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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 06-042-169

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

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

SOLICITANTE: PROCAPS S.A.

APODERADO: REINALDO PINILLA MORENO

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en los argumentos planteados en la oposición referida, los cuales, como se dijo en su momento, demuestran que la solicitud en trámite incumple los requisitos de patentabilidad establecidos por los artículos 14 y

18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- En primer término, la publicación internacional WO 95/07696 publicada el 23 de Marzo de 1995 y titulada "PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS" revela una composición farmacéutica que comprende una solución de un compuesto inhibidor de proteasa HIV en un solvente orgánico farmacéuticamente aceptable que comprende un alcohol farmacéuticamente aceptable; la composición puede opcionalmente comprender un ácido o una combinación de ácidos farmacéuticamente aceptables; adicionalmente, la solución puede ser encapsulada en cápsulas de gelatina dura o de gelatina blanda; con lo que se demuestra que en el estado del arte se encuentran composiciones farmacéuticas de Ritonavir como un agente inhibidor de la proteasa VIH en uno o más solventes orgánicos farmacéuticamente aceptables, junto con antioxidantes adecuados, incluso, puede contener Propilenglicol monolaurato entre sus excipientes, su forma farmacéutica puede ser cápsulas de gelatina blanda y los porcentajes o rangos se encuentran dentro de lo revelado en la solicitud colombiana en trámite.
- La publicación internacional WO 98/22106 publicada el 28 de Mayo de 1998 y titulada "PHARMACEUTICAL COMPOSITION" revela una composición farmacéutica líquida que proporciona una mejorada biodisponibilidad para compuestos inhibidores de proteasa HIV; en particular la composición comprende una solución en un solvente orgánico farmacéuticamente aceptable de a) un inhibidor de proteasa HIV y opcionalmente, b) un surfactante (que podría en nuestra opinión estar mejorando la solubilidad de Ritonavir); y opcionalmente puede ser encapsulada en cápsulas de gelatina dura o en cápsulas blandas elásticas (SEC), tal como se pretende en la solicitud colombiana en trámite.
- La solicitud internacional WO 00/74677 publicada el 14 de diciembre de 2000 y titulada "IMPROVED PHARMACEUTICAL FORMULATIONS" describe composiciones farmacéuticas mejoradas que comprenden uno o más compuestos inhibidores de proteasa HIV que tienen propiedades mejoradas de disolución en una mezcla de ácido graso, etanol y agua; y si bien es cierto que

esta publicación internacional no revela el lleno de características contenidas en la solicitud colombiana en trámite, no lo es menos que se trata de composiciones que comprenden Ritonavir en cápsulas de gelatina, solventes orgánicos adecuados, surfactantes, antioxidantes y agua dentro de la formulación; además, esta anterioridad junto con las otras hasta el momento expuestas, permiten evidenciar y reunir la información necesaria para poder llevar a cabo una formulación como la que se pretende ahora patentar.

- La publicación internacional WO 01/52821 publicada el 26 de Julio de 2000 y titulada "IMPROVES PHARMACEUTICAL FORMULATIONS" revela una vez más el conjunto de características descritas en la solicitud colombiana en trámite, y en consecuencia, se evidencia el incumplimiento de los requisitos de patentabilidad en virtud de lo revelado en dicho documento perteneciente al arte anterior.
- La publicación internacional WO 02/096395 publicada el 05 de Diciembre de 2000 y titulada "SOFT ELASTIC CAPSULES COMPRISING RITONAVIR AND/OR LOPINAVIR" revela con anterioridad, características esenciales que sustentan la invención de la solicitud colombiana en trámite, específicamente lo que se refiere a el inhibidor de proteasa (ritonavir) en el tratamiento de VIH, las características del solvente y el porcentaje del mismo en la formulación, la presencia de antioxidantes, las proporciones del principio activo y demás componentes de la formulación, y finalmente la inclusión de dicha solución en cápsulas de gelatina.
- Finalmente, siendo evidente la anterioridad en la obtención de formulaciones con características idénticas a la de la solicitud colombiana en trámite, es importante resaltar que con la información necesaria para realizar este tipo de formulaciones (capsulas de gelatina blanda) contenida en el estado de la técnica, la producción de las formulaciones reivindicadas por dichas solicitud colombiana en trámite se reduce a la aplicación de todos los ensayos requeridos a nivel de preformulación y formulación reconocidos por cualquier persona versada en la materia¹.

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

II. COMPLEMENTO DE INFORMACIÓN.

Por si no fuesen suficientes los argumentos dados en la oposición presentada anteriormente, se puede demostrar, además, que el uso de “elevadores de la absorción” dentro de la formulación, tales como los que se mencionan en las reivindicaciones 1, 6, 7 y 11, se utilizan con anterioridad y su uso deriva del amplio conocimiento que se tiene respecto a la baja absorción del ritonavir a nivel gástrico y su baja e irregular biodisponibilidad cuando se administra por vía oral, veamos:

- La publicación científica “SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SED DS) FOR IMPROVED ORAL DELIVERY OF LIPOPHILIC DRUGS²” describe:

ABSTRACT: *The oral delivery of hydrophobic drugs presents a major challenge because of the low aqueous solubility of such compounds. Self-emulsifying drug delivery systems (SED DS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. SED DS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil-in-water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids. The efficiency of oral absorption of the drug compound from the SED DS depends on many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-emulsifying systems. Although many studies have been carried out, there are few drug products on the pharmaceutical market formulated as SED DS confirming the difficulty of formulating hydrophobic drug compounds into such formulations. At present, there are four drug products, Sandimmune and Sandimmun Neoral (cyclosporin A), Norvir (ritonavir), and Fortovase (saquinavir) on the pharmaceutical market, the active compounds of which have been*

² Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SED DS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother. 2004 Apr;58(3):173-82.

formulated into specific SEDDS. Significant improvement in the oral bioavailability of these drug compounds has been demonstrated for each case. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SEDDS will continue, and more drug compounds formulated as SEDDS will reach the pharmaceutical market in the future.

Lo anterior demuestra que la incorporación de agentes tensoactivos dentro de una formulación que se va a encapsular con el fin de mejorar la absorción de compuestos con baja solubilidad en los fluidos gástricos, es una alternativa reconocida y ampliamente utilizada con anterioridad en el estado de la técnica, lo que en consecuencia le resta al menos nivel inventivo a lo pretendido en la solicitud colombiana en trámite puesto que en ambos casos se pretende mejorar la biodisponibilidad y la absorción oral del ritonavir.

- La publicación científica "NOVEL APPROACHES TO ISSUES OF DEVELOPABILITY³." Revela:

Considerations of developability, such as 'is the compound drugable', are often left until a lead is selected for trials. Investigating the form and formulation of compounds at the early preclinical stage can save significant costs and time. Here we take a look at how to ensure your candidate is a suitable drug using high-throughput form and formulation technologies.

(...)

these formulations. Two examples of high-profile problems relate to saquinavir (Invirase® and Fortovase®) and ritonavir (Norvir®).

(...)

³ Örn Almarsson & Colin R Gardner. Novel approaches to issues of developability. www.currentdrugdiscovery.com, January 2003.

product. By extensive F&F effort, the new formulation, Fortovase, was engineered in such a way as to emulsify the drug more effectively in gastric fluid than was possible before. One can surmise that having the better performing formulation at the outset could have enhanced saquinavir's market penetration by mitigating the issue of poor bioavailability of the original formulation.

(...)

Ritonavir was originally launched as a semi-solid dosage form, in which the waxy matrix contained dispersed drug in order to achieve acceptable oral bioavailability. In 1998, two years after its introduction, ritonavir exhibited latent crystal polymorphism, which caused the semi-solid capsule formulation of Norvir to be removed from the market. The new drug crystal form did not have sufficient solubility in the formulation and the product therefore began failing dissolution specifications. Knowledge of the crystal form diversity of ritonavir would likely have averted this painful experience. A new formulation was developed; a soft-gelatin capsule containing a liquid excipient mixture in which the new crystal form is soluble.

(...)

Lo anterior muestra nuevamente la utilización de formulaciones tipo cápsula blanda junto con tensoactivos para solucionar los problemas de absorción de las moléculas tipo inhibidor de proteasa.

- La publicación científica **Physicochemical considerations in the preparation of amorphous ritonavir-poly(ethylene glycol) 8000 solid dispersions.**⁴, describe:

A systematic study of the properties of ritonavir and the influence of polyethylene glycol 8000 (PEG) on ritonavir revealed that amorphous

⁴ D Law , S L Krill , E A Schmitt , J J Fort , Y Qiu , W Wang , W R Porter. Physicochemical considerations in the preparation of amorphous ritonavir-poly(ethylene glycol) 8000 solid dispersions J Pharm Sci. 2001 Aug ;90 (8):1015-25 11536205.

ritonavir dispersions in PEG would have an improved dissolution profile and could exhibit long-term stability. Ritonavir, a human immunodeficiency virus (HIV) protease inhibitor, is highly lipophilic [distribution coefficient (log D)= 4.3, 25 degrees C, pH 6.8], poorly water soluble (400 microg/mL in 0.1 N HCl, 1 microg/mL at pH 6.8, 37 degrees C), and exhibits an exceedingly slow dissolution rate (0.03 mg/cm(2)-min in 0.1 N HCl at 37 degrees C). These properties indicated that a solid dispersion containing ritonavir might be useful for overcoming problems associated with slow dissolution. In addition, ritonavir is a good glass former [glass-transition temperature (T(g))/melting point (T(m)) > 0.7]. Amorphous ritonavir has an apparent solubility of 4 mg/mL in 0.1 N HCl at 37 degrees C and shows reasonable stability at 25 degrees C. Amorphous ritonavir, therefore, has properties desirable for preparing a solid dispersion containing this phase. **Since PEG, a commonly used polymer, improved the aqueous solubility of crystalline ritonavir, it was expected to have a positive influence on the dissolution rate of ritonavir. Moreover, PEG was found to have negligible plasticizing effect on amorphous ritonavir, which was beneficial for the stability of the dispersion.** Finally, solid dispersions of amorphous ritonavir in PEG were prepared, and these dispersions had improved in vitro dissolution rate and were physically stable for > 1.5 years at 25 degrees C when protected from moisture. The performance of this solid dispersion has been attributed to the physicochemical properties of amorphous ritonavir.

