtures on a hot plate at 80–85 °C until they were completely melted. The melts were rapidly cooled by immersion in a freezing mixture of ice and sodium chloride, and the solids were stored for 24 h in a desiccator over silica gel before pulverization and sieving. Mura et al.[14] solidified naproxen–PEG melts in an ice bath and the solids were then stored under reduced pressure in a desiccator for 48 h before they were ground into powders with a mortar and pestle. In another study, Owusu-Ababio et al.[15] prepared a mefenamic acid–PEG solid dispersion by heating the drug–carrier mixture on a hot plate to a temperature above the melting point of mefenamic acid (253 °C) and then cooling the melt to room temperature under a controlled environment.

Another commonly used method of preparing a solid dispersion is the dissolution of drug and carrier in a common organic solvent, followed by the removal of solvent by evaporation.[9,16,17] Because the drug used for solid dispersion is usually hydrophobic and the carrier is hydrophilic, it is often difficult to identify a common solvent to dissolve both components. Large volumes of solvents as well as heating may be necessary to enable complete dissolution of both components. Chiou and Riegelman[9] used 500 mL of ethanol to dissolve 0.5 g of griseofulvin and 4.5 g of PEG 6000. Although in most other reported studies the volumes of solvents necessary to prepare solid dispersions were not specified, it is possible that they were similarly large. To minimize the volume of organic solvent necessary, Usui et al.[18] dissolved a basic drug in a hydroalcoholic mixture of 1 N HCl and methanol, with drug-to-cosolvent ratios ranging from 1:48 to 1:20, because as a protonated species, the drug was more soluble in the acidic cosolvent system than in methanol alone. Some other investigators dissolved only the drug in the organic solvent, and the solutions were then added to the melted carriers. Vera et al.[19] dissolved 1 g of oxodipine per 150 mL of ethanol before mixing the solution with melted PEG 6000. In the preparation of piroxicam–PEG 4000 solid dispersion, Fernandez et al.[20] dissolved the drug in chloroform and then mixed the solution with the melt of PEG 4000 at 70 °C. Many different methods were used for the removal of organic solvents from solid dispersions. Simonelli et al.[16] evaporated ethanolic solvent on a steam bath and the residual solvent was then removed by applying reduced pressure. Chiou and Riegelman[9] dried an ethanolic solution of griseofulvin and PEG 6000 in an oil bath at 115 °C until there was no evolution of ethanol bubbles. The viscous mass was then allowed to solidify by cooling in a stream of cold air. Other investigators used such techniques as vacuum-drying,[20,21] spray-drying,[22–25] spraying on sugar-beads using a fluidized bed-coating system,[26] lyophilization,[27] etc., for the removal of organic solvents from solid dispersions. None of the reports, however, addressed how much residual solvents were present in solid dispersions when different solvents, carriers, or drying techniques were used.

Reproducibility of Physicochemical Properties—In their pioneering studies, Sekiguchi and Obi[2] observed that manufacturing conditions might greatly influence the physicochemical properties of solid dispersions formed. They cooled drug–carrier melts under vigorous stirring conditions to obtain fine and uniform drug particles in solid dispersions. Various investigators observed that heating rate, maximum temperature used, holding time at a high temperature, cooling method and rate, method of pulverization, and particle size may greatly influence the properties of solid dispersions prepared by the melt method. McGinity et al.[28] prepared solid dispersions of tolbutamide in urea and PEG 6000 by flash cooling in a bath of dry ice and acetone or by gradual cooling over a period of several hours by immersion in an oil bath. The powder X-ray diffraction patterns of the tolbutamide–urea solid dispersion differed markedly depending on the cooling rate. The slow-cooled solid dispersion of tolbutamide in urea demonstrated a complete lack of crystallinity for both the drug and urea, whereas the flash-cooled dispersions showed only the absence of drug crystallinity. In the powder X-ray diffraction patterns of tolbutamide–PEG 6000 solid dispersions, peaks for both tolbutamide and PEG 6000 were observed; however, their degree of crystallinity in flash-cooled samples was less than that in the slow-cooled

samples. In another study, a metastable amorphous form of nifedipine was formed in its solid dispersions in PEG 4000 and PEG 6000 when the drug–carrier melts were cooled rapidly, whereas slow cooling of melts or powdering of solidified mass resulted in the crystallization of drug.[29] Ginés et al.[30] studied the effect of fusion temperature on oxazepam–PEG 4000 solid dispersions. Microscopic examination revealed the presence of crystalline oxazepam and the spheculitic form of PEG 4000 in solid dispersions prepared by fusion at 100 °C. In contrast, a fusion temperature of 150 °C produced a solid dispersion with no crystalline form of the drug and the presence of PEG 4000 in a hedritic form. Complete dissolution of drug in the carrier at 150 °C in contrast to 100 °C was reported to be responsible for such a difference in physicochemical properties of the solid dispersions produced. Dordunoo et al.[31] also observed a change of triamterene and temazepam from crystalline to amorphous form in poly(ethylene glycol) solid dispersions when the fusion temperature was increased from 100 to 150 °C. Such changes in physical states of drugs in solid dispersions result into differences in drug dissolution rates in aqueous media.[30] Drug-to-carrier ratio and particle size of solid dispersions were also reported to influence the dissolution rate of drug.[32]

The properties of solid dispersions prepared by the solvent method may also vary depending on manufacturing conditions. The solvent method usually leads to amorphous forms of drugs. However, some crystallinity of drug may be observed depending on the drug-to-carrier ratio used.[33] Although no detailed studies were reported in the literature, it is expected that the nature of solvent used, drug-to-solvent and carrier-to-solvent ratios, drying method, and drying rate may significantly influence the physicochemical properties of solid dispersions formed.

