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Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Expediente No. 06-120.230
Solicitud de Patente de Invención titulada: "COMPOSICIONES FARMACEUTICAS INYECTABLES DE POSACONAZOL CON PARTICULAS ESTABILIZADAS"
Solicitante: SCHERING CORPORATION

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 587

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el articulo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de $420.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 del año 2007.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por $420.000 pesos
Sustitución

LMB/P2006/000265 080219

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO DE CONTENIDO Y FIRMA.

NOTARIA 27

EL ANTERIOR ESCRITO DIRIGIDO A:

FUE PRESENTADO PERSONALMENTE ANTE EL SUSCRITO NOTARIO VEINTISIETE DEL CIRCULO DE BOGOTA POR:

Con C.C. 75282[illegible] T.P. [illegible]

Y ADEMAS DECLARO QUE EL CONTENIDO DEL ANTERIOR DOCUMENTO ES CIERTO Y QUE LA FIRMA QUE LO AUTORIZA FUE PUESTA POR EL.

EL DECLARANTE:

HOY: 11 MAR 2008

HUELLA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

REPUBLICA DE COLOMBIA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA

Notaria 27 Bogotá DC

OLARTERAISBECK
OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA.

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Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
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Expediente No. 06-120.230
Solicitud de Patente de Invención titulada: "COMPOSICIONES FARMACEUTICAS INYECTABLES DE POSACONAZOL CON PARTICULAS ESTABILIZADAS"
Solicitante: SCHERING CORPORATION

SUSTITUCIÓN DE PODER

J. IAN RAISBECK LLINAS, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad, en el doctor **CARLOS R. OLARTE**, mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.782.747 de Bogotá y portador de la Tarjeta Profesional No. 74.295 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,

J. IAN RAISBECK
C.C. No. 79.376.996 de Bogotá
T.P. 135.799 del C. S. de la J.

DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA.

NOTARIA 27

EL ANTERIOR ESCRITO DIRIGIDO A

FUE PRESENTADO PERSONALMENTE
ANTE EL SUSCRITO NOTARIA VEINTISIETE
DE BARRANQUILLA POR

Con C.C. y T.P.

Y AFIRMO BAJO GRAVEDAD DE JURAMENTO QUE EL CONTENIDO DEL ANTERIOR
DOCUMENTO ES CIERTO Y QUE LA FIRMA QUE LO
AUTORIZA ES LA PUESTA POR EL

HOY: 21 FEB 2008

HUELLA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

REPÚBLICA DE COLOMBIA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA

Notaría 27 Bogotá D.C

253

255.

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-120230

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **587** DE

FECHA **18 DE ENERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **16 DE ABRIL DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ____X____

US 20030055067A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0055067 A1**

Sharpe et al. (43) **Pub. Date: Mar. 20, 2003**

(54) **ANTIFUNGAL COMPOSITION WITH ENHANCED BIOAVAILABILITY**

(75) Inventors: **Stefan Sharpe**, Jersey City, NJ (US); **Joel Sequeira**, Edison, NJ (US); **David Harris**, New Providence, NJ (US); **Shashank Mahashabde**, Kendall Park, NJ (US)

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(73) Assignee: **SCHERING CORPORATION**

(21) Appl. No.: **10/114,612**

(22) Filed: **Apr. 1, 2002**

Related U.S. Application Data

(60) Provisional application No. 60/281,139, filed on Apr. 3, 2001.

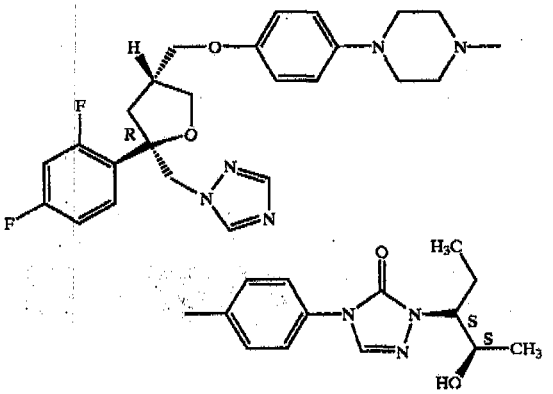
Publication Classification

(51) **Int. Cl.**[7] **A61K 31/497**; A61K 9/14

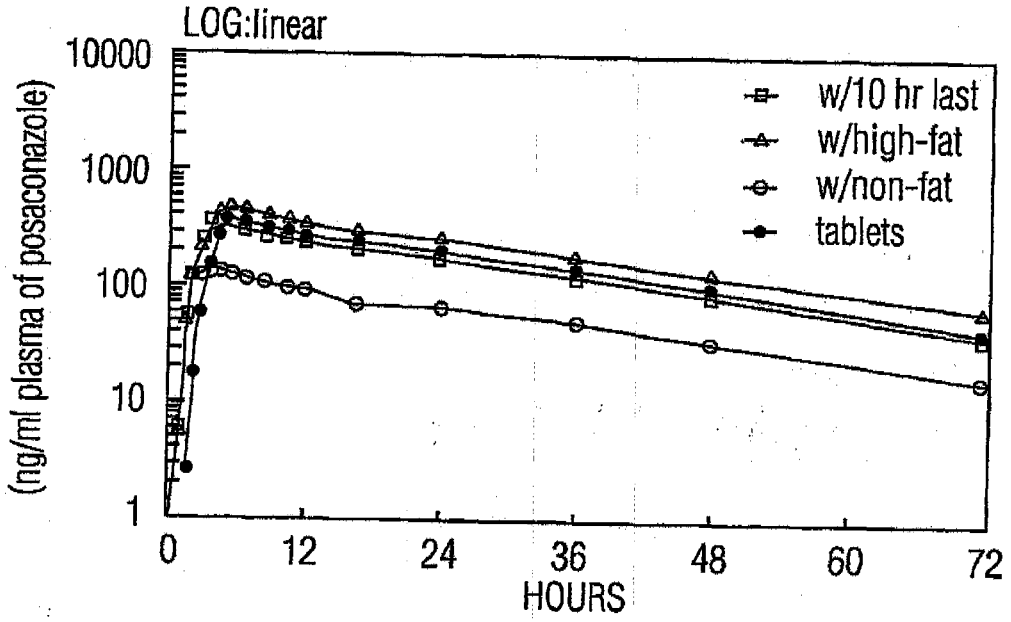
(52) **U.S. Cl.** **514/254.05**; 424/484