En este artículo podemos ver que, para mejorar la solubilidad del principio activo ritonavir se hace uso de un polímero de uso común como es el PEG 8000, si bien es cierto no se refiere a las mismas sustancias que se reportan en la solicitud colombiana en trámite, es importante resaltar que se usan con el mismo fin, es decir, los polietilenglicoles pueden también ser empleados para mejorar la solubilidad acuosa o las características de disolución de compuestos pobremente solubles.

- Ahora bien, si lo supuestamente sorprendente es el empleo de elevadores de la absorción como son el propilenglicol caprilato y monocaprilato, propilenglicol monolaurato, propilenglicol caprilato/caprato, propilenglicol laurato, propilenglicol oleato, propilenglicol miristato, propilenglicol monoestearato y sus mezclas, en una formulación, entonces debemos citar la patente

americana US 6,638,522 de título "MICROEMULSION CONCENTRATE COMPOSITION OF CYCLOSPORIN", publicada el 28 de octubre de 2003 ya que en este documento se describe composiciones farmacéuticas que comprenden Ciclosporina, un fármaco que es substancialmente insoluble en agua. Debido a su limitada solubilidad en agua, la biodisponibilidad de ciclosporina administrada oralmente es extremadamente baja y puede ser altamente dependiente de las condiciones del paciente.

Para vencer los problemas definidos anteriormente, la patente americana describe composiciones farmacéuticas que comprenden ciclosporina y un vehículo lipofílico que comprende a) un **éster de Propilenglicol con ácidos grasos de C₆-C₁₈** que contienen al menos el 60% por peso de monoésteres basado en el peso total del éster de Propilenglicol, dicho éster de propilenglicol está presente en una cantidad suficiente para solubilizar la ciclosporina, y b) un surfactante iónico, en cantidad suficiente para formar una microemulsión con la ciclosporina y el éster de Propilenglicol cuando está en contacto con un medio acuoso, especialmente los encontrados en los mamíferos.

De igual manera describe que, **los ésteres de Propilenglicol de ácidos grasos que contienen los niveles de monoéster indicado arriba, son más compatibles con formas de dosificación orales, como aquellos que involucran cápsulas de gelatina.**

Además, describe que si la forma de dosificación oral es una cápsula, hay una excelente compatibilidad del éster de propilenglicol que tiene al menos el 60% por los monoésteres de peso de C₆-C₁₈ de ácidos grasos basado sobre el peso total del éster con una cápsula de gelatina blanda o dura o con una cápsula de no gelatina, previniendo así la fragilidad y el escape de la formulación durante el almacenaje.

También revela que:

The esters of propylene glycols used in the present invention are commercially available or are prepared by art-recognized techniques, e.g., by esterification of propylene glycol with fatty acids.

Examples of propylene glycol esters useful in the present invention

which are commercially available include propylene glycol monocaprylate, and the like. In the preferred embodiments, the monoester ranges from about 60% to 100% inclusive.

Hasta aquí vemos inequívocamente que sin bien es cierto no se refiere a una formulación basada en Ritonavir, los ésteres de Propilenglicol son útiles para mejorar la solubilidad de fármacos insolubles, en este caso de la ciclosporina y son compatibles con formulaciones orales como cápsulas de gelatina, en consecuencia, su empleo como mejorador de la absorción del RITONAVIR no es sorprendente como se quiere hacer ver en la presente solicitud colombiana.

Para terminar, en los ejemplos de ésta patente americana se encuentran mencionados algunos de los elevadores de la absorción citados en las reivindicaciones 6 y 7 de la solicitud colombiana en trámite:

EXAMPLE 3

INGREDIENT	MG/CAPSULES
Cyclosporin	100
Propylene glycol monocaprylate	200
Polyoxyl 35 Castor oil	<u>550</u>
TOTAL	850

EXAMPLE 7 AND COMPARATIVE EXAMPLES 1 AND 2

The following formulations were prepared:

EXAM- PLE	FORMULATION	INITIAL OBSER- VATION	OBSER- VATION AFTER 1 MONTH
Com- para- tive Exam- ple 1	Cyclosporin 100 mg Propylene glycol Dicaprate-Caprylate, Diester >90% Polyoxyl 35 Castor oil 300 mg (Cremophore EL 35)	Clear	Precipitation and Crystallization (after 1 week)
Com- para- tive Exam- ple 2	Cyclosporin 100 mg Propylene glycol 200 mg Laurate, Monoester about 45 to 50% Polyoxyl 35 Castor oil 300 mg (Cremophore EL 35)	Clear	Precipitation and crystal growth (after 2 weeks)
Exam- ple 7	Cyclosporin 100 mg Propylene glycol 200 mg mono-Caprylate, monoester >90% Polyoxyl 35 Castor oil 300 mg (Cremophore EL 35)	Clear	Clear solution after more than 3 months

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS

- La publicación científica "SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS) FOR IMPROVED ORAL DELIVERY OF LIPOPHILIC DRUGS." Abstract.
- La publicación científica "NOVEL APPROACHES TO ISSUES OF DEVELOPABILITY." Páginas 21 y 25.
- La publicación científica: "Physicochemical considerations in the preparation of amorphous ritonavir-poly(ethylene glycol) 8000 solid dispersions". D Law , S L Krill , E A Schmitt , J J Fort , Y Qiu , W Wang , W R Porter. J Pharm Sci. 2001 Aug;90 (8):1015-25 11536205.

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1: Biomed Pharmacother. 2004 Apr;58(3):173-82.

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Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs.

Gursoy RN, Benita S.

Hacettepe University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 06100 Ankara, Turkey.

The oral delivery of hydrophobic drugs presents a major challenge because of the low aqueous solubility of such compounds. Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. SEDDS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil-in-water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids. The efficiency of oral absorption of the drug compound from the SEDDS depends on many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-emulsifying systems. Although many studies have been carried out, there are few drug products on the pharmaceutical market formulated as SEDDS confirming the difficulty of formulating hydrophobic drug compounds into such formulations. At present, there are four drug products, Sandimmune and Sandimmun Neoral (cyclosporin A), Norvir (ritonavir), and Fortovase (saquinavir) on the pharmaceutical market, the active compounds of which have been formulated into specific SEDDS. Significant improvement in the oral bioavailability of these drug compounds has been demonstrated for each case. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SEDDS will continue, and more drug compounds formulated as SEDDS will reach the pharmaceutical market in the future.

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Novel approaches to issues of developability

Örn Almarsson & Colin R Gardner
TransForm Pharmaceuticals Inc, USA



Considerations of developability, such as 'is the compound drugable', are often left until a lead is selected for trials. Investigating the form and formulation of compounds at the early preclinical stage can save significant costs and time. Here we take a look at how to ensure your candidate is a suitable drug using high-throughput form and formulation technologies.

In recent years, several new technologies have been developed which have enabled great strides in the generation of lead compounds for development into pharmaceuticals. First, the genomic revolution cast a floodlight on the diversity and expression of putative targets for drug discovery. Second, the advent of combinatorial chemistry produced vast libraries from which discovery groups could initiate searches for compounds active at new targets. Third, *in vitro* potency and selectivity assays have become automated with newly available commercial equipment, which is increasingly user-friendly to laboratory personnel. Automation in preclinical research (including metabolic profiling and permeability screening) has facilitated identification of membrane-permeable molecules, the metabolism of which can be characterized at a fairly early stage. These advances were in all cases made possible by high-throughput (HT) methodologies.

Despite this progress, the drug industry finds itself in a productivity crisis as the number of new drugs registered has not kept pace with the increased resource expenditures in discovery. Two elements that exacerbate the issue are the increasing chemical complexity of compounds in discovery and the lack of available technologies to deal with the increased output of compounds downstream of discovery.

Increased chemical complexity is a result of advances in genomics and combinatorial chemistry; there are more plentiful targets that require increasingly elaborate molecules to selectively address the intended target. Combinatorial chemistry has led to the generation of compounds that have progressively more challenging properties; an acute lack of water solubility, as well as poor dissolution characteristics, are frequently a problem in early development.

What is developability?

'Developability' refers to the quest for desirable properties beyond the classical focus on potency and selectivity, ie, does a compound have the desirable pharmaceutical properties to make a drug? The key to efficiently traversing the preclinical stage of drug development involves the marriage of classical criteria with consideration of developability. Limitations of developability raise significant hurdles for advancing compounds into the clinic and for this reason, preclinical development is showing signs of becoming a bottleneck. Due to the mounting pressure on development groups to bring challenging compounds forward to proof-of-principle studies in the clinic, new technologies and capabilities are needed to accelerate preclinical evaluation. In order to increase the chances of identifying a compound with suitable physical proper-

ties and advancing it to development, HT techniques are now being devised for the preclinical space.

