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E. S. D.

Ref.: Expediente No. **04.056.913**
Solicitud de Patente PCT entrada fase nacional para: **COMPOSICIONES FARMACEUTICAS A BASE DE DERIVADOS DE AZETIDINA**
Solicitante: **AVENTIS PHARMA S.A.**

RESPUESTA A EXAMEN DE FONDO

LUIS PATIÑO LEIVA, mayor de edad, identificado y domiciliado como aparece al pié de mi firma, en atención a su oficio No. 4696 notificado el 4 de abril de 2008, atentamente me permito dar repuesta al mismo de la siguiente manera:

Nivel Inventivo

El documento D1 revela un número elevado de derivados de azetdidna utilizados comúnmente en las composiciones farmacéuticas.

Por su parte D2 revela una formulación para agentes farmacéuticos hidrofóbicos y revela un elevado número de excipientes que se pueden utilizar.

Sin embargo, el documento D2 no revela el uso de Labrafil como agente hidrofóbico.

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-En consecuencia, la presente invención está dirigida a una formulación específica de azetidina con agentes específicos no revelados ni sugeridos en las anterioridades.

Argumenta el examinador que el objetivo de la formulación en ambos casos sigue siendo el de mejorar la biodisponibilidad oral de un agente farmacéutico hidrofóbico.

- Sobre este punto pongo de presente que si bien el objetivo de la presente invención es el mismo que D2, el hecho de proveer una formulación más específica y con mejor biodisponibilidad hace a la presente invención inventiva sobre las anterioridades.

Supongamos que un objetivo de diferentes invenciones fuera el tratamiento del cáncer de pulmón. Dichas invenciones logran los **efectos mejorados** mediante la utilización de **diferentes** formulaciones farmacéuticas. El hecho que dichas invenciones estén dirigidas a resolver el mismo problema no puede utilizarse como argumento para desvirtuar su nivel inventivo. El problema a resolver debería enfocarse desde el punto de vista de la formulación farmacéutica como tal.

También argumenta el examinador que el problema técnico planteado se había resuelto previamente mediante el mismo tipo de composiciones ya conocidas. Tanto D1 como D2 divulgaban previamente composiciones similares.

- Sobre este punto expreso mi total desacuerdo ya que como se demostró anteriormente, la presente invención está dirigida a una formulación específica de azetidina con agentes específicos **NO revelados ni sugeridos** en las anterioridades D1 y D2.

En conclusión, solicito que se otorgue el privilegio de patente a la presente invención toda vez que se ha demostrado el nivel inventivo de la misma.

PCT ORGANISATION MONDIALE DE LA PROPRIETE INTELLECTUELLE
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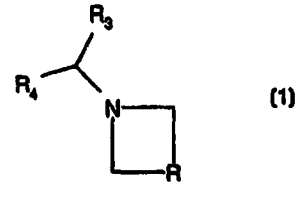

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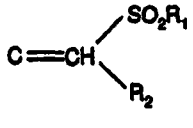

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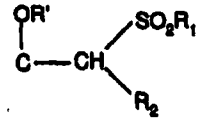

(B)

(57) Abstract

The invention concerns compounds of formula (1) wherein: R represents an chain (A) or (B); R_1 is methyl or ethyl; R_2 is either an optionally substituted aromatic or an optionally substituted heteroaromatic; R_3 and R_4, identical or different, are either an optionally substituted aromatic or an optionally substituted heteroaromatic; R' represents a hydrogen atom or a -CO-alk radical, their optical isomers, their salts, their preparation and medicines containing them.

rométhoxy, nitro, -NR_6R_7, -CO-NH-NR_6R_7, cyano, -$CONHR_9$, alkylsulfanyle, hydroxyalkyle ou alkylthioalkyle,