(57) **ABSTRACT**

A liquid suspension comprising an antifungally effective amount of the micronized compound represented by the chemical structural formula I:



at least one thickening agent, a non-ionic surfactant, and a pharmaceutically acceptable liquid carrier is disclosed.



were analyzed using an analysis of variance (ANOVA). The effects due to subject, phase and treatment were extracted.

[0074] The plasma concentration-time data and pharmacokinetic parameters for the compound of formula I are tabulated in Tables 3 & 4 and depicted graphically in **FIGS. 1 & 2.**

[0075] All subjects had 0-hour concentrations on Day 1 reported as below the LOQ (5 ng/ml) except for Subject 20 in Phases 3 and 4 who had quantifiable levels of posaconazole at 0-hour for Treatments B and A of 8.5 and 22.5 ng/ml, respectively. These levels are most likely due to a carry-over effect from accumulation from previous doses.

[0076] A summary of the mean pharmacokinetic parameters are provided in the table below:

TABLE 3

		Tablet		Suspension					
		High Fat D		10 hr Fast A		High Fat B		Non-Fat C	
Parameter	Unit	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV
Cmax	ng/ml	413	33	132	50	512	34	378	43
Tmax	Hr	5.5	32	5.01	49	4.8	9	4.1	21
AUC(tf)	ng-hr/ml	10304	41	3553	36	13885	41	9511	38
AUC(I)	ng-hr/ml	11832	39	4179	31	15059	26	10753	35
t½	hr	21.0	15	23.5	25	23.0	19	22.2	18

a: Balanced means, n = 20 except for AUC(I) and t½, n = 15.

[0077] Posaconazole was slowly absorbed; the mean Tmax values ranged from 4.1 to 5.5 hr. Posaconazole was slowly eliminated with a mean terminal t½ of about 22 hour which was independent of treatment. This study was conducted to evaluate the bioavailability of posaconazole oral suspension (Treatment B) compared to a tablet formulation (Treatment D), both given with a high-fat food. The results, based on log-transformed data, are shown below:

TABLE 4

Parameter	Treatments Given After High Fat Breakfast	Geometric Mean	Relative Bioavailability (%)[b]	90% Confidence Interval
Cmax	Suspension	485 ng/ml	123.3	104–146
	Tablet	394 ng/ml		
AUC(tf)[a]	Suspension	13141 ng.hr/ml	136.5	119–156
	Tablet	9624 ng.hr/ml		

[a]AUC(tf) was used for statistical comparisons because it could be calculated for all treatments for all subjects.
[b]Suspension relative to tablet.

[0078] On average, the suspension formulation of the present invention resulted in a 23% increase in Cmax and a 36% increase in AUC(tf) compared to the tablet of the prior art.

[0079] The secondary objective of the study was to evaluate the effect of high fat food (Treatment B) and non-fat food (Treatment C) compared to fasting (Treatment A) on the oral bioavailability of posaconazole administered as an oral suspension. The results, based on log-transformed data, are shown below:

TABLE 5

Parameter	Suspension Treatments	Geometric Mean	Relative Bioavailability (%)[a]	90% Confidence Interval
Cmax	High-Fat	485	417	352–493
(ng/ml)	Non-Fat	345	296	250–350
	Fast	116	—	—
AUC(tf)	High-Fat	13141	392	343–448
(ng.hr/ml	Non-Fat	8857	264	231–302
	Fast	3352	—	—

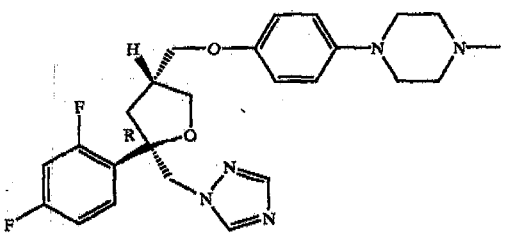
[a]Expressed as a percent of Treatment A - Suspension/Fast.

[0080] A high fat breakfast produced a 4-fold increase in the bioavailability of posaconazole given in a suspension. This was consistent with results from a previous study where food significantly increased the bioavailability of posaconazole by 3-5-fold for both tablet and capsule formulations. The effect of a non-fat breakfast (Treatment C) compared to fasting (Treatment A) was less, with a 2.5-3-fold increase in bioavailability.

[0081] Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to one skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims along with the full scope of equivalents to which such claims are entitled.

We claim:

1. A liquid suspension comprising an antifungally effective amount of the micronized compound represented by the chemical structural formula I comprising:



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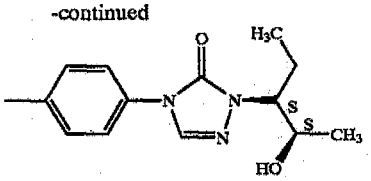


at least one thickening agent, at least one non-ionic surfactant, and a pharmaceutically acceptable liquid carrier.