Two questions are beginning to receive attention across the pharmaceutical industry and they provide the focus of this article: Why is consideration of pharmaceutical properties becoming increasingly critical to drug discovery and preclinical development? And, what HT strategies help to address developability at earlier stages, when amounts of test substance are often limiting?

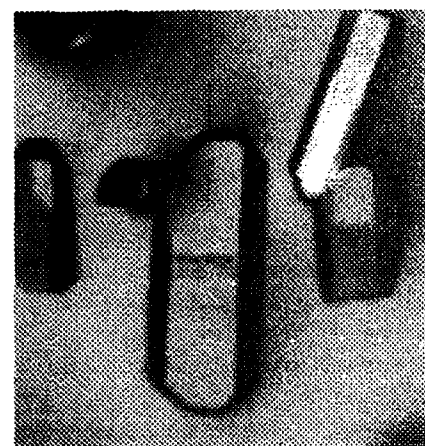


Figure 1. The form of a drug candidate is a critical attribute that determines the physical properties of the compounds and significantly affects pharmaceutical processing, stability and bioavailability.

Impact points

Increasingly, compounds are stalling in development due to issues of form and formulation, and these problems were likely already evident in the discovery phase. Others experience unanticipated biopharmaceutical problems in development or, worse, on the market. The emerging way to avoid these problems is to conduct miniaturized experiments earlier combined with informatics-aided analyses of solubility, solid form diversity, formulation options and biopharmaceutical data. The vision of cross-correlating physical, chemical and biological information for diverse chemical structures is shared by a number of pharmaceutical companies that operate with ever growing sample collections. At present, the best examples of the value of understanding the nature of compounds are historical ones. The examples chosen come from analysis of the pharmaceutical issues with HIV protease inhibitors.

Many will realize that the tremendous strides made in HIV therapy due to the

advent of the protease inhibitors in the mid 1990s would not have occurred without the knowledge and experience gained a half a decade earlier, when several companies were deeply involved in the discovery of renin inhibitors. The latter class of compounds largely comprise peptidomimetics, which are compounds that frequently possess the challenging properties of poor aqueous solubility and meta-

these formulations. Two examples of high-profile problems relate to saquinavir (Invirase® and Fortovase®) and zidovudine (Retrovir®).

It is well known that the utility of saquinavir, the first HIV protease inhibitor on the market, was severely impeded by poor bioavailability. Because bioavailability and pharmacokinetics are crucial determinants of the activity of an anti-infective drug, the original formulation, Invirase showed only modest market performance at its peak. Invirase soon became overshadowed by drugs such as zidovudine (Retrovir) and didanosine (Videx) that had better bioavailability. Three years after initial approval, saquinavir was re-introduced in a formulation with six-fold higher oral bioavailability relative to the original product. By extensive F&F effort, the new formulation, Fortovase, was engineered in such a way as to emulsify the drug more effectively in gastric fluid than was possible before. One can surmise that having the better performing formulation at the outset could have enhanced saquinavir's market penetration by mitigating the issue of poor bioavailability of the original formulation.

Ritonavir was originally launched as a semi-solid dosage form, in which the waxy matrix contained dispersed drug in order to achieve acceptable oral bioavailability. In 1998, two years after its introduction, ritonavir exhibited latent crystal polymorphism, which caused the semi-solid capsule formulation of Norvir to be removed from the market. The new drug crystal form did not have sufficient solubility in the formulation and the product therefore began failing dissolution specifications. Knowledge of the crystal form diversity of ritonavir would likely have averted this painful experience. A new formulation was developed; a soft-gelatin capsule containing a liquid excipient mixture in which the new crystal form is soluble.

The storage label for Norvir capsules indicates refrigeration of the drug prior to dispensing to the patient. The same is

"HT crystallization screening provides a way to address polymorphism issues much earlier and can help to avoid late discoveries of polymorphism in pharmaceutical systems."

bolic instability toward cytochrome P450 enzymes. These issues are prominent in the HIV protease inhibitor class. The types of marketed formulations in this class illustrate the problems that exist with achieving bioavailability (Table 2). In essence, the oral dosage forms consist of drug in an oily solution within soft gelatin capsules or more water-soluble (and in one case amorphous) salt forms in hard gelatin capsules. There were significant challenges along the way to achieving

HIV Protease	Products	Oral formulation(s)
Saquinavir	Invirase® ¹	Hard gelatin capsule containing the mesylate salt form
Saquinavir	Fortovase® ²	Soft gelatin capsule containing the free base drug form
Indinavir	Crixivan®	Hard gelatin capsule of the crystalline sulfate salt
Ritonavir	Norvir®	Soft gelatin capsule; oral solution
Amprenavir	Agenerase®	Soft gelatin capsule; oral solution
Nelfinavir	Viracept®	Hard gelatin capsule of the amorphous mesylate salt
Lopinavir	Kaletra® ³	Soft gelatin capsule; oral solution

¹ Original product.

² Improved product with 6-fold bioavailability relative to Invirase®.

³ Formulated as a fixed-dose combination of Lopinavir with Ritonavir.

Table 2. FDA-approved HIV protease inhibitors.

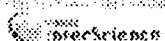
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Links**Physicochemical considerations in the preparation of amorphous ritonavir-poly (ethylene glycol) 8000 solid dispersions.****Law D, Krill SL, Schmitt EA, Fort JJ, Qiu Y, Wang W, Porter WR.**

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A systematic study of the properties of ritonavir and the influence of polyethylene glycol 8000 (PEG) on ritonavir revealed that amorphous ritonavir dispersions in PEG would have an improved dissolution profile and could exhibit long-term stability. Ritonavir, a human immunodeficiency virus (HIV) protease inhibitor, is highly lipophilic [distribution coefficient (log D)= 4.3, 25 degrees C, pH 6.8], poorly water soluble (400 microg/mL in 0.1 N HCl, 1 microg/mL at pH 6.8, 37 degrees C), and exhibits an exceedingly slow dissolution rate (0.03 mg/cm(2)-min in 0.1 N HCl at 37 degrees C). These properties indicated that a solid dispersion containing ritonavir might be useful for overcoming problems associated with slow dissolution. In addition, ritonavir is a good glass former [glass-transition temperature (T(g))/melting point (T(m)) > 0.7]. Amorphous ritonavir has an apparent solubility of 4 mg/mL in 0.1 N HCl at 37 degrees C and shows reasonable stability at 25 degrees C. Amorphous ritonavir, therefore, has properties desirable for preparing a solid dispersion containing this phase. Since PEG, a commonly used polymer, improved the aqueous solubility of crystalline ritonavir, it was expected to have a positive influence on the dissolution rate of ritonavir. Moreover, PEG was found to have negligible plasticizing effect on amorphous ritonavir, which was beneficial for the stability of the dispersion. Finally, solid dispersions of amorphous ritonavir in PEG were prepared, and these dispersions had improved in vitro dissolution rate and were physically stable for > 1.5 years at 25 degrees C when protected from moisture. The performance of this solid dispersion has been attributed to the physicochemical properties of amorphous ritonavir. Copyright 2001 Wiley-Liss, Inc.

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(12) **United States Patent**
Mulye(10) **Patent No.:** **US 6,638,522 B1**
(45) **Date of Patent:** ***Oct. 28, 2003**(54) **MICROEMULSION CONCENTRATE**
COMPOSITION OF CYCLOSPORIN(75) **Inventor:** **Nirmal Mulye, Long Beach, NY (US)**(73) **Assignee:** **Pharmasolutions, Inc., Cranbury, NJ (US)**(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) **Appl. No.:** **09/459,298**(22) **Filed:** **Dec. 10, 1999****Related U.S. Application Data**

(60) Provisional application No. 60/111,951, filed on Dec. 11, 1998.

(51) **Int. Cl.⁷** **A61K 47/00; A61K 9/20**(52) **U.S. Cl.** **424/439; 514/506; 514/937; 424/439; 424/464**(58) **Field of Search** **424/439, 464; 514/506, 937**(56) **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Sabiha Qazi(74) **Attorney, Agent, or Firm**—Scully, Scott, Murphy & Presser(57) **ABSTRACT**

The present invention is directed to a pharmaceutical composition comprising a pharmaceutically effective amount of Cyclosporin, in association with a pharmaceutical carrier, said carrier comprising a cyclosporin solubilizing effective amount of a propylene glycol monoester of C₆–C₁₈ fatty acid having at least 60% by weight monoester based on the total weight of the propylene glycol ester and a non-ionic surfactant.

21 Claims, No Drawings

1

MICROEMULSION CONCENTRATE COMPOSITION OF CYCLOSPORIN

RELATED APPLICATIONS

The present application is claiming benefit of the provisional application, U.S. Ser. No. 60/111,951 filed on Dec. 11, 1998.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising Cyclosporin, a drug which is substantially non-soluble in water.

BACKGROUND OF THE INVENTION

The Cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-Methylated undecapeptides, commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic (in particular anti-protozoal, e.g. anti-malarial) activity. The first of the Cyclosporins to be isolated was the naturally occurring fungal metabolite Cyclosporin or Cyclosporine, also known as cyclosporin A and commercially available under the Registered Trademark SANDIMMUN®.

Cyclosporin is sparingly soluble in water, but dissolves readily in organic solvents, such as methanol, chloroform and the like. Due to its limited solubility in water, the bioavailability of orally administered cyclosporin is extremely low and may be highly dependent on the condition of the patient. Accordingly, it is very difficult to retain an effective therapeutic concentration. Cyclosporin can thus be formulated into a preparation for oral administration only with great difficulty. Accordingly, numerous studies have been extensively conducted to find a cyclosporin preparation effective for oral administration, that is, a preparation which provides both uniform dosage and bioavailability of the active component.

In the prior art preparations of cyclosporin suitable for oral administration, sparingly water-soluble cyclosporin has been usually formulated in the form of an emulsion by combining cyclosporin with a surfactant, an oil and a co-surfactant. For example, U.S. Pat. No. 4,388,307 discloses a liquid formulation of cyclosporin that includes at least one of the following components: (a) a transesterification product of a natural or hydrogenated vegetable oil and a polyalkylene polyol; (b) a saturated fatty acid triglyceride; or (c) a mono- or diglyceride. Component (a) is formed by the transesterification of a triglyceride, e.g., a triglycerides from a vegetable oil, with polyethylene glycol. Component (b) may be obtained by esterifying a triglyceride with saturated fatty acid while component (c) is a mono- or di-glyceride, or a mono- or di-fatty acid glyceride. In these prior art formulations, it is preferred that ethanol be further used as a solubilizing agent. However, since this liquid formulation is administered as an aqueous solution, it is both inconvenient and difficult to administer in an uniform dosage as a result of its limited solubility in water.

In order to mitigate the inconvenience of diluting a cyclosporin liquid composition with water prior to oral administration, a liquid composition has been formulated into a soft capsule preparation, which is now commercially available as SANDIMMUN®. In this preparation, the cyclosporin soft capsule contains a large amount of ethanol as a cosurfactant in order to solubilize the cyclosporin. However, since ethanol permeates the gelatin shell of the capsule and is volatile even at normal temperatures, the

2

constitutional ratio of the contents of the soft capsules may greatly vary during storage. The resulting reduced ethanol content may in turn result in crystallization of the cyclosporin and thus results in a significant variation in the bioavailability of cyclosporin. The variation in cyclosporin concentration in this formulation makes it quite difficult to determine the dosage needed to provide a desired therapeutic effect.

Belgian Patent No. 895,724, which relates to the use of Cyclosporin in the treatment of multiple sclerosis, also describes two oral formulations suitable for the administration of this particular compound. Both of these are based on the commercial Cyclosporin (SANDIMMUN®) drink-solution, with adaption to suit the particular cyclosporin active ingredient. The first comprises 5-10% Cyclosporin, 10-12% ethanol, 30-40% MAISINE®, about 4% CREMOPHORE® and 51-30% LABRAFIL®. This corresponds to the composition of the liquid oral formulation of SANDIMMUN®, but with the replacement of the natural vegetable oil component with MAISINE® and the introduction of a minor percentage of the tenside CREMOPHORE®. MAISINE® is a trans-esterification product of corn oil with glycerol. The ratio of Cyclosporin: tenside in the disclosed composition is 1:0.4-0.8. Inasmuch as ethanol is a key component of the formulation, it does not make any suggestion to replace ethanol as co-solvent/cosurfactant.

U.S. Pat. No. 5,342,625 discloses cyclosporin in association with a hydrophilic phase, lipophilic phase and a surfactant. The hydrophilic phase comprises 1,2-propylene glycol or $R_1-[O-(CH_2)_x]-OR_2$, where R_1 is alkyl containing 1-5 carbon atoms or tetrahydrofuryl, R_2 is hydrogen, alkyl containing 1-5 carbon atoms or tetrahydrofurfuryl and x is 1-6. Such ethers are commercially available under the trade name of Transcutol and Glycofurol; in addition, it may contain C_{1-5} alkanols, such as ethanols.

However, the use of ethanol as well as other hydrophilic solvents such as 1,2-propylene glycol or liquid polyethylene glycols in these sorts of systems creates several problems. Since ethanol permeates the gelatin shell of the capsule and is volatile, even at room temperature, the constitutional ratio of the contents of the soft capsules may greatly vary during storage. The resulting reduced ethanol content may in turn result in crystallization of the cyclosporin, and this results in a significant variation in the bioavailability of cyclosporin when administered to an animal. The variation in cyclosporin concentrate in these types of formulations makes it quite difficult to determine the dosage needed to provide a desired therapeutic effect. Moreover, when solvents such as ethanol, 1,2-propylene glycol and liquid polyethylene glycols are utilized in gelatin capsules, these solvents have a tendency to absorb moisture, thereby rendering brittle the shell walls, especially those in hard gelatin capsules, and thereby resulting in leakage of the contents of the capsules during storage or shipment. Moreover, one of the biggest drawbacks using hydrophilic components, as in U.S. Pat. No. 5,342,625, has been the potential of reprecipitation of the drug from the formulation when it comes into contact with aqueous systems, such as in the stomach or intestine after ingestion by the mammal.

Moreover, the complexity of the ternary formulations as in U.S. Pat. No. 5,342,625 makes them costly and difficult to manufacture. Moreover, U.S. Pat. No. 5,342,625 suggests the use of solvents such as Glycofurol and Transcutol which are restricted for pharmaceutical use by several regulatory agencies worldwide, including the FDA, because they are not considered "Generally Recognized As Safe" (GRAS) for oral use. Further, with hydrophilic solvents there is always

an added risk of precipitation of the cyclosporin on exposure to gastrointestinal fluids in vivo, thereby further affecting bioavailability.

U.S. Pat. No. 4,970,076 discloses the use of GLA (gamma linoleic acid) and DGLA (dihomogammalinolenic acid) and their derivatives as active components in pharmaceutical compositions to counter the adverse side effects of cyclosporin, such as nephrotoxicity and renal side effects. It, however, does not teach or even recognize the use of the lipophilic materials for enhancing the solubility, bioavailability, emulsion or microemulsion capability.

A couple of very recent patents, U.S. Pat. Nos. 5,759,997 and 5,858,401, disclose the use of a mixture of mono-, di- and triglycerides as a carrier for cyclosporin formulations. The formulations therein do not contain a hydrophilic component, such as alcohol, propylene glycol, and the like. However, the formulation therein has several drawbacks. For example, some of the problems encountered with these formulations include the limited solubility of cyclosporin therein. As a result, the size of the capsules necessary to accommodate the required dose, e.g., 100 mg, is very large. This causes a major inconvenience to the patient, resulting in a larger pill or capsule, thereby making it more difficult for the patient to swallow the same. This, in turn, tends to minimize compliance by the patients who have to take multiple capsules per day.

Furthermore, in addition, the stability of this formulation, especially those having a high monoglyceride content when used in hard gelatin capsules, is extremely limited; monoglycerides have a tendency to make the gelatin shells brittle, causing leakage of the contents of such capsules.

It is apparent that there is a need to prepare formulations of cyclosporins which minimize the number of components that are to be administered to the patient. There is also a need to prepare formulations of cyclosporins which provide higher drug loading, and therefore need smaller size capsules, use components considered as GRAS and offer advantageous formulation stabilities, desirable pharmacokinetics and bioavailability and ease of manufacture.

In accordance with the present invention, it is now surprisingly been found that pharmaceutical compositions comprising cyclosporins can be prepared which can overcome the difficulty in dosing and patient compliance/acceptability encountered in the art as discussed above. More specifically, it has been found that the use of a specific lipophilic carrier comprising esters of propylene glycol with C_6 - C_{18} fatty acids containing at least about 60% by weight monoesters based on the total weight of the propylene glycol ester in conjunction with a non-ionic surfactant overcomes the problems described hereinabove. No one heretofore utilized or realized the advantages of this specific carrier in combination with cyclosporins. Unlike the composition of the prior art containing mono-, di- or triglycerides of vegetable oils, the propylene glycol esters of fatty acids containing levels of monoester indicated hereinabove are more compatible with oral dosage forms, such as those involving gelatin capsules.

It has been found that by employing the above defined carrier, it is possible to obtain lipid-based formulations which do not require any additional solvent or co-solvent, such as alcohol, propylene glycol, polyethylene glycol, etc., and therefore, problems associated with these hydrophilic components or solvents mentioned hereinabove are eliminated. Thus, the compositions of the present invention are more stable than those compositions associated with hydrophilic components, such as alcohols.

Due to the greater solubility of Cyclosporin in the carrier of the present invention, the size of the capsule for the delivery of unit doses of the cyclosporin is reduced, providing greater patient acceptance and compliance. Moreover, if the oral dosage form is a capsule, there is an excellent compatibility of the propylene glycol ester having at least 60% by weight monoesters of C_6 - C_{18} fatty acids based on the total weight of the ester with a hard or soft shell gelatin capsule or with a non-gelatin capsule, thereby preventing brittleness and leakage of the formulation during storage. Furthermore, the present composition of cyclosporin forms a microemulsion upon exposure to aqueous fluid (water, e.g., the g.i. tract) which will provide higher and uniform bioavailability. This characteristic will further help reduce the intra- and intersubject variability associated with the absorption of cyclosporin, as well as minimize the effect of food on the absorption and bioavailability thereof in mammals.

SUMMARY OF THE INVENTION

The present invention is directed to a pharmaceutical composition comprising a pharmaceutically effective amount of cyclosporin in association with a carrier, said carrier comprising a mixture of (a) a propylene glycol ester of C_6 - C_{18} fatty acids having at least about 60% by weight monoesters based on the total weight of the propylene glycol ester, said propylene glycol ester being present in an amount sufficient to solubilize the cyclosporin, and (b) a non-ionic surfactant, said surfactant being present in an amount sufficient to form a microemulsion with the cyclosporin and propylene glycol ester when in contact with an aqueous medium, especially those found in mammals.

