



No. 03-095913- -00005-0000

Fecha: 2007-06-14 14:20:28 Dep. 2020 DIR.NUEVASOR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 519 TRASLADOINFORME Folios: 1

85
ff.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Gustavo Tamayo
Apoderado

Oficio N° 000.7347

REFERENCIA	Radicación	03 95913
	Trámite	002
	Evento	001
	Actuación	430
	Folios	012

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 03 95913, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 28-38
- . Ejemplos: folios 38-50
- . Capítulo reivindicatorio estudiado: folios 51-52
- . Se reivindica prioridad, presentada en Estados Unidos el 03.05.01, bajo el número 60/288410

Objeto de la invención

Según las reivindicaciones 1 a 12 de la presente solicitud, se refiere a una forma de dosificación farmacéutica oral unitaria sólida que comprende mesilato de nelfinavir amorfo y un copolímero de oxido de etileno/óxido de propileno, así como su procedimiento de fabricación.

Clasificación internacional de patentes A 61 K 31/472

Claridad de la solicitud

El artículo 30 de la decisión 486 contempla que las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción

La reivindicación 1 es muy amplia, pues no define las cantidades de mesilato de nelfinavir dentro de la composición, y puede incluir cantidades de principio activo que no se encuentran dentro de la descripción.

El término “copolímero en bloque de óxido de etileno y óxido de propileno, sintético, no iónico, soluble en agua...tiene un punto de fusión de al menos 40°C” de la reivindicación 1 es muy amplio y puede incluir copolímeros que no se encuentran dentro de la descripción. Tampoco se especifica la cantidad del copolímero dentro de la composición. De la lectura de la descripción y los ejemplos queda claro que los copolímeros que se utilizan son el poloxámero 188, 237, 338 y 407 y éstos deberían ser incluidos dentro de la reivindicación principal.

La reivindicación 12 se encuentra mal redactada, puesto que ésta es de producto y se remite a una reivindicación de proceso.

Favor hacer las aclaraciones y correcciones del caso.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud – 03.05.01-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	WO 9822106	“Composición farmacéutica”	28.05.98
2	WO 9702017	“Formulaciones de liberación controlada para drogas pobremente solubles”	23.01.97

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación del NIVEL INVENTIVO

El art. 18 de la Decisión 486 contempla *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

La publicación WO 9822106 enseña composiciones en cápsula que comprenden inhibidores de la proteasa de VIH que comprenden:

- Nelfinavir
- Solvente farmacéutico
- Surfactantes como el poloxámero 188

87 89

En los ejemplos se enseña que el surfactante se mezcla con el principio activo con calentamiento.

La publicación WO9702017 enseña composiciones sólidas que contienen principios activos que son pobremente solubles en agua que comprenden una dispersión sólida del activo en un surfactante, como el poloxámero, en alta cantidad mediante calentamiento. Tales composiciones mejoran la biodisponibilidad de los principios activos gracias al uso del poloxámero.

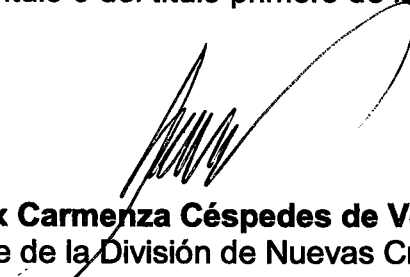
Teniendo en cuenta el objeto de la solicitud, el cual es proporcionar composiciones sólidas de nelfinavir amorfo con biodisponibilidad mejorada gracias al poloxámero, es una derivación evidente del estado de la técnica, ya que una persona versada en la materia combinaría las enseñanzas de estos dos documentos, es decir, combinar nelfinavir con poloxámero y usarlo en composiciones sólidas que mejoran la solubilidad del principio activo, para llegar a formular las composiciones que se reivindican.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9822106	1-12	Nivel Inventivo
2	WO 9702017	1-12	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 15 JUN. 2007

CONCEPTO TÉCNICO Número 0846	EXAMINADOR TÉCNICO Código 202024
---------------------------------	-------------------------------------

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



88 90

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: 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 Hybernia 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).		

89 98

- (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

90 g/l.

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.

91 93

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

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



92 94

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 9/14, 9/20	A1	(11) International Publication Number: WO 97/02017 (43) International Publication Date: 23 January 1997 (23.01.97)
(21) International Application Number: PCT/IE96/00039 (22) International Filing Date: 1 July 1996 (01.07.96) (30) Priority Data: 950492 3 July 1995 (03.07.95) IE 60/000,897 6 July 1995 (06.07.95) US (71) Applicant (for all designated States except US): ELAN CORPORATION, PLC [IE/IE]; Monksland Industrial Estate, Athlone, County Westmeath (IE). (72) Inventors; and (75) Inventors/Applicants (for US only): CLANCY, Maurice, Joseph, Anthony [IE/IE]; 58 Auburn Heights, Athlone, County Westmeath (IE). CUMMING, Kenneth, Iain [GB/IE]; Apartment 19, 46 North Great Georges Street, Dublin 1 (IE). MYERS, Michael [IE/US]; 43514 Golden Meadow Circle, Ashburn, VA 22011 (US). (74) Agent: ANNE RYAN & CO.; 60 Northumberland Road, Ballsbridge, Dublin 4 (IE).		(81) Designated States: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: CONTROLLED RELEASE FORMULATIONS FOR POORLY SOLUBLE DRUGS		
(57) Abstract A controlled release formulation for oral administration comprises a solid dispersion of a poorly soluble active ingredient in a hydrophilic poloxamer, the solid dispersion being a component of a core and the core as such or following coating of the core with a polymeric coating being effective to achieve therapeutic levels of the active ingredient over extended periods of time (24 hours or longer) following oral administration. The formulation can be in a multi-particulate form such as pellets or mini-tablets or in the form of tablets. Examples of active ingredients whose solubility and therapeutic effectiveness can be improved with the formulation are cisapride, cyclosporin, diclofenac, felodipine, ibuprofen, indomethacin, nifedipine, nifedipine, terfenadine and theophylline.		