2. The liquid suspension of claim 1, wherein the at least one non-ionic surfactant is a block copolymer of ethylene oxide and propylene oxide, glycol or glyceryl esters of saturated or unsaturated $C_8$to C_{20} acids, polyoxyethylene esters of saturated or unsaturated $C_8$to C_{20} acids, polyoxyethylene ethers of saturated or unsaturated $C_8$to C_{20} acids, polyvinylalcohols or sorbitan esters of saturated or unsaturated C_{10} to C_{20} acids.

3. The liquid suspension of claim 1, wherein the at least one non-ionic surfactant is a polyoxyethylene derivative of a sorbitan ester of a saturated or unsaturated $C_{10}$to C_{20} acid.

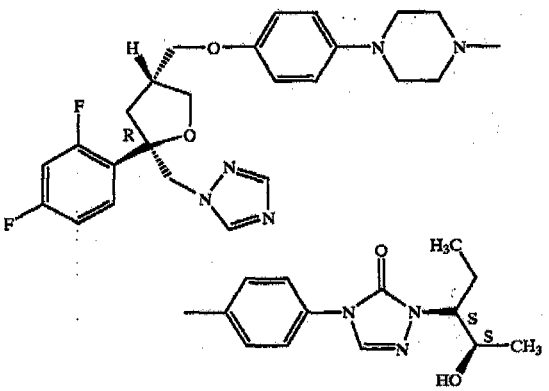
4. The liquid suspension of claim 1, wherein the at least one thickening agent is selected from xanthan gum, liquid sugars, starches, celluloses and mixtures thereof.

5. The liquid suspension of claim 1, wherein a combination of xanthan gum and a liquid sugar are used as the at least one thickening agent.

6. The liquid suspension of claim 1, wherein the micronized compound of formula I has a mean particle size of about 1200 nm to about 1600 nm.

7. A liquid suspension comprising:

(a) an antifungally effective amount of the micronized compound represented by the chemical structural formula I:



(b) an effective amount of at least one thickening agent;

(c) an amount of a buffer system effective to maintain the pH of the system in the range of about 4.0 to about 6.0;

(d) an effective amount of at least one non-ionic surfactant; and

(e) a pharmaceutically acceptable liquid carrier.

8. The liquid suspension of claim 7, wherein the at least one non-ionic surfactant is a polyoxyethylene derivative of a sorbitan ester of a saturated or unsaturated $C_{10}$to C_{20} acid.

9. The liquid suspension of claim 7, wherein the sorbitan ester is a fatty acid ester of sorbitan selected from sorbitan monolaurate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, sorbitan monopalmitate, sorbitan monostearate and sorbitan tristearate, or mixtures thereof.

10. The liquid suspension of claim 7, wherein the at least one thickening agent is selected from gums, liquid sugars, starches, cellulose and mixtures thereof.

11. The liquid suspension of claim 7, wherein a combination of a xanthan gum and a liquid sugar is used as the at least one thickening agent.

12. The liquid suspension of claim 7, wherein a combination of a xanthan gum and a liquid glucose is used as the thickening agent.

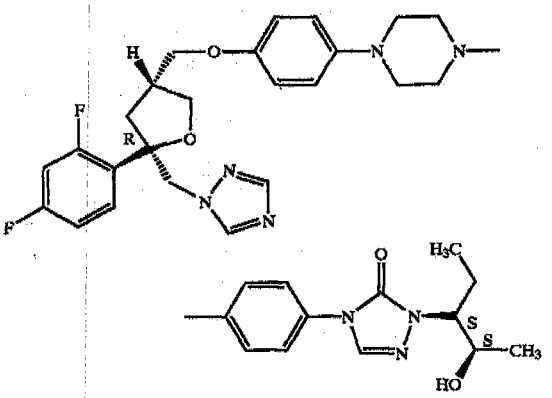
13. The liquid suspension of claim 7, wherein the buffer system comprises sodium citrate and citric acid.

14. The liquid suspension of claim 7, wherein the pharmaceutically acceptable liquid carrier is a combination of purified water, glucose and glycerin.

15. The liquid suspension of claim 7, wherein the micronized compound of formula I has a mean particle size of about 1200 nm to about 1600 nm.

16. A liquid suspension comprising:

(a) an antifungally effective amount of the micronized compound comprising chemical structural formula I:



wherein the micronized compound of formula I has a mean particle size in the range of about 1200 nm to about 1600 nm,

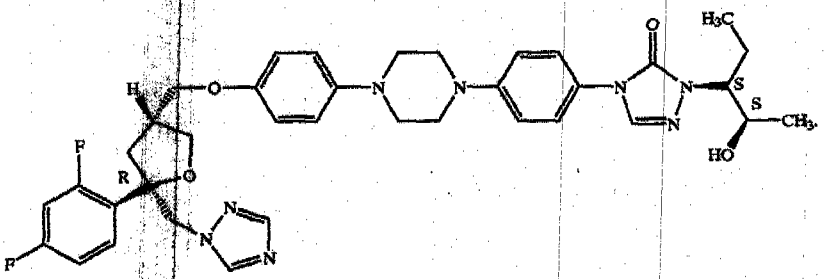
(b) an effective amount of a polyoxyethylene derivative of sorbitan esters of saturated or unsaturated C_{12} to C_{18} acids;

(c) an effective amount of a buffer system sufficient to maintain a pH in the range of about 4.0 to about 6.0;

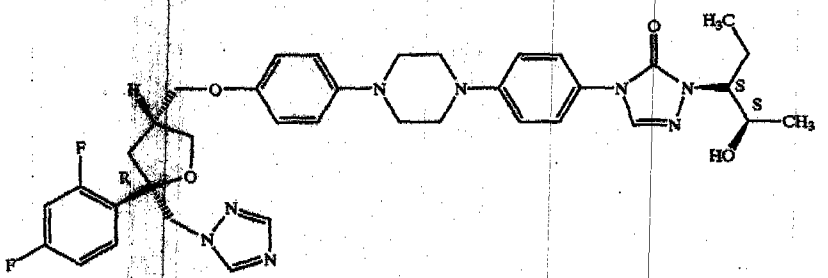
(d) an effective amount of a combination of two thickening agents, wherein one is a liquid sugar; and

(e) a pharmaceutically acceptable liquid carrier.