The present invention is also directed to the pharmaceutically acceptable carrier described hereinabove. Furthermore, the present invention is also directed to a method of forming a microemulsion of a pharmaceutical composition in which cyclosporin is the active medicament, said method comprising (a) thoroughly mixing the cyclosporin with (i) a cyclosporin solubilizing effective amount of a propylene glycol ester of C_6 - C_{18} fatty acid with at least 60% by weight of monoester based on the total weight of the propylene glycol ester; and (ii) a non-ionic surfactant having a HLB value greater than 10, said surfactant being present in sufficient amounts to form a microemulsion with the cyclosporin and said propylene glycol ester when brought in contact with an aqueous medium, and (b) contacting the product of (a) with an aqueous medium, e.g. water.

Another aspect of the present invention is directed to a method of enhancing the bioavailability of cyclosporin in a patient in need of drug therapy, said method comprising orally administering to said patient a pharmaceutical composition comprising a therapeutically effective amount of cyclosporin in association with a carrier, said carrier comprising (a) a cyclosporin solubilizing effective amount of a propylene glycol ester of C_6 - C_{18} fatty acid with at least 60% by weight monoester based on the total weight of the propylene glycol ester and (b) a non-ionic surfactant having a HLB value greater than 10, said surfactant being present in sufficient quantity to form a microemulsion with the cyclosporin and the propylene glycol ester when brought in contact with an aqueous medium. Moreover, the present invention is directed to a method of forming a pharmaceutical composition containing cyclosporin as the active therapeutic agent, which comprises thoroughly mixing cyclosporin with the carrier as defined herein, which when brought in contact with an aqueous medium forms a microemulsion.

5

The present inventions is also directed to a method of increasing the drug loading ability of cyclosporin in a pharmaceutical composition, said method comprising thoroughly mixing cyclosporin with (a) a cyclosporin solubilizing effective amount of a propylene glycol ester of C₆-C₁₈ fatty acid with at least about 60% by weight monoester based on the total weight of the propylene glycol ester and (b) a non-ionic surfactant having a HLB value greater than 10, said surfactant being present in amounts sufficient to form a microemulsion with the cyclosporin and said propylene glycol ester when brought in contact with an aqueous medium.

The present invention is also directed to an improved process for treating a patient in need of cyclosporin therapy comprising administering to said patient the pharmaceutical composition of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The term "carrier" is a term of art. As used, herein, the term "carrier" refers to the composition that transports the cyclosporin across the biological membrane or within a biological fluid. The carrier of the present invention comprises (a) the propylene glycol ester of C₆-C₁₈ fatty acid, having at least 60% by weight monoester, based on the total weight of the propylene glycol ester (b) the surfactant and (c) optionally other adjuvants that normally are present in pharmaceutically acceptable carriers, as described hereinbelow.

As indicated hereinabove, an aspect of the present invention relates to a pharmaceutically acceptable carrier in association with cyclosporin in a pharmaceutical formulation. It is preferred that the formulation be used in oral dosage form, e.g., in hard or soft gelatin capsules (or capsules made of other materials such as starch, cellulose or its derivatives, and the like).

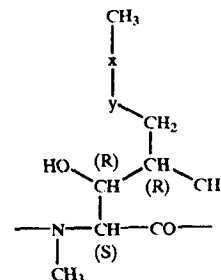
It is preferred that the cyclosporin pharmaceutical formulation is substantially free and more preferably completely free of ethanol and other hydrophilic components. It is also preferred that the cyclosporin pharmaceutical composition is substantially free and more preferably completely free of fatty acid triglycerides.

In a preferred embodiment, the present invention relates to a Cyclosporin pharmaceutical formulation in the absence of a hydrophilic component, such as ethanol, and in the absence of fatty acid triglyceride in oral dosage form, e.g., in hard or soft gelatin capsules (or capsules made of other materials such as starch, cellulose or its derivatives, etc.) or in a parental preparation for intramuscular and intravenous administration.

As used herein, cyclosporin is a cyclic peptide compound. It exhibits, inter alia, immunosuppressive activity and anti-inflammatory activity. Various cyclosporins, such as cyclosporin A, B, C, D, G, M and the like can all be used as the cyclosporin component in the present invention. Cyclosporin A has the formula:

6

wherein MeBmt represents a N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)-threonyl residue of the formula



in which —x—y is CH=CH-(trans).

Since the original discovery of cyclosporin, a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes, for example, the naturally occurring cyclosporins A through Z [c.f. Traber et al. 1, *Helv. Chim. Acta.* 60, 1247-1255 (1997); Traber et al. 2, *Helv. Chim. Acta.* 65 no. 162, 1655-1667 (1982); Kobel et al., *Europ. J. Applied Microbiology and Biotechnology* 14, 273-240 (1982); and von Warburg et al., *Progress in Allergy*, 38, 28-45. (1986).], as well as various non-natural cyclosporin derivatives and artificial or synthetic cyclosporins including the so called dihydro-cyclosporins [in which the moiety —x—y of the MeBmt residue above is saturated to give x—y=CH₂—CH₂]; derivatized cyclosporins (e.g. in which a further substituent is introduced at the α -carbon atom of the sarcosyl residue at the 3-position of the cyclosporin molecule); cyclosporins in which the -MeBmt-residue is present in isomeric form (e.g. in which the configuration across positions 6' and 7' of the -MeBmt-residue is cis rather than trans); and cyclosporins wherein variant amino acids are incorporated at specific positions within the peptide sequence, employing e.g. the total synthetic method for the production of cyclosporins developed by R. Wenger—see e.g. Traber 1, Traber 2 and Kobel loc. cit., U.S. Pat. Nos. 4,108,985, 4,210,581 and 4,220,641; European Patent Publication Nos. 0 034 567, 0 156 782 and 0 296 122; International Patent Publication No. WO 86/02080; Wenger 1, *Transp. Proc.* 15, Suppl. 1:2230 (1983); Wenger 2, *Angew. Chem. Int. Ed.*, 24, 77 (1985); and Wenger 3, *Process in the Chemistry of Organic Natural Products* 50, 123 (1986), the contents of all of which are incorporated by reference.

The class comprised by the cyclosporins includes, for example, [Thr]²-, [Val]²-, [Nva]²- and [Nva]²-[Nva]²-Cyclosporin A (also known as cyclosporins C, D, G, and M respectively), [3'-O-acyl-MeBmt]¹-Cyclosporin A (also known as cyclosporin A acetate), [Dihydro-MeBmt]¹-[Val]²-cyclosporin A (also known as dihydrocyclosporin D), [(1D)Fluoromethyl-Sar]³-Cyclosporin A, [(1D)Ser]⁴-Cyclosporin A, [Melle]¹¹-Cyclosporin A, [(D)MeVal]¹¹-Cyclosporin A (also known as cyclosporin H), [MeAla]²-Cyclosporin A, [(D)Pro]³-Cyclosporin A and so on.

MeBmt	α Abu	Sar	MeLeu	Val	MeLeu	Ala	(D)Ala	MeLeu	MeLeu	MeVal
1	2	3	4	5	6	7	8	9	10	11

[In accordance with now conventional nomenclature for cyclosporins, these are defined by reference to the structure of Cyclosporin A. This is done by first indicating the amino acid residues present which differ from those present in cyclosporin A (e.g. "[D]Pro") to indicate that the cyclosporin in question has a -[D]Pro- rather than -Sar- residue at the 3-position) and then applying the term "Cyclosporin A" to characterize remaining residues which are identical to those present in Cyclosporin A. Individual residues are numbered starting with the residue -MeBmt, dihydroMeBmt- or its equivalent in position 1.]

The preferred cyclosporin utilized in the present invention is cyclosporin A.

The cyclosporin is present in the present formulation in pharmaceutically effective amounts. Of course those of ordinary skill in the art will understand that the amounts of cyclosporin present in the composition will vary with the particular situation, including without limitation, the mode of administration, the size, age and condition of the subject and the like. Moreover, these effective amounts will be easily determined by the physician without an undue amount of experimentation. It is preferred that cyclosporin is present in an amount ranging between 5% and 40% by weight of the pharmaceutical composition. For example, when treating chronic inflammations or provoking an immunosuppressive effect, it is preferred that the daily dose ranges from about 3 mg/kg to about 50 mg/kg of body weight of the patient, e.g., mammal. It is more preferred that it is present in amounts ranging from about 5 to about 35% by weight of the pharmaceutical composition.

The second essential component of the present composition is the lipid, i.e., the propylene glycol esters of C_6 - C_{18} fatty acids with at least 60% by weight monoester based on the total weight of the propylene glycol ester utilized. When using the term "propylene glycol ester" herein, it is to be understood that it refers to this lipid, as defined hereinabove.

The term propylene glycol refers to 1,2-dihydroxypropane as well as 1,3-dihydroxypropane. The preferred propylene glycol is 1,2-dihydroxypropane.

The fatty acids of the propylene glycol ester utilized in the present invention contain C_6 - C_{18} carbon atoms. They may contain carbon-carbon double bonds. If a carbon-carbon double bond is present, it is preferred that it does not contain more than nine carbon-carbon double bond and more preferably no more than four carbon-carbon double bonds. If a carbon-carbon double bond is present, it is more preferred that the fatty acid contains 1, 2 or 3 carbon-carbon double bonds. The fatty acids utilized herein preferably have the formula $RCOOH$, wherein R is a hydrocarbyl group (group containing carbon and hydrogen atoms) containing 6-18 carbon atoms, which hydrocarbyl group is saturated. Although the fatty acid may be branched, it is preferred that a straight chain fatty acid is utilized.