93 9f

following coating of the core with a polymeric coating being effective to achieve therapeutic levels of said active ingredient over extended periods of time following oral administration.

5 To accommodate the varying solubility of different active ingredients of the type referred to above, the solid dispersion may need to include one or more ingredients to further improve the solubility/wettability enhancement of the active ingredient.

10 Accordingly, the solid dispersion may include a surfactant component. The surfactant may be an anionic, cationic or non-ionic surfactant. Preferred surfactant components are selected from sodium lauryl sulphate, a sodium carboxylate, an alkyl sulphate, a polyethylene glycol ester, a polyethylene ether, a sorbitan ester, an ethoxylated sorbitan ester and an alkyl trimethylammonium halide and a mixture thereof.

15 Alternatively, the solid dispersion may include an acid component. Preferred acid components are selected from adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid.

20 Further, alternatively, the solid dispersion may include a base component. Preferred base components are selected from calcium carbonate, calcium hydroxide, magnesium hydroxide, sodium bicarbonate, sodium carbonate, sodium citrate and sodium hydroxide.

Preferably, the surfactant, acid or base component is present in a ratio of 0.01:1.0 to 5.0:1.0 by weight of the active ingredient.

25 Any such surfactant, acid or base components are hereinafter collectively referred to as auxiliary agents.

Further, preferably, the active ingredient and the poloxamer are present in an amount of 0.1:1.0 to 10.0:1.0 by weight.

96
94

By poloxamer herein is meant also a combination of two or more poloxamers.

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide.

5 More specifically, the poloxamer polyols are α -hydro- ω -hydroxypoly(oxyethylene)poly(oxypropylene)poly(oxyethylene) block copolymers, more generally known as polyethylene - propylene glycol copolymer or polyoxyethylene - polyoxypropylene copolymer.

10 Preferred poloxamers are those which contain between 60% and 90%, more especially between 70% and 80%, by weight of the polyoxyethylene portion.

15 The polyoxyethylene segment is hydrophilic whilst the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene oxide and ethylene oxide added during manufacture. The hydrophilic segment can comprise between 15 and 90% of the molecule. As indicated above, those recommended for use in accordance with the invention have between 60% and 90%, more especially between 70% and 80%, by weight of the hydrophilic polyoxyethylene segment or sequence. Such poloxamer polyols, hereinafter referred to as poloxamers, are known by the trade names Lutrol, Monolan and Pluronic.

25 Poloxamers are also defined by a number. The first two digits of the number, when multiplied by 100, correspond to the approximate average molecular weight of the polyoxypropylene (POP) portion of the molecule. The third digit, when multiplied by 10, corresponds to the percentage by weight of the polyoxyethylene (POE) portion. When called by their Pluronic name, the first two digits, when multiplied by 1000 indicate the total molecular weight, and the third digit, multiplied by 10, represents the approximate percentage of POE in the molecule. 30 The associated capital letter indicates the physical state: L = liquid, P =

97 95

paste, and F = solid. For further information, reference can be made to Pharmaceutical Technology Europe May 1994.

5 The preferred poloxamers for use in accordance with the invention are the F series. Especially preferred poloxamers of the F series are F68, F108 and F127, especially those sold under the trade marks Lutrol F 68, Pluronic F 108 and Lutrol F 127 by BASF.

Further information on these poloxamers can be obtained from the technical information sheets supplied by BASF (Ireland) Limited.

10 The poloxamer is melted and then the active ingredient and any auxiliary agents(s) are dispersed in the molten poloxamer.

15 The poloxamer is suitably melted in a stainless steel container. To the molten mass the active ingredient, and any auxiliary agent(s) and the inert filler, if used, are added slowly over time. The mixture is stirred while it is cooled and milled to a median particle size in the range 30-300 μm .

Alternatively, the active ingredient, any auxiliary agent(s), and the poloxamer are dissolved in an organic solvent or solvents; the solvent is evaporated and the molten poloxamer is cooled and milled to a median particle size in the range 30-300 μm .

20 It has been found that various poorly soluble active ingredients are readily dispersible in the melt forms of the poloxamers used in accordance with the invention. When cooled the mixture of active ingredient, auxiliary agent(s), if present, and poloxamer forms a dry, hard solid which can be easily ground or milled. It is for this reason
25 that the poloxamers were chosen herein as the polymer base for the solid dispersion.

The solid dispersion according to the invention can include excipient agents, such as an inert filler. The inert filler is suitably a water soluble inert filler. An example of an inert filler is lactose, more

98 96

Example 7Preparation of solid dispersion

- 5 Lutrol F127 (463 g) was melted by heating to 80°C. Cisapride (237 g), tartaric acid (150 g), and lactose (150 g), were gradually added to, and dispersed in, the molten Lutrol. Mixing was continued for 0.5 hours until the last of the lactose had been added. The resulting solid dispersion was allowed to cool at room temperature, followed by milling thereof.

Preparation of tablet

- 10 A tablet formulation was prepared by blending the solid dispersion with the following tableting ingredients in the indicated proportions:

	<u>Ingredient</u>	<u>Weight %</u>
	Solid dispersion	24.2
15	Methocel K100LV	40.0
	Avicel pH101	35.3
	Magnesium stearate	0.5

The tablet blend was tabletted to a mean hardness of 139 N in a Killian RTS tablet press.

- 20 The *in vitro* dissolution for the tablets so prepared was determined under the conditions specified in Example 6. The following results were obtained:

