



No. 06-042169- -00003-0000

Fecha: 2007-08-30 15:01:06 Dep. 2020 NUECREACIONE
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 400 OPOSIOBSERVTER Folios: 94

**FORMULARIO UNICO DE OPOSICION
2000-12**

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OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

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Número del expediente: 06 042.169

Solicitante: PROCAPS S.A.

**SOLICITUD
PUBLICADA**

Apoderado: REINALDO PINILLA MORENO

Título de la nueva creación o denominación del signo:

"UNA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN

TRANSPARENTE PARA EL TRATAMIENTO DEL SIDA Y PROCESO PARA PREPARAR
DICHA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE".

Gaceta: 576 de 31 de Mayo de 2007, Número de Publicación 71.

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OPOSICION PRESENTADA POR:

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial) y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia).

Justificación: VER ANEXO

2702133

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Comprobante de pago No. 07-70.016 (Oposición) Fecha Agosto 30 de 2007
07-70.013 (Prórroga) Fecha Agosto 30 de 2007

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Anexos:

☒ Comprobante de pago de la tasa

☒ Poderes, si fuere el caso

☒ Pruebas de los fundamentos de la oposición

☒ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas

☐ Documentos que acrediten el legítimo interés, si fuere el caso

☒ Copia de la oposición para el traslado al solicitante.

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 

C.C.No. 79.152.473 T.P. No. 44655

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

EXPEDIENTE 06-042-169

TÍTULO SOLICITADO: "UNA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE PARA EL TRATAMIENTO DEL SIDA Y PROCESO PARA PREPARAR DICHA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE."

PUBLICACIÓN:

GACETA No. 576 de 31 de Mayo de 2007, número de publicación 71.

SOLICITANTE:

PROCAPS S.A.

APODERADO:

REINALDO PINILLA MORENO

TRÁMITE:

PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO LA FRANCOL S.A.**, en desarrollo de lo dispuesto por los artículos 42 y siguientes de la Decisión 486 de 2000 de la Comunidad Andina de Naciones, me permito solicitarle, muy respetuosamente, dar curso a la siguiente

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **06-042-169**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos

14 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUIMICAS S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

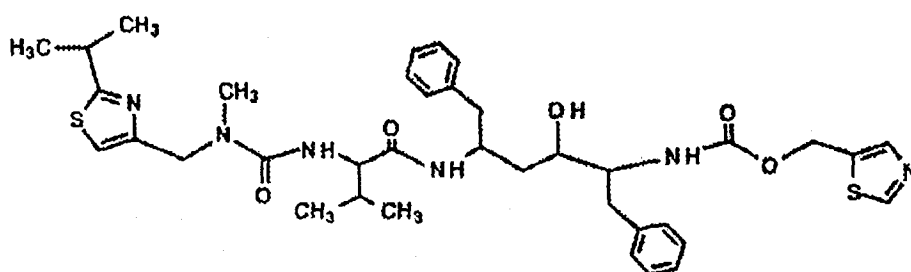
La solicitud Colombiana 06-042-169 en trámite que se refiere a una formulación farmacéutica en solución transparente que contiene ritonavir entre el 1 y 90% del peso total de la formulación, y el proceso de elaboración de la misma para ser depositada finalmente en cápsulas de gelatina, carece de novedad y de nivel inventivo como se argumenta a continuación:

- La publicación internacional WO 95/07696 publicada el 23 de Marzo de 1995 y titulada "PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS" revela una composición farmacéutica que comprende una solución de un compuesto inhibidor de proteasa HIV en un solvente orgánico farmacéuticamente aceptable, que comprende un alcohol farmacéuticamente aceptable; la composición puede opcionalmente comprender un ácido o una combinación de ácidos farmacéuticamente aceptables; adicionalmente, la solución puede ser encapsulada en cápsulas de gelatina dura o de gelatina blanda.

Adicionalmente describe:

In accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Also in accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.



II

(Ritonavir) ✓

(...)

acceptable surfactant or a mixture of pharmaceutically acceptable surfactants. In addition, the solution composition of the invention can comprise an antioxidant (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability. Solutions encapsulated in a SEC may also comprise glycerin for physical stability.

(...)

The term "pharmaceutically acceptable organic solvent" as used herein refers to polypropylene glycol; polyethylene glycol (for example, polyethylene glycol 600, polyethylene glycol 900, polyethylene glycol 540, polyethylene glycol 1450, polyethylene glycol 6000, polyethylene glycol 8000 (all available from Union Carbide) and the like); pharmaceutically acceptable alcohols which are liquids at about room temperature, approximately 20°C, (for example, propylene glycol, ethanol, 2-(2-ethoxyethoxy)ethanol (Transcutol® , Gattefosse, Westwood, NJ 07675), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and the like); polyoxyethylene castor oil derivatives (for example, polyoxyethyleneglyceroltriricinoleate or polyoxyl 35 castor oil (Cremophor®EL, BASF Corp.), polyoxyethyleneglycerol oxystearate (Cremophor®RH 40 (polyethyleneglycol 40 hydrogenated castor oil) or

(...)

Saturated polyglycolized glycerides are described in the French Pharmacopeia 10th Edition. In particular, saturated polyglycolized glycerides are mixtures of mono-, di- and tri-glycerides and polyethylene glycol mono- and di-esters obtained either by partial alcoholysis of hydrogenated vegetable oils using polyethylene glycol of relative molecular weight ranging from 200 - 2000, or by esterification of saturated fatty acids using polyethylene glycol of relative molecular weight ranging from 200 - 2000 and glycerol. Each saturated

(...)

Pharmaceutically acceptable solvents also include pharmaceutically acceptable oils such as mineral oil or a vegetable oil (for example, safflower oil, peanut oil, olive oil, fractionated coconut oil (for example, mixed triglycerides with caprylic acid and capric acid (Miglyol® 812, available from Huls AG, Witten, Germany) and the like), propyleneglycol monolaurate and the like.

(...)

aprox 2.6

A preferred pharmaceutically acceptable solvent is propylene glycol or a mixture of propylene glycol (about 80% v/v) and ethanol (about 20% v/v) or a mixture of propylene glycol (from about 80% to about 90% v/v), ethanol (from about 5% to about 10% v/v) and water (from about 5% to about 10% v/v).

Yet another preferred composition of the invention comprises a solution of (1) a compound of the formula II in the amount of from about 2% to about 30% (preferably, from about 4% to about 30%) by weight of the total solution; and

(...)

Lo anterior demuestra que en el estado del arte se encuentran composiciones farmacéuticas de Ritonavir como un agente inhibidor de la proteasa VIH en uno o más solventes orgánicos farmacéuticamente aceptables, junto con antioxidantes adecuados, incluso, puede contener Propilenglicol monolaurato entre sus excipientes, su forma farmacéutica puede ser cápsulas de gelatina blanda y los porcentajes o rangos se encuentran dentro de lo revelado en la solicitud colombiana en trámite.

Para complementar lo consignado, podemos ver que las reivindicaciones de la solicitud internacional describen:

1. A pharmaceutical composition comprising a solution of an HIV protease inhibiting compound in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.
2. The composition of Claim 1 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.
4. The composition of Claim 1 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.
10. The composition of Claim 9 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

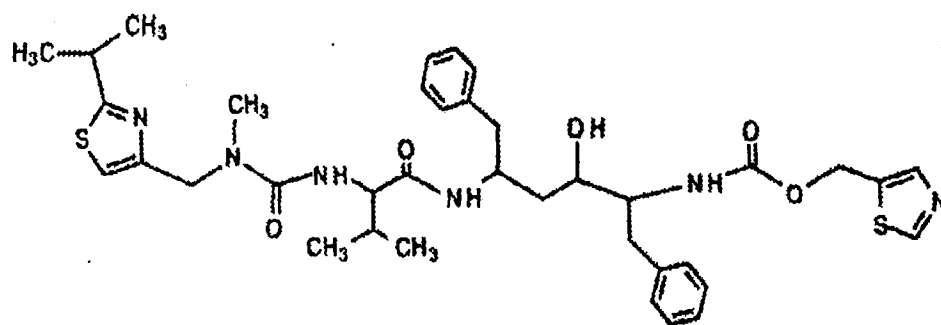
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- La publicación internacional WO 98/22106 publicada el 28 de Mayo de 1998 y titulada "PHARMACEUTICAL COMPOSITION" revela una composición farmacéutica líquida que proporciona una mejorada biodisponibilidad para compuestos inhibidores de proteasa HIV; en particular la composición comprende una solución en un solvente orgánico farmacéuticamente aceptable de a) un inhibidor de proteasa HIV y opcionalmente, b) un surfactante; y opcionalmente puede ser encapsulada en cápsulas de gelatina dura o en cápsulas blandas elásticas (SEC), tal como se pretende en la solicitud colombiana en trámite.

Más específicamente se refiere a:

In accordance with the present invention, there is a pharmaceutical composition which 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 VX-478, more preferably, a compound of the formula III or V or saquinavir or nelfinavir or indinavir or



II

(Ritonavir) ✓

(b) a pharmaceutically acceptable organic solvent which comprises a pharmaceutically acceptable long chain fatty acid or a mixture of a pharmaceutically acceptable long chain fatty acid and a pharmaceutically acceptable alcohol, and, optionally,

(c) a pharmaceutically acceptable surfactant, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

(...)

The solution composition of the invention can also comprise an antioxidant (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 alcohol" as used herein refers to alcohols which are liquids at about room temperature, approximately 20°C, for example, ethanol, propylene glycol, 2-(2-ethoxyethoxy)ethanol (Transcutol® , Gattefosse, Westwood, NJ 07675), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and the like. A preferred pharmaceutically acceptable alcohol is ethanol or propylene glycol or a mixture thereof.

(...)

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 70%; more preferably, from about 40% to about 60%) 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 70%; more preferably, from about 40% to about 60%) by weight of the total solution and

(2) ethanol in the amount of from about 0% to about 12% (preferably, from about 10% to about 12%) by weight of the total solution or propylene glycol in the amount of from about 0% to about 10% (preferably, from about 5% to about 10%) by weight of the total solution or a mixture thereof in the amount of from about 0% to about 15% (preferably, from about 10% to about 15%) by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of from about 0% to about 20% (preferably, from about 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.

(...)

Además reivindica:

4. 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 70% by weight of the total solution and (2) ethanol or propylene glycol in the amount of from about 1% to about 15% by weight of the total solution or a mixture of ethanol and propylene glycol in the amount of from about 1% to about 15% by weight of the total solution.