Moreover, it is preferred that the fatty acid of the propylene glycol monoester contains 6-16 carbon atoms and more preferably 8-12 carbon atoms, and most preferably 8-10 carbon atoms, and even more preferably 8 or 10 carbon atoms. It is also preferred that the fatty acid contains an even number of carbon atoms. In the most preferred embodiments, the fatty acid of propylene glycol ester is a straight chain.

The second component, as indicated hereinabove, is a lipid fatty acid esterified product of propylene glycol containing at least about 60% monoester based on the total weight of propylene glycol ester, i.e., only one of the hydroxy groups is esterified. The term "ester of propylene glycol containing at least about 60% monoester by weight"

signifies that at least about 60% by weight up to a maximum of 100% of the esters formed in the esterification reaction is the monoester. Although the second component may contain any amount of monoester above the 60% level based on the total weight of the propylene glycol ester, including 60%-100% inclusive, e.g. including at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% by weight, it is preferred that the propylene glycol ester contains at least about 70% by weight monoester, and most preferably at least about 90% by weight monoester. However, in a preferred embodiment, it contains at least about 95% by weight monoester and in another preferred embodiment, at least about 99% by weight monoester.

Although a mixture of fatty acids of C_6 - C_{18} may be used to be esterified to the propylene glycol, it is preferred that only one type of fatty acid be esterified to the propylene glycol.

The esters of propylene glycols used in the present invention are commercially available or are prepared by art-recognized techniques, e.g., by esterification of propylene glycol with fatty acids. Examples of propylene glycol esters useful in the present invention which are commercially available include propylene glycol monocaprylate, and the like. In the preferred embodiments, the monoester ranges from about 60% to 100% inclusive.

The propylene glycol esters of C_6 - C_{18} fatty acid with at least about 60% by weight of monoester, based on the total weight of propylene glycol ester of the fatty acids, are used as the lipids in the carrier. They help to solubilize the cyclosporin. The propylene glycol esters used in the present invention having at least 60% monoester content by weight will also be designated as the "cyclosporin solubilizing agent", "lipid", or "solubilizing agent" and these terms will also be used to denote the propylene glycol monoester having at least 60% monoester.

Thus, in the composition of the present invention, it is preferred that the propylene glycol ester of C_6 - C_{18} fatty acid with at least about 60% by weight of monoester based on the total weight of propylene glycol ester be present in amounts sufficient to solubilize the cyclosporin. It is preferred that the weight ratio of cyclosporin to propylene glycol ester ranges from about 1:1 to about 1:500 and more preferably from about 1:1 to about 1:20 and even more preferably from about 1:2 to about 1:4. Most preferably, the weight ratio is about 1:2 or 1:3.

To maximally solubilize the cyclosporin, it is preferred that the lipophilicity of the cyclosporin solubilizing agent, and more specifically, the log of the octanol/saline partition coefficient of the solubilizing agent, i.e., the propylene glycol ester as defined herein, should be substantially identical with that of cyclosporin. More specifically, it is preferred that the octanol/saline partition coefficient of the lipid and cyclosporin is within about 2 log units.

When the propylene glycol ester containing at least about 60% by weight monoester based on the total weight of the propylene glycol ester is present in the amounts indicated hereinabove, the solubility of the cyclosporin is enhanced. As a result, when the propylene glycol ester of C_6 - C_{18} fatty acids having at least about 60% by weight monoesters based on the total weight of the propylene glycol ester is present in solubilizing effective amounts and is combined with an effective amount of the non-ionic surfactant and cyclosporin, in accordance with the present invention, a self emulsifying drug delivery system (SEDDS), as defined hereinbelow, is formed. A microemulsion is formed when the propylene glycol ester used in the present invention, the water soluble non-ionic surfactant and the cyclosporine are

brought in contact with aqueous medium, e.g., g.i. fluids of mammals. Surprisingly, the present inventor has found that the propylene glycol ester of C₆-C₁₈ fatty acids with at least about 60% by weight monoester, based on the total weight of the propylene glycol ester, provides drug solubility and co-surfactant properties essential to form the microemulsion when used in conjunction with the non-ionic water soluble surfactant and cyclosporin when the pharmaceutical composition of the present invention is brought in contact with aqueous medium, e.g., g.i. fluids. The inventor has additionally surprisingly found that propylene glycol diesters of the corresponding fatty acids do not aid in solubilizing the cyclosporin. The present inventor has found that the presence of the propylene glycol ester, as defined herein not only provides the solubilization of the cyclosporin but also aids the SEDDS process.

The third essential component of the composition present is the water soluble non-ionic surfactant. It is preferred that the surfactant has a HLB (Hydrophilic Lipophilic Balance) greater than 10 and more preferably greater than 12 and most preferably greater than 14. The surfactant of the present pharmaceutical composition is capable of forming a stable microemulsion when it is brought into contact with an aqueous fluid, such as in the G.I. tract. Examples of the preferred surfactant according to the present invention include polyoxyethylene products of hydrogenated vegetable oils, polyethoxylated castor oils or polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene castor oil derivatives and the like, for example, NIKKOL HCO-50®, NIKKOL HCO-35®, NIKKOL HCO-40®, NIKKOL HCO-60® (from Nikko Chemicals Co. Ltd.); CREMOPHORE® (from BASF) such as CREMOPHORE RH40®, CREMOPHORE RH60®, CREMOPHORE EL®, TWEENS (from ICI Chemicals) e.g., TWEEN 20®, TWEEN 21®, TWEEN 40®, TWEEN 60®, TWEEN 80®, TWEEN 81®, CREMOPHORE RH 410®, CREMOPHORE RH 455® and the like.

The surfactant can be one surfactant or a combination of two or more surfactants having a HLB value greater than 10. It may include any of the above-mentioned surfactants alone or in a combination with two or more surfactants selected from the above list. In the pharmaceutical composition of the present invention, it is preferred that the propylene glycol ester of C₆-C₁₈ fatty acid with at least about 60% by weight of mono-ester based on the total weight of the propylene glycol ester and surfactant be used in a weight ratio ranging from about 1:1 to about 1:20 and more preferably from about 1:1 to about 1:4 and most preferably about 1:1 or 1:2 or 1:3.

It is also preferred that the ratio of cyclosporin to surfactant ranges from about 1:1 to about 1:20 and more preferably from about 1:1 to about 1:4, and most preferably about 1:2 or about 1:3.

In the composition of the present invention, the three essential components are present preferably in the weight ratio of cyclosporin:propylene glycol ester:surfactant, respectively, from about 1:1-20:1-20, and more preferably from about 1:2-4:2-4.

In a preferred embodiment the surfactant is present in equal to or greater amounts by weight than the propylene glycol ester.

Additives normally utilized in the pharmaceutical arts can also be added to the pharmaceutical composition and especially the carrier or carrier system. These include thickening, granulating, dispersing, flavoring, coloring, and stabilizing agents, other excipients, such as anti-oxidants (e.g., α -tocopherol, BHA, BHT, TBHQ and the like), preservatives (e.g., parabens), and the like.

The present pharmaceutical composition is prepared by uniformly and thoroughly mixing the cyclosporin, the solubilizing agent, and the surfactant together at room temperature or at slightly elevated temperature, such as temperatures up to about 60° C. until a clear solution is obtained, and then the mixture is cooled to room temperature. The other additives indicated hereinabove are then thoroughly admixed therewith. In this preparation, cyclosporin remains in solution and does not crystallize or precipitate out.

An essential aspect of the pharmaceutical formulation of the present invention is that it forms a microemulsion, when brought into contact with water or an aqueous medium. The microemulsion thus formed is thermodynamically stable when it comes into contact with the water or aqueous medium, as in the G.I. fluids of mammals. However, until the present formulation comes in contact with an aqueous medium, it is not a microemulsion; instead, when the various components are mixed, it forms what in the art is known as a preconcentrate of an emulsion (SEDDS), i.e., microemulsion pre-concentrate, i.e., a system capable of forming microemulsion respectively, on contact with water or aqueous system.

The microemulsion consists of substantially uniform and spherical droplets dispersed in a continuous medium. It is substantially non-opaque, i.e., is transparent or opalescent. The average particle size of the droplets in the present microemulsion are submicron. It is preferred that the average particle size is less than about 200 nm, which explains the optical transparency. In a preferred embodiment, the average particle size is less than about 40 nm and more preferably less than about 20 nm. In an even more preferred embodiment, substantially all of the particles are less than about 40 nm and more preferably less than about 20 nm.

Thus, the preconcentrate (SEDDS) of the present invention, when brought in contact with aqueous medium, forms microemulsions and are ideal for oral delivery systems for lipophilic drugs, since they are homogeneous, thermodynamically stable, have uniform droplet sizes of and are optically clear. It is also preferred that the average particle size of the microemulsion formed in the present invention ranges from about 20 to about 40 nanometers.

By forming a microemulsion when in contact with aqueous medium, the present formulation minimizes and essentially eliminates the risk that the cyclosporin will precipitate or crystallize out of the aqueous dispersion, i.e., the microemulsion. In addition, it enhances the absorption of the cyclosporin into the mammal.

Thus, the present formulation not only increases the solubility of the cyclosporin in the pharmaceutical carrier, but also facilitates uniform absorption thereof in the treated mammal and enhances the bioavailability of the cyclosporin.

The present composition is useful as an immunosuppressive agent, in particular in relation to its application to recipients of organ transplants, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, bone-marrow, skin and corneal transplants and in particular, allogenic organ transplants.