Dosage Form Development—Solid dispersion must be developed into convenient dosage forms, such as capsules and tablets, for their clinical use and successful commercialization. As already mentioned, solid dispersions produced by the melt method are usually hardened at very low temperatures and then pulverized with mortars and pestles. Similarly, solid dispersions produced by the solvent method are also pulverized after solvent removal and hardening. Some of the challenges in the dosage form development of such materials are difficulty of pulverization and sifting of the dispersions, which are usually soft and tacky, poor flow and mixing properties of powders thus prepared, poor compressibility, drug–carrier incompatibility, and poor stability of dosage forms. However, there are very few reports in the literature addressing these important issues.[7] Even the limited number of reports describing any dosage form developmental aspects of solid dispersions only confirm that the task of formulating solid dispersions into capsules or tablets may be a very complex and difficult one. In developing a tablet formulation for the indomethacin–PEG 6000 solid dispersion, Ford and Rubinstein[34] reported that the solid dispersion was not amenable to wet granulation because water could disrupt its physical structure. In addition, the dispersion was soft and tacky. To overcome these problems, the authors adopted an in situ dry granulation method where the excipients (calcium hydrogen phosphate and sodium starch glycolate) were preheated and rotated in a water-jacketed blender at 70 °C, and the indomethacin–PEG 6000 mixture that melted at 100 °C was then added to the moving powder. After mixing, the granules were passed through a 20-mesh sieve and allowed to harden at 25 °C for 12 h. Then, the granules were mixed with a relatively high concentration of magnesium stearate (1%) and compressed into tablets. To process 100 mg of solid dispersion, 506 mg of other excipients were used, thus making the final weight of a 25-mg indomethacin tablet 606 mg. Yet, the tablet did not disintegrate in water despite the use of a large amount of excipients. It dissolved slowly by erosion, and the dissolution rate decreased on aging of the tablet. In another study, the same investigators used an essentially similar in situ dry granulation method for the preparation of tablet dosage forms for a chlorpropamide–urea solid dispersion, where the drug, the carrier, and the excipients were mixed in a rotating flask on a water bath maintained at 100 °C.[35] The properties of these formulations also changed with time, and the authors concluded that aging could "limit their usefulness as prospective dosage forms". During the development of a tablet formulation for a furosemide–poly(vinylpyrrolidone) (PVP) solid dispersion, Akbuga et al.[36] observed that method of preparation, choice of disintegrant and particle size of solid dispersions were critical factors in determining the properties of tablets produced. Despite the use of relatively large amounts of disintegrants, the tablets did not disintegrate. Rather, they dissolved by erosion only, and the erosion rate varied depending on the disintegrant used. In addition, the dissolution rate of tablets prepared by double compression (slugging and recompression of dry granules) was much slower than that of the tablets prepared by single compression. The dissolution rate of tablet was also dependent on the particle size of solid dispersion used; the rate decreased by a factor of 5 when 100-mesh particles were used in place of 80-mesh particles. Also, the compressibility of solid dispersion decreased with a decrease in particle size. In another study, Sjökvist and Nystrom [37] overcame the compression difficulties due to sticking of griseofulvin–xylitol solid dispersions to dies and punches by lubricating die wall and punch faces with 1% (w/w) magnesium stearate suspension before the compression of each tablet. The authors observed that the dissolution rate of tablet was highly sensitive to compression pressure. The sticking of solid dispersion to dies and punches might become so problematic that Kaur et al. [38] resorted to placing small pieces of grease-proof paper between metal surfaces and granules before the compression of tablets.

The lack of disintegration and the slow dissolution of tablets prepared from solid dispersions could be related to the soft and waxy nature of carriers used (e.g., PEG) in many of the reported studies. Such carriers essentially act as strong binders within tablets. During compression, the carriers could plasticize, soften, or melt, filling the pores within tablets and thus making them nondisintegrating. It is also possible that the softened and melted carriers coat the disintegrants and other ingredients used in tablets, and such a coating, along with the reduction of porosity of tablets, make the disintegrants ineffective. Use of a very high ratio of solid dispersion to added excipient might alleviate the problem. In one study,[15] 270 mg of microcrystalline cellulose (Avicel) was used to formulate 30 mg of mefenamic acid–PEG solid dispersion into a tablet with good dissolution. The use of such a high ratio of added excipient would, however, greatly increase the size of tablet and might, therefore, be impractical in most formulations.

Scale Up of Manufacturing Processes—Because very few solid dispersion products prepared by melt or solvent methods have been marketed, there are practically no reports on the scale up of such products. It is apparent from the discussion just presented that the scale up of the methods of preparation of solid dispersions and their dosage forms could be very challenging. In most of the studies reported in the literature, solid dispersions by the melt method were prepared in a small scale by heating drug–carrier mixtures in beakers, frying pans, etc. that were placed on hot plates and then cooling the melts in an ice bath, a dry ice-acetone mixture, etc.[2-5,7-14] Because there could be condensation of moisture over solid disper-

sions during cooling to low temperatures, strict protection from moisture was necessary in all cases. The scale up challenges may be illustrated with the example of the preparation of a phenytoin–PEG 4000 solid dispersion by Yakou et al.[39] The drug–carrier mixture was heated at 250 °C under constant stirring until a clear homogeneous melt was obtained, and the melt was air-cooled by spreading on stainless steel trays. The trays were stored in a desiccator for 3 days to enhance solidification of the solid dispersion. The resulting material was then crushed in a cutter mill, and the powders were sieved to collect a sieve fraction of 105–177-μm particle size for use in the dosage form. The scale up of such a method would be difficult and it might even be impractical in many cases because of possible degradation of both drug and carrier at high temperatures used. The scale up might also necessitate a large capital investment because a chemical plant-like facility, rather than a common pharmaceutical dosage form manufacturing plant, would be required to process and manufacture the products. For scale up of the cooling process, Lefebvre et al.[40] recommended such continuous operation as cooling on the surfaces of moving belts or rotating cylinders, and spray congealing. The practical application of the methods, however, was not demonstrated. Kennedy and Niebergall[41] described a hot-melt fluid bed method whereby nonpareils could be coated with PEGs having molecular weights between 1450 and 4600. A similar method can possibly be used to deposit solid dispersions on nonpareils and might in the future find application in the manufacture and scale up of solid dispersion formulations.

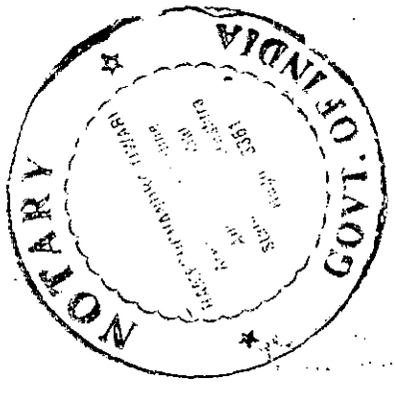
The physicochemical properties and stability of solid dispersions may also be affected by scale up because heating and cooling rates of solid dispersions under large-scale manufacturing conditions may differ greatly from that in small beakers.[28,29] Drug–carrier compatibility at a high temperature also requires careful consideration. Dubois and Ford[42] reported the chain scission of PEG 600 during fusion with disulfiram, furosemide, chlorthiazide, and chlorpropamide.

The scale up of the solvent method of preparing solid dispersions may also be very challenging. A chemical plant environment would be necessary to evaporate hundreds and even thousands of liters of organic solvents necessary to prepare solid dispersions for kilogram quantities of drugs.[17,20] The cost of recovery of these solvents may be very high. Removal of residual amounts of potentially toxic organic solvents such as chloroform and methanol from large masses of material may be difficult because the solid dispersions are usually amorphous and may exist in viscous and waxy forms. Solvates may also be formed with drugs and carriers. Because most dosage form manufacturing facilities are not equipped to handle large volumes of organic solvents, one way to resolve the issue might be the designation of solid dispersion as an active pharmaceutical ingredient or bulk drug substance. In that case, the responsibility of the manufacture of solid dispersion can be shifted to the chemical plant. It would be necessary to conduct all developmental activities using the solid dispersion, so this approach might not be suitable for situations where active pharmaceutical ingredients have multiple uses (e.g., oral and parenteral).

The final step in the manufacturing process, which is the conversion of solid dispersions into stable and marketable dosage forms, may be the most difficult one to scale up, optimize, and validate. Most of the commonly used solid dispersion vehicles are soft and sticky and, as a result, the pulverized forms of solid dispersions produced by such vehicles may not be amenable to processing by high-speed capsule or tablet filling machines.