R_3 et R_4, identiques ou différents, représentent soit un aromatique choisi parmi phényle, naphtyle ou indényle, ces aromatiques étant non substitués ou substitués par un ou plusieurs halogène, alkyle, alcoxy, formyle, hydroxy, trifluorométhyle, trifluorométhoxy, -CO-alk, cyano, -$COOR_9$, -$CONR_{10}R_{11}$, -CO-NH-NR_6R_7, alkylsulfanyle, hydroxyalkyle, -alk-NR_6R_7 ou alkylthioalkyle; soit un hétéroaromatique choisi parmi les cycles benzofuryle, benzothiazolyle, benzothiényle, benzoxazolyle, chromannyle, 2,3-dihydrobenzofuryle, 2,3-dihydrobenzothiényle, furyle, isochromannyle, isoquinolyle, pyrrolyle, quinolyle, 1,2,3,4-tétrahydroisoquinolyle, thiazolyle, thiényle, ces hétéroaromatiques pouvant être non substitués ou substitués par un halogène, alkyle, alcoxy, hydroxy, trifluorométhyle, trifluorométhoxy, cyano, -$COOR_9$, -CO-NH-NR_6R_7, -$CONR_{10}R_{11}$, -alk-NR_6R_7, alkylsulfanyle, hydroxyalkyle ou alkylthioalkyle,

R_5 est un radical alkyle ou phényle éventuellement substitué par un ou plusieurs atomes d'halogène,

R_6 et R_7, identiques ou différents représentent un atome d'hydrogène ou un radical alkyle, -COOalk, cycloalkyle, alkylcycloalkyle, -alk-O-alk, hydroxyalkyle ou bien R_6 et R_7 forment ensemble avec l'atome d'azote auquel ils sont rattachés un hétérocycle mono ou bicyclique saturé ou insaturé ayant 3 à 10 chaînons, contenant éventuellement un autre hétéroatome choisi parmi oxygène, soufre et azote et étant éventuellement substitué par un ou plusieurs radicaux alkyle, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, -CO-alk-$NR_{14}R_{15}$, oxo, hydroxyalkyle, -alk-O-alk, -$CO-NH_2$,

R_8 représente un radical alkyle,

R_9 représente un atome d'hydrogène ou un radical alkyle ou alkyle substitué par dialkylamino, phényle, cycloalkyle (éventuellement substitué par -COOalk) ou un hétérocycle mono ou bicyclique saturé ou insaturé ayant 3 à 10 chaînons, contenant

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

(10) **Patent No.: US 6,294,192 B1**
(45) **Date of Patent: Sep. 25, 2001**

(54) **TRIGLYCERIDE-FREE COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF HYDROPHOBIC THERAPEUTIC AGENTS**

(75) Inventors: **Mahesh V. Patel; Feng-Jing Chen,** both of Salt Lake City, UT (US)

(73) Assignee: **Lipocine, Inc.,** Salt Lake City, UT (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.

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(52) **U.S. Cl.** **424/451**; 424/450; 424/464; 424/489; 514/772; 514/937; 514/962; 514/963; 514/975

(58) **Field of Search** 424/450, 451, 424/455, 489, 464; 514/772, 937, 962, 963, 975

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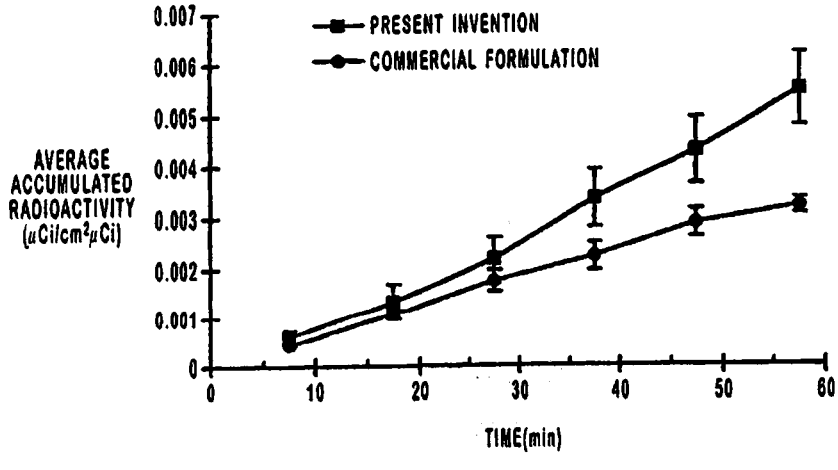
(74) *Attorney, Agent, or Firm*—Dianne E. Reed; Reed & Associates

(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.

