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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Doctora,

ALIX CARMENZA CESPEDES DE VERGUEL

JEFE DE LA DIVISIÓN DE NUEVAS CREACIONES

Superintendente de Industria y Comercio

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Referencia : Expediente N° 06-042169

Asunto : Contestación al Oficio 5494 del 9 de abril de 2010 a la Solicitud de Patente de Invención titulada "UNA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE PARA EL TRATAMIENTO DEL SIDA Y PROCESO PARA PREPARAR DICHA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE".

Solicitante: PROCAPS S.A.

Yo, *REINALDO PINILLA MORENO*, abogado con tarjeta profesional N° 91563 del Consejo Superior de la Judicatura, en mi condición de apoderado de la sociedad *PROCAPS S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, como consta en el documento de poder anexo a la presente, atentamente manifiesto que estando dentro del término de y por orden expresa de mi representada, presento la debida contestación a la oposición presentada contra la solicitud de patente de invención titulada "UNA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE PARA EL TRATAMIENTO DEL SIDA Y PROCESO PARA PREPARAR DICHA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE", solicitada por mi mandante.

1. CLARIDAD DE LA SOLICITUD.

- 1.1. En materia del capítulo reivindicatorio, el Señor Examinador advierte que las cláusulas comprenden términos como "uno más", "al menos", "por lo menos", etc., que no permiten dar

claridad ni concisión y también se refiere a que frases como "*solventes farmacéuticamente aceptables*" y "*elevador de absorción farmacéuticamente aceptable*", etc., son ambiguas y generales.

- 1.2. Así las cosas, conforme se ha solicitado por el Señor Examinador, se propone un pliego de nuevas cláusulas que definen claramente el objeto de la invención, sus componentes y relaciones estructurales acorde con lo definido en la descripción, tal como lo solicita el Señor Examinador. Es preciso aclarar que dicho nuevo capítulo reivindicatorio no implica ampliación alguna de la invención sino por el contrario, su intención es precisar la invención con base en las apreciaciones del señor examinador.

2. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA

- 2.1. La solicitud objeto de la presente fue radicada en la Superintendencia de Industria y Comercio el 5 de mayo de 2006, bajo el número 06042169 y fue publicada en la Gaceta de la Propiedad Industrial N° 576 y fue solicitado el examen de patentabilidad el pasado 7 de noviembre de 2007.
- 2.2. Mediante escrito radicado el 14 de agosto de 2008 el Doctor José Luis Reyes Villamizar en calidad de apoderado de la sociedad LA FRANCOL S.A. con domicilio en la ciudad de Cali, Valle, presento oposición una vez surtida la publicación en la gaceta oficial colombiana.
- 2.3. La solicitud colombiana 06042169, tiene por objeto una composición farmacéutica en solución transparente para el tratamiento del SIDA y un proceso para preparar dicha composición farmacéutica en solución transparente. Particularmente, la invención comprende en combinación: (a) Ritonavir como un agente inhibidor de proteasa VIH o su sal farmacéuticamente aceptable; (b) un solvente que comprende alcohol tetrahidrofurfurílico polietilenglicol éter; (c) un elevador de absorción que comprende propilenglicol monocaprilato; (d) un antioxidante farmacéuticamente aceptable elegido entre butilhidroxianisol o butilhidroxitolueno o una combinación de los mismos; y, (e) agua. Adicionalmente, la invención proporciona el proceso para preparar dicha composición farmacéutica en solución transparente que comprende disolver el Ritonavir como un agente inhibidor de proteasa VIH o su sal farmacéuticamente aceptable para producir una solución transparente; y, encapsular dicha solución transparente.



- 2.4. En el Oficio objeto de la presente se referencia el documento D1: WO9507696 publicado el 23 de marzo de 1995 como el documento más cercano.
- 2.5. Con ánimo de diferenciar aún más los términos mediante los cuales se presenta la solicitud de patente, se ha modificado el capítulo reivindicatorio precisando los elementos que lo caracterizan y que como tal apartan el arte anterior, ofreciendo la característica de novedad.
- 2.6. Como tal, el problema a solucionar como objeto de la presente es que la administración oral de Ritonavir es limitada tanto por disolución como permeabilidad, convirtiéndola en un activo de la Clase IV en el Sistema de Clasificación Biofarmacéutico. Ritonavir, es un activo hidrofóbico y de baja biodisponibilidad oral, que logra mediante la adición del solvente que comprende alcohol tetrahidrofurfurílico polietilenglicol éter, un elevador de absorción, un antioxidante y una cantidad controlada de agua para formar un sistema básico cuya finalidad es la de originar una fina combinación aceite/agua en microemulsión tipo SMEDDS, la cual una vez administrada por vía oral y por la motilidad del estómago y del intestino, provee la agitación requerida para la autoemulsificación en vivo, dando como resultado una perfecta distribución de partículas para su absorción en un rango entre 0.02 y 2000 micrones. Por lo tanto, un sistema SMEDDS en una formulación, se usa como alternativa respecto a formulaciones orales convencionales, para asegurar biodisponibilidad.
- 2.7. Con la formulación de la presente invención, donde normalmente el log P del Ritonavir es 4, se puede bajar a un valor cercano al ideal del log Po, entre 2 y 3, de manera que la formulación de la presente invención puede conseguir máxima absorción en el Tracto Gastro Intestinal.
- 2.8. Como tal, el arte anterior basa su composición con base en glicerinas y surfactantes y para solubilizar el activo el arte anterior D1 usa (1) propilenglicol; (2) etano; y, (3) polietilenglicol 540. A diferencia, la presente sólo utiliza alcohol tetrahidrofurfurílico polietilenglicol éter.
- 2.9. Ahora bien, comparando este documento anterior referenciado en el Oficio, tenemos que:

06042169	D1: WO9507696
(a) Ritonavir como un agente inhibidor de proteasa VIH o su sal farmacéuticamente aceptable;	Una composición farmacéutica en solución que comprende (folios 230, 293; pág. 5, 12) Ritonavir o su sal farmacéuticamente aceptable entre (2-30%)
(b) un solvente que comprende alcohol tetrahidrofurfurílico polietilenglicol éter	Mezcla de solventes orgánicos farmacéuticamente aceptables (50-95)% (folios 191-292 y 293; pág. 6-7 y 12)



	2-(2-etoxyeto)etanol (Trancutol ® ó dietilenglicol monoetil éter) Propilenglicol monolaurato y similares
(c) un elevador de absorción que comprende propilenglicol monocaprilato	
(d) un antioxidante farmacéuticamente aceptable elegido entre butilhidroxianisol o butilhidroxitolueno o una combinación de los mismos	Antioxidantes farmacéuticamente aceptables como ácido ascórbico, BHA, BHT, vitamina E, vitamina E PEG 1000 succinato, entre otros (folio 291; pág. 6).
Agua	Agua
	Aditivos
	Glicerina
	Surfactante: Glicérido poliglicolizado

2.10. Este documento anterior D1 se refiere composiciones que comprenden un inhibidor de proteasa HIV. Evidentemente este documento D1, no revela el mismo solvente y no utiliza un elevador de absorción además que D1 requiere de aditivos, glicerina y Glicérido poliglicolizado como surfactante, por lo que a luz de dicha comparación no soluciona el objeto principal de la presente solicitud, conformar una composición de rápida disolución y consecuentemente mayor actividad terapéutica del activo en el organismo. Por lo tanto, esta anterioridad no es revelante y comparable desde el punto de vista de novedad y/o altura o nivel inventivo con la presente solicitud.

2.11. Así las cosas, el documento D1 del arte es relevante como compuesto farmacéuticos con condiciones de elevación de absorción de inhibidores de proteasa HIV que son solubilizados mediante el alcohol tetrahidrofurfurilico polietilenglicol éter. Se evidencia en dichos documentos, que aunque se relacionan con inhibidores de proteasa HIV, ninguno se refiere a solucionar sus condiciones de absorción y solubilidad.

2.12. Dado que la presente solicitud en relación con el documento aportado por no están relacionado con el mismo objeto, solicito a usted se sirva declarar novedosa, de altura inventiva y de aplicación industrial con base en el nuevo capítulo reivindicatorio aquí anexo, presentado a la presente invención y continuar con el proceso de registro de Patente de invención denominada "UNA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE PARA EL TRATAMIENTO DEL SIDA Y PROCESO PARA PREPARAR DICHA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE".