17. A method of treating and/or preventing a fungal infection in a patient comprising administering to a patient in need of such treating and/or preventing an antifungally effective amount of micronized particles of of the compound of formula I in the form of an oral suspension I:

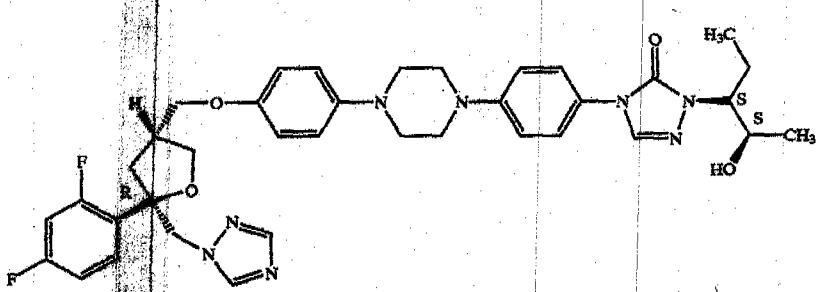


18. A suspension comprising an antifungally effective amount of the micronized particles of the compound comprising chemical structural formula I:



at least one thickening agent and a non-ionic surfactant in a pharmaceutically acceptable liquid carrier.

19. A composition of matter comprising micronized particles of the compound represented by structural formula I



US005091188A

United States Patent [19]

Haynes

[11] Patent Number: 5,091,188

[45] Date of Patent: Feb. 25, 1992

[54] **PHOSPHOLIPID-COATED MICROCRYSTALS: INJECTABLE FORMULATIONS OF WATER-INSOLUBLE DRUGS**

[76] Inventor: **Duncan H. Haynes**, 4051 Barbarossa Ave., Miami, Fla. 33133

[21] Appl. No.: **514,012**

[22] Filed: **Apr. 26, 1990**

[51] **Int. Cl.**[5] **A61K 37/22; A61F 13/00**

[52] **U.S. Cl.** **424/450**; 424/422; 424/405; 424/408; 424/409

[58] **Field of Search** 424/450, 422, 405, 408, 424/409

[56] **References Cited**

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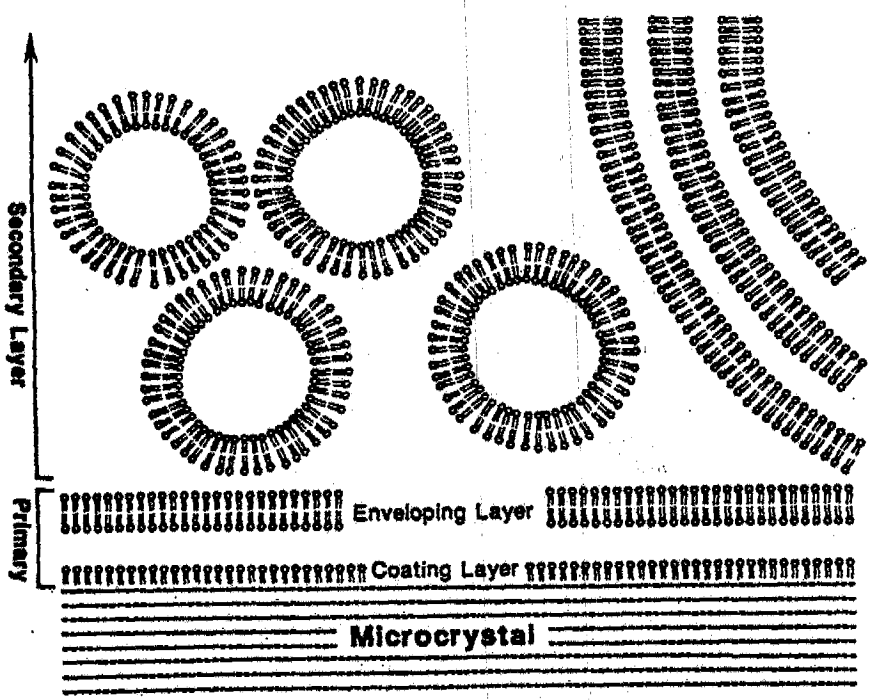
Primary Examiner—Thurman K. Page
Assistant Examiner—G. S. Kishore
Attorney, Agent, or Firm—Nixon & Vanderhye

[57] **ABSTRACT**

Water-insoluble drugs are rendered injectable by formulation as aqueous suspensions of phospholipid-coated microcrystals. The crystalline drug is reduced to 50 nm to 10 μm dimensions by sonication or other processes inducing high shear in the presence of phospholipid or other membrane-forming amphipathic lipid. The membrane-forming lipid stabilizes the microcrystal by both hydrophobic and hydrophilic interactions, coating and enveloping it and thus protecting it from coalescence, and rendering the drug substance in solid form less irritating to tissue. Additional protection against coalescence is obtained by a secondary coating by additional membrane-forming lipid in vesicular form associated with and surrounding but not enveloping the lipid-encapsulated drug particles. Tissue-compatible formulations containing drug in concentrations up to 40% (w/v) are described. The preparations can be injected intra-lesionally and in numerous other sites, including intra-venous, intra-arterial, intra-muscular, intra-dermal, etc. The disclosure describes examples of formulations and pharmacokinetic data with antibiotics, anthelmintic drugs, anti-inflammatory drugs, local and general anesthetics, and biologicals.