74 Claims, 1 Drawing Sheet



when used in combination with digestible oils in emulsion preparations, can substantially decrease the lipolysis-inhibiting effect of some common pharmaceutical surfactants (see, U.S. Pat. No. 5,645,856), such formulations are still subject to the other disadvantages of pharmaceutical emulsions and triglyceride-based formulations.

Yet another approach is based on formation of "microemulsions." Like an emulsion., a microemulsion is a liquid dispersion of oil in water, stabilized by surfactants. The microemulsion particles are smaller than those of an emulsion, rendering the microemulsion essentially optically clear. Microemulsions, however, are thermodynamically stable, and are not subject to the particle agglomeration problems of conventional emulsions. It is generally believed that microemulsions are micelle-like particles, having an essentially micellar structure but containing a distinct oil phase in the micelle "core". These micelle-like particles are often referred to as "swollen micelles", a term which emphasizes their close relationship 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 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 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.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide pharmaceutical compositions capable of solubilizing therapeutically effective amounts of hydrophobic therapeutic agents.

It is another object of the invention to provide pharmaceutical compositions that are homogeneous and thermodynamically stable.

It is yet another object of the invention to provide pharmaceutical compositions having a small and narrow particle size distribution.

It is still another object of the invention to provide pharmaceutical compositions of a hydrophobic therapeutic agent that are not dependent upon lipolysis for bioabsorption.

It is still another object of the invention to provide methods of treating a patient with a hydrophobic therapeutic agent.

It is still another object of the invention to provide less greasy pharmaceutical compositions for topical/transdermal delivery.

In accordance with these and other objects and features, 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 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 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 clear aqueous dispersion, and a second amount of the hydrophobic therapeutic agent that remains non-solubilized but dispersed.

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.

These and other objects and 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

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:

FIG. 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

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

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
PEG 400 distearate	Cithrol 4DS series (Croda)	>10
PEG 100,200, 300 monolaurate	Cithrol ML series (Croda)	>10
PEG 100,200, 300 monooleate	Cithrol MO series (Croda)	>10
PEG 400 dioleate	Cithrol 4DO series (Croda)	>10
PEG 400–1000 monostearate	Cithrol MS series (Croda)	>10
PEG-1 stearate	Nikkol MYS-1EX (Nikko), Coster K1 (Condea)	2
PEG-2 stearate	Nikkol MYS-2 (Nikko)	4
PEG-2 oleate	Nikkol MYO-2 (Nikko)	4.5
PEG-4 laurate	Mapeg ® 200 ML (PPG), Kessco ® PEG 200 ML (Stepan), LIPOPEG 2 L (LIPO Chem.)	9.3
PEG-4 oleate	Mapeg ® 200 MO (PPG), Kessco ® PEG 200 MO (Stepan),	8.3
PEG-4 stearate	Kessco ® PEG 200 MS (Stepan), Hodag 20 S (Calgene), Nikkol MYS-4 (Nikko)	6.5
PEG-5 stearate	Nikkol TMGS-5 (Nikko)	9.5
PEG-5 oleate	Nikkol TMGO-5 (Nikko)	9.5
PEG-6 oleate	Algon OL 60 (Auschem SpA), Kessco ® PEG 300 MO (Stepan), Nikkol MYO-6 (Nikko), Emulgante A6 (Condea)	8.5
PEG-7 oleate	Algon OL 70 (Auschem SpA)	10.4
PEG-6 laurate	Kessco ® PEG300 ML (Stepan)	11.4
PEG-7 laurate	Lauridac 7 (Condea)	13
PEG-6 stearate	Kessco ® PEG300 MS (Stepan)	9.7
PEG-8 laurate	Mapeg ® 400 ML (PPG), LIPOPEG 4DL(Lipo Chem.)	13