2.13. Con lo anterior esperamos haber cumplido con los requerimientos exigidos por este despacho y solicitamos se practique un nuevo examen de fondo conforme el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina y en consecuencia sea concedida la presente conforme el nuevo capítulo reivindicatorio anexo a la presente.

3. FUNDAMENTO DE DERECHO

Fundamento esta remisión en las normas legales siguientes:

- 3.1. Numeral 1 del artículo 586 del Código de Comercio.
- 3.2. Artículo 43 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 3.3. En las demás normas concordantes.

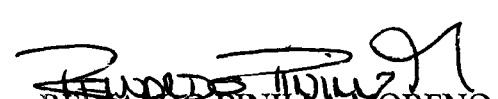
4. ANEXOS.

- 4.1. NUEVAS REIVINDICACIONES.

5. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas de abogado situadas en la Carrera 13 N° 119-95 Oficina 104 de esta ciudad de Bogotá.

Señor Superintendente,


REINALDO PINILLA MORENO

C.C. 80'425.609

T.P. 91563 del C.S.J.

REIVINDICACIONES

- 1- Una composición farmacéutica en solución transparente **CARACTERIZADA PORQUE** comprende en combinación: (a) Ritonavir como un agente inhibidor de proteasa VIH o su sal farmacéuticamente aceptable; (b) un solvente que comprende alcohol tetrahidrofurfúrico polietilenglicol éter; (c) un elevador de absorción que comprende propilenglicol monocaprilato; (d) un antioxidante farmacéuticamente aceptable elegido entre butilhidroxianisol o butilhidroxitolueno o una combinación de los mismos; y, (e) agua.
- 2- Una composición farmacéutica en solución transparente según la reivindicación 1 **● CARACTERIZADO PORQUE** dicho inhibidor de proteasa VIH está presente en dicha composición farmacéutica, en una cantidad entre el 5% y el 60% del peso total de la composición.
- 3- Una composición farmacéutica en solución transparente según la reivindicación 2 **CARACTERIZADO PORQUE** para solubilizar el Ritonavir, el solvente está presente en una cantidad de 5% a 68% del peso total de la composición.
- 4- Una composición farmacéutica en solución transparente según la reivindicación 3 **CARACTERIZADO PORQUE** dicho elevador de absorción está presente en una cantidad entre 15% a 50% por peso total de la composición.
- 5- Una composición farmacéutica en solución transparente según la reivindicación 4 **● CARACTERIZADO PORQUE** dicho antioxidante está presente en una cantidad de 0.001% a 0.1% del peso total de la composición.
- 6- Proceso para preparar la composición farmacéutica en solución transparente definida en cualquiera de las reivindicaciones 1 a 5, donde dicho proceso está **CARACTERIZADO PORQUE** en un primer paso, se solubiliza el (a) Ritonavir como un agente inhibidor de proteasa VIH o su sal farmacéuticamente aceptable en una cantidad entre el 5% y el 60% por peso total de la composición; (c) el elevador de absorción que comprende propilenglicol monocaprilato entre 15% a 50% por peso total de la composición; (d) el antioxidante farmacéuticamente aceptable elegido entre butilhidroxianisol o butilhidroxitolueno o una combinación de los mismos entre el 0.001% a 0.1% del peso total de la composición; y (e) agua, solubilizados en (b) alcohol

tetrahidrofurfurilico polietilenglicol éter entre el 5% a 68% del peso total de la composición.

- 7- Proceso para preparar la composición farmacéutica en solución transparente según la reivindicación 6 **CARACTERIZADO PORQUE** un segundo paso de mezcla hasta obtener una solución transparente.
- 8- Proceso para preparar la composición farmacéutica en solución según la reivindicación 12 **CARACTERIZADO PORQUE** un tercer paso de encapsulado donde la solución transparente es encapsulada en cápsulas de gelatina.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 9/127, 9/107, 38/13	A1	(11) International Publication Number: WO 00/50007 (43) International Publication Date: 31 August 2000 (31.08.00)
(21) International Application Number: PCT/US00/00165 (22) International Filing Date: 5 January 2000 (05.01.00) (30) Priority Data: 09/258,654 26 February 1999 (26.02.99) US (71) Applicant: LIPOCINE, INC. [US/US]; Suite 314, 800 North 350 West, Salt Lake City, UT 84103 (US). (72) Inventors: PATEL, Manesh, V.; 1515 South Preston, Salt Lake City, UT 84108 (US). CHEN, Feng-Jing; 201 East South Temple, Salt Lake City, UT 84111 (US). (74) Agents: REED, Diane, E. et al.; Reed & Associates, 3282 Alpine Road, Portola Valley, CA 94028 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF HYDROPHOBIC THERAPEUTIC AGENTS		
(57) Abstract The present invention relates to triglyceride-free pharmaceutical compositions for delivery of hydrophobic therapeutic agents. Compositions of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the surfactants containing the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compositions.		

1 to true micellar particles. Despite their close relationship to micelles, microemulsions
function quite differently in drug delivery systems. The majority of hydrophobic therapeutic
agents are lipophilic, and have greater solubility in triglycerides than in surfactants. As a
5 result, the hydrophobic therapeutic agent in a microemulsion-based delivery system is
preferentially solvated in the triglyceride phase, which is in turn encapsulated in the swollen
micelle. The preferential partitioning in the triglyceride phase results in higher loading
capacities than in comparable micelle-based systems, but at the cost of introducing into the
delivery system the lipolysis-dependence and other disadvantages associated with the
10 presence of triglycerides. In addition, the larger size of microemulsion particles, relative to
true micelles, results in a slower rate of particle diffusion, and thus a slower rate of
therapeutic agent absorption.

Thus, there is a need for pharmaceutical compositions that overcome the limitations
of conventional micelle formulations, but without suffering from the disadvantages of
triglyceride-containing formulations.

15 SUMMARY OF THE INVENTION

The present invention provides pharmaceutical compositions for improved delivery of
hydrophobic therapeutic agents. In one embodiment, the present invention provides a
triglyceride-free pharmaceutical composition including a hydrophobic therapeutic agent and a
carrier. The carrier includes a hydrophilic surfactant and a hydrophobic surfactant in
20 amounts such that upon dilution with an aqueous solution such as simulated gastrointestinal
fluids the carrier forms a clear aqueous dispersion of the hydrophilic and hydrophobic
surfactants containing the hydrophobic therapeutic agent.

In another embodiment, the present invention provides a clear aqueous dispersion
containing a hydrophilic surfactant, a hydrophobic surfactant and a hydrophobic therapeutic
25 agent. The dispersion is substantially free of triglycerides.

In another embodiment, the present invention relates to a triglyceride-free
pharmaceutical composition which includes a hydrophilic surfactant and a hydrophobic
surfactant in amounts such that upon dilution with an aqueous solution a clear aqueous
dispersion is formed, a first amount of a hydrophobic therapeutic agent solubilized in the
30 clear aqueous dispersion, and a second amount of the hydrophobic therapeutic agent that
remains non-solubilized but dispersed.

1 In another embodiment, the present invention relates to methods of increasing the rate and/or extent of absorption of hydrophobic therapeutic agents by administering to a patient a pharmaceutical composition of the present invention.

5 These features of the present invention will become more fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

10 In order to illustrate the manner in which the above-recited and other advantages and objects of the invention are obtained, a more particular description of the invention briefly described above will be rendered by reference to the specific embodiments shown in the appended drawings. Understanding that these drawings depict only typical embodiments of the invention and are not therefore limiting of its scope, the invention will be described and explained with additional specificity and detail through the use of the accompanying drawing, in which:

15 Figure 1 shows the enhanced bioabsorption of a hydrophobic therapeutic agent in the compositions of the present invention, relative to a commercial formulation.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

20 The present invention overcomes the problems described above characteristic of conventional formulations such as micelle formulations, emulsions, and microemulsions, by providing unique triglyceride-free pharmaceutical compositions. Surprisingly, the present inventors have found that compositions including a combination of a hydrophilic surfactant and a hydrophobic surfactant can solubilize therapeutically effective amounts of hydrophobic therapeutic agents without recourse to the use of triglycerides, thereby avoiding the lipolysis dependence and other disadvantages of conventional formulations. Use of these formulations results in an enhanced rate and/or extent of absorption of the hydrophobic therapeutic agent.

A. Pharmaceutical Compositions

30 In one embodiment, the present invention provides a pharmaceutical composition including a carrier and a hydrophobic therapeutic agent. The carrier includes a hydrophilic surfactant and a hydrophobic surfactant in amounts such that upon dilution with an aqueous solution the carrier forms a clear aqueous dispersion of the hydrophilic and hydrophobic surfactants containing the hydrophobic therapeutic agent. It is a particular feature of the present invention that the carrier is substantially free of triglycerides, thereby providing surprising and important advantages over conventional, triglyceride-containing formulations.

1. Surfactants

The carrier includes at least one hydrophilic surfactant and at least one hydrophobic surfactant. As is well known in the art, the terms "hydrophilic" and "hydrophobic" are relative terms. To function as a surfactant, a compound must necessarily include polar or charged hydrophilic moieties as well as non-polar hydrophobic (lipophilic) moieties; *i.e.*, a surfactant compound must be amphiphilic. An empirical parameter commonly used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions.

Using HLB values as a rough guide, hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, hydrophobic surfactants are compounds having an HLB value less than about 10.

It should be appreciated that the HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions. For many important surfactants, including several polyethoxylated surfactants, it has been reported that HLB values can differ by as much as about 8 HLB units, depending upon the empirical method chosen to determine the HLB value (Schott, *J. Pharm. Sciences*, 79(1), 87-88 (1990)). Likewise, for certain polypropylene oxide containing block copolymers (PLURONIC® surfactants, BASF Corp.), the HLB values may not accurately reflect the true physical chemical nature of the compounds. Finally, commercial surfactant products are generally not pure compounds, but are complex mixtures of compounds, and the HLB value reported for a particular compound may more accurately be characteristic of the commercial product of which the compound is a major component. Different commercial products having the same primary surfactant component can, and typically do, have different HLB values. In addition, a certain amount of lot-to-lot variability is expected even for a single commercial surfactant product. Keeping these inherent difficulties in mind, and using HLB values as a guide, one skilled in the art can readily identify surfactants having suitable hydrophilicity or hydrophobicity for use in the present invention, as described herein.

The hydrophilic surfactant can be any hydrophilic surfactant suitable for use in pharmaceutical compositions. Such surfactants can be anionic, cationic, zwitterionic or non-ionic, although non-ionic hydrophilic surfactants are presently preferred. As discussed

above, these non-ionic hydrophilic surfactants will generally have HLB values greater than about 10. Mixtures of hydrophilic surfactants are also within the scope of the invention.

Similarly, the hydrophobic surfactant can be any hydrophobic surfactant suitable for use in pharmaceutical compositions. In general, suitable hydrophobic surfactants will have an HLB value less than about 10. Mixtures of hydrophobic surfactants are also within the scope of the invention.

The choice of specific hydrophobic and hydrophilic surfactants should be made keeping in mind the particular hydrophobic therapeutic agent to be used in the composition, and the range of polarity appropriate for the chosen therapeutic agent, as discussed in more detail below. With these general principles in mind, a very broad range of surfactants is suitable for use in the present invention. Such surfactants can be grouped into the following general chemical classes detailed in the Tables below. The HLB values given in the Tables below generally represent the HLB value as reported by the manufacturer of the corresponding commercial product. In cases where more than one commercial product is listed, the HLB value in the Tables is the value as reported for one of the commercial products, a rough average of the reported values, or a value that, in the judgment of the present inventors, is more reliable. It should be emphasized that the invention is not limited to the surfactants in the following Tables, which show representative, but not exclusive, lists of available surfactants.

1.1. Polyethoxylated Fatty Acids

Although polyethylene glycol (PEG) itself does not function as a surfactant, a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Among the surfactants of Table 1, preferred hydrophilic surfactants include PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate and PEG-20 oleate. Examples of polyethoxylated fatty acid monoester surfactants commercially available are shown in Table 1.

Table 1: PEG-Fatty Acid Monoester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG 4-100 monolaurate	Crodet L series (Croda)	>9
PEG 4-100 monooleate	Crodet O series (Croda)	>8
PEG 4-100 monostearate	Crodet S series (Croda), Myrj Series (Atlas/ICI)	>6

1	Polyglyceryl-10 laurate	Nikkol Decaglyn 1-L (Nikko)	15
	Polyglyceryl-10 oleate	Nikkol Decaglyn 1-O (Nikko)	14
	Polyglyceryl-10 stearate	Nikkol Decaglyn 1-S (Nikko)	12
5	Polyglyceryl-6 ricinoleate	Nikkol Hexaglyn PR-15 (Nikko)	>8
	Polyglyceryl-10 linoleate	Nikkol Decaglyn 1-LN (Nikko)	12
	Polyglyceryl-6 pentaoleate	Nikkol Hexaglyn 5-O (Nikko)	<10
	Polyglyceryl-3 dioleate	Cremophor GO32 (BASF)	<10
10	Polyglyceryl-3 distearate	Cremophor GS32 (BASF)	<10
	Polyglyceryl-4 pentaoleate	Nikkol Tetraglyn 5-O (Nikko)	<10
	Polyglyceryl-6 dioleate	Caprol® 6G20 (ABITEC); Hodag PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)	8.5
	Polyglyceryl-2 dioleate	Nikkol DGDO (Nikko)	7
15	Polyglyceryl-10 trioleate	Nikkol Decaglyn 3-O (Nikko)	7
	Polyglyceryl-10 pentaoleate	Nikkol Decaglyn 5-O (Nikko)	3.5
	Polyglyceryl-10 septaoleate	Nikkol Decaglyn 7-O (Nikko)	3
20	Polyglyceryl-10 tetraoleate	Caprol® 10G40 (ABITEC); Hodag PGO-62 (CALGENE), Drewpol 10-4-O (Stepan)	6.2
	Polyglyceryl-10 decaisostearate	Nikkol Decaglyn 10-IS (Nikko)	<10
	Polyglyceryl-10l decaoleate	Drewpol 10-10-O (Stepan), Caprol 10G10O (ABITEC), Nikkol Decaglyn 10-O	3.5
25	Polyglyceryl-10 mono, dioleate	Caprol® PGE 860 (ABITEC)	11
	Polyglyceryl polyricinoleate	Polymuls (Henkel)	3-20

30 1.7. Propylene Glycol Fatty Acid Esters

Esters of propylene glycol and fatty acids are suitable surfactants for use in the present invention. In this surfactant class, preferred hydrophobic surfactants include propylene glycol monolaurate (Lauroglycol FCC), propylene glycol ricinoleate (Propymuls),

EN SOCIEDAD
↑ de absorción

propylene glycol monooleate (Myverol P-O6), propylene glycol dicaprylate/dicaprate (Captex® 200), and propylene glycol dioctanoate (Captex® 800). Examples of surfactants of this class are given in Table 7.

Table 7: Propylene Glycol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Propylene glycol monocaprylate ✓	Capryol 90 (Gattefosse), Nikkol Sefsol 218 (Nikko)	<10
Propylene glycol monolaurate ✓	Lauroglycol 90 (Gattefosse), Lauroglycol FCC (Gattefosse)	<10
Propylene glycol oleate	Lutrol OP2000 (BASF)	<10
Propylene glycol myristate	Mirpyl	<10
Propylene glycol monostearate ✓	ADM PGME-03 (ADM), LIPO PGMS (Lipo Chem.), Aldo® PGHMS (Lonza)	3-4
Propylene glycol hydroxy stearate		<10
Propylene glycol ricinoleate	PROPYMULS (Henkel)	<10
Propylene glycol isostearate		<10
Propylene glycol monooleate ✓	Myverol P-O6 (Eastman)	<10
Propylene glycol dicaprylate/dicaprate	Captex® 200 (ABITEC), Miglyol® 840 (Hüls), Neobee® M-20 (Stepan)	>6
Propylene glycol dioctanoate	Captex® 800 (ABITEC)	>6
Propylene glycol caprylate/caprate ✓	LABRAFAC PG (Gattefosse)	>6
Propylene glycol dilaurate ×		>6
Propylene glycol distearate	Kessco® PGDS (Stepan)	>6
Propylene glycol dicaprylate	Nikkol Sefsol 228 (Nikko)	>6
Propylene glycol dicaprate	Nikkol PDD (Nikko)	>6

1.19 Surfactant Concentrations

The hydrophilic and hydrophobic surfactants are present in the pharmaceutical compositions of the present invention in amounts such that upon dilution with an aqueous solution, the carrier forms a clear, aqueous dispersion of the hydrophilic and hydrophobic surfactants, containing the hydrophobic therapeutic agent. The relative amounts of hydrophilic and hydrophobic surfactants are readily determined by observing the properties of the resultant dispersion; *i.e.*, when the relative amounts of the hydrophobic and hydrophilic surfactants are within a suitable range, the resultant aqueous dispersion is optically clear. When the relative amount of hydrophobic surfactant is too great, the resulting dispersion is visibly "cloudy", resembling a conventional emulsion or multiple phase system. Although a visibly cloudy solution may be potentially useful for some applications, such a system would suffer from many of the same disadvantages as conventional prior art formulations, as described above.

A convenient method of determining the appropriate relative concentrations for any hydrophilic surfactant - hydrophobic surfactant pair is as follows. A convenient working amount of a hydrophilic surfactant is provided, and a known amount of a hydrophobic surfactant is added. The surfactants are stirred to form a homogeneous mixture, with the aid of gentle heating if desired. The resulting mixture is diluted with purified water to prepare an aqueous dispersion. Any dilution amount can be chosen, but convenient dilutions are those within the range expected *in vivo*, about a 10 to 250-fold dilution. The aqueous dispersion is then assessed qualitatively for optical clarity. The procedure can be repeated with incremental variations in the relative amount of hydrophobic surfactant added, to determine the maximum relative amount of hydrophobic surfactant that can be present for a given surfactant pair.

Alternatively, the optical clarity of the aqueous dispersion can be measured using standard quantitative techniques for turbidity assessment. One convenient procedure to measure turbidity is to measure the amount of light of a given wavelength transmitted by the solution, using, for example, a UV-visible spectrophotometer. Using this measure, optical clarity corresponds to high transmittance, since cloudier solutions will scatter more of the incident radiation, resulting in lower transmittance measurements. If this procedure is used, care should be taken to insure that the surfactant mixture does not itself absorb light of the chosen wavelength, as any true absorbance necessarily reduces the amount of transmitted light and falsely increases the quantitative turbidity value. In the absence of chromophores at

1 the chosen wavelength, suitable dispersions at a dilution of 10X should have an apparent
absorbance of less than about 0.3, preferably less than about 0.2, and more preferably less
than about 0.1. At a dilution of 100X, suitable dispersions should have an apparent
absorbance of less than about 0.1, preferably less than about 0.05, and more preferably less
5 than about 0.01.

A third method of determining optical clarity and carrier diffusivity through the
aqueous boundary layer is to quantitatively measure the size of the particles of which the
dispersion is composed. These measurements can be performed on commercially available
particle size analyzers, such as, for example, a Nicomp particle size analyzer available from
10 Particle Size Systems, Inc., of Santa Barbara, CA. Using this measure, clear aqueous
dispersions according to the present invention have average particle sizes much smaller than
the wavelength of visible light, whereas dispersions containing excessive relative amounts of
the hydrophobic surfactant have more complex particle size distributions, with much greater
average particle sizes. It is desirable that the average particle size be less than about 100 nm,
15 preferably less than about 50 nm, more preferably less than about 30 nm, and still more
preferably less than about 20 nm. It is also preferred that the particle size distribution be
mono-modal. As is shown in more detail in the Examples herein, dispersions having an
undesirably large relative amount of hydrophobic surfactant typically display bimodal
particle size distributions, such distributions having a small particle size component, typically
20 less than about 30 nm, and a large particle size component, typically on the order of 100 nm
or more. It should be emphasized that these particle sizes are appropriate for the carrier
particles in aqueous solution, in the absence of a hydrophobic therapeutic agent. It is
expected that the presence of the hydrophobic therapeutic agent may result in an increase in
the average particle size.

25 Other methods of determining optical clarity or particle size can be used as desired.
Such methods are well known to those skilled in the art.

It should be emphasized that any or all of the available methods may be used to
ensure that the resulting aqueous dispersions possess the requisite optical clarity. For
convenience, however, the present inventors prefer to use the simple qualitative procedure;
30 i.e., simple visible observation. However, in order to more fully illustrate the practice of the
present invention, all three of the above measures are used to assess the dispersion clarity in
the Examples herein.

1 Although it should be understood that any aqueous dispersion having the properties
described above is within the scope of the present invention regardless of the specific relative
amounts of hydrophobic and hydrophilic surfactants, it is expected that the amount of
hydrophobic surfactant will generally be less than about 200% by weight, based on the
5 amount of hydrophilic surfactant, and more specifically, in the range of about 1% to 200%.
Further, based on observations reported in the Examples herein, it is expected that the amount
of hydrophobic surfactant will generally be less than about 100%, and more specifically in
the range of about 5% to about 100% by weight, or about 10% to about 100% by weight,
based on the amount of hydrophilic surfactant. For some particular surfactant combinations,
10 cloudy solutions result when the amount of hydrophobic surfactant is greater than about 60%
by weight, based on the amount of hydrophilic surfactant. A preferred range for these
surfactants is about 1% to about 60%, preferably about 5% to about 60%, and more
preferably about 10% to about 60%. Addition of optional excipients as described below can
further increase the maximum relative amount of hydrophobic surfactant that can be used.

15 Other considerations well known to those skilled in the art will further inform the
choice of specific proportions of hydrophobic and hydrophilic surfactants. These
considerations include the degree of bioacceptability of the surfactants, and the desired
dosage of hydrophobic therapeutic agent to be provided. In some cases, the amount of
hydrophobic surfactant actually used in a pharmaceutical composition according to the
20 present invention will be less than the maximum that can be used, and it should be apparent
that such compositions are also within the scope of the present invention.

2. Hydrophobic Therapeutic Agents

Hydrophobic therapeutic agents suitable for use in the pharmaceutical compositions
of the present invention are not particularly limited, as the carrier is surprisingly capable of
25 solubilizing and delivering a wide variety of hydrophobic therapeutic agents. Hydrophobic
therapeutic agents are compounds with little or no water solubility. Intrinsic water
solubilities (*i.e.*, water solubility of the unionized form) for hydrophobic therapeutic agents
usable in the present invention are less than about 1% by weight, and typically less than about
0.1% or 0.01% by weight. Such therapeutic agents can be any agents having therapeutic or
30 other value when administered to an animal, particularly to a mammal, such as drugs,
nutrients, and cosmetics (cosmeceuticals). It should be understood that while the invention is
described with particular reference to its value in the form of aqueous dispersions, the
invention is not so limited. Thus, hydrophobic drugs, nutrients or cosmetics which derive

1 their therapeutic or other value from, for example, topical or transdermal administration, are still considered to be suitable for use in the present invention.

Specific non-limiting examples of hydrophobic therapeutic agents that can be used in the pharmaceutical compositions of the present invention include the following representative
5 compounds, as well as their pharmaceutically acceptable salts, isomers, esters, ethers and other derivatives:

analgesics and anti-inflammatory agents, such as aloxiprin, auranofin, azapropazone, benorylate, capsaicin, celecoxib, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, leflunomide,
10 meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, refocoxib, sulindac, tetrahydrocannabinol, tramadol and tromethamine;

anthelmintics, such as albendazole, bephenium hydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel embonate,
15 praziquantel, pyrantel embonate and thiabendazole;

anti-arrhythmic agents, such as amiodarone HCl, disopyramide, flecainide acetate and quinidine sulfate;

anti-asthma agents, such as zileuton, zafirlukast, terbutaline sulfate, montelukast, and albuterol;

anti-bacterial agents, such as alatrofloxacin, azithromycin, baclofen, benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, dirithromycin, doxycycline, erythromycin, ethionamide, furazolidone, grepafloxacin, imipenem, levofloxacin, loxofloxacin, moxifloxacin HCl, nalidixic acid, nitrofurantoin, norfloxacin, ofloxacin, rifampicin, rifabutin, rifapentine, sparfloxacin,
20 spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim, trovafloxacin, and vancomycin;

anti-viral agents, such as abacavir, amprenavir, delavirdine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, and stavudine;

anti-coagulants, such as cilostazol, clopidogrel, dicoumarol, dipyridamole, nicoumalone, oprelvekin, phenindione, ticlidopine, and tirofiban;

anti-depressants, such as amoxapine, bupropion, citalopram, clomipramine, fluoxetine HCl, maprotiline HCl, mianserin HCl, nortriptyline HCl, paroxetine HCl, sertraline HCl,

1 HCl, oxatomide, and terenadine;

keratolytics, such as acutretin, calciprotiene, calcifediol, calcitriol, cholecalciferol, ergocalciferol, etretinate, retinoids, targretin, and tazarotene;

5 lipid regulating agents, such as atorvastatin, bezafibrate, cerivastatin, clinofibrate, clofibrate, fenofibrate, fluvastatin, gemfibrozil, pravastatin, probucol, and simvastatin;

muscle relaxants, such as dantrolene sodium and tizanidine HCl;

nitrates and other anti-anginal agents, such as amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate and pentaerythritol tetranitrate;

10 nutritional agents, such as calcitriol, carotenes, dihydrotachysterol, essential fatty acids, non-essential fatty acids, phytonadione, vitamin A, vitamin B₂, vitamin D, vitamin E and vitamin K.

opioid analgesics, such as codeine, dextropropoxyphene, diamorphine, dihydrocodeine, fentanyl, meptazinol, methadone, morphine, nalbuphine and pentazocine;

15 sex hormones, such as clomiphene citrate, cortisone acetate, danazol, dihydro epiandrosterone, ethinylestradiol, finasteride, fludrocortisone, fluoxymesterone, medroxyprogesterone acetate, megestrol acetate, mestranol, methyltestosterone, norethisterone, norgestrel, oestradiol, conjugated estrogens, progesterone, rimexolone, stanozolol, stibioestrol, testosterone and tibolone;

20 stimulants, such as amphetamine, dexamphetamine, dexfenfluramine, fenfluramine and mazindol;

and others, such as becaplermin, donepezil HCl, L-thyroxine, methoxsalen, nerteporfin, physostigmine, pyridostigmine, raloxifene HCl, sibutramine HCl, sildenafil citrate, tacrine, tamsulosin HCl, and tolterodine.

25 Preferred hydrophobic therapeutic agents include sildenafil citrate, amlodipine, tramadol, celecoxib, refocoxib, oxaprozin, nabumetone, ibuprofen, terbenafine, itraconazole, zileuton, zafirlukast, cisapride, fenofibrate, tizanidine, nizatidine, fexofenadine, loratadine, famotidine, paricalcitol, atovaquone, nabumetone, tetrahydrocannabinol, megestrol acetate, repaglinide, progesterone, rimexolone, cyclosporine, tacrolimus, sirolimus, teniposide, paclitaxel, pseudo-ephedrine, troglitazone, rosiglitazone, finasteride, vitamin A, vitamin D, 30 vitamin E, and pharmaceutically acceptable salts, isomers and derivatives thereof. Particularly preferred hydrophobic therapeutic agents are progesterone and cyclosporin.

It should be appreciated that this listing of hydrophobic therapeutic agents and their therapeutic classes is merely illustrative. Indeed, a particular feature, and surprising

1 advantage, of the compositions of the present invention is the ability of the present
compositions to solubilize and deliver a broad range of hydrophobic therapeutic agents,
regardless of functional class. Of course, mixtures of hydrophobic therapeutic agents may
also be used where desired.

5 3. Solubilizers

If desired, the pharmaceutical compositions of the present invention can optionally
include additional compounds to enhance the solubility of the hydrophobic therapeutic agent
in the carrier system. Examples of such compounds, referred to as "solubilizers", include:

10 alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene
glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol,
mannitol, transcitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol,
polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives,
cyclodextrins and cyclodextrin derivatives;

15 ethers of polyethylene glycols having an average molecular weight of about 200 to
about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol, available commercially
from BASF under the trade name Tetraglycol) or methoxy PEG (Union Carbide);

amides, such as 2-pyrrolidone, 2-piperidone, ϵ -caprolactam, N-alkylpyrrolidone, N-
hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, and
polyvinylpyrrolidone;

20 esters, such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl
citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol
monoacetate, propylene glycol diacetate, ϵ -caprolactone and isomers thereof, δ -valerolactone
and isomers thereof, β -butyrolactone and isomers thereof;

25 and other solubilizers known in the art, such as dimethyl acetamide, dimethyl
isosorbide (Arlasolve DMI (ICI)), N-methyl pyrrolidones (Pharmasolve (ISP)),
monooctanoin, diethylene glycol monoethyl ether (available from Gattefosse under the trade
name Transcutol), and water.

Mixtures of solubilizers are also within the scope of the invention. Except as
indicated, these compounds are readily available from standard commercial sources.

30 Preferred solubilizers include triacetin, triethylcitrate, ethyl oleate, ethyl caprylate,
dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone,
hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol

1 200-600, glycofurol, transcitol, propylene glycol, and dimethyl isosorbide. Particularly {
preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol
and propylene glycol.

5 The amount of solubilizer that can be included in compositions of the present {
invention is not particularly limited. Of course, when such compositions are ultimately
administered to a patient, the amount of a given solubilizer is limited to a bioacceptable
amount, which is readily determined by one of skill in the art. In some circumstances, it may {
be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts in
order to maximize the concentration of hydrophobic therapeutic agent, with excess solubilizer
10 removed prior to providing the composition to a patient using conventional techniques, such
as distillation or evaporation. Thus, if present, the solubilizer can be in a concentration of
50%, 100%, 200%, or up to about 400% by weight, based on the amount of surfactant. If
desired, very small amounts of solubilizers may also be used, such as 25%, 10%, 5%, 1% or
even less. Typically, the solubilizer will be present in an amount of about 1% to about 100%,
15 more typically about 5% to about 25% by weight.

4. Other Additives

Other additives conventionally used in pharmaceutical compositions can be included,
and these additives are well known in the art. Such additives include antioxidants,
preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants odorants,
20 opacifiers, suspending agents, binders, and mixtures thereof. The amounts of such additives
can be readily determined by one skilled in the art, according to the particular properties
desired.

5. Dosage Forms

25 The pharmaceutical compositions of the present invention can be provided in the form
of a solution concentrate; *i.e.*, a composition as described above, and intended to be
dispersed with water, either prior to administration, in the form of a drink, or dispersed *in*
vivo. Alternatively, the compositions can be provided in the form of a diluted concentrate
(*i.e.*, an aqueous dispersion), a semi-solid dispersion or a solid dispersion. If desired, the
compositions may be encapsulated in a hard or soft gelatin capsule, a starch capsule or an {
30 enteric coated capsule. The term "enteric coated capsule" as used herein means a capsule
coated with a coating resistant to acid; *i.e.*, an acid resistant enteric coating. Although {
solubilizers are typically used to enhance the solubility of a hydrophobic therapeutic agent, {
they may also render the compositions more suitable for encapsulation in hard or soft gelatin

1 capsules. Thus, the use of a solubilizer such as those described above is particularly preferred in capsule dosage forms of the pharmaceutical compositions. If present, these solubilizers should be added in amounts sufficient to impart to the compositions the desired solubility enhancement or encapsulation properties.

5 Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration, in the form of a triglyceride-free cream, lotion, ointment, suppository, gel or the like. If such a formulation is desired, other additives may be included, such as are well-known in the art, to
10 impart the desired consistency and other properties to the formulation. The compositions of the present invention can also be formulated as a spray or an aerosol. In particular, the compositions may be formulated as a sprayable solution, and such formulation is particularly useful for spraying to coat a multiparticulate carrier, such as a bead. Such multiparticulate carriers are well known in the art.

15 6. Preparation of Pharmaceutical Compositions

The pharmaceutical compositions of the present invention can be prepared by conventional methods well known to those skilled in the art. Of course, the specific method of preparation will depend upon the ultimate dosage form. For dosage forms substantially free of water, *i.e.*, when the composition is provided in a pre-concentrated form for later
20 dispersion in an aqueous system, the composition is prepared by simple mixing of the components to form a pre-concentrate. The mixing process can be aided by gentle heating, if desired. For compositions in the form of an aqueous dispersion, the pre-concentrate form is prepared, then the appropriate amount of purified water is added. Upon gentle mixing, a clear aqueous dispersion is formed. If any water-soluble additives are included, these may be
25 added first as part of the pre-concentrate, or added later to the clear aqueous dispersion, as desired.

In another embodiment, the present invention includes a multi-phase dispersion. In this embodiment, a pharmaceutical composition includes a carrier which forms a clear aqueous dispersion upon mixing with an aqueous solution, and an additional amount of non-solubilized hydrophobic therapeutic agent. Thus, the term "multi-phase" as used herein to
30 describe these compositions of the present invention means a composition which when mixed with an aqueous solution forms a clear aqueous phase and a particulate dispersion phase. The carrier is as described above, and can include any of the surfactants, hydrophobic therapeutic

agents, solubilizers and additives previously described. An additional amount of hydrophobic therapeutic agent is included in the composition. This additional amount is not solubilized by the carrier, and upon mixing with an aqueous system is present as a separate dispersion phase. The additional amount is optionally a milled, micronized, or precipitated form. Thus, upon dilution, the composition contains two phases: a clear aqueous dispersion of the hydrophilic and hydrophobic surfactants containing a first, solubilized amount of the hydrophobic therapeutic agent, and a second, non-solubilized amount of the hydrophobic therapeutic agent dispersed therein. It should be emphasized that the resultant multi-phase dispersion will not have the optical clarity of a dispersion in which the hydrophobic therapeutic agent is fully solubilized, but will appear to be cloudy, due to the presence of the non-solubilized phase. Such a formulation may be useful, for example, when the desired dosage of a hydrophobic therapeutic agent exceeds that which can be solubilized in the carrier of the present invention. The formulation may also contain additives, as described above.

One skilled in the art will appreciate that a hydrophobic therapeutic agent may have a greater solubility in the pre-concentrate carrier than in the aqueous dispersion, so that meta-stable, supersaturated solutions having apparent optical clarity but containing a hydrophobic therapeutic agent in an amount in excess of its solubility in the aqueous dispersion can be formed. Such super-saturated solutions, whether characterized as clear aqueous dispersions (as initially formed) or as multi-phase solutions (as would be expected if the meta-stable state breaks down), are also within the scope of the present invention.

The multi-phase formulation can be prepared by the methods described above. A pre-concentrate is prepared by simple mixing of the components, with the aid of gentle heating, if desired. It is convenient to consider the hydrophobic therapeutic agent as divided into two portions, a first solubilizable portion which will be solubilized by the carrier and contained within the clear aqueous dispersion upon dilution, and a second non-solubilizable portion which will remain non-solubilized. When the ultimate dosage form is non-aqueous, the first and second portions of the hydrophobic therapeutic agent are both included in the pre-concentrate mixture. When the ultimate dosage form is aqueous, the composition can be prepared in the same manner, and upon dilution in an aqueous system, the composition will form the two phases as described above, with the second non-solubilizable portion of the hydrophobic therapeutic agent dispersed or suspended in the aqueous system, and the first solubilizable portion of the hydrophobic therapeutic agent solubilized in the mixed surfactant

1 carrier. Alternatively, when the ultimate dosage form is aqueous, the pre-concentrate can be
prepared including only the first, solubilizable portion of the hydrophobic therapeutic agent.
This pre-concentrate can then be diluted in an aqueous system to form a clear aqueous
dispersion, to which is then added the second, non-solubilizable portion of the hydrophobic
5 therapeutic agent to form a multi-phase aqueous composition.

The amount of hydrophobic therapeutic agent included in the pharmaceutical
compositions of the present invention can be any amount desired by the formulator, up to the
maximum amount that can be solubilized or suspended in a given carrier system. In general,
the amount of hydrophobic therapeutic agent will be about 0.1% to about 60% by weight,
10 based on the total weight of the pharmaceutical composition. In another aspect of the
invention, described below, excess hydrophobic therapeutic agent can also be added, in a
multi-phase dispersion.

B. Methods of Improved Delivery

15 In another aspect, the present invention relates to methods of improving delivery of
hydrophobic therapeutic agents in an animal by administering to the animal a dosage form of
the pharmaceutical compositions described herein. Preferably the animal is a mammal, and
more preferably, a human. It has been found that the pharmaceutical compositions of the
present invention when administered to an animal enable the hydrophobic therapeutic agent
20 contained therein to be absorbed more rapidly than in conventional pharmaceutical
compositions. Thus, in this aspect the invention relates to a method of increasing the rate of
and/or extent of bioabsorption of a hydrophobic therapeutic agent by administering the
hydrophobic therapeutic agent to an animal in the pharmaceutical compositions described
herein.

C. Characteristics of the Pharmaceutical Compositions

25 The dispersions formed upon dilution of the pharmaceutical compositions of the
present invention have the following characteristics:

Rapid formation: upon dilution with an aqueous solution, the carrier forms a clear
dispersion very rapidly; *i.e.*, the clear dispersion appears to form instantaneously.

30 Optical clarity: the dispersions are essentially optically clear to the naked eye, and
show no readily observable signs of heterogeneity, such as turbidity or cloudiness. More
quantitatively, dispersions of the pharmaceutical compositions of the present invention show
a mono-modal distribution of very small particles sizes, typically 20 nm or less in average
diameter; absorbances of less than about 0.3, typically less than about 0.1, at 10X dilution;

and absorbances of less than about 0.1, typically less than about 0.01, at 100X dilution, as described more fully in the Examples herein. In the multi-phase embodiment of the compositions described herein, it should be appreciated that the optical clarity of the aqueous carrier dispersion phase will be obscured by the dispersed particulate non-solubilized hydrophobic therapeutic agent.

Robustness to dilution: the dispersions are surprisingly stable to dilution in aqueous solution, including aqueous solutions simulating physiological fluids such as enzyme-free simulated gastric fluid (SGF) and enzyme-free simulated intestinal fluid (SIF). The hydrophobic therapeutic agent remains solubilized for at least the period of time relevant for absorption.

Triglyceride-free: It is a particular feature of the present invention that the pharmaceutical compositions are substantially triglyceride-free. The term "triglyceride" as used herein means glycerol triesters of C₆ to about C₂₅ fatty acids. Unlike conventional compositions such as oil-based solutions, emulsions, and microemulsions, which rely on the solubilizing power of triglycerides, the present compositions surprisingly solubilize hydrophobic therapeutic agents using combinations of substantially triglyceride-free surfactants.

As used herein, the term "substantially triglyceride-free" means compositions which contain triglycerides, if at all, only as minor components or impurities in surfactant mixtures. It is well known in the art that commercially available surfactants often are complex mixtures of compounds. For example, one preferred surfactant is Capmul® GMO-K, a widely-used blend of glyceryl mono- and dioleates. Due to difficulties in separating complex product mixtures, however, a typical lot of Capmul® GMO-K, as reported by the manufacturer's certificate of analysis, contains the following distribution of glyceryl esters, in percent by weight based on the total weight of glyceryl esters:

Palmitic acid	3.3%
Stearic acid	4.0%
Oleic acid	81.0%
Linoleic acid	9.7%
Linolenic acid	0.3%

In addition, the surfactant mixture in the particular lot reported contains 0.10% water and 0.95% free, unesterified glycerol. These specific percentages are expected to vary, lot-by-lot, as well, and it is expected that commercial surfactant products will generally possess similar

1 variability, regardless of the specific major component and the specific manufacturer. Thus,
the present invention does not include surfactants which contain triglycerides as an intended
component. Indeed, such surfactants are not common, since triglycerides themselves have no
surfactant properties. However, it should be appreciated that the present invention does not
5 exclude the use of surfactant products which contain small amounts of triglycerides as
impurities or as unreacted starting material. It is expected that commercial mixtures suitable
for use in the present invention may contain as much as 5% triglycerides by weight as
unintended components. Thus, "substantially triglyceride-free" should be understood as
meaning free of added triglycerides, and containing less than 5%, preferably essentially 0%,
10 triglyceride impurities.

Without wishing to be bound by theory, it is believed that the observed properties of
the clear, aqueous dispersions formed by the compositions of the present invention are
consistent with, and best explained by, the formation of mixed micelles of the hydrophobic
and hydrophilic surfactants, with the hydrophobic therapeutic agent solubilized by the
15 micelles. It should be emphasized that these dispersions are characterized by the properties
described herein, regardless of the precise microscopic physical form of the dispersed
particles. Nevertheless, in order to more fully explain the invention, and to illustrate its
unexpected and important advantages, the following discussion is offered in terms consistent
with the theoretical principles believed to be correct.

20 It is believed that the hydrophobic and hydrophilic surfactants form mixed micelles in
aqueous solution. In this model, each micelle is composed of molecules (or ions) of both the
hydrophilic and hydrophobic surfactants. Depending upon the detailed three-dimensional
structure of the hydrophobic therapeutic agent, its distribution of polar moieties, if any, its
polarizability in local regions, and other molecule-specific and complex factors, the
25 hydrophobic therapeutic agent may be distributed in any part of the micelle, such as near the
outer, more hydrophilic region, near the inner, more hydrophobic region, or at various points
in between. Further, it is known that micelles exist in dynamic equilibrium with their
component molecules, and it is expected that this equilibrium will include dynamic
redistribution of the hydrophobic therapeutic agent.

30 As discussed above, triglyceride-containing formulations suffer the disadvantage that
bioabsorption of the hydrophobic therapeutic agents contained therein is dependent upon
enzymatic degradation (lipolysis) of the triglyceride components. The pharmaceutical
compositions of the present invention, however, are substantially free of triglycerides, and

1 hydrophobic therapeutic agent to more closely match the polarity distribution of the
therapeutic agent, resulting in still further enhanced solubilization.

5 Faster dissolution and release: Due to the robustness of compositions of the present
invention to dilution, the hydrophobic therapeutic agents remain solubilized and thus do not
suffer problems of precipitation of the therapeutic agent in the time frame relevant for
absorption. In addition, the therapeutic agent is presented in small particle carriers, and is not
limited in dilution rate by entrapment in emulsion carriers. These factors avoid liabilities
associated with the poor partitioning of lipid solubilized drug in to the aqueous phase, such as
large emulsion droplet surface area, and high interfacial transfer resistance, and enable rapid
10 completion of the critical partitioning step.

Consistent performance: Aqueous dispersions of the present invention are
thermodynamically stable for the time period relevant for absorption, and can be more
predictably reproduced, thereby limiting variability in bioavailability-- a particularly
important advantage for therapeutic agents with a narrow therapeutic index.

15 Efficient release: The compositions of the present invention are designed with
components that help to keep the hydrophobic therapeutic agent solubilized for transport to
the absorption site, but readily available for absorption, thus providing a more efficient
transport and release.

20 Less prone to gastric emptying delays: Unlike triglyceride-containing formulations,
the present compositions are less prone to gastric emptying delays, resulting in faster
absorption. Further, the particles in dispersions of the present invention are less prone to
unwanted retention in the gastro-intestinal tract.

25 Small size: Because of the small particle size in aqueous dispersion, the
pharmaceutical compositions of the present invention allow for faster transport of the
hydrophobic therapeutic agent through the aqueous boundary layer.

These and other advantages of the present invention, as well as aspects of preferred
embodiments, are illustrated more fully in the Examples which follow.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
✓ REINALDO PINILLA MORENO

ASUNTO	Radicación	06-42169
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	112501
	Folios	025

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☒		

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción:	Folios 3-10	como se radicó inicialmente
Reivindicaciones:	Folios 11-14	como se radicó inicialmente
	Folios 308-309	como se radicó el 27-07-2010
Oposiciones:	Folio 123-140	como se radicó el 14-08-2007
	Folios 29-46	como se radicó el 30-08-2007
	Folios 228-237	como se radicó el 28-11-2007
	Folios 252-262	como se radicó el 28-11-2007
Respuesta del solicitante:	Folios 278-287	como se radicó el 04-03-2008
	Folios 303-307	como se radicó el 27-07-2010

2. Objeto de la invención

Título de la solicitud: UNA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE PARA EL TRATAMIENTO DEL SIDA Y PROCESO PARA PREPARAR DICHA COMPOSICIÓN FARMACÉUTICA EN SOLUCIÓN TRANSPARENTE (folio 1).

El problema técnico planteado en esta solicitud esta relacionado con la necesidad de obtener una composición farmacéutica de ritonavir (agente inhibidor de proteasa VIH) en forma de solución que permita aumentar la absorción y biodisponibilidad del fármaco (folios 6-8; pág. 4-6)

Para solucionar este problema técnico la solicitud en estudio proporciona en

Reivindicaciones 1-5: una composición farmacéutica en solución que comprende

- a) Ritonavir o su sal farmacéuticamente aceptable
- b) Un solvente que comprende alcohol tetrahydrofurfurílico polietilenglicol éter
- c) Un elevador de absorción que comprende propilenglicol monocaprilato
- d) Un antioxidante farmacéuticamente aceptable elegido entre butilhidroxianisol o butilhidroxitolueno o una combinación de los mismos, y
- e) Agua

Reivindicaciones 6-8: un proceso para preparar la composición farmacéutica de las reivindicaciones 1-5.

Clasificación Internacional de Patentes (IPC): A61K31/425, A61P31/18.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

Se encuentra que la materia solicitada no tiene sustento como una invención real (desarrollada), ya que en la solicitud no existe ninguna composición ejemplificada que permita reconocerla como soporte de la invención con la que se logre obtener una composición que permita aumentar la absorción y biodisponibilidad del fármaco tal como se asegura en la solicitud (folios 6-8; pág. 4-6)

Así, aunque ahora la composición que se reclama tiene elementos específicos para los elementos (b), (c), y (d) junto ritonavir (a) y agua (d), se encuentra que en la descripción simplemente se listan una serie de compuestos opcionales para cada uno de los elementos (b), (c), y (d) en composiciones que contenga ritonavir (a) y agua (d), representando así solo ser información para formulaciones potenciales.

Por lo anterior, el capítulo reivindicatorio no cumple con el requisito de sustento de acuerdo con las exigencias de los artículos 30 de la Decisión 486.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente 05-05-2006], se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	WO9507696	Pharmaceutical composition of HIV-protease inhibitors	23-03-1995
D2	WO0050007	Compositions and methods for improved delivery of hydrophobic therapeutics agents	21-08-2000

Anterioridad D1 en folios 288-296 y D2 en folios 310-329.

5. Análisis de patentabilidad (artículo 14 D486)

5.1 Nivel inventivo (artículo 18 D486)

Se solicita en las reivindicaciones 1-5 una composición farmacéutica en solución que comprende:

- a) Ritonavir o su sal farmacéuticamente aceptable
- b) Un solvente que comprende alcohol tetrahidrofurfurílico polietilenglicol éter
- c) Un elevador de absorción que comprende propilenglicol monocaprilato
- d) Un antioxidante farmacéuticamente aceptable elegido entre butilhidroxianisol o butilhidroxitolueno o una combinación de los mismos, y
- e) Agua

SOLICITUD	D1	D2
Una composición farmacéutica en solución	Una composición farmacéutica en solución (folios 290; pág. 5)	Una composición farmacéutica acuosa clara (folio 312; pág. 5)
Ritonavir o su sal farmacéuticamente aceptable	Ritonavir o su sal farmacéuticamente aceptable, entre	Agente activo hidrofóbico Como ritonavir (folios 320; pág. 33)
El solvente alcohol tetrahidrofurfurílico polietilenglicol éter	Mezcla de solventes orgánicos farmacéuticamente aceptables como: 2-(2,-etoxietoxi)etanol (Transcutol ® ó dietilenglicol monoetil éter)	Solubilizadores seleccionados de Alcoholes y polioles como dietilenglicol monoetil éter (Transcutol) Éteres de polietilenglicol como alcohol tetrahidrofurfurílico polietilenglicol éter (Glycofural o Tetraglycol) ó metoxi polietilenglicol (folio 322; pág. 37)
El elevador de absorción propilenglicol monocaprilato	Propilenglicol monolaurato y similares. (folios 191-292; pág. 6-7)	Surfactantes Como Propilenglicol ésteres de ácidos grasos como propilenglicol monocaprilato, propilenglicol monolaurato, propilenglicol oleato, propilenglicol miristato, propilenglicol monoesterato, propilenglicol laurato, propilenglicol caprilato/caprato (folio 316; pág. 17)
Un antioxidante elegido entre butilhidroxianisol ó butilhidroxitolueno ó una combinación de los mismos	Antioxidantes farmacéuticamente aceptables como BHA (butilhidroxianisol) ó BHT (butilhidroxitolueno), entre otros (folio 291; pág. 6)	Antioxidantes farmacéuticamente aceptables (folio 323; pág. 38)
Agua	Agua (folio 291; pág. 6)	Agua (folio 312; pág. 5)

D1 enseña composiciones farmacéuticas en solución de ritonavir en un solvente o mezcla de solventes orgánicos como 2-(2,-etoxietoxi)etanol (Transcutol ® ó dietilenglicol monoetil éter), propilenglicol monolaurato y similares, entre otros; conteniendo antioxidantes farmacéuticamente aceptables como BHA (butilhidroxianisol) ó BHT (butilhidroxitolueno) y agua, tal como se señala arriba en la tabla comparativa.

La solicitud se diferencia de D1 en que indica específicamente el alcohol tetrahidrofurfurílico polietilenglicol éter como solvente y propilenglicol monocaprilato como elevador de absorción.

El efecto técnico que provee tal diferencia es obtener una composición farmacéutica en solución de ritonavir que permite aumentar la absorción y biodisponibilidad del fármaco (folios 6-8; pág. 4-6).

Por tanto, el problema técnico objetivo de la solicitud está relacionado con la necesidad de obtener una composición farmacéutica de ritonavir en forma de solución que permita aumentar su absorción y biodisponibilidad.

Sin embargo, D2 enseña que el alcohol tetrahidrofurfurílico polietilenglicol éter como un agente solubilizante y el propilenglicol monocaprilato (entre los surfactantes de propilenglicol ésteres de ácidos grasos) son adecuados en composiciones acuosas para solubilizar agentes hidrofóbicos como ritonavir, tal como se enseña en el cuadro comparativo, permitiendo lograr composiciones acuosas claras que tienen una velocidad de absorción incrementada y mejor biodisponibilidad del fármaco (folios 312,322, 329; pág. 5, 37, 45).

Adicionalmente, se observa que la solicitud (folios 7-8; pág. 5-6) establece que la invención también se puede llevar a cabo con otros agentes solubilizantes como el dietilenglicol monoetil éter -*Transcutol*®- (señalado en D1 y D2), metoxi polietilenglicol (señalado en D2) y otros agentes elevadores de la absorción de los propilenglicol ésteres de ácidos grasos como propilenglicol monolaurato (señalado en D1 y D2), u otros como propilenglicol monocaprilato, propilenglicol monolaurato, propilenglicol oleato, propilenglicol miristato, propilenglicol monoesterato, propilenglicol laurato, propilenglicol caprilato/caprato (señalados en D2).

Por ende, de acuerdo con las enseñanzas de D1 y D2 para un experto en la materia la formulación farmacéutica reclamada no tiene nivel inventivo.

- Se solicita en las reivindicaciones 6-8 un proceso para preparar la composición farmacéutica en solución de las reivindicaciones 1-5, que comprende:
 - solubilizar el ritonavir, el elevador de absorción (propilenglicol monocaprilato), el antioxidante (butilhidroxianisol ó butilhidroxitolueno o su mezcla) y agua en el solvente (alcohol tetrahidrofurfurílico polietilenglicol éter), mezclar hasta obtener una solución transparente y encapsular tal solución en capsulas de gelatina.

Sin embargo, se encuentra que tal proceso para obtener una solución en una forma encapsulada esta caracterizado por los pasos comúnmente conocidos por un experto en la materia: disolver el agente activo y excipientes en el solvente, mezclar hasta lograr la solución transparente y luego encapsular la misma, tal como lo indica D1 en la preparación de una composición en solución de ritonavir al disolver el agente activo y demás aditivos, agua y antioxidantes en el solvente o mezcla de solventes, agitar o mezclar hasta lograr una solución clara que posteriormente es encapsulada (folios 294-295; pág. 19-20); por lo que el proceso solicitado no cumple el requisito de nivel inventivo.

6. Respuesta al solicitante

- El solicitante anexa un nuevo capítulo reivindicatorio (folio308-309) en el que ha eliminado los términos generales y ambiguos, y ha limitado la materia a una composición (que contiene ritonavir, alcohol tetrahidrofurfurílico polietilenglicol éter, propilenglicol monocaprilato y un antioxidante farmacéuticamente aceptable elegido entre butilhidroxianisol o butilhidroxitolueno o una combinación de los mismos y agua) y un proceso de prepararla; capítulo que es aceptado por esta Oficina.

No obstante, se reitera que la materia solicitada no tiene sustento como una invención real (desarrollada); ya que, aunque ahora la composición que se reclama tiene elementos específicos para los elementos (b), (c), y (d) junto ritonavir (a) y agua (d), se encuentra que en la descripción simplemente se listan una serie de compuestos opcionales para cada uno de los elementos (b), (c) y (d) en composiciones que contienen ritonavir (a) y agua (d), representando así sólo ser información para formulaciones potenciales, sin que exista ninguna composición ejemplificada con la que se logre obtener una composición que aumente la absorción y biodisponibilidad del fármaco tal como se asegura en la solicitud (folios 6-8; pág. 4-6)

- En cuanto a la objeción por novedad, el solicitante señala:

Que en D1 la composición tiene glicerinas, surfactantes y para solubilizar el activo se usa propilenglicol, etanol y polietilenglicol a diferencia de la solicitud que solo usa alcohol tetrahidrofurfurilico polietilenglicol éter; así, D1 no revela el mismo solvente y no utiliza un elevador de absorción, requiriendo de otros aditivos como la glicerina y el glicérido poliglicolizado como surfactante; por lo tanto D1 no es relevante y comparable para novedad y nivel inventivo de la solicitud (folio 306; pág. 3-4 de respuesta).

Al respecto, se aclara primero, que puesto que el capítulo ha sido restringido a una composición más concreta D1 ya no afecta la novedad; sin embargo, ahora D1 junto con D2 afectan el nivel inventivo de la materia reclamada, ya que:

D1 enseña composiciones farmacéuticas en solución de ritonavir en un solvente o mezcla de solventes orgánicos como 2-(2,-etoxietoxi)etanol (Transcutol ® ó dietilenglicol monoetil éter), propilenglicol monolaurato y similares, entre otros; conteniendo antioxidantes farmacéuticamente aceptables como BHA (butilhidroxianisol) ó BHT (butilhidroxitolueno) y agua (folios 290-292; pág. 5-7).

Siendo entonces la diferencia de la solicitud con D1 el alcohol tetrahidrofurfurilico polietilenglicol éter y el propilenglicol monocaprilato. Pero, dado que D2 enseña que el alcohol tetrahidrofurfurilico polietilenglicol éter como un agente solubilizante y el propilenglicol monocaprilato (entre los surfactantes de propilenglicol ésteres de ácidos grasos) son adecuados en composiciones acuosas para solubilizar agentes hidrofóbicos como ritonavir (folios 316, 322; pág. 17, 37) y que permiten lograr composiciones acuosas claras que tienen una velocidad de absorción incrementada y mejor biodisponibilidad del fármaco (folios 312, 322, 329; pág. 5, 37, 45), la composición farmacéutica reclamada no tiene nivel inventivo, tal como se explica en el respectivo numeral.

Segundo, se aclara que D1 señala entre los solventes adecuados el propilenglicol monolaurato y similares, es decir propilenglicol ésteres de ácidos grasos; y se señala que aunque D1 no los defina como un agentes elevadores de la absorción es conocido que éstos agentes tiene también tal función, tal como se reconoce en la solicitud al indicar que los propilenglicol ésteres de ácidos grasos además de solubilizar el agente activo son elevadores de la absorción del mismo (folio 8; pág. 6).

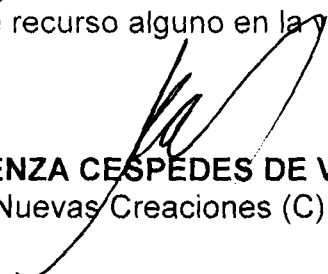
7. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO9507696	1-8	Nivel inventivo
D2	WO0050007	1-5	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 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 artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
23 SET. 2010

CONCEPTO TECNICO No. 3112	EXAMINADOR TECNICO Código No. 202079
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