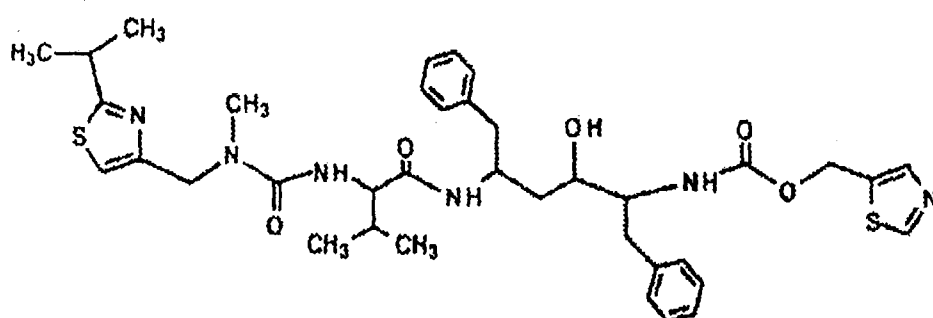
9. The composition of Claim 1 wherein the HIV protease inhibiting compound is ritonavir or a combination of ritonavir and another HIV protease inhibiting compound.

De nuevo vemos que el conjunto de características reveladas y descritas en la solicitud colombiana en trámite ya habían sido tenidas en cuenta en la solicitud internacional WO 98/22106, en consecuencia, los requisitos de patentabilidad, en especial el art 14 y 18, no se cumplen en virtud de lo revelado en dicho documento perteneciente al arte anterior.

- La solicitud internacional WO 00/74677 publicada el 14 de diciembre de 2000 y titulada "IMPROVED PHARMACEUTICAL FORMULATIONS" describe composiciones farmacéuticas mejoradas que comprenden uno o más compuestos inhibidores de proteasa HIV que tienen propiedades mejoradas de disolución en una mezcla de ácido graso, etanol y agua.

Luego en la parte descriptiva señala que:

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



II

(Ritonavir)

(...)

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

(...)

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.

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.

(...)

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,

(...)

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%.

Además reivindica:

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

Si bien es cierto que esta publicación internacional no revela el lleno de características contenidas en la solicitud colombiana en trámite, no lo es menos

que se trata de composiciones que comprenden Ritonavir en cápsulas de gelatina, solventes orgánicos adecuados, surfactantes, antioxidantes y agua dentro de la formulación; además, esta anterioridad junto con las otras hasta el momento expuestas, permiten evidenciar y reunir la información necesaria para poder llevar a cabo una formulación como la que se pretende ahora patentar.

- La publicación internacional WO 01/52821 publicada el 26 de Julio de 2000 y titulada "IMPROVES PHARMACEUTICAL FORMULATIONS" revela:

(57) Abstract: Improved pharmaceutical compositions are provided comprising one or more solubilized HIV protease inhibiting compounds having improved solubility properties in a medium and/or long chain fatty acid, or mixtures thereof, a pharmaceutically acceptable alcohol, and water.

(...)

The term "pharmaceutically acceptable alcohol" as used herein refers to alcohols which are liquid at room temperature, for example ethanol, propylene glycol, 2-(ethoxyethoxy)ethanol (Transcutol[®], Gattefosse, Westwood, NJ), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400, and the like, or mixtures thereof.

(...)

In one embodiment of the invention, a more preferred composition of the invention is a solution comprising (a) solubilized 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

(...)

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

(...)

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.

(...)

75% by weight of the total solution and (2) propylene glycol in the amount of from about 1% to about 15% by weight of the total solution, (c) water in the amount of from about 0.4% to about 3.5% and (d) a pharmaceutically

Además reivindica:

1. A pharmaceutical composition comprising:

- (a) a solubilized HIV protease inhibiting compound or a combination of solubilized HIV protease inhibiting compounds, or pharmaceutically acceptable salts thereof;
- (b) a pharmaceutically acceptable organic solvent which comprises a medium and/or long chain fatty acid or a mixture thereof, and propylene glycol;
- (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)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir).

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) propylene glycol 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) propylene glycol 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.

Quiero no decir

Una vez más se observa que el conjunto de características reveladas y descritas en la solicitud colombiana en trámite ya habían sido tenidas en cuenta en la solicitud internacional en mención, en consecuencia, los requisitos de patentabilidad no se cumplen en virtud de lo revelado en dicho documento perteneciente al arte anterior.

- La publicación internacional WO 02/096395 publicada el 05 de Diciembre de 2000 y titulada "SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR" revela:

(57) Abstract: A soft elastic capsule is described containing a pharmaceutical agent or a mixture of pharmaceutical agents. The soft elastic capsule is prepared from a fill composition and a shell composition that impart acceptable physical characteristics to the soft elastic capsule when in an equilibrium state. The pharmaceutical agents of the fill composition are also soluble when the soft elastic capsule is in the equilibrium state.

(...)

Preferably, the initial fill composition is prepared at temperatures that avoid the degradation of a HIV protease inhibitor, for example, ritonavir.

(...)

The alcohol of the fill composition can be propylene glycol, another suitable alcohol, or mixtures thereof. Suitable alcohols include, for example, ethanol, 2-2(ethoxyethoxy)ethanol, benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, and polyethylene glycol 400. Preferably, propylene glycol, a suitable alcohol, or a mixture thereof, is present in the initial fill composition, as measured by weight, in a range of 3-20%. More preferably, propylene glycol, a suitable alcohol, or a mixture thereof, is present in a range of 9-14%. Most preferably, propylene glycol, a suitable alcohol, or a mixture thereof, is present in the range of 10-13% in the initial fill composition. Propylene

(...)

En el capítulo reivindicatorio se revela:

1. A soft elastic capsule having a fill and a shell, the fill comprising:

a pharmaceutical agent or combination of pharmaceutical agents,
an alcohol,
a fatty acid, and

the shell comprising:

gelatin, and
at least one plasticizing agent,

wherein said shell has an initial state and an equilibrium state, wherein said initial state shell is underplasticized and said fill contains an alcohol amount in excess of an alcohol amount necessary to solubilize said pharmaceutical agent and said alcohol is not present in the initial state shell composition, and wherein said equilibrium state said shell becomes plasticized by the alcohol from said fill to provide suitable capsule hardness and said fill retains sufficient alcohol to maintain said pharmaceutical agent in solution.

The soft elastic capsule of claim 4 wherein said HIV inhibiting compound 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-1,6-diphenyl-3-hydroxyhexane (ritonavir).

7. The soft elastic capsule of claim 4 wherein said solubilized HIV inhibiting compound or said combination of solubilized HIV inhibiting compounds is present in said fill in a range of 10-35% by weight.

8. The soft elastic capsule of claim 1 wherein said alcohol is propylene glycol or ethanol.
9. The soft elastic capsule of claim 8 wherein propylene glycol or ethanol are present in said fill in initial state in a range of 3-20% by weight.

Como se puede apreciar, estas anterioridades contienen y reivindican las características esenciales que sustentan la invención de la solicitud colombiana en trámite, específicamente lo que se refiere a el inhibidor de proteasa (ritonavir) en el tratamiento de VIH, las características del solvente y el porcentaje del mismo en la formulación, la presencia de antioxidantes, las proporciones del principio activo y demás componentes de la formulación, y finalmente la inclusión de dicha solución en cápsulas de gelatina.

Siendo evidente la anterioridad en la obtención de formulaciones con características idénticas a la de la solicitud colombiana en trámite, es importante resaltar que con la información necesaria para realizar este tipo de formulaciones (capsulas de gelatina blanda) contenida en el estado de la técnica, la producción de las formulaciones reivindicadas por dichas solicitud colombiana en trámite se reduce a la aplicación de todos los ensayos requeridos a nivel de preformulación y formulación reconocidos por cualquier persona versada en la materia¹.

Por lo expuesto respetuosamente llamo la atención sobre el hecho de que la solicitud de la referencia, en todas sus reivindicaciones, no cumple con los requisitos dispuestos en la Decisión 486 de 2000, por tal razón no puede ser objeto de privilegio de patente de invención.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14 y 18 (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para

¹ Vila Jato J.L. TECNOLOGIA FARMACÉUTICA. Vol. II. Parte 1, Cap. 2. Páginas 62 a 67.

sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI PRUEBAS

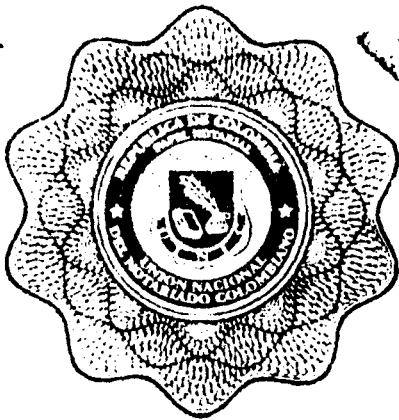
Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La publicación internacional WO 95/07696 publicada el 23 de Marzo de 1995 y titulada "PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS" páginas 5, 6, 7, 11 y capítulo reivindicatorio.
- La publicación internacional WO 98/22106 publicada el 28 de Mayo de 1998 y titulada "PHARMACEUTICAL COMPOSITION" páginas 8, 9, 19, 11, 12 y capítulo reivindicatorio.
- La publicación internacional WO 00/74677 publicada el 14 de diciembre de 2000 y titulada "IMPROVED PHARMACEUTICALS FORMULATIONS" páginas 11, 18, 22, 23 y capítulo reivindicatorio.
- La publicación internacional WO 01/52821 publicada el 26 de Julio de 2000 y titulada "IMPROVES PHARMACEUTICAL FORMULATIONS" páginas 17, 18, 20 y capítulo reivindicatorio.
- La publicación internacional WO 02/096395 publicada el 05 de Diciembre de 2000 y titulada "SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR" página 13 y capítulo reivindicatorio.

VII. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Lafranco S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. El mencionado en el acápite de pruebas.



165- B

AA 8567146

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REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE JULIO - - - -

DEL AÑO DOS MIL DOS (2002).

ACTO:

Como Acta de Verificación del Circulo de Bogotá, consta que esta copia con original que se ha presentado para su autenticación. Bogotá, D.C. Colombia

22 FEB. 2006

1.- PODER ESPECIAL.

OTORGADO POR: LAFRANCOL S.A., con Nit. No.

GONZALO L DELGADO CASTRO
NOTARIO 26 ENCARGADO

890.301.463-8

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No. 79.152.473 de Usaquén - Bogotá.

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL, DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA, ANTE MI, DIANA BEATRIZ LOPEZ,

NOTARIA TREINTA Y TRES (33)

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE SE CONSIGNA EN LOS SIGUIENTES TERMINOS:

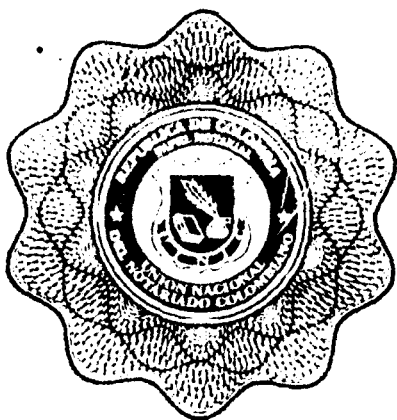
COMPARECIO: JUAN MARIA RENDON, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 17.125.100

Expedida en Bogotá

Y manifestó:

PRIMERO: Que obra en su carácter de Representante Legal de en nombre y representación de LAFRANCOL S.A, sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Cali - Valle, constituida mediante escritura pública número

De la Notaría
De fecha
Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.-----
SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a JOSE LUIS REYES VILLAMIZAR , mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C, República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo, contencioso, administrativo y judicial, en todo lo concerniente a los siguientes asuntos:-----
a.- Obtención, formulación de oberservaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos.-----
b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- administrativos relacionados con estos derechos u otros de diferente naturaleza, acciones y procesos que



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AA 8567152

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promueva Lafrancol S.A., o se promuevan contra esta y.-----

c.- Para que en todos los asuntos arriba determinados, tanto en los términos señalados por los artículos 42 y complementarios

de la decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C. pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.-----

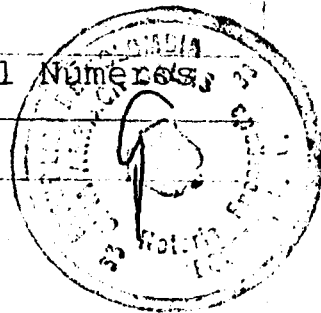
Manifestamos que de la veracidad de las declaraciones del contenido y autenticidad de los documentos anexos en éste instrumento público sólo respondemos los comparecientes.-

HASTA AQUI LA MINUTA PRESENTADA

OTORGAMIENTO Y AUTORIZACION: Leído el presente instrumento Público por los comparecientes y advertidos de la formalidad de su contenido, dentro del término legal, lo hallaron conforme con sus intenciones y lo aprobaron en todas sus partes y firmaron junto con la Suscrita Notaria quien da fe y lo autoriza. -----

Se utilizaron las hojas de papel Notarial Números

AA 8567146, 8567152.



DERECHOS NOTARIALES: \$ 49.600.00

RESOLUCION No. 4188 del 28 de Diciembre del 2001

Juan Maria Rendon
JUAN MARIA RENDON

C.C. No. 17.125.100 de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

Como Notario Veintiséis del Circuito de Bogotá, he de constar que esta copia es una copia con original que se ha expedido para su autenticación. Bogotá, D.C. Colombia

22 FEB. 2006

BONZALO L. DELGADO CASTRO
NOTARIO 26 ENCARGADO

JOSE LUIS REYES VILLAMIZAR

C.C. No. 29.152.473

TEL: 621-2631

Diana Beatriz Lopez
DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

n.c.a.

Es segunda COPIA (FOTOCOPIA)

tomada de su original que se expide conforme al

Artículo 79 del Decreto 960 de 1970 en 06

hojas útiles con destino a Jose Luis Reyes

Villamizar

Santafé de Bogotá

BOG: Dcto. 1772/79

05 JUL. 2002

Qui Amun





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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070830

Hora Certificado 11:27:25

Operacion : 02CP20830006

PAGINA No. 1

null

CERTIFICA:

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. ✓
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL : ---K 1 46 84
DIRECCION NOTIFICACION JUDICIAL: ---K 1 46 84
CIUDAD: CALI
MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTUBRE DE 1958
DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net
AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

REFORMAS DOCUMENTO INS LIBRO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
E.P. 1104 19467	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	
E.P. 2309 20089	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	
E.P. 1725 24528	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	
E.P. 1824 26360	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	
E.P. 2422 26717	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963	
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964	

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070830

Hora Certificado 11:27:25

Operacion : 02CP20830006

PAGINA No. 2

28406					
E.P. 101	31/01/1966	NOTARIA	CUARTA	DE CALI	01/02/1966
31039					
E.P. 552	21/03/1968	NOTARIA	CUARTA	DE CALI	01/04/1968
35711					
E.P. 4964	12/12/1972	NOTARIA	CUARTA	DE CALI	16/01/1973
2975 IX					
E.P. 1956	30/05/1973	NOTARIA	CUARTA	DE CALI	13/06/1973
4337 IX					
E.P. 4964	12/12/1972	NOTARIA	CUARTA	DE CALI	28/11/1973
5994 IX					
E.P. 5579	12/11/1973	NOTARIA	CUARTA	DE CALI	28/11/1973
5995 IX					
E.P. 4406	30/09/1974	NOTARIA	CUARTA	DE CALI	28/11/1974
10887 IX					
E.P. 192	03/02/1978	NOTARIA	CUARTA	DE CALI	14/02/1978
25355 IX					
E.P. 3479	07/09/1979	NOTARIA	CUARTA	DE CALI	19/09/1979
34204 IX					
E.P. 4274	12/12/1984	NOTARIA	NOVENA	DE CALI	19/12/1984
73088 IX					
E.P. 1155	21/05/1985	NOTARIA	SEPTIMA	DE CALI	03/06/1985
76917 IX					
E.P. 1553	20/06/1986	NOTARIA	SEPTIMA	DE CALI	08/07/1986
85997 IX					
E.P. 1458	09/06/1987	NOTARIA	SEPTIMA	DE CALI	24/12/1987
3508 IX					
E.P. 7222	14/12/1988	NOTARIA	TERCERA	DE CALI	19/12/1988
13847 IX					
E.P. 4530	04/09/1989	NOTARIA	TERCERA	DE CALI	07/09/1989
21508 IX					
E.P. 3865	02/08/1990	NOTARIA	TERCERA	DE CALI	13/08/1990
31708 IX					
E.P. 8305	13/12/1995	NOTARIA	TERCERA	DE CALI	23/01/1996
557 IX					
E.P. 4559	16/11/1999	NOTARIA	TERCERA	DE CALI	26/11/1999
7911 IX					
E.P. 6.004	02/12/2004	NOTARIA	TERCERA	DE CALI	14/12/2004
13371 IX					
E.P. 6241	27/12/2006	NOTARIA	TERCERA	DE CALI	19/01/2007
625 IX					

CERTIFICA:

VIGENCIA: 29 DE SEPTIEMBRE DEL A?O 2057

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070830

Hora Certificado 11:27:25

Operacion : 02CP20830006

PAGINA No. 3

CERTIFICA:

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISIOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) AÑOS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTE: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTE: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMMVLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y

*** CONTINUA ***

REPUBLICA DE COLOMBIA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070830

Hora Certificado 11:27:25

Operacion : 02CP20830006

PAGINA No. 4

DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS.
EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

GERENTE GENERAL Y REPRESENTANTE LEGAL
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

PRIMER SUPLENTE DEL GERENTE
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE
ROBERTO M. VENTURA CRISPINO
C.C.9086003

*** CONTINUA ***



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154

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070830

Hora Certificado 11:27:25

Operacion : 02CP20830006

PAGINA No. 5

PRESIDENTE

ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

VICEPRESIDENTE

ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2032 DEL LIBRO IX

FUE(ON) NOMBRADO(S) :

TERCER SUPLENTE DEL GERENTE
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2031 DEL LIBRO IX

FUE(ON) _NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO RENGLON

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070830

Hora Certificado 11:27:25

Operacion : 02CP20830006

PAGINA No. 6

ROSA VICTORIA VENTURA DE VISBAL
C.C.38992048

TERCER RENGLON
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

SUPLENTES

PRIMER RENGLON
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

SEGUNDO RENGLON
ROBERTO M. VENTURA CRISPINO
C.C.9086003

TERCER RENGLON
ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL
ALFREDO LOPEZ & CIA. LTDA
NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 20 DE OCTUBRE DE 2006
ORIGEN: ALFREDO LOPEZ & CIA LTDA
INSCRIPCION: 07 DE NOVIEMBRE DE 2006 No. 12672 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL
ALFREDO LOPEZ CAMPO

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070830

Hora Certificado 11:27:25

Operacion : 02CP20830006

PAGINA No. 7

C.C.8241912

REVISOR FISCAL SUPLENTE
GEOVANA GONZALEZ GALINDO
C.C.66959852

CERTIFICA:

CAPITAL AUTORIZADO: \$7,500,000,000
NUMERO DE ACCIONES: 750,000,000
VALOR NOMINAL: \$10
CAPITAL SUSCRITO: \$6,000,000,000
NUMERO DE ACCIONES: 600,000,000
VALOR NOMINAL: \$10
CAPITAL PAGADO: \$6,000,000,000
NUMERO DE ACCIONES: 600,000,000
VALOR NOMINAL: \$10

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL
UBICADO EN: ---K 1 46 84 DE CALI
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A
UBICADO EN: --K 1 46A 70 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO

*** CONTINUA ***

CAMARA DE COMERCIO DE CALI

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070830

Hora Certificado 11:27:25

Operacion : 02CP20830006

PAGINA No. 8

EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A

UBICADO EN: ---K 1A 46 A 32 DE CALI

FECHA MATRICULA : 29 DE ABRIL DE 1994

RENOVO : POR EL A?O 2007

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 29 DE
MARZO DE 2007 .

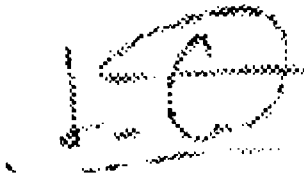
CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL
PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES
DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO
TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR
LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A
CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 30 DIAS DEL MES DE AGOSTO DEL A?O 2007 HORA: 11:07:58



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/425, 38/55, 9/48, 47/02, 47/12, 47/10		(11) International Publication Number: WO 95/07696
A1		(43) International Publication Date: 23 March 1995 (23.03.95)
(21) International Application Number: PCT/US94/09788		(81) Designated States: AU, CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(22) International Filing Date: 30 August 1994 (30.08.94)		
(30) Priority Data: 08/120,886 13 September 1993 (13.09.93) US 08/188,511 28 January 1994 (28.01.94) US 08/267,331 28 June 1994 (28.06.94) US 08/288,873 15 August 1994 (15.08.94) US		
(71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).		
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(54) Title: PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS		
(57) Abstract A pharmaceutical composition is disclosed which comprises a solution of an HIV protease inhibiting compound in a pharmaceutically acceptable organic solvent comprising a pharmaceutically acceptable alcohol. The composition can optionally comprise a pharmaceutically acceptable acid or a combination of pharmaceutically acceptable acids. The solution can optionally be encapsulated in hard gelating capsule or soft elastic gelating capsules. The solution can optionally be granulated with a pharmaceutically acceptable granulating agent.		