tants are PEG-35 castor oil (Incrocas-35), PEG-40 hydrogenated castor oil (Cremophor RH 40), PEG-25 trioleate (TAGAT® TO), PEG-60 corn glycerides (Crovol M70), PEG-60 almond oil (Crovol A70), PEG-40 palm kernel oil (Crovol PK70), PEG-50 castor oil (Emalex C-50), PEG-50 hydrogenated castor oil (Emalex HC-50), PEG-8 caprylick-capric glycerides (Labrasol), and PEG-6 caprylic/capric glycerides (Softigen 767). Preferred hydrophobic surfactants in this class include PEG-5 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-9 hydrogenated castor oil, PEG-6 corn oil (Labrafil® M 2125 CS), PEG-6 almond oil (Labrafil® M 1966 CS), PEG-6 apricot kernel oil (Labrafil® M 1944 CS), PEG-6 olive oil (Labrafil® M 1980 CS), PEG-6 peanut oil (Labrafil® M 1969 CS), PEG-6 hydrogenated palm kernel oil (Labrafil® M 2130 BS), PEG-6 palm kernel oil (Labrafil® M 2130 CS), PEG-6 triolein (Labrafil® M 2735 CS), PEG-8 corn oil (Labrafil® WL 2609 BS), PEG-20 corn glycerides (Crovol M40), and PEG-20 almond glycerides (Crovol A40). The latter two surfactants are reported to have HLB values of 10, which is generally considered to be the approximate border line between hydrophilic and hydrophobic surfactants. For purposes of the present invention, these two surfactants are considered to be hydrophobic.

Representative surfactants of this class suitable for use in the present invention are shown in Table 5.

TABLE 5

Transesterification Products of Oils and Alcohols

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-3 castor oil	Nikkol CO-3 (Nikko)	3
PEG-5, 9, and 16 castor oil	ACCONON CA series (ABITEC)	6–7
PEG-20 castor oil	Emalex C-20 (Nihon Emulsion), Nikkol CO-20 TX (Nikko)	11
PEG-23 castor oil	Emulgante EL23	>10
PEG-30 castor oil	Emalex C-30 (Nihon Emulsion), Alkamuls ® EL 620 (Rhone-Poulenc), Incrocas 30 (Croda)	11
PEG-35 castor oil	Cremophor EL and EL-P (BASF), Emulphor EL, Incrocas-35 (Croda), Emulgin RO 35 (Henkel)	
PEG-38 castor oil	Emulgante EL 65 (Condea)	
PEG-40 castor oil	Emalex C-40 (Nihon Emulsion), Alkamuls ® EL 719 (Rhone-Poulenc)	13
PEG-50 castor oil	Emalex C-50 (Nihon Emulsion)	14
PEG-56 castor oil	Emulgin ® PRT 56 (Pulcra SA)	>10
PEG-60 castor oil	Nikkol CO-60TX (Nikko)	14
PEG-100 castor oil	Thomley	>10
PEG-200 castor oil	Emulgin ® PRT 200 (Pulcra SA)	>10
PEG-5 hydrogenated castor oil	Nikkol HCO-5 (Nikko)	6
PEG-7 hydrogenated castor oil	Simnsol ® 989 (Seppic), Cremophor WO7 (BASF)	6
PEG-10 hydrogenated castor oil	Nikkol HCO-10 (Nikko)	6.5
PEG-20 hydrogenated castor oil	Nikkol HCO-20 (Nikko)	11
PEG-25 hydrogenated castor oil	Simulsol ® 1292 (Seppic), Cerex ELS 250 (Anschem SpA)	11
PEG-30 hydrogenated castor oil	Nikkol HCO-30 (Nikko)	11
PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13
PEG-45 hydrogenated castor oil	Cerex ELS 450 (Anschem Spa)	14
PEG-50 hydrogenated castor oil	Emalex HC-50 (Nihon Emulsion)	14
PEG-60 hydrogenated castor oil	Nikkol HCO-60 (Nikko); Cremophor RH 60 (BASF)	15
PEG-80 hydrogenated castor oil	Nikkol HCO-80 (Nikko)	15
PEG-100 hydrogenated castor oil	Nikkol HCO-100 (Nikko)	17
PEG-6 corn oil	Labrafil ® M 2125 CS (Gattefosse)	4
PEG-6 almond oil	Labrafil ® M 1966 CS (Gattefosse)	4
PEG-6 apricot kernel oil	Labrafil ® M 1944 CS (Gattefosse)	4
PEG-6 olive oil	Labrafil ® M 1980 CS (Gattefosse)	4
PEG-6 peanut oil	Labrafil ® M 1969 CS (Gattefosse)	4
PEG-6 hydrogenated palm kernel oil	Labrafil ® M 2130 BS (Gattefosse)	4
PEG-6 palm kernel oil	Labrafil ® M 2130 CS (Gattefosse)	4
PEG-6 triolein	Labrafil ® M 2735 CS (Gattefosse)	4
PEG-8 corn oil	Labrafil ® WL 2609 BS (Gattefosse)	6–7
PEG-20 corn glycerides	Crovol M40 (Croda)	10
PEG-20 almond glycerides	Crovol A40 (Croda)	10
PEG-25 trioleate	TAGAT ® TO (Goldschmidt)	11
PEG-40 palm kernel oil	Crovol PK-70	>10
PEG-60 corn glycerides	Crovol M70(Croda)	15
PEG-60 almond glycerides	Crovol A70 (Croda)	15
PEG-4 caprylic/capric triglyceride	Labrafac ® Hydro (Gattefosse),	4–5
PEG-8 caprylic/capric glycerides	Labrasol (Gattefosse), Labrafac CM 10 (Gattefosse)	>10
PEG-6 caprylic/capric glycerides	SOFTIGEN ® 767 (Hüls), Glycerox 767 (Croda)	19
Lauroyl macrogol-32 glyceride	GELUCIRE 44/14 (Gattefosse)	14
Stearoyl macrogol glyceride	GELUCIRE 50/13 (Gattefosse)	13
Mono, di, tri, tetra esters of vegetable oils and sorbitol	SorbitoGlyceride (Gattefosse)	<10
Pentaerythrityl tetraisostearate	Crodamol PTIS (Croda)	<10
Pentaerythrityl distearate	Albunol DS (Taiwan Surf.)	<10
Pentaerythrityl tetraoleate	Liponate PO-4 (Lipo Chem.)	<10
Pentaerythrityl tetrastearate	Liponate PS-4 (Lipo Chem.)	<10