Stability—The physical instability of solid dispersions due to crystallization of drugs was the subject of most published reports in the literature.[3,7] In a solid dispersion prepared by the melt method, a certain fraction of the drug may remain molecularly dispersed, depending on its solubility in the carrier used, thus forming a solid solution. How the excess drug exists may greatly depend on the method of manufacture of the system: it may, as a whole or in part, form a supersaturated solution, separate out as an amorphous phase, or crystallize out. The supersaturated and amorphous forms may, in turn, crystallize out on aging. Similarly, certain carriers may also exist in thermodynamically unstable states in solid dispersions and undergo changes with time. Chiou[43] reported that griseofulvin precipitated out in an amorphous form in a griseofulvin–PEG 6000 solid dispersion during the time of its preparation. The amorphous material crystallized out on aging, except when the drug concentration in the dispersion was 5% or less. Ford and Rubinstein[44] attributed similar crystallization as the cause for a decrease in dissolution rate of drug from indomethacin–PEG 6000 solid dispersions with time. The decrease in the dissolution rate of indomethacin was also dependent on drug concentration in the solid dispersion. The decrease was greater for a higher drug concentration because a larger fraction of drug crystallized out. In another study, Suzuki and Sunada[45] observed that on exposure of a nifedipine–nicotinamide–hydroxypropylmethylcellulose (HPMC) solid dispersion to 60% RH at 30 °C or 75% RH at 40 °C for 1 month, nifedipine converted from the amorphous to the crystalline state, thus lowering the dissolution rate of nifedipine drastically. No conversion of nifedipine to the crystalline state was observed when the solid dispersion was stored at an elevated temperature in the absence of humidity. Although the presence of HPMC facilitated the conversion of nifedipine to an amorphous state during the cooling of drug–nicotinamide melt to room temperature at the time of manufacturing, it did not prevent the subsequent crystallization of drug under humid conditions. Pronounced decreases in dissolution rates due to drug crystallization were also reported for tablets prepared from solid dispersions.[34,35] No such decrease in dissolution rate on aging was observed by Khalil et al.[46] in corticosteroid–PEG solid dispersions prepared with a drug-to-carrier ratio of 1:99, possibly because most of the drug was molecularly dispersed in the carrier. The corticosteroid, however, exhibited chemical degradation due to oxidation by the peroxides present in PEG. The cooling rate of solid dispersions may also significantly influence their aging behavior. It has been reported that the crystallinity of drug in solid dispersions is less influenced by aging when a slow cooling rate is used because thermodynamically more stable systems are produced during the time of preparation.[47,48]

The conversion of drug to crystalline state is also the primary stability issue with solid dispersions prepared by the solvent method. PVP, which is commonly used as a carrier in such solid dispersions, is amorphous and does not convert to a crystalline state. However, certain other carriers may convert from their amorphous states to crystalline states in solid dispersions. Zografi and coworkers[49,50] extensively studied the physicochemical properties of the amorphous states of drugs and excipients and observed that the crystallization of amorphous materials is facilitated by moisture. This effect is why strict protection from moisture is necessary during the preparation and storage of most solid dispersions. Doherty and York[51] studied the stability of furosemide–PVP solid dispersion in the temperature range of 0 to 45 °C and 40% RH for up to 1 year. They did not observe any crystallization of furosemide and suggested that PVP may indeed act as a



stabilizer in the solid dispersion by retarding crystallization of drug at a relatively low humidity. Rapid crystallization of furosemide in the solid dispersion was, however, evident when the humidity was raised to 75% RH. Similar observations were also made by Guillaume et al.[52] for an oxodipine–PVP solid dispersion where no crystallization of oxodipine was observed in 18 months when samples were stored under 55% RH at various temperatures, but the drug crystallized out at 80% RH. The stabilization of drugs in amorphous forms in solid dispersions is an active area of research in the pharmaceutical field. For an indomethacin–PVP solid dispersion system, Taylor and Zografi[53] suggested that hydrogen bonding between the drug and PVP might offer an explanation for the absence of drug crystallization. Lu and Zografi[54] recently demonstrated that indomethacin forms a completely miscible amorphous mixture with citric acid and PVP when the weight fraction of PVP in the ternary mixture exceeds 0.3 weight fraction. Thus, both the choice of carrier and the drug-to-carrier ratio are important considerations in the stabilization of solid dispersions.

Breakthroughs in Solid Dispersion Technology

Because of the various limitations just mentioned, it is not surprising that the solid dispersion system, despite its many potential advantages, has not been widely used in pharmaceutical dosage forms. Under the present health care economic climate, the goal of any drug development program in the pharmaceutical industry is to rapidly progress a new chemical entity from the discovery stage to clinical testing to determine whether it is safe and clinically effective. The limited supply of the bulk drug substance at the early drug development phase and the accelerated time lines would not allow a formulator to address most of the challenges (vide supra) of a solid dispersion formulation. Most importantly, if a compound proves promising in early clinical testing, the scale up of complex manufacturing processes for the development of marketable dosage forms cannot be ensured.

Two recent breakthroughs in the formulation of solid dispersion systems involve (1) the development of technologies to fill solid dispersions directly into hard gelatin capsules and (2) the availability of surface-active and self-emulsifying carriers. As a result, there is renewed interest in such systems for use in commercial development of drug products.[6,55]

Direct Capsule-Filling—Although the filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature, was first described by Francois and Jones in 1978,[56] it was not until much later that the potential application of the technique for solid dispersions was fully realized. Chathani[57] reported the possibility of preparing PEG-based solid dispersions by filling drug–PEG melts in hard gelatin capsules. By using PEG with molecular weights ranging from 000 to 8000, Serajuddin et al.,[58] however, demonstrated that a PEG by itself might not be a suitable carrier for solid dispersion of poorly water-soluble drugs intended for direct filling into hard gelatin capsules. They dissolved a poorly water-soluble drug, REV5901, in molten PEG 1000, PEG 1450, and PEG 8000 and filled the hot solutions into hard gelatin capsules such that each size 0 capsule contained 100 mg of drug and 550 mg of PEG. At room temperature, solid plugs were formed inside the capsules, where the drug remained molecularly dispersed in the carriers. Although a sink condition existed for the dissolution of 100 mg of the weakly basic REV5901 ($pK_a \sim 3.6$) in 900 mL of simulated gastric fluid (drug solubility = 0.7 mg/mL at 37 °C), the dissolution of drug from all PEG-based solid dispersions was incomplete.

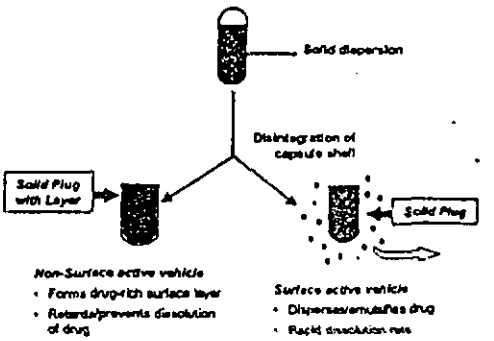


Figure 2—A schematic representation of the comparative dissolution of a poorly water-soluble drug from surface-active versus nonsurface-active vehicles.

Because the water-soluble carrier dissolved more rapidly than the drug, drug-rich layers were formed over the surfaces of dissolving plugs, which prevented further dissolution of drug from solid dispersions. The dissolution was practically zero at pH > 2, where the solubility of drug was low and a drug layer coated the surface of the solid plug as soon as the capsule shell disintegrated. Corrigan[59] also reported the possibility of such a retardation of drug dissolution from solid dispersions.

Surface-Active Carriers—The direct filling of melts into hard gelatin capsules would not be a viable method for the preparation of solid dispersions unless the formation of drug-rich layers on the surfaces of dissolving plugs could be prevented. Serajuddin et al.[58,60] achieved a complete dissolution of drug from solid dispersions by using surface-active or self-emulsifying carriers. The vehicles acted as dispersing or emulsifying agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers. Although the liberated drug remained undissolved in the dissolution medium when its concentration exceeded its saturation solubility, it was dispersed or emulsified in a finely divided state because of surface activity of the dissolved vehicle.[58,60] The high surface area of a drug produced in this way would facilitate its dissolution in the gastrointestinal fluid, especially in the presence of bile salts, lecithin, and lipid digestion mixtures.[61]

The advantage of a surface-active carrier over a nonsurface-active one in the dissolution of drug from a capsule formulation is shown schematically in Figure 2.[6] The physical state of drug in a solid dispersion must, however, be carefully considered in evaluating the advantage of a surface-active vehicle. As mentioned earlier, the drug can be molecularly dispersed in the carrier to form a solid solution or it can be dispersed as particles. It can also be both partially dissolved and partially dispersed in the carrier. The potential for the formation of a continuous drug-rich surface layer is possibly greater if the drug is molecularly dispersed, whereas the drug dispersed as particulates may be more prone to dissociation from the water-soluble matrix. It is, however, rare that the drug is dispersed just as particulates and is not at least partially dissolved in the vehicle. Therefore, a surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs.

The interest in surface-active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs increased greatly in recent years.[58,62-67] For ease of manufacturing, the carriers must be amenable to liquid filling into hard gelatin capsules as melts. The melting temperatures of carriers should be such that the solutions do not exceed ~70 °C, which is the maximum acceptable temperature for hard gelatin capsule shells.[68] Some of the manufacturing difficulties mentioned earlier may be en-

countered if solid dispersion products using surface-active carriers are prepared by methods other than direct filling into hard gelatin capsules; for examples, the solvent evaporation method,[69] compaction into tablets from granules,[37] etc.

One surface-active carrier that has commonly been used in solid dispersion for the bioavailability enhancement of drugs is Gelucire 44/14 (Gattefossé Corp., France).[58,62-65,67] It is a mixture of glyceryl and PEG 1500 esters of long-chain fatty acids and is official in the European Pharmacopeia as lauryl macrogolglycerides; the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophilic–lipophilic balance (HLB) value. Another surface-active carrier that generated certain interest in recent years is Vitamin E TPGS NF (Eastman, Kingsport, TN),[70] which is prepared by the esterification of the acid group of *d*-α-tocopheryl acid succinate by PEG 1000. The material has an HLB value of 13 and is miscible with water in all parts. Its melting point is, however, relatively low (38 °C) and it may require mixing with other carriers to increase melting temperatures of formulations.

In search of alternative surface-active carriers, Serajuddin and co-workers[60,71] demonstrated that a commonly used surfactant, polysorbate 80, could be used in solid dispersions by mixing it with solid PEG. Although polysorbate 80 is liquid at room temperature, it forms a solid matrix when it is mixed with a PEG because it incorporates within the amorphous regions of PEG solid structure. As high as 50% (w/w) polysorbate 80 could be incorporated in a PEG with a lowering of <6 °C in its melting point. Even when 75% (w/w) polysorbate 80 was incorporated, PEG remained semisolid, and the lowering of the melting temperature of the PEG used was <12 °C.[71] The crystalline structure of solid PEG was minimally affected by polysorbate 80 because the two compounds have low miscibility in each other. Other investigators also reported enhanced dissolution[72] and bioavailability[65] of drugs from PEG–polysorbate carriers. Law et al.[73] reported a >2-fold increase in the dissolution rate of nifedipine from a PEG-based solid dispersion after incorporation of 5% (w/w) phosphatidylcholine. Increased dissolution rate of drug from solid dispersions in PEG containing varying amounts of ionic and nonionic surfactants, including sodium dodecyl sulfate and polysorbate 80, were also reported by Sjökvist et al.[74] The authors, however, pulverized the waxy material instead of filling them into hard gelatin capsules as melts.

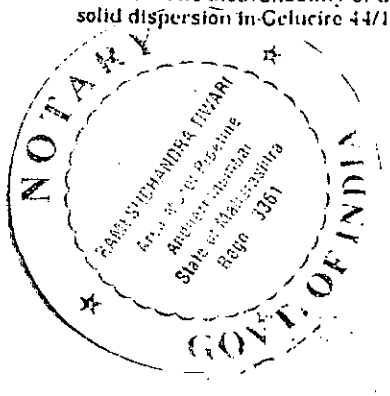
Ease of Manufacturing—Cadé and Madt[75] and Shah et al.[76] reviewed various formulation and processing considerations for liquid-filled hard gelatin capsules. Initial formulation development studies can be conducted by filling hot solutions or dispersions into hard gelatin capsule shells manually by using pipets or by using laboratory scale semiautomatic equipment.[77] Equipment is also available to scale up the manufacturing process and for large scale manufacturing.[78] As mentioned earlier, the temperature of solutions during the filling of hard gelatin capsules should not exceed 70 °C.[68] Solutions can also be filled into soft gelatin capsules for which the solution temperature should remain <40 °C.[79] Several hard gelatin[80,81] and soft gelatin[82] capsule products prepared according to these techniques have been marketed in recent years.

Bioavailability Enhancement—The reports on the bioavailability enhancement by solid dispersion in surface-active carriers are promising. The human bioavailability of the poorly soluble REV5901 from a solid dispersion in Gelucire 44/14 under a fasting regimen was much higher than that of a tablet formulation even though the micronized form of drug and a wetting agent were used in the tablet.[83] The bioavailability of ubidecarenone in dogs from solid dispersion in Gelucire 44/14 and the Gelucire 44/14–lecithin mixture were, respectively, two and three times higher than that of commercially available tablet.[63] The bioavailability of another poorly water-soluble drug, RP69698, in dogs was 4.5 times higher (27.6% versus 6%) from its solid dispersion in a PEG 3350–Labrasol–polysorbate 80 system than from an aqueous suspension in 0.5% methylcellulose.[65] Aungst et al.[67] reported that the bioavailability of an HIV protease inhibitor, DMP323, in dogs from a PEG-based formulation decreased from 49.6 to 5.2% when the dose was increased from 100 to 350 mg. No such drastic decrease in bioavailability was observed in a Gelucire 44/14-based formulation of DMP323; the bioavailability values were 68.9 and 49.5% after doses of 85 and 350 mg, respectively. The bioavailability of ritonavir (Norvir, Abbott), another poorly soluble HIV protease inhibitor (solubility <1 μg/mL at pH > 2), was enhanced by formulation as a solid dispersion in a mixture of such surface-active carriers as Gelucire 50/13, polysorbate 80 and polyoxyl 35 castor oil.[84]

Special Considerations for Surfactant-Based Solid Dispersions—Solid dispersion in surface-active carriers may not be the answer to all bioavailability problems with poorly water-soluble drugs. One of the limitations of bioavailability enhancement by this method might be the low solubility of drug in available carriers.[64,85] The desired doses of a drug cannot be solubilized and filled into hard gelatin capsules if adequate solubility in a carrier cannot be obtained. Dordunoo et al.[64] reported that the particle size of a drug in a solid dispersion remained unchanged if it is just mixed with the carrier instead of dissolving in it. On the other hand, if the drug is dissolved by heating in excess of its solubility in the carrier under normal storage condition, it may subsequently crystallize out from the solid dispersion. Either situation would defeat the purpose of bioavailability enhancement of poorly water-soluble drugs by solid dispersion, as described in Figure 1.

