BAKER & MCKENZIE

Rajabock, Lara, Rodriguez & Rueda
Av. 82 No. 10 - 62 Piso 6
Bogotá, Colombia

NIT: 860.066.840-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

105
101

Señora
Alix Carmenza Céspedes de Vergel
Jefe de División de Nuevas Creaciones
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S.

SUPERINDUSTRIA Y COMERCIO
Radicación : 03088515 [illegible] Folios: 2
Fecha (AMD): 2005-12-26 16:57:36
Trámite : 001 PCT-PATENTE 379 FASE NAL 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Referencia: Expediente No. 03.088.515
Solicitud de Patente de Invención titulada: "Suspensión de partículas micronizadas de un compuesto antifungal."

Solicitante: Schering Corporation

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISIÓN 486. GACETA NO. 553

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad en referencia, solicito que se examine si la invención de la referencia es patentable según los requisitos de patentabilidad previstos en la Decisión 486 de la Comisión de la Comunidad Andina de Naciones. Adjunto recibo de caja por valor de $186,000 para cubrir la tasa correspondiente según la Resolución 31980 del 24 de diciembre de 2004.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281
Anexo: Recibo de caja No.05-71,219 por valor de $186,000 del 15-sep-05

BOGYND/BOGDMS-938435-V1.DOC

102 (84

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05005515 00000003 Folios: 2
Fecha (AMD): 2005-12-06 16:57:36
Tramite : 011 PCI-PATENT 379 FASE RACI 538 PETICION
Dependencia: 2000 DIVISION DE NUEVAS CONEXIONES

RECIBO OFICIAL DE CAJA : 5 - 71,219
FECHA : SEPTIEMBRE 15 DE 2005

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CORREA ORDONEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	27550373	15/09/2005	78,736,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114	PTC CAP-II EXAMEN DE PATENTIBILID	186,000.00
			TOTAL : $	186,000.00

SON: CIENTO OCHENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL ASUNTO No.

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **03- 88515**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION - PCT,** FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **553,** DE FECHA **30** DE **JUNIO** DE **2005**, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **27** DE **SEPTIEMBRE** DE **2005.**

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 _____

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

106
109

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor **Oficio N° - 6402**
Álvaro Correa Ordóñez
Apoderado

REFERENCIA	**Radicación**	**03 88515**
	Trámite	**002**
	Evento	**001**
	Actuación	**430**
	Folios	**009**

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 03 88515, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

. Descripción: folios 31-45
. Ejemplos: folios 45-58
. Capítulo reivindicatorio estudiado: folios 59-64
. Se reivindica prioridad presentada en Estados Unidos, el 03.04.01, bajo el número 60/281139

Objeto de la invención

Según las reivindicaciones 1 a 20 de la presente solicitud, se refiere a una suspensión líquida que comprende posaconazol micronizado, un agente espesante, un surfactante no iónico y un portador líquido farmacéuticamente aceptable.

Clasificación internacional de patentes A 61 K 31/496

Claridad de la solicitud

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

457
105

Teniendo en cuenta lo anterior, el término "portador líquido farmacéuticamente aceptable" de las reivindicaciones 1, 7, 16 y 18 es muy amplio y puede incluir portadores que no se encuentran revelados en la descripción.

El término "aproximadamente" es muy vago y no delimita de manera correcta la materia que se desea proteger.

El término "cantidad antifungal eficaz" es relativa y depende de la condición particular del paciente, por lo tanto es inexacta y no delimita la materia que se pretende proteger.

El término "cantidad eficaz" no delimita de manera correcta la cantidad de espesante, buffer o surfactante que se encuentran en la descripción.

Se le recuerda al solicitante que una composición se caracteriza por sus componentes específicos y la proporción de los mismos para que se diferencien de manera clara de aquellas que se encuentran en el estado de la técnica.

La dependencia entre las reivindicaciones 9 y 7 no es posible porque el ester de sorbitan no se encuentra en el texto de la reivindicación 7

Favor revisar la fórmula del compuesto posaconazol

Favor hacer las aclaraciones y correcciones del caso.

Excepciones a la patentabilidad

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

Teniendo en cuenta lo anterior, el contenido de la reivindicación 17, que trata de "El uso de partículas...", no es patentable.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la presente solicitud -03.04.01-, relacionados con la materia de la presente solicitud:

N°	Documento	Título	Fecha de publicación
1	US 5834472	"Composición antifungal con biodisponibilidad aumentada"	10.11.98
2	EP 0499299	"Nanopartículas de droga modificada de superficie modificada"	19.08.92

Evaluación de los requisitos de patentabilidad:

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

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

Evaluación de la NOVEDAD

El artículo 16 de la decisión 486 contempla que *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La patente US 5834472 revela una composición farmacéutica que comprende:

- posaconazol
- un surfactante lónico
- un diluyente como azúcares.