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.

Other methods of determining optical clarity or particle size can be used as desired. Such methods are well know 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; 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.

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 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, 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.

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 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 solubilizing and delivering a wide variety of hydrophobic therapeutic agents. Hydrophobic therapeutic agents are compounds with little or no water solubility. Intrinsic water solubilities (ie., 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 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 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 compounds, as well as their pharmaceutically acceptable salts, isomers, esters, ethers and other derivatives:

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

antihelminthics, such as albendazole, bephenium hydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel embonate, 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, benzathine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, dirithromycin, doxycycline, erythromycin, ethionamide, furazolidone, grepafloxacin, imipenem, levofloxacin, lorefloxacin, moxifloxacin HCl, nalidixic acid, nitrofurantoin, norfloxacin, ofloxacin, rifampicin, rifabutine, rifapentine, sparfloxacin, 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, dicumarol, dipyridamole, nicoumalone, oprelvekin, phenindione, ticlopidine, and tirofiban;

anti-depressants, such as amoxapine, bupropion, citalopram, clomipramine, fluoxetine HCl, maprotiline HCl, mianserin HCl, nortriptyline HCl, paroxetine HCl, sertraline HCl, trazodone HCl, trimipramine maleate, and venlafaxine HCl;

anti-diabetics, such as acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, glimepiride, miglitol, pioglitazone, repaglinide, rosiglitazone, tolazamide, tolbutamide and troglitazone;

anti-epileptics, such as beclamide, carbamazepine, clonazepam, ethotoin, felbamate, fosphenytoin sodium, lamotrigine, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone, phenytoin, phensuximide, primidone, sulthiame, tiagabine HCl, topiramate, valproic acid, and vigabatrin;

anti-fimnpal agents, such as amphotericin, butenafine HCl, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, oxiconazole, terbinafine HCl, terconazole, tioconazole and undecenoic acid;

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 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.

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.

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.

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.

EXAMPLES

Example 1

Preparation of Compositions

A simple pre-concentrate of a hydrophobic surfactant and a hydrophilic surfactant is prepared as follows. Predetermined weighed amounts of hydrophilic and hydrophobic surfactants are stirred together to form a homogeneous mixture. For surfactant combinations that are poorly miscible, the mixture can be gently heated to aid in formation of the homogeneous mixture. A chosen hydrophobic therapeutic agent in a predetermined amount is added and stirred until solubilized. Optionally, solubilizers or additives are included by simple mixing.