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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 compound III, the oral bioavailability of compound III should be at least 20%. Preferably, the oral bioavailability of compound III from the dosage form should be greater than about 40% and, more preferably, greater than about 50%.

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 compound III has good solubility in pharmaceutically acceptable organic solvents and that the solubility in such solvents is enhanced by at least four times in the presence of a pharmaceutically acceptable acid. Unexpectedly, these solutions of compound III in organic solvents provide an oral bioavailability of from about 20% to about 40% in dogs. Quite unexpectedly, 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 90% or more. In addition, quite unexpectedly, when certain solution compositions of compound III are granulated by mixing with a pharmaceutically acceptable granulating agent and the resulting solid composition is administered to dogs, an acceptable oral bioavailability is observed.

Disclosure of the Invention

In accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Also in accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

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The solution composition of the invention can also comprise from about 0 to about 3 molar equivalents (based on the amount of the HIV protease inhibiting compound in the composition) of a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids. Preferably, the pharmaceutically acceptable acid or mixture of pharmaceutically acceptable acids is present in a total amount of from about 0.2 to about 2.0 molar equivalents (based on the amount of the HIV protease inhibiting compound in the composition).

The solution composition of the invention can also comprise from about 0% to about 10% (by weight of the total solution) of water. In addition, the solution composition of the invention can comprise a pharmaceutically acceptable surfactant or a mixture of pharmaceutically acceptable surfactants. In addition, the solution composition of the invention can comprise an antioxidant (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability. Solutions encapsulated in a SEC may also comprise glycerin for physical stability.

The compositions of this invention (solution or encapsulated solution) provide improved oral bioavailability for compound II when compared to non-formulated compound II (base) or non-formulated compound II (acid addition salt), or even when compared to a mixed aqueous/organic solution (50% water, 20% ethanol, 30% propylene glycol) of compound II (methanesulfonate acid addition salt).

The term "pharmaceutically acceptable organic solvent" as used herein refers to polypropylene glycol; polyethylene glycol (for example, polyethylene glycol 600, polyethylene glycol 900, polyethylene glycol 540, polyethylene glycol 1450, polyethylene glycol 6000, polyethylene glycol 8000 (all available from Union Carbide) and the like); pharmaceutically acceptable alcohols which are liquids at about room temperature, approximately 20°C, (for example, propylene glycol, ethanol, 2-(2-ethoxyethoxy)ethanol (Transcutol® , Gattefosse, Westwood, NJ 07675), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and the like); polyoxyethylene castor oil derivatives (for example, polyoxyethyleneglyceroltriricinoleate or polyoxyl 35 castor oil (Cremophor®EL, BASF Corp.), polyoxyethyleneglycerol oxystearate (Cremophor®RH 40 (polyethyleneglycol 40 hydrogenated castor oil) or

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Cremophor®RH 60 (polyethyleneglycol 60 hydrogenated castor oil), BASF Corp.) and the like); saturated polyglycolized glycerides (for example, Gelucire® 35/10, Gelucire® 44/14, Gelucire® 46/07, Gelucire® 50/13 or Gelucire® 53/10 and the like, available from Gattefosse, Westwood, NJ 07675); polyoxyethylene alkyl ethers (for example, cetomacrogol 1000 and the like); polyoxyethylene stearates (for example, PEG-6 stearate, PEG-8 stearate, polyoxyl 40 stearate NF, polyoxyethyl 50 stearate NF, PEG-12 stearate, PEG-20 stearate, PEG-100 stearate, PEG-12 distearate, PEG-32 distearate, PEG-150 distearate and the like); ethyl oleate, isopropyl palmitate, isopropyl myristate and the like; N-methylpyrrolidinone; parafin; cholesterol; lecithin; suppository bases; pharmaceutically acceptable waxes (for example, carnauba wax, yellow wax, white wax, microcrystalline wax, emulsifying wax and the like); pharmaceutically acceptable silicon fluids; sorbitan fatty acid esters (including sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan stearate and the like); pharmaceutically acceptable saturated fats or pharmaceutically acceptable saturated oils (for example, hydrogenated castor oil (glyceryl-tris-12-hydroxystearate), cetyl esters wax (a mixture of primarily C14-C18 saturated esters of C14-C18 saturated fatty acids having a melting range of about 43-47°C), glyceryl monostearate and the like); and the like.

Pharmaceutically acceptable solvents also include pharmaceutically acceptable oils such as mineral oil or a vegetable oil (for example, safflower oil, peanut oil, olive oil, fractionated coconut oil (for example, mixed triglycerides with caprylic acid and capric acid (Miglyol® 812, available from Huls AG, Witten, Germany) and the like), propyleneglycol monolaurate and the like.

Saturated polyglycolized glycerides are described in the French Pharmacopeia 10th Edition. In particular, saturated polyglycolized glycerides are mixtures of mono-, di- and tri-glycerides and polyethylene glycol mono- and di-esters obtained either by partial alcoholysis of hydrogenated vegetable oils using polyethylene glycol of relative molecular weight ranging from 200 - 2000, or by esterification of saturated fatty acids using polyethylene glycol of relative molecular weight ranging from 200 - 2000 and glycerol. Each saturated polyglycolized glyceride is characterized by its nominal drop point, its nominal hydroxyl and saponification values and its nominal composition in fatty acids. The free glycerol content is less than 1%.

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room temperature; or it refers to semi-solid solutions wherein the pharmaceutically active agent is dissolved in a pharmaceutically acceptable solvent or mixture of solvents which is a liquid at temperatures above about room temperature (particularly, at about the temperature of the human body) but is a solid or semi-solid at about room temperature.

A preferred composition of the invention comprises a solution of (1) an HIV protease inhibiting compound (preferably, a compound of the formula II); and (2) a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Another preferred composition of the invention comprises a solution of (1) a compound of the formula II in the amount of from about 2% to about 30% (preferably, from about 4% to about 30%) by weight of the total solution; and (2) a total of from about 0.2 molar equivalent to about 3 molar equivalents (based on compound II) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Yet another preferred composition of the invention comprises a solution of (1) an HIV protease inhibiting compound (preferably, a compound of the formula II); and (2) a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

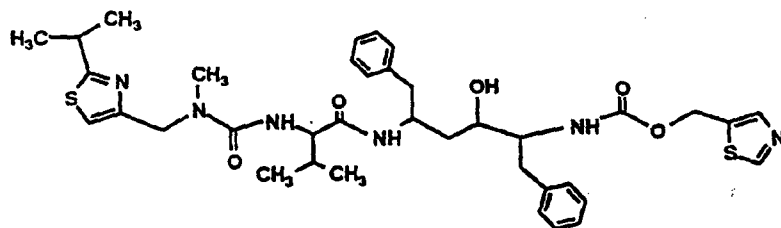
Yet another preferred composition of the invention comprises a solution of (1) a compound of the formula II in the amount of from about 2% to about 30% (preferably, from about 4% to about 30%) by weight of the total solution; and (2) a total of from about 0.2 molar equivalent to about 3 molar equivalents (based on compound II) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent

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CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a solution of an HIV protease inhibiting compound in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.
2. The composition of Claim 1 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.
3. The composition of Claim 1 further comprising a pharmaceutically acceptable acid.
4. The composition of Claim 1 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.
5. A pharmaceutical composition comprising a solution of a compound of the formula:



in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

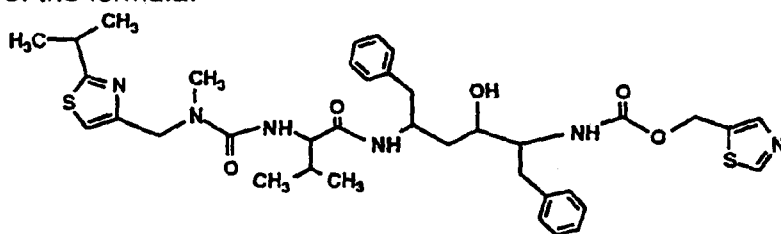
6. The composition of Claim 5 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.
7. The composition of Claim 5 further comprising a pharmaceutically acceptable acid.

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8. The composition of Claim 5 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.

9. A pharmaceutical composition comprising a solution of (a) a compound of the formula:



; and

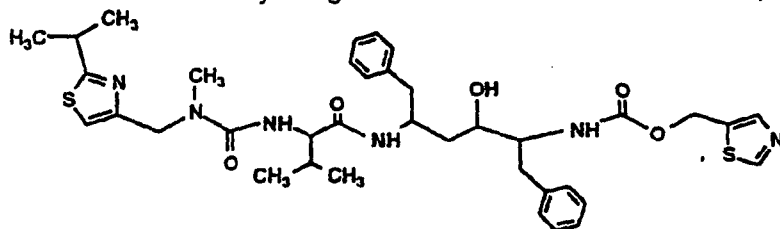
(b) a pharmaceutically acceptable acid or a combination of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

10. The composition of Claim 9 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

11. The composition of Claim 9 further comprising water.

12. The composition of Claim 9 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.

13. The composition of Claim 9 comprising a solution of (a) from about 2% to about 30% by weight of the total solution of a compound of the formula:



; and

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(b) from about 0.2 molar equivalent to about 3 molar equivalents, based upon the amount of the compound of part (a), of a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol and the solvent comprising from about 50 % to about 95 % by weight of the total solution.