Las partículas pueden ser micronizadas a un nivel menor de 100 micrones, la composición puede ser formulada suspendida en agua (portador líquido).

La presente solicitud comprende:

- posaconazol micronizado
- un surfactante
- un espesante como azúcar
- un portador líquido.

Comparando elemento por elemento, las composiciones de las reivindicaciones 1-4 y 18-20 son iguales a las del documento citado y pueden afectar la novedad de la presente solicitud.

Evaluación del NIVEL INVENTIVO

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

La patente US 5834472 revela una composición farmacéutica de posaconazol que comprende un surfactante iónico y un diluyente como azúcares. Las partículas pueden ser micronizadas a un nivel menor de 100 micrones, la composición puede ser formulada suspendida en agua.

La publicación EP 0499299 enseña que la biodisponibilidad de un principio activo es fuertemente influenciada por su tasa de disolución y que la tasa de disolución puede ser aumentada por una disminución del tamaño de partícula.

Teniendo en cuenta el objeto de la solicitud, el cual es proveer suspensiones de posaconazol de bajo tamaño de partícula que tienen una biodisponibilidad aumentada, es una derivación evidente del estado de la técnica ya que una persona versada en la materia tomaría las composiciones de posaconazol reveladas en US 5834472 y disminuiría el tamaño de partícula del principio activo para aumentar su biodisponibilidad, tal como se enseña en EP 0499299, y llegar a las composiciones que se desean proteger.

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

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 5834472	1-4, 18-20	Nivel Inventivo
2	EP 0499299	1-16, 18-20	Nivel Inventivo

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única Nº 10 de 2001

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

El anterior requerimiento fue notificado por fijación en lista, de fecha 25 MAYO 2007

CONCEPTO TÉCNICO Número 0734	**EXAMINADOR TÉCNICO** Código 202024

US005834472A

United States Patent [19]

Sangekar et al.

[11] Patent Number: 5,834,472

[45] Date of Patent: Nov. 10, 1998

[54] **ANTIFUNGAL COMPOSITION WITH ENHANCED BIOAVAILABILITY**

[75] Inventors: **Surendra A. Sangekar**, Union; **Winston A. Vadino**, Whitehouse Station, both of N.J.; **Ping L. Lee**, Radnor, Pa.

[73] Assignee: **Schering Corporation**, Kenilworth, N.J.

[21] Appl. No.: **861,250**

[22] Filed: **May 21, 1997**

[51] Int. Cl.[6] **A61K 31/50; A61K 31/495**

[52] U.S. Cl. **514/252; 514/772.3**

[58] Field of Search 514/252

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,791,111	12/1988	Heeres et al.	514/252
4,853,223	8/1989	Graf et al.	424/405
4,883,808	11/1989	Fodor et al.	514/468
4,916,478	3/1990	Valentino et al.	424/682
5,039,676	8/1991	Saksena et al.	514/254
5,272,137	12/1993	Blase et al.	514/54
5,411,745	5/1995	Oshlack et al.	424/456
5,506,248	4/1996	Nikafar et al.	514/374
5,580,578	12/1996	Oshlacket	424/468
5,661,151	8/1997	Saksena et al.	514/252

FOREIGN PATENT DOCUMENTS

0539938A1	5/1993	European Pat. Off. .
WO 89/04829	5/1989	WIPO .
WO 95/17407	6/1995	WIPO .

OTHER PUBLICATIONS

Yamasaki et. al. Chemical Abstracts vol. 121: 117721u, 1994.

Jon E. Lutz et al., Activity of the Triazole 56592 against Disseminated Murine Coccidioidomycosis, Antimicrobial Agents and Chemotherapy, Jul. 1997, pp. 1558–1561.

Peter G. Welling, Pharmacokinetics, Processes and Mathematics, American Chemical Society, Washington, DC, ACS Monograph 185, (1986), p. 57.

J.G. nairn, Remington's Pharmaceutical Sciences, 18th edition, (1990), Mack Publishing Co., Chapter 83, p. 1519.

A.A. Nomeir et al., Bioavailability of SCH56592, a new broad spectrum triazole antifungl agent, from various formulations; Abstract of paper presented at 36th ICAAC, New Orleans, Louisiana, (Sep. 15–18, 1996); 1 page.