To form an aqueous dispersion of the pre-concentrate, a predetermined amount of purified water, buffer solution, or aqueous simulated physiological solution, is added to the pre-concentrate, and the resultant mixture is stirred to form a clear, aqueous dispersion.

Example 2

Surfactant Combinations Giving Clear Aqueous Dispersions

Surfactant mixtures giving clear, aqueous dispersions were prepared according to the method of Example 1. Seven hydrophilic surfactants and sixteen hydrophobic surfactants were used to produce approximately one hundred clear aqueous dispersions suitable for use in the present invention. For simplicity, no hydrophobic therapeutic agent was included in these compositions, since it is believed that the presence of the hydrophobic therapeutic agent does not substantially affect the clear, aqueous nature of composition. For the same reason, these compositions were free of additional solubilizers and other additives.

Multiple solutions were prepared for each surfactant combination, to determine the approximate maximum amount of hydrophobic therapeutic agent giving a clear aqueous dispersion with a given amount of hydrophilic therapeutic agent. Thus, for each gram of the hydrophilic surfactant, a predetermined amount of hydrophobic agent was used to prepare a 10× aqueous dispersion. If the dispersion appeared to be optically clear, a new dispersion was prepared according to Example 1, using a larger amount of hydrophobic surfactant. Similarly, if the dispersion appeared to be cloudy, a new dispersion was prepared using a smaller amount of hydrophobic surfactant. The results are shown in Table 19.

TABLE 19

	Surfactant Combinations Giving Clear Dispersions						
	Hydrophilic Surfactant						
Hydrophobic Surfactant	PEG-35 Castor Oil (Incrocas 35)	PEG-40H Castor Oil (Cremophor RH-40)	Polysorbate-20 (Tween 20)	Polysorbate 80 (Tween 80)	PEG-60 Corn Oil (Crovol M-70)	PEG-8 Capric/ Caprylic (Labrasol)	PEG-25 Glyceryl trioleate (Tagat TO)
Glyceryl/Propylene Glycol Oleate (Arlacel 186)	20	20	20	8	15	25	10
Glyceryl Oleate (Peceol)	15	40	10	12	10	35	10
Acetylated Monoglycerides (Myvacet 9-45)	80	80	20	15	10	10	10
PEG-6 Corn Oil (Labmfil M2125CS)	50	95	10	10	20	10	10
Sorbitan Monooleate (Span 80)	25	65	5	5	20	15	10
Sorbitan Monolaurate (Arlacel 20)	30	20	20	10	15	30	10
Polyglyceryl oleate (Plurol Oleique CC497)	10	5	35	10	10	35	10

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Doctor
LUIS PATIÑO LEYVA
Apoderado

ASUNTO		
	Radicación	04-056913
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	16 R 06426

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: 38 a 50 como se radicó inicialmente

Reivindicaciones: 1 a 17, Folios 51 a 54 como se radicó inicialmente
1 a 17, Folios 160 a 163 (según modificación radicada el 20 de Noviembre de 20006)

Oposiciones: José Luis Reyes (apoderado Tecnoquímicas)
Folios 153 a 156

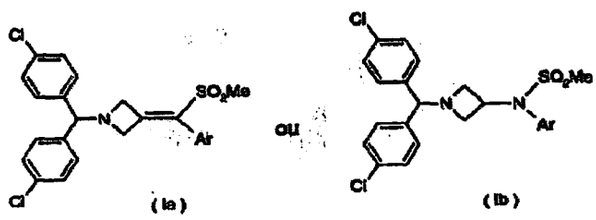
Prioridad: Folios: 17 a 35
21 de Diciembre de 2001, Francia, 01 16638.

Respuesta del solicitante: Folios 189 a 191

2. Objeto de la invención

Título de la solicitud: **COMPOSICIONES FARMACEUTICAS A BASE DE DERIVADOS DE AZETIDINA** (folio 1).

La presente solicitud se refiere a una composición farmacéutica estable que comprende por lo menos un derivado de azetidina de fórmula general (I a) o (I b), combinado opcionalmente con otro principio activo capaz de potenciar el efecto, en un sistema coloidal binario.



Se plantea como problema técnico que los derivados de azetidina son productos muy poco hidrosolubles (folio 38, línea 23) por lo que su bio-disponibilidad es muy reducida (líneas 28 y29).