The cyclosporin pharmaceutical composition is also useful in treating various autoimmune diseases and inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific auto-immune diseases for which Cyclosporin therapy is useful include, inter alia, autoimmune hematological disorder (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic

thrombocytopaenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and lomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic, nephrotic syndrome or minimal change nephropathy).

Cyclosporin is also useful as an anti-parasitic, in particular as an anti-protozoal agent. It is also useful in the treatment of malaria, coccidiomycosis and schistosomiasis. It is also useful in cancer therapy, e.g. as an agent for reversing or abrogating resistance to the other anti-neoplastic or cytostatic therapy.

Compositions of the present invention are preferably administered to mammals, such as dog, cat, horse, pig, mice, rat and especially humans. It is preferred that the pharmaceutical compositions of the present invention are administered orally in capsule, tablet, liquid-oral, powder, or the like or liquid for parental composition for intramuscular or intravenous administration. In a preferred embodiment, the invention provides a composition in a form appropriate or adapted for oral administration, in particular, in oral unit dosage form, e.g., in the form of tablets, capsules, drink solutions or dry powder for reconstitution; or a soxhlet form prepared by standard techniques known in the art, such as by spray coating on deposition. Especially suitable unit dosage forms for oral administration include encapsulated forms, e.g., soft or hard gelatin encapsulated forms, which is the preferred oral dosage forms or capsules made from non-gelatin materials.

Oral unit dosage forms in accordance with the present invention will suitably comprise from 5 to 400 mg and more preferably from 20 to 300 mg, e.g., 25, 50 or 100, 150, 200, 250 and 300 mg of cyclosporin. The dosage of the drug and the number of times administered to the patient will vary depending on several factors, the age of the patient, the severity of the condition of the patient, past medical history, among other factors, and will be determined by the physician in his sound discretion without an undue amount of experimentation.

When the composition of the present invention is prepared in the form of a soft or hard capsule, the composition may be encapsulated in a gelatin shell which contains any conventional plasticizer. As the plasticizer which can be included in the gelatin capsule shell, one or more selected from the group consisting of glycerine, sorbitol, hexanetriol propylene carbonate, hexane glycol, sorbitans, tetrahydrofuryl alcohol ether, diethylene glycol monoethyl ether, 1,3-trimethyl-2-imidazolidone, dimethylisorbide, etc. can be used without any limitation. However, it should be understood that the plasticizer which can be used in the present invention is not restricted to those mentioned above.

Capsule preparation according to the present invention can be prepared in a conventional machine by encapsulating the resulting preconcentrates of the microemulsion of the present invention, e.g., the self-emulsifying pre-concentrate with or without the above-mentioned pharmaceutically acceptable additives.

Ethanol and other hydrophilic components are preferably substantially absent and even more preferably completely

absent from the carrier of the present invention. Since ethanol is preferably not present, especially in amounts sufficient to solubilize the cyclosporin, there is less risk of precipitating or crystallizing cyclosporin in the pharmaceutical composition. If ethanol were present, and if it were present in the amounts usually found in cyclosporin pharmaceutical formulations described in the prior art, it would evaporate even when standing at room temperature, thereby causing possible crystallization and/or precipitation of the cyclosporin. The absence of ethanol in these amounts in the present formulation prevents possible crystallization and precipitation of the cyclosporin, thereby ensuring dosage uniformity, accurate blood levels of the cyclosporin and consistent therapeutic performance.

The present pharmaceutical composition has several advantageous properties. It is non-volatile and non-hygroscopic and has a high boiling point. It has excellent compatibility with both soft and hard gelatin shell capsules, as well as with the other dosage forms, thereby providing excellent storage stability. Additionally, it provides greater solubility with higher drug loading, thereby providing smaller capsule size per unit dose of cyclosporin and resulting in greater patient acceptance and compliance. Moreover, if the oral dosage form is a capsule, there is an excellent compatibility of the carrier of the present invention with hard or soft shell gelatin capsules, thereby preventing brittleness and leakage of the formulation during storage. Furthermore, the present pharmaceutical composition is a preconcentrate (SEDDS) which forms a microemulsion upon exposure to aqueous fluid (water, in e.g., the g.i. tract) which provides higher and uniform bioavailability. This characteristic further helps reduce the intra- and intersubject variability associated with the absorption of the cyclosporin in the mammal, as well as minimizes the effect of food on the absorption and bioavailability of the drug in mammals. Moreover, there is no need for special precaution and procedure for the manufacturing, packaging and handling requirement during the preparation, storage and shipping of the product since ethanol is not present.

In addition, the compositions of the invention exhibit improved stability on storage as compared with compositions based on the use of ethanol or equivalent alkanols, such as those having 1-10 carbon atoms, and are, in particular, better adapted, e.g., for presentation in capsule, e.g. hard or soft gelatin capsule form. Preferred compositions in accordance with the present invention which are free or substantially free of ethanol or other hydrophilic components have the particular advantage of eliminating or substantially reducing packaging difficulties, e.g. in relation to the packaging of soft gelatin encapsulated forms.

The present pharmaceutical forms a more stable system and is capable of holding a larger amount of cyclosporin than prior art formulations.

The present invention exhibits additional advantages over other carrier system which are comprised of glycerides including those having significant amounts of monoglycerides. The present inventor has found that there is greater compatibility between the carrier and cyclosporin when propylene glycol esters comprising at least 60% by weight monoester, is utilized than when the carrier comprises monoglyceride, even if the monoglycerides are present in larger amounts.

Moreover, the present inventor has found that the present carrier system has advantages over those carrier systems comprising diesters. In the latter case, the diester does not exhibit the drug loading capabilities achieved by the present carrier system, and thus, as a result, the size of the unit dosage form in the present invention is significantly smaller.

13

Moreover, unlike other systems which contain glycofural and other components which are non-GRAS, the present formulation contemplated by the present invention has GRAS status.

Furthermore, the present formulation can also be administered as a parenteral preparation for intra-muscular or even intravenous use with higher drug loading.

Moreover, in the formulations of the present invention in which a hydrophilic component is substantially absent, there is even better compatibility between the cyclosporin and the carrier, and in case of capsules as the oral dosage form, between the pharmaceutical compositions as defined herein and the capsules, and particularly hard gelatin capsules. Moreover, in a preferred embodiment, it is preferred that fatty acid triglycerides are absent. The inventor has noted that the fatty acid triglycerides do not aid in solubilizing the cyclosporin; instead, their presence results in a larger oral dosage form, e.g., tablet or capsule. Consequently, it is preferred that the fatty acid triglycerides are substantially absent or even more preferably completely absent from the present pharmaceutical composition.

Thus the present pharmaceutical formulation has several advantages. It exhibits (I) an enhanced solubility of the cyclosporin, thereby providing for higher drug loading and reducing the size of oral unit dosage of same (e.g., the size of the capsule will be reduced); (II) greater and uniform bioavailability; (III) better storage stability; (IV) greater compatibility with hard and soft gelatin capsules; (V) reduced inter and intra-subject variability, and (VI) minimal effect of food on the oral absorption of the drug. Furthermore, administration of the present formulation in the reduced size dosage forms, such as capsules, will facilitate greater patient acceptance and compliance. Moreover, unlike pharmaceutical compositions of the prior art containing alcohol, the present formulation, as defined herein, does not require special handling during manufacturing or expensive specialized packaging.

The term "aqueous medium" as used herein, includes water, fluids containing water and in vivo media in mammals, such as the aqueous fluid present in the G.I. tract thereof.

Unless indicated to the contrary, the singular implies the plural and vice versa.

Moreover, it is to be understood, that in the preferred ratios given between cyclosporin and the propylene glycol esters, it is to be understood that the term, propylene glycol ester, unless indicated to the contrary, refers to the propylene glycol ester of C_6 - C_{18} fatty acid containing at least 60% monoester by weight based upon the total weight of propylene glycol ester. The ratio is not to be understood to be a ratio of the cyclosporin to monoesters in the propylene glycol ester. The same is true with respect to the ratio of propylene glycol ester to surfactant and the ratio of drug:propylene glycol ester:surfactant.

Unless indicated to the contrary, all percentages and ratios are by weight.

The following examples further illustrate the present invention.

In examples 1-6, the monoester content of the propylene glycol ester utilized is preferably greater than 60% by weight and more preferably 90% or greater.

14

EXAMPLE 1

INGREDIENT	MG/CAPSULES
Cyclosporin	25
Propyleneglycol Monoester of Caprylic Acid	100
Polyoxyethylene (20)	250
sorbitan ester	
TOTAL	375

Procedure

Cyclosporin is dissolved in the propylene glycol monoester. The polyoxyethylene (20) sorbitan ester is added, and the components are mixed until a clear solution is obtained.

EXAMPLE 2

INGREDIENT	MG/CAPSULES
Cyclosporin	100
Propylene glycol monoester of Caprylic Acid	175
Polyoxyl 40 hydrogenated	525
Castor oil	
TOTAL	800

Procedure

Cyclosporin is dissolved in the propylene glycol monoester of Caprylic Acid. Polyoxyl 40 hydrogenated Castor oil is added thereto. The components are mixed until a clear solution is obtained.

EXAMPLE 3

INGREDIENT	MG/CAPSULES
Cyclosporin	100
Propylene glycol monocaprylate	200
Polyoxyl 35 Castor oil	550
TOTAL	850

Procedure

Cyclosporin is dissolved in the propylene glycol monocaprylate. Polyoxyl 35 Castor oil is added thereto and the components are mixed until a clear solution is obtained.