18 Claims, 9 Drawing Sheets



PRESERVATIVES

Oil-soluble preservatives can be added in process during the primary or coating phase. These include, but are not limited to, benzalkonium chloride, propylparabum, butylparaben, and chlorobutanol. There are also numerous water- and oil-soluble agents which can be added to the finished product as preservatives, including, benzyl alcohol, phenol, sodium benzoate, EDTA, etc.

OPTIONAL LYOPHILIZATION AND RECONSTITUTION

Aqueous microcrystal preparations can be lyophilized to give a dry product which can be reconstituted with water (Example 6). This is particularly useful for a drug which does not have long-term stability in an aqueous environment. It is also possible to conduct the sonication or shear process in a volatile organic solvent in which the crystalline drug is not substantially soluble, and to prepare dry coated microcrystals by solvent evaporation (Example 8). These procedures give microcrystals surrounded by layers of phospholipid in the anhydrous state. Such forms are suitable for oral administration or for reconstitution with water and injection.

DESIGN OF THE FINAL PRODUCT

One skilled in the art following the instructions provided herein will have no difficulty in empirically determining the:

Most convenient method of preparation:

Sonication vs. high pressure and shear vs. methods involving organic solvents vs. impact in air vs. in-flight crystallization vs. solvent dilution

Most advantageous form of the drug:

Crystal of neutral drug vs. crystal of charged drug vs. more complex solid forms of the drug

Optimal membrane forming lipid:

Based on reactivity and stability of membranes, blood and tissue compatibility and price

Optimal conditions for manufacture, including:

Input drug and phospholipid ratio; incorporation of small amounts of oils or waxes as modifying agents; duration of sonication, shear, etc; use of sedimentation as a means of size selection; addition of more peripheral lipid in unilamellar or multi-lamellar form; addition of osmotic or viscosity-affecting agents.

Optimal particle size:

Which can be controlled to a certain extent by the power supplied, the duration of processing, the drug and phospholipid concentrations,

And which can be selected between 50 nm and 10 um by sedimentation velocity

Optimal compositions to achieve the desired shelf life and pharmacokinetics:

Including study of the effect of the above factors on the pharmacokinetics after injection. Particularly important are the particle size, primary and secondary phospholipid content, and additives to avoid compaction after injection into a tissue.

Most advantageous mode of administration:

Including injection (IV, IA, IM, etc.), oral, topical administration, inhalation, etc.

WEIGHTS AND MEASURES

All parts and percentages reported herein are by weight (w/w) or weight/volume (w/v) percentage, in which the weight or volume in the denominator represents the total weight or volume of the system. Concentrations of water soluble constituents in aqueous solution (e.g. glucose) are given in millimolar concentration (mM=millimoles per liter) referred to the volume of water in the system. All temperatures are reported in degrees Celsius. Diameters or dimensions are given in millimeters (mm=10^{-3} meters), micrometers (um=10^{-6} meters), nanometers (nm=10^{-9} meters) or Angstrom units (=0.1 nm). The compositions of the invention can comprise, consist essentially of or consist of the materials set forth and the process or method can comprise, consist essentially of or consist of the steps set forth with such materials.

DETAILED DESCRIPTION OF THE INVENTION

EXAMPLE 1

Lecithin-coated microcrystals of oxytetracycline (OTC) were prepared by sonication in the following manner:

Into a 150 ml glass beaker, 4.4 gm oxytetracycline dihydrate (Sigma, 0-5750) and 16.0 gm egg lecithin (L-alpha-phosphatidylcholine from egg, Type XV-E, Sigma, P-9671) were added coarsely mixed using a glass stirring rod. Next, an aqueous solution of 300 mM glucose, 10 mM tris adjusted to pH 7.4, was added to give a final volume of 80 ml. The beaker was jacketed with a larger beaker filled with water which was kept in motion by means of a magnetic stirring bar. This, and occasional interruptions of the sonication, allowed for dissipation of heat produced by sonication process. The 1.0 cm diameter probe of a Sonifier ® Cell Disrupter, Model W185D (Heat System and Ultrasonics, Plainview, N.Y.) was immersed in the liquid and mixture was sonicated for a total of 60 min at power stage 10 (nominally 100–150 watts). The temperature of the mixture was not allowed to exceed 60° C. During the sonication, the preparation was titrated with 1.2M HCl to achieve a final pH of 5.0. Sonication resulted in an opaque yellowish-beige suspension. Next, the preparation was covered and allowed to settle for 24 hrs. The bottom 11 ml contained a visible precipitate of OTC at a concentration of 40% (w/v). The supernatant contained phospholipid vesicles. Bottom 22 ml were collected and the precipitate was resuspended with gentle shaking. It contained lecithin-coated microcrystals of OTC. It behaved as a somewhat viscous but syringable liquid.

Fluorimetric analysis and high pressure liquid chromatographic (HPLC) showed that the top phase contained very little oxytetracycline. The bottom phase sampled as the bottom 22 ml contained ≅98% of the added oxytetracycline. It was 20% (w/v) in OTC and 20% (w/v) lecithin. Aliquots were taken from both phases and were diluted into OTC-saturated buffer and were analyzed for diameter (±SD) using a Coulter N4-MD Submicron Particle Analyzer. The top phase was analyzed for particle size was found to have diameters of 30.5±8 nm (77%) and <3,000 nm corresponding to unilamellar and multilamellar phospholipid vesicles, respectively. The top phase was discarded. The lecithin-coated OTC microcrystal fraction had the following weight-averaged particle size distribution: 980±460 (SD) nm, 59%; 2,880±400 (SD) nm, 41%. Analysis of the preparation by electron microscopy using negative staining corroborated the above findings. Several preparations were made as described above and were filled into rubber-stoppered glass ampules and glass bottles.