14. The composition of Claim 13 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

15. The composition of Claim 13 comprising a solution of (1) (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 in the amount of from about 2% to about 30% by weight of the total solution and (2) a total of from about 0.2 to about 2 molar equivalents (based on the compound of part (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) a pharmaceutically acceptable alcohol or mixture of pharmaceutically acceptable alcohols in a total amount of from about 2% to about 50% by weight of the total solution, said alcohol or mixture of alcohols being a liquid at room temperature and (b) a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents in a total amount of from about 20% to about 60% by weight of the total solution, said solvent or mixture of solvents having a melting point between about 20°C and about 60°C, said solvent or mixture of solvents being miscible with the alcohol or mixture of alcohols and providing a homogeneous mixture with the alcohol or mixture of alcohols, said homogeneous mixture being a solid or semi-solid at about 20°C, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

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16. The composition of Claim 15 comprising a solution of (1) (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 in the amount of from about 2% to about 30% by weight of the total solution and (2) a total of from about 0.2 to about 2 molar equivalents (based on the compound of part (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 5% to about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 20% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 20% to about 60% by weight of the total solution or a total amount of from about 20% to about 60% by weight of the total solution of (i) a saturated polyglycolized glyceride or (ii) a mixture of saturated polyglycolized glycerides, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

17. The composition of Claim 16 comprising a solution of (1) (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 in the amount of from about 20% to about 25% by weight of the total solution and (2) a total of from about 1.5 to about 2 molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 20 % to about 22% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

18. The composition of Claim 16 comprising a solution of (1) (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 in the amount of from about 15% to about 20% by

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weight of the total solution and (2) a total of from about 0.3 to about 0.6 molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

19. The composition of Claim 16 comprising a solution of: (1) (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 in the amount of from about 15% to about 20% by weight of the total solution in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 40% by weight of the total solution, (b) ethanol in the amount of about 2% to about 3% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

20. The composition of Claim 16 comprising a solution of (1) (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 in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of from about 0.3 to about 0.6 molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 10% to about 15% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

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21. The composition of Claim 13 comprising a solution of (a) about 8.8 % by weight of the total solution of (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 ; and (b) about 2 molar equivalents, based upon the amount of the compound of part (a), of hydrochloric acid in a mixture comprising about 82 % by weight of the total solution of propylene glycol, about 3.5 % by weight of the total weight of the solution of ethanol and about 4.4 % by weight of the total solution of water.

22. The composition of Claim 21 wherein the solution is encapsulated in a hard gelatin capsule.

23. The composition of Claim 16 comprising a solution of (1) (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 in the amount of from about 4% to about 30% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 10% to about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 8% , and (c) polyethylene glycol 540 in the amount of from about 25% to about 60% by weight of the total solution or saturated polyglycolized glyceride in the amount of from about 25% to about 60% by weight of the total solution.

24. The composition of Claim 23 wherein the solution is encapsulated in a hard gelatin capsule.

25. The composition of Claim 16 comprising a solution of (1) (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 in the amount of from about 20% to about 25% by weight of the

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total solution and (2) a total of about two molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 22% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

26. The composition of Claim 25 wherein the solution is encapsulated in a hard gelatin capsule.

27. The composition of Claim 16 comprising a solution of: (1) (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 in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound (1)) of a mixture of citric acid and hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

28. The composition of Claim 27 wherein the solution is encapsulated in a hard gelatin capsule.

29. The composition of Claim 16 comprising a solution of (1) (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 in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound (1)) of p-toluene- sulfonic acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 40% by weight of the total solution, (b) ethanol in the amount of from about

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2% to about 3% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 30% to about 35% by weight of the total solution.

30. The composition of Claim 29 wherein the solution is encapsulated in a hard gelatin capsule.

31. The composition of Claim 16 comprising a solution of: (1) (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 in the amount of about 22% by weight of the total solution and (2) a total of about 1.6 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 20% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

32. The composition of Claim 31 wherein the solution is encapsulated in a hard gelatin capsule.

33. The composition of Claim 16 comprising a solution of: (1) (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 in the amount of about 18% by weight of the total solution and (2) a total of about 0.5 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

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34. The composition of Claim 33 wherein the solution is encapsulated in a hard gelatin capsule.

35. The composition of Claim 16 comprising a solution of: (1) (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 in the amount of about 22% by weight of the total solution and (2) a total of about 1.8 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 20% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

36. The composition of Claim 35 wherein the solution is encapsulated in a hard gelatin capsule.

37. The composition of Claim 16 comprising a solution of: (1) (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 in the amount of about 17% by weight of the total solution and (2) a total of about 0.4 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 14% by weight of the total solution, (b) ethanol in the amount of about 12% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

38. The composition of Claim 37 wherein the solution is encapsulated in a hard gelatin capsule.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶ : A61K 31/425, 31/535, 31/55, 47/10, 47/12, 9/48	A1	(11) International Publication Number: WO 98/22106 (43) International Publication Date: 28 May 1998 (28.05.98)
(21) International Application Number: PCT/US97/20794 (22) International Filing Date: 12 November 1997 (12.11.97) (30) Priority Data: 08/754,390 21 November 1996 (21.11.96) US (71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US). (72) Inventors: LIPARI, John; 6600 Apollo Drive, Racine, WI 53406 (US). AL-RAZZAK, Laman, A.; 2325 Hybernian Drive, Highland Park, IL 60035 (US). GHOSH, Soumojeet; Apartment 2A, 219 Dittmer Lane, Lindenhurst, IL 60046 (US). GAO, Rong; Apartment 201, 4255 Greenleaf Court, Park City, IL 60085 (US). KAUL, Dilip; 4334 Buckingham Drive, Gurnee, IL 60031 (US). (74) Agents: CROWLEY, Steven, R. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), 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 <i>With international search report.</i>
(54) Title: PHARMACEUTICAL COMPOSITION		
(57) Abstract A liquid pharmaceutical composition providing improved oral bioavailability is disclosed for compounds which are inhibitors of HIV protease. In particular, the composition comprises a solution in a pharmaceutically acceptable organic solvent of (a) the HIV protease inhibitor and optionally, (b) a surfactant. The composition can optionally be encapsulated in either hard gelating capsules or soft elastic capsules (SEC).		

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Compound 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, compound III in the free base form would be expected to provide very low oral bioavailability. In fact, the free base form 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.

Acid addition salts of compound III (for example, bis-hydrochloride, bis-tosylate, 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 compound 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 compound III, the oral bioavailability of compound III should be at least 20%. Preferably, the oral bioavailability of compound III from the dosage form should be greater than about 40% and, more preferably, greater than about 50%.

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 compound 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.

Disclosure of the Invention

In accordance with the present invention, there is a pharmaceutical composition which is a solution comprising

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- (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 VX-478, more preferably, a compound of the formula III or V or saquinavir or nelfinavir or indinavir or VX-478, 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 VX-478), 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 VX-478)),
- (b) a pharmaceutically acceptable organic solvent which comprises a pharmaceutically acceptable long chain fatty acid or a mixture of a pharmaceutically acceptable long chain fatty acid and a pharmaceutically acceptable alcohol,
- and, optionally,
- (c) a pharmaceutically acceptable surfactant.

In the above solution composition, preferred HIV protease inhibitors as individual compounds are the compound of the formula III or V or saquinavir or nelfinavir or indinavir or VX-478. In the above composition, preferred combinations of HIV protease inhibitors are the compound of formula III and the compound of formula V, the compound of formula III and saquinavir, the compound of formula III and indinavir, the compound of formula III and nelfinavir, the compound of formula III and VX-478, nelfinavir and the compound of formula V, nelfinavir and saquinavir, nelfinavir and indinavir, nelfinavir and VX-478.

Also in accordance with the present invention, there is a pharmaceutical composition which 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 VX-478, more preferably, a compound of the formula III or V or saquinavir or nelfinavir or indinavir or VX-478, 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 VX-478), or, more preferably, a

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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 VX-478)),

(b) a pharmaceutically acceptable organic solvent which comprises a pharmaceutically acceptable long chain fatty acid or a mixture of a pharmaceutically acceptable long chain fatty acid and a pharmaceutically acceptable alcohol, and, optionally,

(c) a pharmaceutically acceptable surfactant, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

In the above encapsulated solution composition, preferred HIV protease inhibitors as individual compounds are the compound of the formula III or V or saquinavir or nelfinavir or indinavir or VX-478. In the above composition, preferred combinations of HIV protease inhibitors are the compound of formula III and the compound of formula V, the compound of formula III and saquinavir, the compound of formula III and indinavir, the compound of formula III and nelfinavir, the compound of formula III and VX-478, nelfinavir and the compound of formula V, nelfinavir and saquinavir, nelfinavir and indinavir, nelfinavir and VX-478.

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

The compositions of this invention (solution or encapsulated solution) provide improved oral bioavailability for HIV protease inhibitors. In particular, the compositions of this invention (solution or encapsulated solution) provide improved oral bioavailability for compound III when compared to non-formulated compound III (base) or non-formulated compound III (acid addition salt).

The term "pharmaceutically acceptable long chain fatty acid" as used herein refers to saturated, mono-unsaturated or di-unsaturated C₁₂ to C₁₈ carboxylic acids which are liquids at room temperature. Preferred long chain fatty acids are mono-unsaturated C₁₆-C₂₀ carboxylic acids which are liquids at room temperature. A most preferred long chain fatty acid is oleic acid.

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The term "pharmaceutically acceptable alcohol" as used herein refers to alcohols which are liquids at about room temperature, approximately 20°C, for example, ethanol, propylene glycol, 2-(2-ethoxyethoxy)ethanol (Transcutol® , Gattefosse, Westwood, NJ 07675), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and the like. A preferred pharmaceutically acceptable alcohol is ethanol or propylene glycol or a mixture thereof.

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 (Cremophor®RH 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, Poloxamer®188, Poloxamer®237, Poloxamer®388, Poloxamer®407 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 (Tween® 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 (Cremophor®EL, BASF Corp.).

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

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saquinavir or nelfinavir or indinavir or, more preferably, a compound of the 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%; most preferably, from about 15% 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 70%; more preferably, from about 40% to about 60%) 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 70%; more preferably, from about 40% to about 60%) by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% (preferably, from about 6% to about 12%) by weight of the total solution and

(c) 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 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.

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CLAIMS

What is claimed is:

1. A pharmaceutical composition which is a solution comprising
 - (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds,
 - (b) a pharmaceutically acceptable organic solvent which comprises a pharmaceutically acceptable long chain fatty acid or a mixture of a pharmaceutically acceptable long chain fatty acid and a pharmaceutically acceptable alcohol,
 - and, optionally,
 - (c) a pharmaceutically acceptable surfactant.
2. The composition of Claim 1 comprising
 - (a) an HIV protease inhibiting compound or a combination of HIV protease inhibiting compounds in the amount of from about 1% to about 50% 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% 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% by weight of the total solution and
 - (2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% by weight of the total solution and
 - (c) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 40% by weight of the total solution.
3. The composition of Claim 1 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.
4. 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 70% by weight of the total solution and (2) ethanol or propylene

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glycol in the amount of from about 1% to about 15% by weight of the total solution or a mixture of ethanol and propylene glycol in the amount of from about 1% to about 15% by weight of the total solution.

5. 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 70% by weight of the total solution and (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture of ethanol and propylene glycol in the amount of from about 5% to about 15% by weight of the total solution.

6. The composition of Claim 1 wherein the solvent comprises (1) oleic acid in the amount of from about 40% to about 70% by weight of the total solution and (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture of ethanol and propylene glycol in the amount of from about 10% to about 15% by weight of the total solution.

7. The composition of Claim 1 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)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)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;

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);

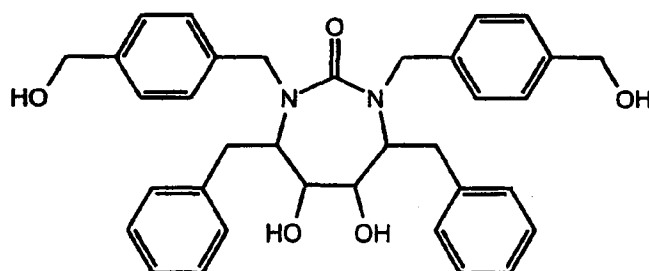
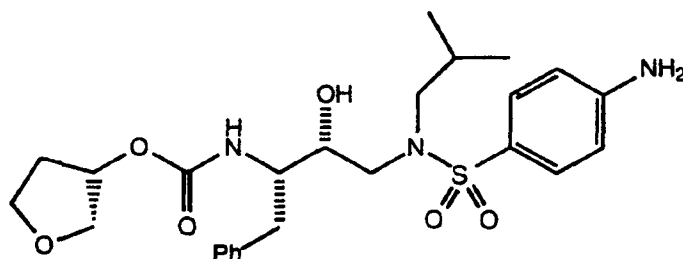
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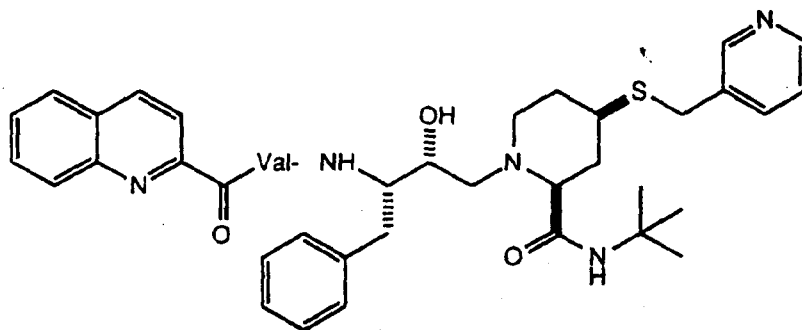
5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

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

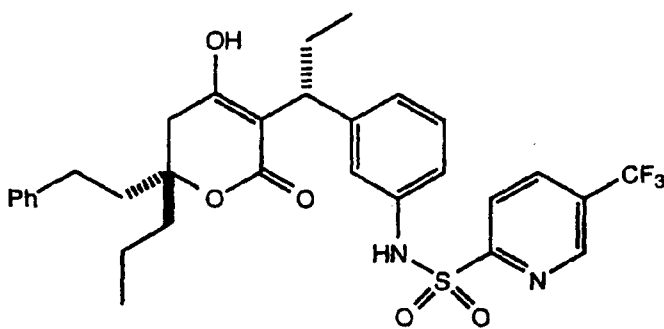
5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

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





; and



or a pharmaceutically acceptable salt of any of the above.

8. The composition of Claim 1 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-methyl butanoyl) amino-1,6-diphenylhexane, indinavir, saquinavir, nelfinavir or VX-478.

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

10. The composition of Claim 1 wherein the combination of HIV protease inhibiting compounds is:
 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;
 ritonavir and indinavir;

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ritonavir and saquinavir;
ritonavir and nelfinavir;
ritonavir and VX-478;
saquinavir and nelfinavir;
indinavir and nelfinavir;
nelfinavir 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; or
nelfinavir and VX-478.

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

12. The composition of Claim 1 comprising

- (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) a pharmaceutically acceptable long chain fatty acid in the amount of from about 40% to about 99% 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% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% by weight of the total solution and
- (c) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 20% by weight of the total solution.

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

14. The composition of Claim 12 comprising

- (a) ritonavir in the amount of from about 5% to about 25% by weight of the total solution,

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(b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable long chain fatty acid in the amount of from about 30% to about 70% 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 30% to about 70% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 6% to about 12% by weight of the total solution and

(c) a pharmaceutically acceptable surfactant in the amount of from about 5% to about 10% by weight of the total solution.

15. The composition of Claim 14 wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC).

16. The composition of Claim 1 comprising

(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 or (ii) a mixture of (1) 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 0% to about 12% by weight of the total solution or propylene glycol in the amount of from about 0% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 0% to about 15% by weight of the total solution and

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

17. The composition of Claim 16 comprising

(a) ritonavir in the amount of 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 30% to about 70% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 30% to about 70% by weight of the total solution and

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- (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 10% to about 15% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 5% to about 10% by weight of the total solution.

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

19. The composition of Claim 16 comprising

- (a) ritonavir in the amount of about 20% 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 62% to about 64% by weight of the total solution and (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 6% by weight of the total solution.

20. The composition of Claim 16 comprising

- (a) ritonavir in the amount of about 20% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 65% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 5% by weight of the total solution.

21. The composition of Claim 16 comprising

- (a) ritonavir in the amount of about 20% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 60% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

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(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

22. The composition of Claim 1 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 1% to about 50% 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% 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% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% by weight of the total solution and
- (c) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 40% by weight of the total solution.

23. The composition of Claim 22 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 5% to about 35% 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 30% to about 70% 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 30% to about 70% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 6% to about 12% by weight of the total solution and
- (c) a pharmaceutically acceptable surfactant in the amount of from about 2% to about 20% by weight of the total solution.

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24. The composition of Claim 22 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 1% to about 50% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 20% to about 99% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 20% to about 99% by weight of the total solution and (2) ethanol in the amount of from about 0% to about 12% by weight of the total solution or propylene glycol in the amount of from about 0% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 0% to about 15% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 0% to about 20% by weight of the total solution

25. The composition of Claim 24 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of from about 5% to about 35% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 30% to about 70% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 30% to about 70% by weight of the total solution and (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture thereof in the amount of about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 5% to about 10% by weight of the total solution.

26. The composition of Claim 22 comprising

- (a) (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 30% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises

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a mixture of (1) oleic acid in the amount of about 50% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

27. The composition of Claim 1 comprising

(a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution and another HIV protease inhibitor in the amount of from about 1% to about 50% 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 10% to about 98% 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 98% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 0% to about 15% by weight of the total solution and

(c) a pharmaceutically acceptable surfactant in the amount of from about 0% to about 20% by weight of the total solution.

28. The composition of Claim 27 comprising

(a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution and another HIV protease inhibitor in the amount of from about 5% 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 30% to about 70% 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 30% to about 70% by weight of the total solution and (2) a pharmaceutically acceptable alcohol in the amount of from about 6% to about 120% by weight of the total solution and

(c) a pharmaceutically acceptable surfactant in the amount of from about 5% to about 10% by weight of the total solution.

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29. The composition of Claim 27 comprising

- (a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution and another HIV protease inhibitor in the amount of from about 1% to about 50% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 10% to about 98% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 10% to about 98% by weight of the total solution and (2) ethanol in the amount of from about 0% to about 12% by weight of the total solution or propylene glycol in the amount of from about 0% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 0% to about 15% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 0% to about 20% by weight of the total solution.

30. The composition of Claim 29 comprising

- (a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution and another HIV protease inhibitor in the amount of from about 5% to about 40% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises (i) oleic acid in the amount of from about 30% to about 70% by weight of the total solution or (ii) a mixture of (1) oleic acid in the amount of from about 30% to about 70% by weight of the total solution and
- (2) ethanol in the amount of from about 10% to about 12% by weight of the total solution or propylene glycol in the amount of from about 5% to about 10% by weight of the total solution or a mixture thereof in the amount of from about 10% to about 15% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of from about 5% to about 10% by weight of the total solution.

31. The composition of Claim 29 comprising

- (a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-

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diphenylhexane in the amount of from about 1% to about 50% 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 10% to about 88% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

32. The composition of Claim 31 comprising

(a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution 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 in the amount of from about 5% to about 40% 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 40% to about 65% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution, in .

33. The composition of Claim 27 comprising

(a) a mixture of ritonavir in the amount of about 5% by weight of the total solution 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 in the amount of about 30% by weight of the total solution,

(b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 45% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and

(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

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34. The composition of Claim 27 comprising

- (a) a mixture of ritonavir in the amount of about 15% by weight of the total solution 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 in the amount of about 15% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 50% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

35. The composition of Claim 27 comprising

- (a) a mixture of ritonavir in the amount of about 15% by weight of the total solution 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 in the amount of about 5% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 60% by weight of the total solution and (2) ethanol in the amount of about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

36. The composition of Claim 27 comprising a mixture of 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, the ratio (w/w) of ritonavir to (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane being from about 1:16 to about 5:1.

37. The composition of Claim 36 comprising a mixture of 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, the

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ratio (w/w) of ritonavir to (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane being from about 1:8 to about 3:1.

38. The composition of Claim 1 comprising

- (a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution and another HIV protease inhibiting compound in the amount of from about 1% to about 50% 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 10% to about 88% by weight of the total solution and (2) propylene glycol in the amount of from about 5% to about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

39. The composition of Claim 38 comprising

- (a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution 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 in the amount of from about 5% to about 40% 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 40% to about 65% by weight of the total solution and (2) propylene glycol in the amount of from about 6% to about 8% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

40. The composition of Claim 38 comprising

- (a) a mixture of ritonavir in the amount of from about 1% to about 30% by weight of the total solution 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 in the amount of from about 1% to about 50% by weight of the total solution,

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- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of
- (1) oleic acid in the amount of from about 10% to about 88% by weight of the total solution and (2) propylene glycol in the amount of from about 5% to about 10% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

41. The composition of Claim 40 comprising

- (a) a mixture of ritonavir in the amount of from about 5% to about 25% by weight of the total solution 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 in the amount of from about 5% to about 40% 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 40% to about 65% by weight of the total solution and (2) propylene glycol in the amount of from about 6% to about 8% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

42. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 6.0% by weight of the total solution 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 in the amount of about 24% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of
- (1) oleic acid in the amount of about 52.5% by weight of the total solution and
- (2) propylene glycol in the amount of about 7.5% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

43. The composition of Claim 41 comprising a solution of (a) a mixture of ritonavir in the amount of about 5% by weight of the total solution and (2S, 3S,

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5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in the amount of about 25% by weight of the total solution and (b) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution, in a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 52.5% by weight of the total solution and (2) propylene glycol in the amount of about 7.5% by weight of the total solution.

44. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 8% by weight of the total solution 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 in the amount of about 24% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 50.5% by weight of the total solution and (2) propylene glycol in the amount of about 7.5% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

45. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 8.25% by weight of the total solution 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 in the amount of about 22% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of (1) oleic acid in the amount of about 52.25% by weight of the total solution and (2) propylene glycol in the amount of about 7.5% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

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46. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 5% by weight of the total solution 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 in the amount of about 30% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of
 - (1) oleic acid in the amount of about 47.5% by weight of the total solution and
 - (2) propylene glycol in the amount of about 7.5% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

47. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 15% by weight of the total solution 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 in the amount of about 15% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of
 - (1) oleic acid in the amount of about 52.5% by weight of the total solution and
 - (2) propylene glycol in the amount of about 7.5% by weight of the total solution and
- (c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

48. The composition of Claim 41 comprising

- (a) a mixture of ritonavir in the amount of about 13% by weight of the total solution 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 in the amount of about 17% by weight of the total solution,
- (b) a pharmaceutically acceptable organic solvent which comprises a mixture of
 - (1) oleic acid in the amount of about 52.5% by weight of the total solution and
 - (2) propylene glycol in the amount of about 7.5% by weight of the total solution and

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(c) polyoxyl 35 castor oil in the amount of about 10% by weight of the total solution.

49. The composition of Claim 41 comprising a mixture of 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, the ratio (w/w) of ritonavir to (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane being from about 1:16 to about 5:1.

50. The composition of Claim 47 comprising a mixture of 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, the ratio (w/w) of ritonavir to (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane being from about 1:8 to about 3:1.

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

(19) World Intellectual Property Organization
International Bureau



INTERNATIONAL BUREAU OF PATENT COOPERATION
358, RUE DE LA FOIRE
CHAMBELEN, SUISSE

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

PCT

(10) International Publication Number
WO 00/74677 A2

(51) International Patent Classification⁷: A61K 31/425.
9/48, A61P 31/18

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Park, IL 60064-6050 (US).

(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

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377, Building AP6D, 100 Abbott Park Road, Abbott Park,
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(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).

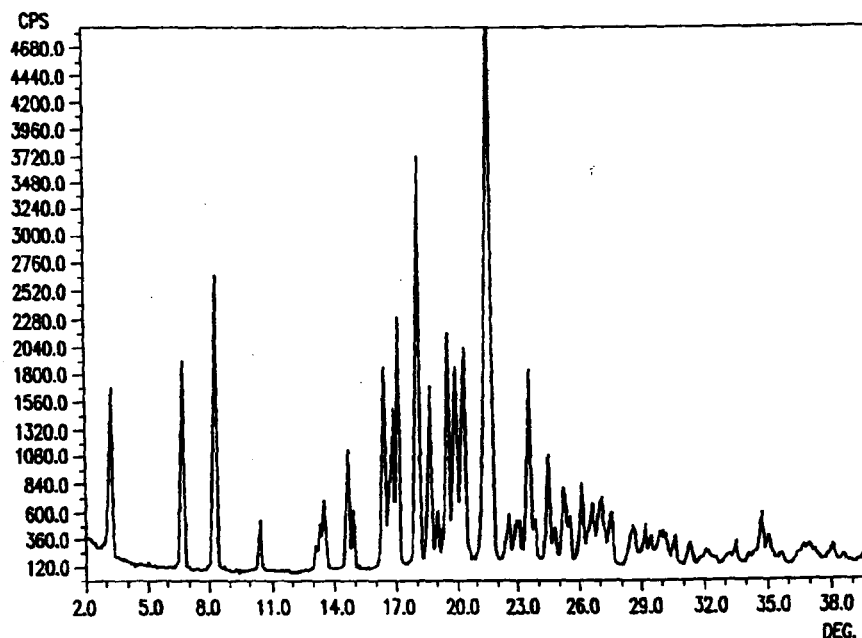
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Published:

— 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.

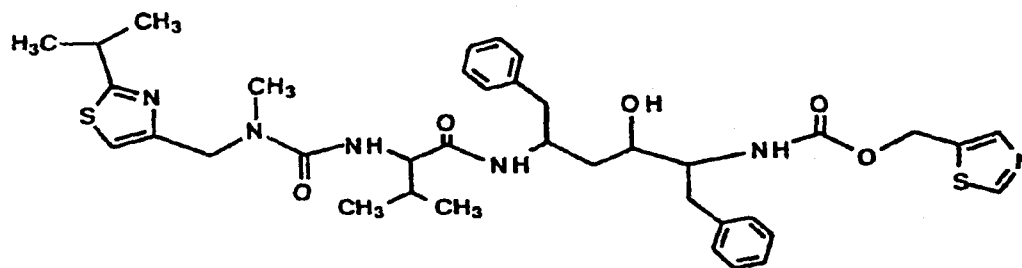
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wherein R1 is lower alkyl and R2 and R3 are phenyl and related compounds or a pharmaceutically acceptable salt thereof, disclosed in PCT Patent Application No. W0 94/14436, published July 7, 1994 and U.S. Patent No. 5,541,206, issued July 30, 1996, 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.



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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:

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197Summary 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

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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

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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,

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200CLAIMS

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-methylbutanoyl] amino-1,6-diphenylhexane.

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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)) -penta neamide (indinavir);

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

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

1 -Naphthoxyacetyl-beta-methylthio-Ala- (2S, 3S) -3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-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*]] -N¹ [3- [[[(1, 1 -dimethylethyl) amino] carbonyl] (2-methylpropyl) amino] -2-

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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

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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-methylbutanoyl] 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))-penta neamide (indinavir);

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

S(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-

phenylmethylexanoyl-(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*]]-N¹ [3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinoliny]carbonyl)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-methyl

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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.

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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).

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are mono-unsaturated C₁₆-C₂₀ fatty acids which are liquids at room temperature. A most preferred fatty acid is oleic acid, with or without additional medium and/or long chain fatty acids in the mixture. One suitable source of said
5 oleic acid is Henkel Corporation.

The term "pharmaceutically acceptable alcohol" as used herein refers to alcohols which are liquid at room temperature, for example ethanol, propylene glycol, 2-2(ethoxyethoxy)ethanol (Transcutol[®], Gattefosse, Westwood,
10 NJ), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400, and the like, or mixtures thereof.

Preferred pharmaceutically acceptable solvents comprise (1) pharmaceutically acceptable medium and/or long
15 chain fatty acid in the amount of from about 40% to about 75% by weight of the total solution; (2) ethanol or propylene glycol 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
20 total solution. More preferred pharmaceutically acceptable solvents comprise (1) a pharmaceutically acceptable medium and/or long chain fatty acid in the amount of from about 40% to about 75% by weight of the total solution and (2) ethanol or propylene glycol in the amount of from about 3%
25 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 or propylene glycol in the amount of from about 3% to about 12% by
30 weight of the total solution.

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In one embodiment of the invention, a more preferred composition of the invention is a solution comprising (a) solubilized 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 medium and/or 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) solubilized 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

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In one embodiment of the invention, a more preferred composition of the invention is a solution comprising (a) a combination of solubilized HIV protease inhibiting compounds which are ritonavir and ABT-378 in the amount of
5 from about 1% to about 45% (preferably, from about 5% to about 45%) by weight of the total solution, and (b) a pharmaceutically acceptable organic solvent which comprises (i) a pharmaceutically acceptable medium and/or long chain fatty acid in the amount of from about 40% to about 99%
10 (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) propylene
15 glycol in the amount of from about 1% to about 15% 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
20 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
25 a solution comprising (a) a combination of solubilized HIV protease inhibiting compounds which are ritonavir and ABT-378 in the amount of from about 1% to about 45% (preferably, from about 5% to about 45%) by weight of the total solution, (b) a pharmaceutically acceptable organic
30 solvent which comprises (i) oleic acid in the amount of

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210CLAIMS

What is claimed is:

- 5 1. A pharmaceutical composition comprising:
- (a) a solubilized HIV protease inhibiting compound or a combination of solubilized HIV protease inhibiting compounds, or pharmaceutically acceptable salts thereof;
 - 10 (b) a pharmaceutically acceptable organic solvent which comprises a medium and/or long chain fatty acid or a mixture thereof, and propylene glycol;
 - (c) water; and
 - (d) optionally, a pharmaceutically acceptable
 - 15 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)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir).

20

3. The composition according to Claim 1 wherein said combination of HIV protease inhibiting compounds is

25 (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)-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-

30 tetrahydropyrimid-2-onyl)-3-methyl-

butanoyl) amino-1,6-diphenylhexane (ABT-378).

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) -L-valinyl) amino-2- (N- ((5-thiazolyl) methoxy-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-tetrahydropyrimid-2-onyl) -3-methylbutanoyl) 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-asparaginy] amino] butyl] - (4aS,8aS) -isoquinoline-3(S) -carboxamide (saquinavir);
- 5(S) -Boc-amino-4(S) -hydroxy-6-phenyl-2(R) -phenylmethylhexanoyl- (L) -Val- (L) -Phe-morpholin-4-ylamide;
- 1 -Naphthoxyacetyl-beta-methylthio-Ala- (2S, 3S) -3-amino-2-hydroxy-4-butanoyl
- 1,3-thiazolidine-4-t-butylamide;
- 5-isoquinolinoxyacetyl-beta-methylthio-Ala- (2S,3S) -3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

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

5 VX-478;

DMP-323;

DMP-450;

AG1343 (nelfinavir);

BMS 186,318;

10 SC-55389a;

BILA 1096 BS; and

U-140690 (tipranavir),

or a pharmaceutically acceptable salt thereof.

15 5. The composition according to Claim 1 wherein said
medium and/or long chain fatty acid is oleic acid.

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

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

25 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) propylene glycol in the
amount of from about 3% to about 12% by weight of the total

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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
5 comprises (1) oleic acid in the amount of from about 40% to about 75% by weight of the total solution; (2) propylene glycol 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
10 solution.

10. The composition of Claim 9 wherein the HIV protease inhibiting compound is selected from the group consisting of:

15 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-

20 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

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

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

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- quinoline-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)-
5 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*)]-N¹ [3-[[[(1,1'-
10 dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-
hydroxy-1-(phenylmethyl)propyl]-2-[(2-
quinolinylcarbonyl)amino]-butanediamide;
VX-478;
DMP-323;
15 DMP-450;
AG1343 (nelfinavir);
BMS 186,318;
SC-55389a;
BILA 1096 BS; and
20 U-140690 (tipranavir),
or a pharmaceutically acceptable salt thereof.