The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abbott) from the market.[86] The crystallization of drug adversely influenced the dissolution of the ritonavir capsule, and the product was switched to a thermodynamically stable solution formulation. Aungst et al.[67] also stressed the importance of drug solubility in carriers in the development of capsule formulations. They prepared high-dose formulations of a water-insoluble HIV protease inhibitor by dissolving it in carriers at an elevated temperature only, and the formulations were used for bioavailability testing in dogs within 24 h of preparation when no crystallization occurred. The authors cautioned that precipitation of drug could occur upon storage at room temperature over a longer period of time, and that lowering of drug concentration in the carrier would be necessary to ensure long-term physical stability of the formulation.

To ensure that a drug would not crystallize out of solid dispersion at the desired storage temperature, it is important to screen the drug solubility in different carriers at such a temperature. However, no practical method for determining or estimating drug solubility in a carrier at a relatively low temperature, where the carrier exists in a solid state, has been reported in the literature. The relative solubility of a drug in different carriers may be determined by equilibrating the drug at an elevated temperature where all the carriers exist in a liquid state.[87] If the solubility of a drug in a carrier at an elevated temperature is much higher than the concentration required for solid dispersion, an accurate estimation of solubility at room temperature might not be necessary and a reasonable assumption might be made that the drug would not precipitate out. When a better estimation of solubility is needed, one practical



approach is the determination of solubility–temperature relationship of drug in a chemically related carrier that exists as liquid at a wider range of temperature. For example, for the purpose of estimating the solubility of a drug in a solid PEG at room temperature, the solubility may be determined at an elevated temperature where the PEG exists in a liquid state. Then the solubility of drug at a lower temperature may be estimated from the solubility–temperature relationship in a related vehicle, PEG 400, which remains liquid at a wider range of temperature. This method assumes, however, that similar temperature–solubility relationships for the drug would exist in both PEGs and that the relationship would not change when one of them solidifies. The solubility may also be estimated by microscopic examination of solid solutions with increasing drug concentration for any possible crystallization of drug, assuming that the drug does not exist as a separate amorphous phase and the crystallization occurs in a relatively short period of time. A similar microscopic technique was use for determining the solubility of diazepam in liquid crystalline phases of lecithin.[67]

Another possible limitation of the use of surface-active carrier reported by Aungst et al.[67] is that the bioavailability of a drug may vary depending on the amount of carrier administered along with it. This variation is because different amounts of a surface-active carrier may have different solubilization or dispersion effects on a drug in the gastrointestinal fluid. Serajuddin et al.[58,60] reported a method whereby the rate and efficiency of dispersion of drug in aqueous media from different formulations can be studied.

In addition to the solubility, careful attention must be given to the drug-to-carrier ratio in the successful development of a formulation. When the solubility of a particular drug is relatively low, a high drug-to-carrier ratio is necessary to deliver it in a solubilized state, and, therefore, the dose has to be low if it is desired that the total dose is delivered as a single unit. As mentioned earlier, any attempt to supersaturate the drug in solid dispersion to reduce drug-to-carrier ratio may lead to stability problems and, ultimately, to product failure.

Attention should also be given to optimization and validation of the manufacturing process. It is not only that the physicochemical properties of the drug is affected by the cooling rate, the properties of carriers in a solid dispersion might also be influenced by the solidification rate of the product.[84,89] The implication of this observation on bioavailability and stability of drug product is not known.

Future Prospects

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful development of solid dispersion systems for preclinical, clinical, and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drugs in melted carriers and the filling of the hot solutions into hard gelatin capsules. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and, as a result, the bioavailability of solid dispersions are not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts of drug substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation.

One major focus of future research will be the identification of new surface-active and self-emulsifying carriers for solid dispersions. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may the inadequate drug solubility in carriers, so a wider choice of carriers will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention must also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipidic in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP3-based drug metabolism and *p*-glycoprotein-mediated drug efflux, will require careful consideration.[99]

In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed toward the development of extended-release dosage forms. Although a review of literature on this aspect of solid dispersion is outside the scope of the present article, it may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsule-filling processes. Because the formulation of solid dispersions for bioavailability enhancement and extended release of drugs may employ essentially similar processes except for the use of slower dissolving carriers for the latter case,[91] it is expected that the research in these two areas will progress simultaneously and be complementary to each other.

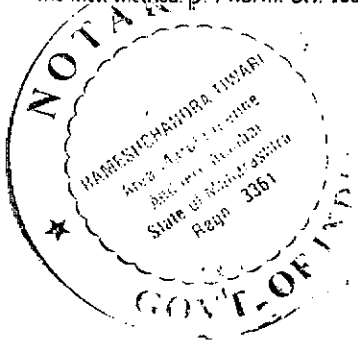
Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, as exemplified by the recent withdrawal of ritonavir capsules from the market,[86] so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problems that might not be seen in other types of solid dosage forms. Predictive methods will be necessary for the investigation of any potential crystallization of drugs and its impact on dissolution and bioavailability. Possible drug–carrier interactions must also be investigated.

Although, as mentioned earlier, the direct filling of solid dispersion into hard gelatin capsules is a relatively simple process, there are very limited reports on the scale up of the technology. Further studies on scale up and validation of the process will be essential. Many problems and challenges still remain with solid dispersion systems. Nevertheless, as a result of recent breakthroughs, it will continue to be one of the exciting frontiers of drug development.

References and Notes

1. Wadke, D. A.; Serajuddin, A. T. M.; Jacobson, H. Preformulation testing. In *Pharmaceutical Dosage Forms: Tablets, Vol. 1*; Lieberman, H. A.; Lachman, L.; Schwartz, J. B.; Eds.; Marcel Dekker: New York, 1989; pp 1–73.
2. Sekiguchi, K.; Obi, N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem. Pharm. Bull.* 1961, *9*, 866–872.