EXAMPLE 4

INGREDIENT	MG/CAPSULES
Cyclosporin	100
Propylene glycol monoester of Caprylic Acid	250
Polyoxyl 35 Castor oil	510
TOTAL	860

Procedure

Cyclosporin is dissolved in the propylene glycol monoester. Polyoxyl 35 Castor oil is added thereto and the components are mixed until a clear solution is obtained.

Informe de fallo de energia

NOV-16-2007 02:24 PM VIE

Numero de fax: 6212542
Nombre : REYES ABOGADOS

1. Hora del fallo de energia : NOV-16-2007 02:23 PM VIE

2. Marcacion diferida eliminada

Num	Hora	Numero de fax	Nombre	E/R	Pag.	Modo
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3. Datos recibidos memoria borrados

Num	Nombre/numero	Hora recep	Hora	Modo	Pag.	Resultado
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4. Ha fallado la operacion de envio o recepcion

E/R	Nombre/numero	H. inicio	Pag.	Resultado
E	35373120363130323739352020202020202020	11-16 02:11PM	000	[Fallo energia]

15
EXAMPLE 5

INGREDIENT	MG/CAPSULES
Cyclosporin	25
Propylene glycol monocaprylate	75
Polyoxyl 30 Castor oil	130
TOTAL	230

Procedure

Cyclosporin is dissolved in the propylene glycol monocaprylate. Polyoxyl 30 Castor oil is added thereto, and the components are mixed until a clear solution is obtained.

EXAMPLE 6

INGREDIENT	MG/CAPSULES
Cyclosporin	25
Propylene glycol monoester of Caprylic Acid	100
Polyoxyl 30 Castor oil	130
TOTAL	255

Procedure

Cyclosporin is dissolved in the propylene glycol monoester of Caprylic Acid. Polyoxyl 30 Castor oil is added thereto and the components are mixed until a clear solution is obtained.

EXAMPLE 7 AND COMPARATIVE
EXAMPLES 1 AND 2

The following formulations were prepared:

EXAM- PLE	FORMULATION	INITIAL OBSER- VATION	OBSER- VATION AFTER 1 MONTH
Com- para- tive Exam- ple 1	Cyclosporin 100 mg Propylene glycol Dicaprylate-Caprylate, Diester >90% Polyoxyl 35 Castor oil 300 mg (Cremophore EL 35)	Clear	Precipitation and Crystallization (after 1 week)
Com- para- tive Exam- ple 2	Cyclosporin 100 mg Propylene glycol 200 mg Laurate, Monoester about 45 to 50% Polyoxyl 35 Castor oil 300 mg (Cremophore EL 35)	Clear	Precipitation and crystal growth (after 2 weeks)
Exam- ple 7	Cyclosporin 100 mg Propylene glycol 200 mg mono-Caprylate, monoester >90% Polyoxyl 35 Castor oil 300 mg (Cremophore EL 35)	Clear	Clear solution after more than 3 months

In each example, the cyclosporins were dissolved in the propylene glycol ester. The polyoxyl 35 castor oil was added thereto and the components were mixed until a clear solution was obtained.

The results are also tabulated in the above table.

When the pharmaceutical formulation contained the propylene glycol ester component as substantially the diester, as

16

in Comparative Example 1, the cyclosporin precipitated and crystallized after 1 week of storage at 25° C. Thus, the presence of the diester did not aid in stabilizing the drug or solubilizing the drug in the carrier system. Moreover, the precipitated cyclosporin has poor and variable absorption in the g.i. fluid, and as a result of the precipitation of the cyclosporin, the composition of the unit dosage form containing this formulation lacks uniformity. Therefore, the formulation in Comparative Example 1 is not suitable for any commercial use.

The above data also illustrate that there is criticality in the percentage of the monoester content present in the propylene glycol ester. The percentage of the monoester present plays, among other things, a significant role in maintaining the solubility of Cyclosporins in the formulation. For example, as shown by the data in Comparative Example 2, when the pharmaceutical formulation contained a propylene glycol ester having a monoester content of 45 to 50% by weight, the cyclosporin crystallized out of the formulation within about 2 weeks of storage at 25° C., thereby making it unsuitable for practical commercial formulation.

However, the inventor has surprisingly found that when the propylene glycol ester having a monoester content of at least 60%, and preferably more than 90%, the formulation remained clear and there was no sign of precipitation or crystallization even after more than three months of storage at 25° C. This formulation therefore was deemed suitable for commercial use. Moreover, it was observed that the formulation of Example 7 further formed a self-emulsifying system, and more specifically, a microemulsion, when it was brought in contact with the aqueous medium as in the gastric fluid of the stomach.

The above results clearly indicate that the monoester content of Propylene glycol ester of C₆-C₁₈ fatty acids as described herein plays a significant role in the acceptable formulation of cyclosporins.

Thus, it is to be concluded from the experimental findings that the carrier of the present invention provides maximum solubility or the highest drug loading capability for cyclosporin. Further, it did not show any precipitation and crystal growth on storage at 25° C., unlike the results found when the carrier system contained propylene glycol ester having mostly diester or 50% monoester by weight of the propylene glycol ester. Additionally, when combined with a surfactant having an HLB of at least 10, the present pharmaceutical formulation forms a self-emulsifying drug delivery system and preferably a microemulsion when brought in contact with the aqueous medium such as gastric fluids of stomach. This ability to form an emulsion is necessary for the uniform and maximum absorption of cyclosporin.

The above preferred embodiments and examples are given to illustrate the scope and spirit of the present invention. These embodiments and examples will make apparent to those skilled in the art other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention.

Therefore, the present invention should be limited only by the appended claims.

What is claimed is:

1. A pharmaceutical composition comprising a pharmaceutically effective amount of a cyclosporin in association with a pharmaceutical carrier, said carrier comprising (a) a cyclosporin solubilizing effective amount of a propylene glycol ester of C₆-C₁₈ fatty acid having at least about 60% by weight of monoester based on the total weight of the propylene glycol ester and (b) a non-ionic surfactant, said

17

non-ionic surfactant being present in an amount sufficient to form a microemulsion with the propylene glycol ester and cyclosporin when brought into contact with an aqueous medium, wherein said cyclosporin is cyclosporin A.

2. The pharmaceutical composition of claim 1 where the surfactant is polyoxyethylene sorbitan ester or the polyethoxylated product of hydrogenated vegetable oils, polyethoxylated castor oil or polyethoxylated hydrogenated castor oil.

3. The pharmaceutical composition according to claim 1 wherein the cyclosporin and the propylene glycol ester of C_6-C_{18} fatty acid with at least 60% by weight monoester, based on the total weight of propylene glycol ester, is present in a weight ratio ranging from about 1:1 to about 1:20, respectively.

4. The pharmaceutical composition according to claim 3 wherein the weight ratio ranges from about 1:1 to about 1:4.

5. The pharmaceutical composition according to claim 1 wherein the cyclosporin and the surfactant are present in a weight ratio ranging from about 1:1 to about 1:20, respectively.

6. The pharmaceutical composition according to claim 5 wherein the weight ratio ranges from about 1:1 to about 1:4.

7. The pharmaceutical composition according to claim 1 wherein the weight ratio of propylene glycol ester to surfactant ranges from about 1:1 to about 1:20.

8. The pharmaceutical composition according to claim 1 wherein the weight ratio of propylene glycol ester to surfactant ranges from about 1:1 to about 1:4.

9. The Pharmaceutical composition according to claim 1 wherein the fatty acid of the propylene glycol ester contains 8 to 12 carbon atoms.

10. The pharmaceutical composition according to claim 9 wherein the fatty acid of the propylene glycol ester contains 8 to 10 carbon atoms.

18

11. The pharmaceutical composition according to claim 10 wherein the fatty acid of the propylene glycol ester contains 8 carbon atoms.

12. The pharmaceutical composition according to claim 10 wherein the fatty acid of the propylene glycol ester contains 10 carbon atoms.

13. The pharmaceutical composition according claim 1 wherein the propylene glycol ester contains at least about 70% by weight monoester based on the total weight of the propylene glycol ester.

14. The pharmaceutical composition according to claim 1 wherein the propylene glycol ester contains at least about 90% by weight monoester based on the total weight of the propylene glycol ester.

15. The pharmaceutical composition according to claim 1 wherein the propylene glycol ester of C_6-C_{18} fatty acid contain at least about 95% monoester by weight based on the total weight of the propylene glycol ester.

16. The pharmaceutical composition according to claim 1 wherein the surfactant has an HLB value greater than 10.

17. A microemulsion of the pharmaceutical composition of claim 1.

18. A microemulsion of the pharmaceutical composition according to claim 14.

19. The pharmaceutical composition according to claim 1 which is in oral dosage form.

20. The pharmaceutical composition according to claim 1 which is present in an injectable form or in a drink-solution.

21. The pharmaceutical composition according to claim 1 wherein the cyclosporin, the propylene glycol ester of C_6-C_8 fatty acid having at least greater than about 60% by weight monoester based on the total weight of the propylene glycol ester and surfactant are present in a weight ratio of 1:1-20:1-20, respectively, wherein the surfactant is present in equal to or greater amounts by weight than the propylene glycol ester.

* * * * *

277

2020
Bogotá, D.C.,

Doctor:
Reinaldo Pinilla Moreno
Apoderado

Oficio N°: 15841

ASUNTO:	Radicación N°	06-42169
	Trámite	002
	Evento	001
	Actuación	440
	Folios	111

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, quien actúa en calidad de apoderado del Laboratorio Franco-Colombiano, Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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



ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

97 DIC. 2007

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021