Pluronic® and Tetronic® Surfactants, publication of BASF Corporation, Mount Olive, New Jersey (1989), 29 pages.

Pluronic®Block Copolymer NF Grade (Poloxamer NF Grades); Technical Bulletin of BASF Corporation, (1995), 2 pages.

W. C. Gunsel and J. L. Kanig, Chapter 11, Tablets from The Theory and Practice of Industrial Pharmacy, 2nd Edition, Lea&Febiger, Philadelphia, (1976), pp. 321–344.

Van Hoetelier and J.Q. Bellard, Chapter 13, Part I. Hard Tablets, from The Theory and Practice of Industrial Pharmacy, 2nd Edition, Lea&Febiger, Philadelphia, 1976, pp. 389–404.

A. K. Saksena et al., Concise Asymmetric Routes to 2,2,4–Trisubstituted Tetrahydrofurans via Chiral Titanium Imide Enolates: Key Intermediates Towards Synthesis of Highly Active Azole Antifungals SCH51048 and SCH56592, Tetrahedron Letters, vol. 37, No. 32, (1996), pp. 5657–5660.

D. Loebenberg et al., #46, Formulation studies with SCH56592, a new broad spectrum antifungal triazole, abstract of paper submitted at "Focus on Fungal Infections 6" in New Orleans, Louisiana, Mar. 6–8, 1996, 4 pages.

Primary Examiner—Leonard Schenkman
Attorney, Agent, or Firm—Joseph T. Majka

[57] **ABSTRACT**

A pharmaceutical composition comprising:

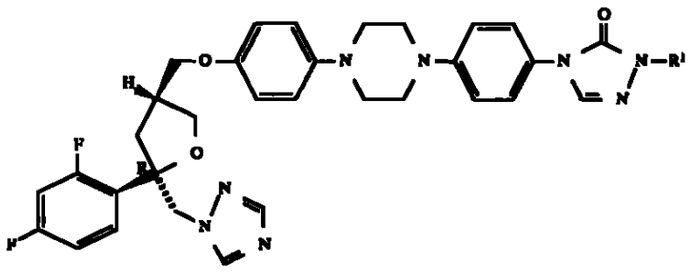
i) an antifungal agent which is (–)-(2R-cis)-4-[4-[4-[4-[[-5-(2,4-difluorophenyl)-tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)furan-3-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-[(S)-1-ethyl-2(S)-hydroxypropyl]-3H-1,2,4-triazol-3-one;

ii) at least one non-ionic surfactant; and

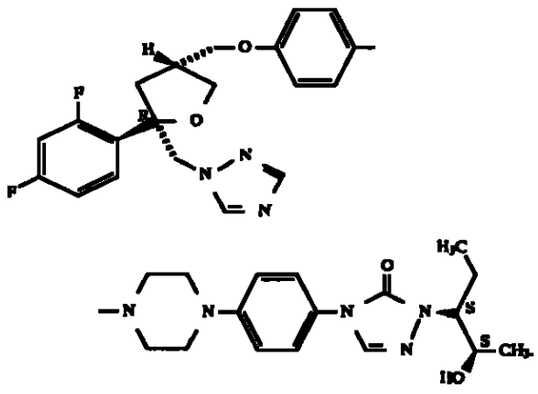
iii) a diluent.

The composition enables the antifungal compound, which has very low water solubility, to have enhanced bioavailability in mammals, such as humans.

39 Claims, No Drawings



wherein R^1 is a straight or branch chain (C3 to C8) alkyl group substituted by one or two hydroxy moieties; esters and ethers thereof or a pharmaceutically acceptable salt thereof. An especially preferred compound of the above group taught in Examples 24 and 32 of WO 95/17407 is the antifungal compound, (−)-(2R-cis)-4-[4-[4-[4-[[-5-(2,4-difluorophenyl)-tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl) furan-3-yl]methoxy]phenyl]-1-piperazinyl]phenyl]2,-4-dihydro-2-[(S)-1-ethyl-2(S)-hydroxypropyl]-3H-1,2,4-triazol-3-one (hereinafter the antifungal compound); Formula: $C_{37}H_{42}F_2N_8O_4$; Molecular weight: 700.8; m.p. 164°–165° C., $[\alpha]_D^{25}$ −29° C.±3° (c=1.0, $CHCl_3$), whose structure is depicted below:



Micron-sized particles of the antifungal compound can be obtained either by the final step during the manufacture of the antifungal compound or by the use of conventional micronizing techniques after the conventional crystallization procedure(s).