3. Chiou, W. L.; Riegelman, S. Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* 1971, *60*, 1281–1302.
4. Goldberg, A. H.; Gibaldi, M.; Kanig, J. L. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II. Experimental evaluation of eutectic mixtures: urea-acetaminophen system. *J. Pharm. Sci.* 1966, *55*, 482–487.
5. Goldberg, A. H.; Gibaldi, M.; Kanig, J. L. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures III. Experimental evaluation of griseofulvin-succinic acid solution. *J. Pharm. Sci.* 1966, *55*, 487–492.
6. Serajuddin, A. T. M. Bioavailability enhancement of poorly water-soluble drugs by solid dispersion in surface active and self-emulsifying vehicles. *Bull. Technique Gattefossé* 1997, *90*, 43–50.
7. Ford, J. L. The current status of solid dispersions. *Pharm. Acta Helv.* 1986, *61*, 69–88.
8. Goldberg, A. H.; Gibaldi, M.; Kanig, J. L.; Mayersohn, M. Increasing dissolution rates and gastrointestinal absorption of drugs via solid dispersion in eutectic mixtures IV. Chloramphenicol-urea system. *J. Pharm. Sci.* 1966, *55*, 581–583.
9. Chiou, W. L.; Riegelman, S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.* 1969, *58*, 1505–1509.
10. Summers, M. P.; Enever, R. P. Preparation and properties of solid dispersion system containing citric acid and primidone. *J. Pharm. Sci.* 1976, *65*, 1613–161.
11. Allen, L. V.; Yanchick, V. A.; Maness, D. D. Dissolution rates of corticosteroids utilizing sugar glass dispersions. *J. Pharm. Sci.* 1977, *66*, 494–497.
12. Timko, R. J.; Lordi, N. G. Thermal characterization of citric acid solid dispersions with benzoic acid and phenobarbital. *J. Pharm. Sci.* 1979, *68*, 601–605.
13. Lin, C. W.; Cham, T. M. Effect of particle size on the available surface area of nifedipine from nifedipine-poly(ethylene glycol) 6000 solid dispersions. *Int. J. Pharm.* 1996, *127*, 261–272.
14. Mura, P.; Manderioli, A.; Bramanti, G.; Ceccarelli, L. Properties of solid dispersion of naproxen in various poly(ethylene glycol)s. *Drug Dev. Ind. Pharm.* 1996, *22*, 909–916.
15. Owusu-Ababio, G.; Eboka, N. K.; Reams, R.; Habib, M. Comparative dissolution studies for mefenamic acid-poly(ethylene glycol) solid dispersion systems and tablets. *Pharm. Dev. Technol.* 1998, *3*, 405–412.
16. Simonelli, A. P.; Mehta, S. C.; Higuchi, W. I. Dissolution rates of high energy poly(vinylpyrrolidone)(PVP)-sulfathiazole coprecipitates. *J. Pharm. Sci.* 1969, *58*, 538–549.
17. Thakkar, A. L.; Hirsch, C. A.; Page, J. G. Solid dispersion approach for overcoming bioavailability problems due to polymorphism of nabilone, a cannabinoid derivative. *J. Pharm. Pharmacol.* 1977, *29*, 783–784.
18. Usui, F.; Maeda, K.; Kusai, A.; Ikeda, M.; Nishimura, K.; Yamamoto, K. Dissolution improvement of RS-8359 by the solid dispersion prepared by the solvent method. *Int. J. Pharm.* 1998, *170*, 247–256.
19. Vera, N.; Veiga, M. D.; Cadorniga, R. Solid dispersions of oxodipine/PEG 6000 characterization and dissolution study. *S. T. P. Pharma Sci.* 1991, *1*, 125–129.
20. Fernandez, M.; Rodriguez, I. C.; Margarit, M. V.; Cerezo, A. Characterization of solid dispersions of piroxicam/poly(ethylene glycol) 4000. *Int. J. Pharm.* 1992, *84*, 197–202.
21. Singla, A. K.; Vijan, T. Dissolution of sulfamethoxazole from poly(ethylene glycol) and poly(vinylpyrrolidone) solid dispersions. *Drug Dev. Ind. Pharm.* 1990, *16*, 875–882.
22. Corrigan, O. I.; Holohan, E. M. Amorphous spray-dried hydroflumethiazide-poly(vinylpyrrolidone) systems: physicochemical properties. *J. Pharm Pharmacol.* 1984, *36*, 217–221.
23. Takahashi, Y.; Tsukuda, T.; Izumi, C.; Ikemoto, K.; Kokubun, K.; Yagi, N.; Takada, M. Preparation of solid dispersion systems of disopyramide with poly(vinylpyrrolidone) and γ-cyclodextrin. *Chem. Pharm. Bull.* 1988, *36*, 2708–2710.
24. Jachowicz, R.; Nürnberg, E.; Hoppe, R. Solid dispersions of oxazepam. *Int. J. Pharm.* 1993, *99*, 321–325.
25. Kai, T.; Akiyama, Y.; Nomura, S.; Sato, M. Oral absorption improvement of poorly soluble drug using solid dispersion technique. *Chem. Pharm. Bull.* 1996, *44*, 568–571.
26. Ho, H. O.; Sho, H. L.; Tsai, T.; Sheu, M. T. The preparation and characterization of solid dispersions on pellets using a fluidized bed system. *Int. J. Pharm.* 1996, *139*, 223–229.
27. Betageri, G. V.; Makarla, K. R. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. *Int. J. Pharm.* 1995, *126*, 155–160.
28. McGinity, J. W.; Maincent, P.; Steinfink, H. Crystallinity and dissolution rate of tolbutamide solid dispersions prepared by the melt method. *J. Pharm. Sci.* 1984, *73*, 1441–1444.
29. Save, T.; Venkitachalam, P. Studies on solid dispersions of nifedipine. *Drug Dev. Ind. Pharm.* 1992, *18*, 1663–1679.
30. Ginés, J. M.; Arias, M. J.; Moyano, J. R.; Sanchez-Soto, P. J. Thermal investigation of crystallization of poly(ethylene glycol)s in solid dispersions containing oxazepam. *Int. J. Pharm.* 1996, *143*, 247–253.
31. Dordunoo, S. K.; Ford, J. L.; Rubinstein, M. H. Physical stability of solid dispersions containing triamterene or temazepam in poly(ethylene glycol)s. *J. Pharm. Pharmacol.* 1997, *49*, 390–396.
32. Ford, J. L.; Elliott, P. N. C. The effect of particle size on some in vitro and in vivo properties of indomethacin-poly(ethylene glycol) 6000 solid dispersions. *Drug Dev. Ind. Pharm.* 1985, *11*, 537–549.
33. Tantishaiyakul, V.; Kaewnopparat, N.; Ingkatawornwong, S. Properties of solid dispersions of piroxicam in poly(vinylpyrrolidone) K-30. *Int. J. Pharm.* 1996, *143*, 59–66.
34. Ford, J. L.; Rubinstein, M. H. Formulation and aging of tablets prepared from indomethacin-polyethylene glycol) 6000 solid dispersions. *Pharm. Acta Helv.* 1980, *55*, 1–7.
35. Ford, J. L.; Rubinstein, M. H. Preparation: properties and aging of tablets prepared from the chlorpropamide-urea solid dispersion. *Int. J. Pharm.* 1981, *8*, 311–322.
36. Akbuğa, J.; Gürsoy, A.; Yetimoğlu, F. Preparation and properties of tablets prepared from furosemide-PVP solid dispersion systems. *Drug Dev. Ind. Pharm.* 1988, *14*, 2091–2108.
37. Sjökvist, E.; Nyström, C. Physicochemical aspects of drug release. XI. Tableting properties of solid dispersions using xylitol as carrier material. *Int. J. Pharm.* 1991, *67*, 139–153.
38. Kaur, R.; Grant, D. J. W.; Eaves, T. Comparison of poly(ethylene glycol) and polyoxyethylene stearate as excipients for solid dispersion systems of griseofulvin and tolbutamide II: Dissolution and solubility studies. *J. Pharm. Sci.* 1980, *69*, 1321–1326.
39. Yukou, S.; Umehara, K.; Sonobe, T.; Nagai, T.; Sughihara, M.; Fukuyama, Y. Particle size dependency of dissolution rate and human bioavailability of phenytoin powders and phenytoin-poly(ethylene glycol) solid dispersions. *Chem. Pharm. Bull.* 1984, *32*, 4150–4156.
40. Lefebvre, C.; Brazier, M.; Robert, H.; Guyot-Hermann, A. M. Les dispersions solides, pourquoi et comment? Aspect industriel. *S. T. P. Pharma.* 1985, *1*, 300–322.
41. Kennedy, J. P.; Niebergall, P. J. Development and optimization of a solid dispersion hot-bed fluid bed coating method. *Pharm. Dev. Technol.* 1996, *1*, 51–61.
42. Dubois, J. L.; Ford, J. L. Similarities in the release rates of different drugs from poly(ethylene glycol) 600 solid dispersions. *J. Pharm. Pharmacol.* 1985, *37*, 494–496.
43. Chiou, W. L. Pharmaceutical applications of solid dispersion systems: X-ray diffraction and aqueous solubility studies on griseofulvin-poly(ethylene glycol) 6000 systems. *J. Pharm. Sci.* 1977, *66*, 989–991.
44. Ford, J. L.; Rubinstein, M. H. Aging of indomethacin-poly(ethylene glycol) 6000 solid dispersion. *Pharm. Acta Helv.* 1979, *54*, 353–358.
45. Suzuki, H.; Sunada, H. Some factors influencing the dissolution of solid dispersions with nicotinamide and hydroxypropylmethylcellulose as combined carriers. *Chem. Pharm. Bull.* 1998, *46*, 1015–1020.
46. Khalil, S. A. H.; El-Fattah, S. A.; Mortada, L. M. Stability and dissolution rates of corticosteroids in poly(ethylene glycol) solid dispersions. *Drug Dev. Ind. Pharm.* 1984, *10*, 771–787.
47. Duclos, R.; Grenet, J.; Salter, J. M.; Besançon, P.; Orecchioni, A. M. Effect of aging on progesterone-poly(ethylene glycol) 6000 dispersions. X-ray study. *Drug Dev. Ind. Pharm.* 1990, *16*, 255–265.
48. Saers, E. S.; Nyström, C.; Aldén, M. Physicochemical aspects of drug release. XVI. The effect of storage on drug dissolution from solid dispersions and the influence of cooling rate and incorporation of surfactant. *Int. J. Pharm.* 1993, *90*, 105–118.
49. Hancock, B. C.; Zografi, G. Characteristics and significance of the amorphous state in pharmaceutical systems. *J. Pharm. Sci.* 1997, *86*, 1–12.
50. Andronis, V.; Yoshioka, M.; Zografi, G. Effects of sorbed water on the crystallization of indomethacin from the amorphous state. *J. Pharm. Sci.* 1997, *86*, 346–351.
51. Doherty, C.; York, P. Accelerated stability of an X-ray amorphous furesemide-poly(vinylpyrrolidone) solid dispersion. *Drug Dev. Ind. Pharm.* 1989, *15*, 1969–1987.
52. Guillaume, F.; Guyot-Herman, A. M.; Duclos, R.; Besançon, P.; Orechioni, A. M.; Drache, M.; Conflour, P.; Gadefait, A.; Bécourt, P. Elaboration and physical study of an oxodipine solid dispersion in order to formulate tablets. *Drug Dev. Ind. Pharm.* 1992, *18*, 811–827.