Como solución la presente invención propone un sistema de máximo dos excipientes para solución, estabilización y bio-disposición de dichos derivados.

La presente invención se catalogó, según la Clasificación Internacional de Patentes (IPC) en la categoría A61K31/397.

3. De la solicitud de Patente

Reivindicaciones *(artículo 30 D 486)*
No se encuentran sustentadas las composiciones, cuando se emplea Gelucire®.
La reivindicación 11 se refiere a: "y, si ello es apropiado, el ingrediente activo capaz de potenciar los efectos del derivado de azetidina", el cual no se encuentra definido ni caracterizado en el capítulo reivindicatorio.

4. Análisis de la(s) Oposición(es): *(artículo 43 D. 486)*:

Opositor: Tecnoquímicas

El opositor en primer término se refiere a la combinación de un primer principio activo derivado de azetidina y sibutramina en la composición farmacéutica y anexa los siguientes documentos:

- Colombo G, et al. *Appetite suppresion and weigth loss after the cannabinoid antagonist SR 141716.* Life Sci 1998; 63 (8): PL 113.7
- Simian et al. *SR 141716, a CB1 cannabinoid receptor antagonist, selectively reduce sweet food intake in marmoset.* Behav Paharmacol 1998, Mar 9(2):179-81
- Freedland et al. *Effects of SR141716A, a central cannabinoid receptor antagonist, on food-maintened responding.*Pharmacol Behav 2000, Oct; 67 (2):265-70

Los anteriores documentos, revelan el compuesto rimonabant (SR 141716), como antagonista del receptor canabinoide CB1 y su uso en el tratamiento de la obesidad.

Frente a dichas anterioridades el compuesto rimonabant, no es un derivado de azetidina

- Kirkman et al.*Synergistic effects of opioid and cannabinoid antagonists on food intake Psycopharmacology*, 2001 Jan 1; 153 (2): 267-70

Este documento revela el efecto sinergístico de un opiode como naloxona y rimonabant

- US 4,935,243 Fecha: 19-06-1990 (Folios 68-72)

Este documento revela cápsulas de gelatina blanda masticables las cuales comprenden agua (15-30%), gelatina (20-45%), plastificante (17.5-35%) y una cantidad de hidrolisado de almidón hidrogenado (5-25%) (Ver columna 2, líneas 54-57-Reivindicación 1) y donde la gelatina puede ser obtenida de la piel de pescado de

agua fría (Ver columna 3, líneas 28-29). La diferencia con la solicitud presentada, es la caracterización de la gelatina por su temperatura de transición sol-gel.

Este documento no afecta la novedad de la solicitud presentada, pero si afecta su nivel inventivo puesto que ya se enseñaban cápsulas de gelatina blanda de pescado, con gelatina, un plastificante y una agente anti-adhesión.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 21 de Diciembre de 2001, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

N°	Documento	Título	Fecha de publicación
D1	WO 00/15609	Pharmaceutical compositions based on azetidine derivatives	23/03/2000
D3	US 6,294,192	Triglyceride-free compositions and methods for improved delivery of hydrophobic therapeutic agents	25/09/2001

6. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo18 D486)

La reivindicación 1 consiste en:

Una composición farmacéutica estable, la cual comprende un derivado de azetidina:-N-{1-[bis-(4-clorofenil)metil]azetidin-3-il}-N-(3,5difluorofenil)-metilsulfonamida *(en adelante citado como derivado de azetidina)*, en un sistema que comprende a lo sumo 2 excipientes principales escogidos entre un surfactante no iónico de carácter hidrofílico capaz de solubilizar el derivado de azetidina y capaz de causar la formación de un sistema coloidal, opcionalmente suplementado con un segundo excipiente de naturaleza lipofílica estabilizante de la formulación.