Where micronizing techniques are employed, the antifungal compound may be micronized to the desired particle size range by conventional techniques, for example, using a ball mill, ultrasonic means, or preferably using fluid energy attrition mills such as the trost fluid energy mill from Plastomer Products, Newton, Pa. 18940. When using a fluid energy attrition mill, the desired particle size can be obtained by varying the feed rate of the antifungal into the mill.

About 99% of the of the micronized antifungal particle are less than or equal to 100 microns in length, of which 95% are less than or equal to 90 microns. Preferably, about 99% of the micronized particles are less than or equal to 50 microns, of which 95% are less than or equal to 40 microns. More preferably, 99% of the micronized particles are less than or equal to 20 microns, of which 95 are less than or equal to 10 microns.

The antifungal compound is employed in the composition in amounts effective to control the fungi of interest. Such amounts can range from about 2% to about 85% by weight of the composition, more preferably from 5% to about 80%, most preferably from about 18 to about 50% by weight. The amount of composition in the particular dosage form, e.g. capsule, tablet, etc., can range from about 10 to about 500 milligrams (mg) antifungal compound per dosage form, preferably from about 50 to about 200 mg. For example, the dosage form of a capsule can have about 50 or about 100 mg of the antifungal agent. Similarly, the dosage form of a tablet can have about 50 mg, about 100 mg or about 200 mg of the antifungal compound.

The pharmaceutical composition of the present invention can be formulated into any suitable dosage form, such as capsules (either solid-filled, semi-solid filled or liquid filled), tablets, powders for constitution or oral gels.

The following terms are used to describe the present pharmaceutical compositions, ingredients which can be employed in its formulation and methods for assessing its bioactivity or bioavailability.

Dosage form—composition containing the antifungal compound formulated into a delivery system, i.e., tablet, capsule, oral gel, powder for constitution or suspension in association with inactive ingredients.

Capsule—refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active antifungal compound. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet—refers to a compressed or molded solid dosage form containing the active ingredient (antifungal compound) with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gels—refers to the antifungal drug dispersed or solubilized in a hydrophillic semi-solid matrix.

Powders for constitution refers to powder blends containing the antifungal drug and suitable diluents which can be suspended in water or juices.

Surfactant—refers to a compound that can reduce the *interfacial tension between two immiscible phases and this* is due to the molecule containing two localized regions, one being hydrophilic in nature and the other hydrophobic.

Non-ionic surfactant—refers to a surfactant which lacks a net ionic charge and do not dissociate to an appreciable extent in aqueous media. The properties of non-ionic surfactants are largely dependent upon the proportions of the hydrophilic and hydrophobic groups in the molecule. Hydrophilic groups include the oxyethylene group

(—OCH_2CH_2—) and the hydroxy group. By varying the number of these groups in a hydrophobic molecule, such as a fatty acid, substances are obtained which range from strongly hydrophobic and water insoluble compounds, such as glyceryl monostearate, to strongly hydrophilic and water-soluble compounds, such as the macrogols. Between these two extremes types include those in which the proportions of the hydrophilic and hydrophobic groups are more evenly balanced, such as the macrogol esters and ethers and sorbitan derivatives. Suitable non-ionic surfactants may be found in Martindale, The Extra Pharmacopoeia, 28th Edition, 1982, The Pharmaceutical Press, London, Great Britain, pp. 370 to 379. Such non-ionic surfactants include block copolymers of ethylene oxide and propylene oxide, glycol and glyceryl esters of fatty acids and their derivatives, polyoxyethylene esters of fatty acids (macrogol esters), polyoxyethylene ethers of fatty acids and their derivatives (macrogol ethers), polyvinyl alcohols, and sorbitan esters. Preferably, the non-ionic surfactant is a block copolymer of ethylene oxide and propylene oxide.

Suitable block copolymers of ethylene oxide and propylene oxide generically called "Poloxamers" and include those represented by the following chemical structure:

wherein a is an integer ranging from about 10 to about 110, preferably from about 12 to 101; more preferably from about 12 to 80; and

b is an integer ranging from about 20 to about 60, more preferably from about 20 to about 56; also from about 20 to 27. Most preferably, a is 80 and b is 27, otherwise known as Pluronic®F68 surfactant, trademark of the BASF Corporation, Mount Olive, N.J., USA. Pluronic®F68 surfactant is also known as Poloxamer 188. This surfactant has an average molecular weight of 8400, is a solid at 20° C., has a viscosity (Brookfield) of 1000 cps at 77° C. Other suitable block copolymers of ethylene oxide and propylene oxide include Pluronic F87, also known as Poloxamer 237 wherein a is 64 and b is 37; and Pluronic F127, also known as Poloxamer 407 wherein a is 101 and b is 56.