53. Taylor, L. S.; Zografi, G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.* 1997, *14*, 1691–1698.
54. Lu, Q.; Zografi, G. Phase behavior of binary and ternary amorphous mixtures containing indomethacin, citric acid, and PVP. *Pharm. Res.* 1998, *15*, 1202–1206.
55. Serajuddin, A. T. M. Bioavailability enhancement of poorly water-soluble drugs by solid dispersion in surface-active vehicles: A recent breakthrough. *La Gazette de l'ApGI* (France) 1997, *14*, 144–145.
56. Francois, D.; Jones, B. E. The hard capsule with the soft center. *European Capsule Technology Symposium*. Constance, October 11–13, 1978; pp 55–61.
57. Chatham, S. M. The use of bases in SSM formulations. *S. T. P. Pharma.* 1987, *3*, 575–582.
58. Serajuddin, A. T. M.; Sheen, P. C.; Mufson, D.; Bernstein, D. F.; Augustine, M. A. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. *J. Pharm. Sci.* 1988, *77*, 414–417.
59. Corrigan, O. E. Mechanism of dissolution of fast release solid dispersions. *Drug Dev. Ind. Pharm.* 1985, *11*, 697–724.
60. Serajuddin, A. T. M.; Sheen, P. C.; Augustine, M. A. Improved dissolution of a poorly water-soluble drug from solid dispersions in poly(ethylene glycol):polysorbate 80 mixtures. *J. Pharm. Sci.* 1990, *79*, 463–464.
61. Serajuddin, A. T. M.; Sheen, P. C.; Mufson, D.; Bernstein, D. F.; Augustine, M. A. Physicochemical basis of increased bioavailability of a poorly water-soluble drug following oral administration as organic solutions. *J. Pharm. Sci.* 1988, *77*, 325–329.
62. Dennis, A. B.; Farr, S. J.; Kellaway, I. W.; Taylor, G.; Davidson, R. In vivo evaluation of rapid release and sustained release Gelucire capsule formulations. *Int. J. Pharm.* 1990, *65*, 85–100.
63. Pozzi, F.; Longo, A.; Lazzarini, C.; Carenzi, A. Formulations of ubidecarenone with improved bioavailability. *Eur. J. Pharm. Biopharm.* 1991, *37*, 243–246.
64. Dordunoo, S. K.; Ford, J. L.; Rubinstein, M. H. Preformulation studies on solid dispersions containing triamterene or temazepam in polyethylene glycols or Gelucire 44/14 for liquid filling of hard gelatin capsules. *Drug Dev. Ind. Pharm.* 1991, *17*, 1685–1713.
65. Sheen, P. C.; Khetarpal, V. K.; Cariola, C. M.; Rowlings, C. E. Formulation studies of a poorly water-soluble drug in solid dispersions to improve bioavailability. *Int. J. Pharm.* 1995, *18*, 221–227.
66. Porter, C. J. H.; Charman, S. A.; Williams, R. D.; Bakalova, M. V.; Charman, W. N. Evaluation of emulsifiable glasses for the oral administration of cyclosporin in beagle dogs. *Int. J. Pharm.* 1996, *141*, 227–237.
67. Aungst, B. J.; Nguyen, N. H.; Rogers, N. J.; Rowe, S. M.; Hussain, M. A.; White, S. J.; Shum, L. Amphiphilic vehicles improve the oral bioavailability of a poorly soluble HIV protease inhibitor at high doses. *Int. J. Pharm.* 1997, *156*, 79–88.
68. Cole, E. T. Liquid-filled hard gelatin capsules. *Pharm. Technol.* 1989, *September*, 124–140.
69. Hahn, L.; Sucker, H. Solid Surfactant solutions of active ingredients in sugar esters. *Pharm. Res.* 1989, *6*, 958–960.
70. Product literature. *Eastman Vitamin E TPGS NF properties and applications*; Eastman, Kingsport, TN; 1998.
71. Morris, K. R.; Knipp, G. T.; Serajuddin, A. T. M. Structural properties of poly(ethylene glycol)-polysorbate 80 mixture, a solid dispersion vehicle. *J. Pharm. Sci.* 1992, *81*, 1185–1188.
72. Velga, M. D.; Escobar, C.; Bernard, M. J. Dissolution behavior of drugs from binary and ternary systems. *Int. J. Pharm.* 1993, *93*, 215–220.
73. Law, S. L.; Lo, W. Y.; Lin, F. M.; Chang, C. H. Dissolution and absorption of nifedipine in poly(ethylene glycol) solid dispersion containing phosphatidylcholine. *Int. J. Pharm.* 1992, *84*, 161–166.
74. Sjökvist, E.; Nystrom, C.; Aldén, M.; Caram-Lelham, N. Physicochemical aspects of drug release. XIV. The effects of some ionic and nonionic surfactants on properties of a sparingly soluble drug in solid dispersions. *Int. J. Pharm.* 1992, *79*, 23–133.
75. Cadé, D.; Mudit, N. Liquid filling in hard gelatin capsules – preliminary steps. *Bull. Technique Gattefossé* 1996, *89*, 15–19.
76. Shah, N. H.; Phuapradit, W.; Ahmed, H. Liquid/semisolid filling in hard gelatin capsules: Formulation and processing considerations. *Bull. Technique Gattefossé* 1996, *89*, 27–31.
77. Wiley, G. J.; Ullah, I.; Agharkar, S. N. Development of a semiautomatic system for R&D and clinical use for liquid-filled hard gelatin encapsulation. *Pharm. Technol.* 1995, *May*, 72–76.
78. Cole, E. T. Equipment for filling and sealing liquids in hard gelatin capsules. *Bull. Technique Gattefossé* 1996, *89*, 87–88.
79. Serajuddin, A. T. M.; Sheen, P. C.; Augustine, M. A. Water migration from soft gelatin capsule shell to fill material and its effect on drug solubility. *J. Pharm. Sci.* 1986, *75*, 62–64.
80. Maes, P.; Brusselmans, J.; Sereno, A.; Pitti, C.; Sonck, M.; Coffiner, M. In vitro and in vivo behavior of some liquid or semisolid filled hard gelatin capsules. *Bull. Technique Gattefossé* 1996, *89*, 63–69.
81. Al-Razzak, L. A.; Dias, L.; Kaul, D.; Ghosh, S. Lipid based systems for oral delivery: Physiological, mechanistic, and product development perspectives. *Symposia Abstracts and Biographies*, AAPS Annual Meeting, Boston, 1997; AAPS, Alexandria, VA, 1997; p 18.
82. Zantac Capsules. *Physicians' Desk Reference 1997*, Medical Economics Company: Montvale, NJ.
83. Sheen, P. C.; Kim, S. I.; Petillo, J. J.; Serajuddin, A. T. M. Bioavailability of a poorly water-soluble drug from tablet and solid dispersion in humans. *J. Pharm. Sci.* 1991, *80*, 712–714.
84. Norvir capsules. *Physician's Desk Reference 1997*; Medical Economics Company: Montvale, NJ.
85. Cinés, J. M.; Velga, M. D.; Arias, M. J.; Rabasco, A. M. Elaboration and thermal study of interactions between cinnarizine and Gelucire 33/10 physical mixtures and solid dispersions. *Int. J. Pharm.* 1995, *126*, 287–291.
86. Press release. *Abbott to Substitute Norvir Capsules with Liquid Formulation*, Abbott Laboratories, July 29, 1998.
87. Rosoff, M.; Serajuddin, A. T. M. Solubilization of diazepam in bile salts and in sodium cholate-lecithin-water phases. *Int. J. Pharm.* 1980, *6*, 137–148.
88. Sutananta, W.; Craig, D. Q. M.; Newton, J. M. An investigation into the effects of preparation conditions and storage on the rate of drug release from pharmaceutical glyceride bases. *J. Pharm. Pharmacol.* 1995, *47*, 355–359.
89. Dordunoo, S. K.; Ford, J. L.; Rubinstein, M. H. Solidification studies of poly(ethylene glycol)s. Gelucire 44/14 or their dispersions with triamterene or temazepam. *J. Pharm. Pharmacol.* 1996, *48*, 782–789.
90. Charman, W. N. Lipids and oral bioavailability: Are there yet-to-be realised opportunities? *Bull. Technique Gattefossé* 1998, *91*, 51–62.
91. Serajuddin, A. T. M.; Fakes, M. G. Sustained release formulation containing captopril and method. U. S. Patent 5,433,951, July 18, 1995, assigned to Bristol-Myers Squibb.