11. The composition of Claim 9 wherein the HIV
protease inhibiting compound is ritonavir, (2S, 3S,
25 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-
hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl
butanoyl) amino-1,6diphenylhexane, indinavir, saquinavir,
nelfinavir, or VX-478.

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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.

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

10 14. The composition of Claim 1 which comprises:
(a) ritonavir and ABT-378 in the amount of from about 1% to about 45% by weight of the total solution;

15 (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) propylene glycol in the amount of from about 1% to about 15% by weight of the total solution; and

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

15. The composition of Claim 14 which comprises:
(a) ritonavir and ABT-378 in the amount of from
25 about 1% to about 45% 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) propylene glycol in the amount of from about 1% about 8% by
30 weight of the total solution; and

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 December 2002 (05.12.2002)

PCT

(10) International Publication Number
WO 02/096395 A1

(51) International Patent Classification:
31/513, 31/427, A61P 31/18

A61K 9/48.

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(21) International Application Number: PCT/US02/15955

(22) International Filing Date: 21 May 2002 (21.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/866,285 25 May 2001 (25.05.2001) US

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(US).

(81) Designated States (national): AU, AC, 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, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN,
YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SI, 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).

Published:
with international search report

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



WO 02/096395 A1

(54) Title: SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR

(57) Abstract: A soft elastic capsule is described containing a pharmaceutical agent or a mixture of pharmaceutical agents. The soft elastic capsule is prepared from a fill composition and a shell composition that impart acceptable physical characteristics to the soft elastic capsule when in an equilibrium state. The pharmaceutical agents of the fill composition are also soluble when the soft elastic capsule is in the equilibrium state.

In the current invention, a portion of the amount of alcohol present in the initial fill composition will migrate into the shell of the soft elastic capsule upon equilibrium of the fill components with the shell components. A substantially smaller portion, if any, of the amounts of the other components of the fill composition, for example, the pharmaceutical agents, the fatty acid, and the surfactant, will migrate into the shell upon equilibrium. Therefore, the ranges by percentage weight in the fill composition of the pharmaceutical agents, the fatty acid, and the surfactant, as described herein, sufficiently reflect the concentration of these components of the fill composition in both the initial state and the equilibrium state.

Included in this embodiment, the increased amount of alcohol in the initial fill composition is also sufficient to retain the solubility of the pharmaceutical agent or combination of pharmaceutical agents upon equilibration of the fill composition with the shell composition. The initial fill composition is also formulated to include an amount of alcohol, for example, propylene glycol, sufficient to solubilize the pharmaceutical agent or pharmaceutical agents, for example, HIV protease inhibitors, without the addition of heat. Preferably, the initial fill composition is prepared at temperatures that avoid the degradation of a HIV protease inhibitor, for example, ritonavir.

Included in this embodiment, the increased amount of alcohol in the fill composition is also sufficient to properly plasticize the shell of the soft elastic capsule upon equilibrium of the fill composition and the shell composition. The amount of plasticizing agent in the initial shell composition is not sufficient to provide proper plasticity to the shell if no additional plasticizing agent(s), for example, alcohol, migrates into the shell during equilibrium or is otherwise added. For example, a initial shell composition formulated to be underplasticized will produce a soft elastic capsule having a shell that is too brittle if no additional alcohol, for example, polypropylene glycol, migrates into the shell. In the current invention, the excess alcohol contained in the initial fill composition can contribute to the plasticity of the shell and can become a plasticizing agent in the shell upon equilibrium.

The alcohol of the fill composition can be propylene glycol, another suitable alcohol, or mixtures thereof. Suitable alcohols include, for example, ethanol, 2-(ethoxyethoxy)ethanol, benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, and polyethylene glycol 400. Preferably, propylene glycol, a suitable alcohol, or a mixture thereof, is present in the initial fill composition, as measured by weight, in a range

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WE CLAIM:

1. A soft elastic capsule having a fill and a shell, the fill comprising:
a pharmaceutical agent or combination of pharmaceutical agents,
an alcohol,
a fatty acid, and
the shell comprising:
gelatin, and
at least one plasticizing agent,
wherein said shell has an initial state and an equilibrium state, wherein said initial state shell is underplasticized and said fill contains an alcohol amount in excess of an alcohol amount necessary to solubilize said pharmaceutical agent and said alcohol is not present in the initial state shell composition, and wherein said equilibrium state said shell becomes plasticized by the alcohol from said fill to provide suitable capsule hardness and said fill retains sufficient alcohol to maintain said pharmaceutical agent in solution.
2. The soft elastic capsule of claim 1 wherein the amount of alcohol present in said fill in initial state is in the range of 100-200% greater than the amount necessary to solubilize said pharmaceutical agent.
3. The soft elastic capsule of claim 1 wherein a portion in the range of 40-50% of the amount of alcohol present in said fill in initial state migrates into the shell upon equilibrium state.
4. The soft elastic capsule of claim 1 wherein said pharmaceutical agent comprises a solubilized HIV inhibiting compound or a combination of solubilized HIV inhibiting compounds.
5. The soft elastic capsule of claim 4 wherein said HIV inhibiting compound is (2S, 3S, 5S)-5-(N-(N-(N-methyl-N-N-(2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-

valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

6. The soft elastic capsule of claim 4 wherein said combination of solubilized HIV inhibiting compounds is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-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-methyl-butanoyl)amino-1,6-diphenylhexane (lopinavir).
7. The soft elastic capsule of claim 4 wherein said solubilized HIV inhibiting compound or said combination of solubilized HIV inhibiting compounds is present in said fill in a range of 10-35% by weight.
8. The soft elastic capsule of claim 1 wherein said alcohol is propylene glycol or ethanol.
9. The soft elastic capsule of claim 8 wherein propylene glycol or ethanol are present in said fill in initial state in a range of 3-20% by weight.
10. The soft elastic capsule of claim 1 wherein said alcohol concentration in the fill decreases by not more than 20% after reaching said equilibrium state.
11. The soft elastic capsule of claim 10 wherein after reaching said equilibrium state said shell has acceptable physical characteristics.
12. The soft elastic capsule of claim 11 wherein the acceptable physical characteristics of said shell comprise
 - a hardness in the range of about 4.5 to about 9 Newtons,
 - a total weight of said capsule within 95% of initial weight of capsule and total weight of said fill within 85% of initial weight of said fill,
 - a moisture content of not more than 2% of said fill weight of said capsule,

a disintegration time of not more than 30 minutes, and
an alcohol concentration of at least 40 mg per gram of said MgSO_4 .

13. The soft elastic capsule of claim 1 wherein said fatty acid is oleic acid.
14. The soft elastic capsule of claim 13 wherein said oleic acid is present in initial state composition in initial state in the range of 50-80% by weight.
15. The soft elastic capsule of claim 1 wherein said fill further comprises Polyoxyl 6 (Cremophor EL®).
16. The soft elastic capsule of claim 15 wherein said surfactant is present in initial state composition in initial state in the range of 0-10% by weight of the fill.
17. The soft elastic capsule of claim 1 wherein the gelatin in said capsule is present in initial state composition in initial state in the range of 30-60 % by weight of the shell.
18. The soft elastic capsule of claim 1 wherein the plasticizing agent is polyvinylpyrrolidone, macrogols, or Andrisorb™.
19. The soft elastic capsule of claim 19 wherein the plasticizing agent is present in initial state composition in initial state in the range of 4-18% by weight of the shell.
20. The soft elastic capsule of claim 1 wherein the ratio of the weight percent of gelatin to plasticizing agent at said equilibrium state is in the range of 1:1 to 1:10.
21. The soft elastic capsule of claim 1 wherein the fill in an initial state composition is (2S, 3S, 5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methyl)carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5R)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methyl)carbonyl)-amino-1,6-diphenyl-3-hydroxyhexane (nelfinavir).

2-(2,6 dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane (lopinavir) in the range of 10–35% by weight of the fill composition; polyethylene glycol in the range of 3–20% by weight of the fill composition; oleic acid in the range of 50–80% by weight of the fill; and wherein the shell in an initial state comprises: gelatin in the range of 30–60% by weight of the shell, and Andrisorb in the range of 4–18% by weight of the shell.

23. A method for making soft elastic capsules containing a pharmaceutical agent or a combination of pharmaceutical agents, the method comprising the steps of:
- preparing a fill composition wherein the fill composition comprises
 - a pharmaceutical agent or combination of pharmaceutical agents,
 - a fill alcohol, and
 - a fatty acid;
 - preparing a shell composition wherein the shell composition comprises
 - gelatin, and
 - at least one plasticizing compound;
 - forming an soft elastic capsule wherein said shell has an initial state and an equilibrium state, wherein said initial state shell is underplasticized and said fill contains an alcohol amount in excess of an alcohol amount necessary to solubilize said pharmaceutical agent and said alcohol is not present in the initial state shell composition; and
 - equilibrating said soft elastic capsule wherein equilibrium state said shell becomes plasticized by the alcohol from said fill to provide suitable capsule hardness and said fill retains sufficient alcohol to maintain said pharmaceutical agent in solution.
24. The method of claim 23 wherein said pharmaceutical agent comprises a solubilized HIV inhibiting compound or a combination of solubilized HIV inhibiting compounds.
25. The method of claim 23 wherein said alcohol is propylene glycol or ethanol.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-042169- -00003-0000

Fecha: 2007-08-30 15:01:06 Dep. 2020 NUECREACIONE
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 400 OPOSIOBSERVTER Folios: 94

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 07 - 70,016
FECHA : AGOSTO 30 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69815610	30/08/2007	768,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69815611	30/08/2007	256,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69815612	30/08/2007	216,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LE MAS COMERCIALES	256,000.00
		TOTAL :	\$ 256,000.00

EN: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

94
128 225

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



Nº. 06-042169- -00003-0000

Fecha: 2007-08-30 15:01:06 Dep. 2020 NUECREACIONE
Tra 2 PATENTES Eve: 1 REGDEPOSITO
Act. 400 OPOSIOBSERVTER Folios: 94

RECIBO OFICIAL DE CAJA : 07 - 70,013
FECHA : AGOSTO 30 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69815610	30/08/2007	768,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69815611	30/08/2007	256,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69815612	30/08/2007	216,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	72,000.00
		31 PRORROGA DE TERMINOS	72,000.00
		TOTAL :	\$ 72,000.00

W: SETENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE Nº. _____