Suitable glycol and glyceryl esters of fatty acids and their derivatives include glyceryl monooleate and similar water soluble derivatives;

Suitable polyoxyethylene esters of fatty acids (macrogol esters) include polyoxyethylene castor oil and hydrogenated castor oil derivatives;

Suitable polyoxyethylene ethers of fatty acids and their derivatives (macrogol ethers) include Cetomacrogol 1000, Lauromacrogols (a series of lauryl ethers of macrogols of differing chain lengths) e.g. Laureth 4, Laureth 9 and Lauromacrogol 400.

Suitable Sorbitan esters (esters of one or more of the hydroxyl groups in the sorbitans, with a fatty acid, such as stearic, palmitic, oleic or lauric acid) include, e.g. Polysorbate 20, Polysorbate 40, Polysorbate 60, Polysorbate 65, Polysorbate 80, Polysorbate 85, Sorbitan Monolaurate, Sorbitan Mono-oleate, Sorbitan Monopalmitate, Sorbitan Monostearate, Sorbitan Sesquioleate, Sorbitan Trioleate and Sorbitan Tristearate.

The amount of non-ionic surfactant in the composition can range from about 5 to about 50% by weight of the total composition, more preferably from about 5 to about 25% by weight.

Optionally, the present composition may also contain an anionic surfactant, e.g. sodium lauryl sulfate, the amount of which can range from about 1 to about 10% by weight of the total composition, more preferably from about 3 to about 8% by weight.

Diluent—refers to to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrants—refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binders—refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant—refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glidents—materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents—excipients that provide coloration to the composition or the dosage form. Such excipients can include

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 499 299 A2**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 92200163.2

(22) Date of filing: 20.01.92

(51) Int. Cl.5: A61K 47/48, A61K 9/51

(30) Priority: 25.01.91 US 647105

(43) Date of publication of application:
19.08.92 Bulletin 92/34

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE

(71) Applicant: STERLING WINTHROP INC.
90 Park Avenue
New York, NY 10016(US)

(72) Inventor: Liversidge, Gary, c/o Sterling Winthrop Inc.
Patent Department, 90 Park Avenue
New York, New York 10016(US)
Inventor: Cundy, Kenneth, c/o Sterling Winthrop Inc.
Patent Department, 90 Park Avenue
New York, New York 10016(US)
Inventor: Bishop, John, c/o Sterling Winthrop Inc.
Patent Department, 90 Park Avenue
New York, New York 10016(US)
Inventor: Czekai, David, c/o Sterling Winthrop Inc.
Patent Department, 90 Park Avenue
New York, New York 10016(US)

(74) Representative: Halls, Helen Cynthia et al
Kodak Limited Patent Department Headstone Drive
Harrow, Middlesex HA1 4TY(GB)

(54) Surface modified drug nanoparticles.

(57) Dispersible particles consisting essentially of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm, methods for the preparation of such particles and dispersions containing the particles. Pharmaceutical compositions containing the particles exhibit unexpected bioavailability and are useful in methods of treating mammals.

EP 0 499 299 A2

This invention relates to drug particles, methods for the preparation thereof and dispersions containing the particles. This invention further relates to the use of such particles in pharmaceutical compositions and methods of treating mammals.

Bioavailability is the degree to which a drug becomes available to the target tissue after administration. Many factors can affect bioavailability including the dosage form and various properties, e.g., dissolution rate of the drug. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. Poorly water soluble drugs, i.e., those having a solubility less than about 10 mg/ml, tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. Moreover, poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with fully soluble drug substances.

It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption. However, in conventional dry milling, as discussed by Lachman et al, *The Theory and Practice of Industrial Pharmacy*, Chapter 2, "Milling", p. 45, (1986), the limit of fineness is reached in the region of 100 microns (100,000 nm) when material cakes on the milling chamber. Lachman et al note that wet grinding is beneficial in further reducing particle size, but that flocculation restricts the lower particle size limit to approximately 10 microns (10,000 nm). However, there tends to be a bias in the pharmaceutical art against wet milling due to concerns associated with contamination. Commercial airjet milling techniques have provided particles ranging in average particle size from as low as about 1 to 50 µm (1,000 - 50,000 nm). However, such dry milling techniques can cause unacceptable levels of dust.