With storage over a period of weeks some settling was observed, but the preparation could be rendered homogeneous with three inversions. The preparation retained its properties, including size distribution, OTC concentration, chemical integrity and syringability (20 gauge or narrower) for over 9 months.

The importance of the lecithin coating was demonstrated as follows: 4.4 gm OTC and 75.6 ml glucose solution were sonicated for 60 min as described above, but in absence of lecithin. A coarse suspension was obtained with the following characteristics: (a) Immediate sampling and 1,000-fold dilution into OTC-saturated water gave particles visible to the naked eye. Analysis by the Coulter Submicron Particle Analyzer reported that the particles were "out of range" (>3 um). The analysis did not reveal any particles with diameters <3 um. (b) Within 10 minutes after sonication, all of the OTC had settled to the bottom. The bottom phase was not free-flowing and was not syringable. Within 1 hr after settling, it became a solid mass which could not be resuspended with shaking. Similarly, it was impossible to stabilize this preparation by adding pre-formed phospholipid vesicles to the sonicated OTC immediately after cessation of sonication. Thus sonication with lecithin (or other membrane-forming lipid) is shown to be a critical step in the method of preparation.

EXAMPLE 2

The preparation of Example 1 was repeated with the following alterations: The preparation was scaled to a total volume of 5.0 ml, the microtip sonicator probe was used and 0.15 mg Nile Red was added at the same time as the lipid. This dye binds to phospholipids and serves as a fluorescent marker for the lecithin. A drop of the 20% (w/v) preparation was spread on a glass slide and observed with a fluorescent microscope (Leitz Wetzlar Dialux 20) at high power. FIG. 2 is a black and white drawing of a typical field. White indicates high fluorescence. With ultra-violet excitation, OTC particles were observed by their intense yellow-green fluorescence. The upper panel of FIG. 2 shows depicts the fluorescent image of OTC. Discrete particles with diameters ranging from approx. 0.2 um and ca. 3 um were observed. The majority of the particles were ≦1 um diameter (number average). The particles had clear boundries, but were surrounded by diffuse yellow-green halo's. The identical field was observed with near ultraviolet excitation to give the Nile Red image associated with the lecithin in the preparation (bottom panel). The Nile Red image shows the lecithin to be surrounding the OTC particles. A halo red fluorescence surrounded the particles, extending 0.3 um to 3 um beyond the boundry of the OTC microcrystal. Empty spaces devoid of both OTC and lecithin, could be readily discerned around all particles situated near the edge of the smear. Occasionally configurations were observed suggesting that two OTC particles were sharing a single phospholipid halo.

Brownian Motion was observed in the sample. The larger (>1 um diameter) particles which settled on the glass slide showed no Brownian Motion, or highly restricted motion. Particles of ≦1 um diameter showed Brownian Motion, moving between the larger particles. Observations in regions of low concentration showed that no particle could move a distance greater than approx. ½ its diameter without its halo experiencing a corresponding movement. Furthermore, direct collisions of the particles were never observed. These observations explain the remarkable stability of the microcrystal suspensions of my invention: The lecithin coats the microcrystal, supplying both a hydrophobic surface for contact with the crystalline surface and a hydrophilic surface for contact with water. The coated surface is enveloped by numerous layers of lecithin in membrane form, as revealed by the Nile Red staining. The stability of the envelopment is shown by the fact that the microcrystal always remains within its lecithin halo, as revealed by their respective fluorescence signals. The outer lecithin layers guarantee that the coated microcrystals do not approach closely enough to fuse.

The dissolution behavior of the lecithin-coated microcrystals was observed under the fluorescent microscope by adding a large quantity of distilled water. The cover slip was raised and a drop of water was balanced next to it, making contact with the smear. The cover slip was floated, and the behavior of the preparation was observed. The smaller particles (approx. 0.2–1.0 um) moved with the water flow. The Nile Red fluorescent halo moved together with the fluorescent OTC particle, and the brightness of the two fluorescent signals initially remained in constant proportion. As the particle moved into the distilled water, the OTC signal dimmed, suggesting that the microcrystal was dissolving. Only a small fraction of the Nile Red image and intensity was lost, suggesting that the lecithin coating was a persisting structure. The dissolution behavior of the larger particles which were generally more firmly attached to the slide was somewhat different. The streaming caused them to shed a large portion of their lipid. The larger microcrystals were then observed to crack, splitting off shards each of which carried away a portion of the Nile Red halo with it.

Dissociation behavior was also studied using the Coulter N4-MD Submicron Particle Sizer. As stated in Example 1, when the preparation is diluted 1,000× into isotonic glucose buffer saturated with OTC, the preparation is stable and particles sizes of 980±460 nm and 2,880±400 nm were observed. When the dilution was made 1,000× into distilled water, rapid alteration of the preparation was observed. Dissolution was expected since the final OTC concentration becomes 0.2 mg/ml, which is lower than the aqueous solubility of the drug (about 1 mg/ml). Dissolution was observed, but it was accompanied by the formation of some particles with diameters greater than 3 um.

EXAMPLE 3

A Nile Red "doped" lecithin-coated microcrystal preparation of oxytetracycline was made and the following fractionation experiment was carried out to delineate the relationship between the primary and secondary phospholipid coatings for the larger-diameter (1.0–1.9 um) coated microcrystals.