JS980403L

महाराष्ट्र MAHARASHTRA

CK 052003

General Stamp Office Mumbai
L. S. V. No. 840
16 NOV 2009
Paper Officer

SHRI. L. S. BAMBLE

खिडकी नं. १
अंधेरी कोर्ट बार एसोसिएशन मुंबई एसोसिएटेड मुद्रांक वेंडर्स
अंधेरी (पू.), मुंबई
दिनांक 19 NOV
सर्वश्री. S. MAJUMDAR & CO.
यांना न्यायीकेतर मुद्रांक विक्रेता
परवाना धारक मुद्रांक विक्रेता

010423

GENERAL POWER OF ATTORNEY

In the matter of The Patents Act, 1970 *as amended by* The Patents (Amendment) Act of 1999 and 2002, and The Patents Amendment Act, 2005,

And

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

And

In the matter of CIPLA LIMITED, Mumbai Central, Mumbai 400 008, India

TRUE COPY
05/08/2010.

Original filed with opposition u/s 25(1) against 2221/Del No/2008. dated. 14/03/2008

5 AUG 2010

We, the above named **CIPLA LIMITED** do hereby retain, constitute and appoint **S. MAJUMDAR, M. MAJUMDAR, DR. SANCHITA GANGULI, ABHISHEK SEN, AMIT CHAKRABORTY, A. MUKHERJEE, MYTHILI VENKATESH, N. R. SETH, MRIGANKI DUTTA, SULTANA SHAIKH, AMRITA MAJUMDAR** representatives of the Firm of S. MAJUMDAR & CO., 5, Harish Mukherjee Road, Calcutta – 700 025, India, all of Indian nationality, jointly and severally to be our Agents and Attorneys for the purpose of all acts under the Patents Act, 1970 (as amended by the Patents (Amendment) Act, 2005 or as may be amended hereafter) for all matters in which the name of the said firm of S. MAJUMDAR & CO., appears in the address for service in the respective matters and we authorize any of them to sign our name and on our behalf on all applications and other papers and writings and do such acts, as may be necessary or expedient and lastly we request that all official communications now or hereafter relating to the same may be addressed to them at their office in Calcutta and that they be recognized as our authorized Agents in all proceedings incidental thereto. Cipla Limited retains the power to revoke this Power of Attorney at any time at its own discretion.

We authorize them to appoint agents, advocates and attorneys on Cipla's expressed consent. We hereby confirm all actions, if any, already taken by them in this matter. This Power of Attorney supercedes all previous Powers of Attorney given in favour of said firm of S. MAJUMDAR & CO.

Dated this 29th day of January 2010

Name: Mr. Amar Lulla

Status: Joint Managing Director

L: 5 AUG 2010