Other techniques for preparing pharmaceutical compositions include loading drugs into liposomes or polymers, e.g., during emulsion polymerization. However, such techniques have problems and limitations. For example, a lipid soluble drug is often required in preparing suitable liposomes. Further, unacceptably large amounts of the liposome or polymer are often required to prepare unit drug doses. Further still, techniques for preparing such pharmaceutical compositions tend to be complex. A principal technical difficulty encountered with emulsion polymerization is the removal of contaminants, such as unreacted monomer or initiator, which can be toxic, at the end of the manufacturing process.

U. S. Patent 4,540,602 (Motoyama et al) discloses a solid drug pulverized in an aqueous solution of a water-soluble high molecular substance using a wet grinding machine. Motoyama et al teach that as a result of such wet grinding, the drug is formed into finely divided particles ranging from 0.5 µm (500 nm) or less to 5 µm (5,000 nm) in diameter. However, there is no suggestion that particles having an average particle size of less than about 400 nm can be obtained. Attempts to reproduce the wet grinding process described by Motoyama et al resulted in particles having an average particle size much greater than 1 µm.

EPO 275,796 describes the production of colloidally dispersible systems comprising a substance in the form of spherical particles smaller than 500 nm. However, the method involves a precipitation effected by mixing a solution of the substance and a miscible non-solvent for the substance and results in the formation of non-crystalline nanoparticles. Furthermore, precipitation techniques for preparing particles tend to provide particles contaminated with solvents. Such solvents are often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical.

U. S. Patent 4,107,288 describes particles in the size range from 10 to 1,000 nm containing a biologically or pharmacodynamically active material. However, the particles comprise a crosslinked matrix of macromolecules having the active material supported on or incorporated into the matrix.

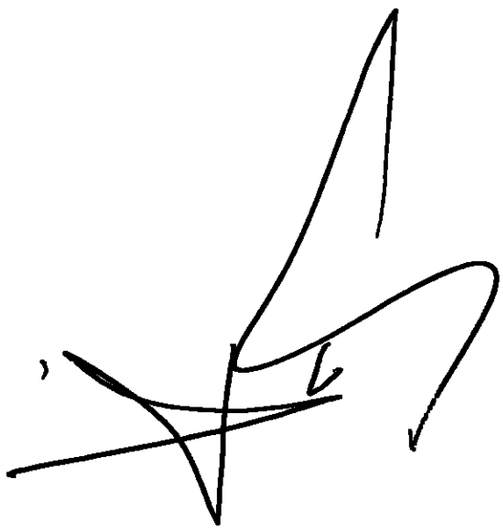
It would be desirable to provide stable dispersible drug particles in the submicron size range which can be readily prepared and which do not appreciably flocculate or agglomerate due to interparticle attractive forces and do not require the presence of a crosslinked matrix. Moreover, it would be highly desirable to provide pharmaceutical compositions having enhanced bioavailability.

We have discovered stable, dispersible drug nanoparticles and a method for preparing such particles by wet milling in the presence of grinding media in conjunction with a surface modifier. The particles can be formulated into pharmaceutical compositions exhibiting remarkably high bioavailability.

More specifically, in accordance with this invention, there are provided particles consisting essentially of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm.

This invention also provides a stable dispersion consisting essentially of a liquid dispersion medium and the above-described particles dispersed therein.

In another embodiment of the invention, there is provided a method of preparing the above-described



113

EXAMEN TECNICO DE FONDO

Nº Radicación	03-8851	Fecha de presentación	02.10.03
Nº Prioridad	US 60/421159	Fecha de Prioridad	03.04.03

Peticiones de la solicitud

Reivindicaciones

Memoria descriptiva

Dibujos

CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA

A61K 31/496			

DOCUMENTOS CORRESPONDIENTES EN OTROS PAISES

US 0280670			
Patente Original			

BASES DE DATOS CONSULTADAS

Epoline			
Espacenet			
USPTO			

INFORMES DE EXAMENES EN OTRAS OFICINAS

Oficina	Fecha	Reivindicaciones

ANTERIORIDADES ENCONTRADAS

Documento	Fecha	Reivindicaciones
US 5814627	No aplica	(1)
EP 0449799		

LITERATURA NO PATENTES

Documento	Fecha	Reivindicaciones

Observaciones: Falta claridad, (1)

Fecha del examen: 15-05-07