Oxytetracycline (2.0 gm), lecithin (8.0 gm) and Nile Red (1.5 mg) were added to 40 ml of isotonic glucose and sonicated for 30 min. The preparation was allowed to concentrate to 20% (w/v) OTC by sedimentation overnight. The volume of this preparation was 10 ml. Small aliquots were taken for fluorimetric assay of Nile Red concentration, phospholipid analysis (by ammonium ferrothiocyanate extraction) and for observation under a fluorescence microscope. Then the preparation was centrifuged with a clinical centrifuge at medium speed for 15 min. This resulted in a visible precipitate of 2.0 ml volume. The top phase was separated, and a aliquots were analyzed (1st supernate). The bottom phase was resuspended to a final volume of 10 ml by

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., 07/07/2009

Abogado
Carlos Reinaldo Olarte
(Apoderado)

ASUNTO	Radicación	**06 120230**
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	007712
	Folios	006

Patente de Invención	[X]	Patente de Modelo de Utilidad	[ ]		
Vía Nacional	[ ]				
Vía PCT (fase nacional)	[X]	Cap. I	[X]	Cap. II	[ ]

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

1.1.	Descripción:	Folios: 95 a 161	
1.2.	Reivindicaciones:	Folios: 162 a 180	
1.3.	Datos PCT:	Solicitud Internacional:	PCT/US05/018945
		Capítulo II	
		Fecha Sol. Internacional:	27/05/2005
		Publicación. Internacional:	WO05/117831
		Fecha Pub. Internacional:	15/12/2005
		Fecha Inicio Fase Nacional:	28/12/2006
		Fecha Sol. Nacional:	28/11/2006
1.4.	Prioridad:	US60/575.126 de 28/05/2004	

2. Objeto de la invención

Título de la solicitud

Composiciones farmacéuticas inyectables de posaconazol con partículas estabilizadas

Reivindicaciones

Reivindicaciones 1 a 36: Se reivindica una formulación que comprende una suspensión de posaconazol estabilizada por un fosfolípido en una mezcla que contiene un protector térmico y un sistema tampón.

Reivindicaciones 37 a 46 y 74 a 80: Se reivindica el método de tratamiento o de prevención de una infección en un animal que lo necesite que comprende la administración a dicho animal de una cantidad efectiva de las formulaciones definidas en cláusulas precedentes.

Reivindicaciones 47 a 50: Se reivindican las formulaciones farmacéuticas que comprenden además del principio activo posaconazol un segundo ingrediente activo seleccionado entre antifúngicos, antibacterianos, antivirales, esteroides, AINEs, quimioterapéuticos y antieméticos.

Reivindicaciones 51 a 73: Se reivindican las formulaciones farmacéuticas en términos de parámetros farmacocinéticos como Cmax, Volumen de distribución, Vida media plasmática, entre otros.

Sustento Descriptivo

La solicitud hace referencia a formulaciones útiles para el tratamiento de infecciones que se encuentran en sistemas inyectables tipo suspensión estéril.

En general, el estado de la técnica no divulga suspensiones que posaconazol estables cuando se someten a esterilización terminal por vapor y estables durante la vida en almacenamiento del producto.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K $^{31}/_{496}$ // A 61 P $^{33}/_{00}$** de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1. Reivindicaciones (*artículo 30 D. 486*)

Teniendo en cuenta la materia definida en las cláusulas 1 a 36, 47 a 50 y 51 a 73 esta Dependencia se permite señalar lo siguiente:

- La formulación de la cláusula independiente 1 se define en términos de la función técnica que ejerce cada uno de los excipientes adicionados, por ejemplo: un agente estabilizador, un agente protector térmico y un sistema tampón o regulador de pH sin que se defina claramente la clase de excipiente que cumple la función esperada.

Esta forma de definir la materia evoca un resultado que se pretende alcanzar, es decir, un sistema de entrega o vehículo farmacéutico que permita formular el agente activo posaconazol y sus combinaciones farmacológicas con antifúngicos, antibacterianos, antivirales, esteroides, AINEs, quimioterapéuticos y antieméticos y que presente estabilidad durante la vida útil del producto y cuando se somete a esterilización con vapor, sin que se precise claramente, tal y como en la cláusula dependiente número 20, las características químicas y las proporciones y cantidades de las especies que constituyen la formulación.

En razón a los argumentos expuestos se recomienda al señor solicitante definir con precisión los elementos característicos de las formulaciones evitando hacer uso de expresiones que evocan la función farmacotécnica de los excipientes.

- Por otra parte, las cláusulas 47 y 50 hacen referencia a las composiciones medicamentosas que contienen combinaciones farmacológicas de Posaconazol con antifúngicos, antibacterianos, antivirales, esteroides, entre otros. Sin embargo, la materia no se define en términos de las especies farmacológicas combinadas sino por géneros terapéuticos, situación que no permite una interpretación inequívoca del alcance de la invención y por otra parte, no todas las combinaciones que se derivan de la definición señalada por el señor solicitante encuentran sustento técnico en el aparte descriptivo de la solicitud, por lo que en virtud del presente examen técnico se requiere al interesado para que reivindique con precisión las combinaciones farmacológicas que fueron objeto de comprobación técnica y que se encuentran debidamente sustentadas en capítulo descriptivo.

- En cuanto al contenido de las cláusulas 51 a 73 es preciso señalar que los parámetros farmacocinéticos no son características que definan con precisión los elementos sustanciales de la composición medicamentosa, por el contrario, se relacionan con propiedades intrínsecas de la formulación que sólo evocan el resultado que se pretende alcanzar con la composición cuali-cuantitativa de las formulaciones. Y debido a que la protección por patente se otorga sobre productos tangibles y no sobre propiedades atribuidas a las formulaciones, es preciso que el señor solicitante defina las formulaciones exclusivamente en términos de las especies químicas que las componen, sus cantidades y proporciones y evite reivindicar el efecto técnico que se consigue con las composiciones.

4. Excepción a la patentabilidad *(artículo 20 D. 486 literal a)-d))*

Las cláusulas 37 a 46 y 74 a 80 de los folios 168 a 180 hacen referencia a un método para el tratamiento de una infección en un animal que lo necesite que comprende la administración a dicho animal de una cantidad efectiva de las formulaciones que contienen posaconazol en un medio compuesto por un fosfolípido, fosfato sódico dibásico, fosfato sódico monobásico, trehalosa y agua para inyección.