El Estado de la Técnica más cercano es **D1,** pues enseña el compuesto de la formulación objeto de solicitud: N-{1-[bis-(4-clorofenil)metil]azetidin-3-il}-N-(3,5difluorofenil)-metilsulfonamida y sus composiciones. (Ver página 202 y 203, reivindicación1)

La composición objeto de esta solicitud se diferencia de las composiciones de **D1**, en que no contienen, un sistema que comprende a lo sumo 2 excipientes, escogidos entre un surfactante no iónico de carácter hidrofílico capaz de solubilizar el derivado de azetidina y opcionalmente un excipiente de naturaleza lipofílica estabilizante de la formulación

El hecho de incluir en las composiciones del compuesto de **D1**, un sistema que comprende a lo sumo 2 excipientes, escogidos entre un surfactante no iónico de carácter hidrofílico capaz de solubilizar el derivado de azetidina y opcionalmente un excipiente de naturaleza lipofílica estabilizante; causa que las composiciones tengan mayor biodisponibilidad en comparación con las anteriormente divulgadas.

El Problema Técnico Objetivo era cómo obtener composiciones de un compuesto de azetidina con una mayor biodisponibilidad.

D3 describe una manera de solucionar el problema técnico pues da a conocer composiciones farmacéuticas, para la liberación de agentes terapéuticos hidrofóbicos (Ver columnas 21-25) cuyo soporte es formado por la combinación de un surfactante hidrofílico y un surfactante hidrofóbico (Ver resumen) y donde el empleo de estas formulaciones resulta en una velocidad aumentada y/o absorción extendida del agente terapéutico hidrofóbico (Ver columna 3, líneas 43-62 y columna 4, líneas 60-63)

Entre los surfactantes empleados se encuentra PEG-6 (Labrafil®) y PEG-8 (Labrasol®) (Ver columnas 9 y 10, tabla 5) y donde se enseña la combinación de estos dos surfactantes con el fin de obtener dispersiones claras (Ver columna 31 y 32, tabla 19)

D3 además divulga que las composiciones empleadas como soporte, pueden contener cualquier fármaco, los cuales se incluyen desde analgésicos hasta ciclosporinas entre otros (Ver columnas 22 a 25).

La reivindicación es obvia, porque el Experto en la Materia enfrentado al problema de "obtener composiciones de un compuesto de azetidina con una mayor biodisponibilidad", incluiría "el compuesto que se enseña en **D1**" en la composición que combina un tensioactivo hidrofílico solubilizante y un excipiente lipofílico estabilizante como soporte farmacéutico" que se revela en **D3**, logrando de esta forma la composición objeto de esta solicitud. Por tanto, la reivindicación 1 no tiene Nivel Inventivo. Las reivindicaciones dependientes 2–11, no mencionan alguna característica que haga inventiva a la composición de la reivindicación 1, por lo cual se considera que no tienen nivel inventivo.

7. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO00/15609	1-11	Nivel Inventivo
D3	US 6,294,192	1-11	Nivel Inventivo

8. Respuesta a los argumentos del solicitante:

El solicitante se refiere en el Folio 189 "el documento **D2** no revela el uso de Labrafil® como agente hidrofóbico"

*De acuerdo con lo anterior es claro que el solicitante se refiere a un agente lipofílico como opcional (Ver Folio 182, reivindicación 1) por lo tanto el documento **D2** sólo aplica para las formulaciones que contienen el agente hidrofílico, como lo enunció en la reivindicación 1; siendo este documento pertinente, cuando la composición sólo contiene un surfactante o tensioactivo hidrofílico tal como Labrasol® para emplear con agentes activos hidrofóbicos con el fin de mejorar la biodisponibilidad y sin emplear el agente denominado como opcional.*

El solicitante afirma en el Folio 190, "el objetivo de la formulación en ambos casos sigue siendo el de mejorar la biodisponibilidad oral de un agente farmacéutico hidrofóbico y que el hecho de proveer una formulación más específica y con mejor biodisponibilidad hace a la presente invención inventiva sobre las anterioridades"

*Al respecto, el problema técnico de cómo mejorar la biodisponibilidad en fármacos hidrofóbicos con el empleo de tensioactivos o surfactantes hidrofílicos, tal como es el uso de Labrasol®, ya se encontraba resuelto en el documento **D2**, siendo evidente para el experto en la materia derivar de forma obvia dichos excipientes en las composiciones que contienen el fármaco de **D1**.*

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 numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

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

El anterior requerimiento fue notificado por fijación en lista, de fecha 14 MAYO 2010

CONCEPTO TÉCNICO No.01068	**EXAMINADOR TÉCNICO** Código No.202070