Al respecto es preciso señalar que el artículo 20 literal d) de la Decisión 486 contempla la excepción a la patentabilidad para los métodos de tratamiento humano y animal, razón por la cual, el contenido de las cláusulas no constituye un objeto patentable conforme a la disposición legal, por lo que mediante el presente concepto técnico se le comunica al señor solicitante que en tratándose de un método como el reivindicado esta Dependencia se encuentra impedida, en virtud de la ley, para realizar el estudio de patentabilidad en razón a la excepción señalada.

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: 28/05/2004, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	US2003/0055067	"Antifungal composition with enhanced bioavailability"	20/03/2003

D2	**US5091188**	"Phospholipid-coated microcrystals: injectable formulations of water-insoluble drugs"	25/02/1992

Anterioridades **D1** y **D2** en los folios 256 a 263

6. Análisis de patentabilidad *(artículo 14 D. 486)*

6.1 Nivel inventivo *(artículo18 D. 486)*

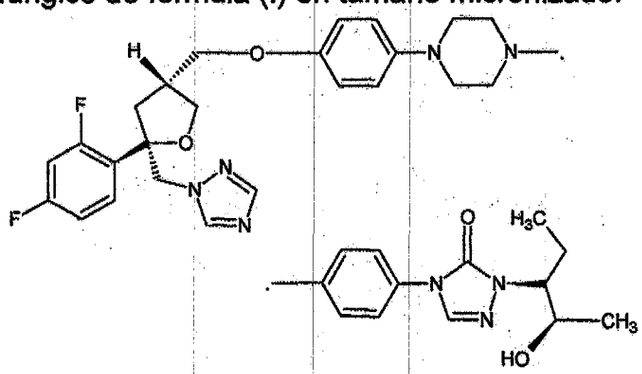
El nivel inventivo del objeto reclamado se evaluó por comparación entre las características esenciales que definen las composiciones reivindicadas y las reveladas por el arte previo.

- **Se reivindica:**

Una formulación que comprende una suspensión de posaconazol estabilizada por un fosfolípido en una mezcla que contiene un protector térmico y un sistema tampón

- **El estado del arte previo a la invención presenta los siguientes documentos:**

Anterioridad D1:
La publicación **D1** revela composiciones tipo suspensiones líquidas que comprenden un agente antifúngico de fórmula (I) en tamaño micronizado:



Anterioridad D2:
La publicación **D2** revela composiciones tipo suspensión de Oxitetraciclina dihidrato que presentan tamaños micronizados, a las que se adiciona lecitina de huevo (L-α-fosfatidilcolina), una solución acuosa de glucosa y un sistema para ajuste de pH.

Diferencias Técnicas:

De esta manera, al evaluar los elementos característicos de las composiciones reivindicadas a la luz de las enseñanzas que revelan los documentos del estado del arte **D1** y **D2**, es posible concluir que las diferencias entre ellos estriban en lo siguiente:

Con respecto al documento **D1** la falta de un agente fosfolípido que estabilice y proteja la formulación.

Con respecto al documento **D2** la falta de un agente protector térmico que evite la descomposición de la fórmula por efecto de la esterilización con vapor.

Tabla 1. Elementos característicos

Materia Reivindicada	Antecedente D1 (US2003/0055067)	Antecedente D2 (US5091188)
Formulación en suspensión de Posaconazol	Formulación en suspensión del antifúngico de fórmula (I) –Posaconazol -	Formulación inyectable heterodispersa tipo suspensión de Oxitetraciclina
Fosfolípido		Fosfolípido como agente de recubrimiento de los microcristales (lecitina)
Agente protector térmico	Copolímero de óxido de etileno y óxido de propileno	
Sistema tampón	Sistema citrato/ácido cítrico	Sistema Tris pH 7,4

Del efecto técnico y el problema objetivo:

Teniendo en cuenta que el problema técnico objetivo tiene que ver con la necesidad de aumentar la estabilidad de la formulación de Posaconazol en sistemas tipo suspensión y que el estado del arte ya utilizaba medios para aumentar dicha estabilidad mediante la adición de un fosfolípido y un agente protector térmico, tal y como lo señalan los documentos del estado del arte **D1** y **D2**, esta Dependencia considera que la materia objeto de análisis carece de altura inventiva, toda vez que el documento **D1** ya señalaba el camino para resolver los problemas derivados de la descomposición causada por el variabilidad en la temperatura mediante la adición de copolímeros de óxido de etileno y propileno que eviten la agregación de las partículas y el documento **D2** indicaba la posibilidad de adicionar fosfolípidos con el fin de evitar que las sustancias activas en tamaños micronizados formaran apastelamientos y sólidos de difícil redispersión, así como la adición de sistemas reguladores de pH para estabilizar el agente de recubrimiento fosfolipídico.

En consecuencia, el diseño propuesto por el solicitante se deriva de manera evidente del contenido de las publicaciones de la referencia por lo que para un conocedor de la materia técnica resulta evidente la solución propuesta por el señor solicitante para las formulaciones convencionales de Posaconazol que presentan estabilidad disminuida por efecto de la temperatura y el tiempo de almacenamiento.

Por las razones expuestas anteriormente esta dependencia encuentra que el arte previo afecta la altura inventiva de la materia reclamada y por consiguiente considera que existe incumplimiento de las disposiciones contempladas en el artículo 18 del ordenamiento jurídico andino.

7. Conclusión:

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	US2003/0055067	1 a 73	Nivel Inventivo
D2	US5091188	1 a 73	Nivel Inventivo

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

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 10 JUL. 2009

CONCEPTO TÉCNICO No. 2274	**EXAMINADOR TÉCNICO** Código No. **202044**