78

SEÑORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S.

Ref.: Expediente Nº 06-096.376
Solicitud de Patente de Invención Titulada: "COMPOSICIONES FARMACEUTICAS SECADAS POR ATOMIZACIÓN"
Solicitante: SMITHKLINE BEECHAM CORPORATION

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 581

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 sustituto tal como consta en la sustitución adjunta, 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 un recibo que de $202.000 pesos para cubrir la tasa correspondiente, según la Resolución 36155 del año 2006.

Atentamente,

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

Anexo: Recibo por $202.000 pesos
Sustitución

LMB/P2006/000169 07120

Industria y Comercio

Carlos Olaik

79782747 Bk 1974295

13 DIC. 2007

REPÚBLICA DE COLOMBIA

MARIA EUGENIA ROJAS DE URUETA

NOTARIA

Notaría 22 Bogotá

79

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Ref.: Expediente Nº 06-096.376

Solicitud de Patente de Invención Titulada: "COMPOSICIONES FARMACEUTICAS SECADAS POR ATOMIZACIÓN"

Solicitante: SMITHKLINE BEECHAM 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 EL ANTERIOR ESCRITO DIRIGIDO A:

27 FUE PRESENTADO PERSONALMENTE
ANTE EL DESPACHO NOTARIO VEINTISIETE
DE SANTAFE DE BOGOTA POR:

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

Y ADEMAS DECLARO QUE EL CONTENIDO DE [illegible]
DOCUMENTO ES CIERTO Y QUE LA FIRMA QUE LO
AUTORIZA FUE PUESTA POR EL.

EL DECLARANTE:

HUELLA

HOY: 4

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MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

REPUBLICA DE COLOMBIA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA
No. 27 Bogotá D.C.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-096376- -00003-0000
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Act 338 [illegible] Folios 3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 99,878
FECHA : DICIEMBRE 7 DE 2007

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

[illegible]POSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	DEVOLUCION TASA			780	07/12/2007	202,000.00

***** 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	202,000.00
		TOTAL : $	202,000.00

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : ______________________

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. ______________________

Industria y Comercio
SUPERINTENDENCIA

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81

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-96376

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **581** DE

FECHA **31 DE OCTUBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **31 DE ENERO 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____

US006608083B1

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

(10) **Patent No.: US 6,608,083 B1**
(45) **Date of Patent: Aug. 19, 2003**

(54) **QUINOLINE DERIVATIVES(2)**

(75) Inventors: **Carlo Farina; Giuseppe Arnaldo Maria Giardina**, both of Milan; **Mario Grugni**, Domodossola; **Luca Francesco Raveglia**, Milan, all of (IT)

(73) Assignee: **SmithKline Beecham Farmaceutici S.p.A**, Milan (IT)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/450,437**

(22) Filed: **May 25, 1995**

(30) **Foreign Application Priority Data**

May 27, 1994 (IT) MI94A1099
Mar. 14, 1995 (IT) MI95A0494

(51) **Int. Cl.**[7] **C07D 215/00**

(52) **U.S. Cl.** **514/311**; 514/312; 514/314; 514/331; 546/152; 546/153; 546/156; 546/155; 546/169

(58) **Field of Search** 514/331, 311, 514/312, 314; 546/152, 153, 156, 169, 155

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,711,890 A 12/1987 Dubroeucq et al.

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

EP 0 112 776 A2 7/1984
EP 0 384 313 A1 8/1990

OTHER PUBLICATIONS

Chemical Abstracts Vol 101, 1984; 101:191716z *4-Quinolinecarboxamide derivatives*, Dubroeucq et al.

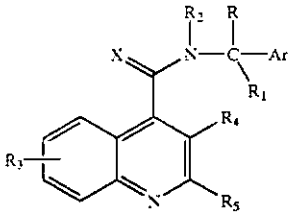
(List continued on next page.)

Primary Examiner—Jeffrey Mullis
(74) *Attorney, Agent, or Firm*—Nora Stein-Fernandez; Stepehen A. Venetianer; Charles M. Kinzig

(57) **ABSTRACT**

NK_3 receptor antagonists of formula (I):

(I)



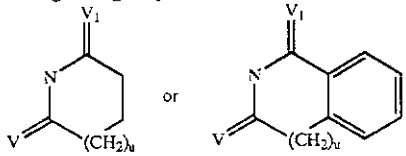
in which:

Ar is an optionally substituted phenyl group, or a naphthyl or C_{5-7} cycloalkdienyl group, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

R is linear or branched C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, an optionally substituted phenyl group or a phenyl C_{1-6} alkyl group, an optionally substituted five-membered heteroaromatic ring comprising up to four heteroatoms selected from O and N, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkylaminoalkyl, di C_{1-6} alkylaminoalkyl, C_{1-6} acylaminoalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylcarbonyl, carboxy, C_{1-6} alkoxyxcarbonyl, C_{1-6} alkoxycarbonyl C_{1-6} alkyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, halogeno C_{1-6} alkyl; or is a group $-(CH_2)_p-$ when cyclized onto Ar, where p is 2 or 3;

R_1 and R_2, which may be the same or different, are independently hydrogen or C_{1-6} linear or branched alkyl, or together form a $-(CH_2)_n-$ group in which n represents 3, 4, or 5; or R_1 together with R forms a group $-(CH2)_q-$, in which q is 2, 3, 4 or 5;

R_3 and R_4, which may be the same or different are independently hydrogen, C_{1-6} linear or branched alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino, mono- and di-C_{1-6} alkylamino, $-O(CH_2)_r-NT_2$, in which r is 2, 3, or 4 and T is hydrogen or C_{1-6} alkyl or it forms with the adjacent nitrogen a group



in which V and V_1 are independently hydrogen or oxygen and u is 0,1 or 2; $-O(CH_2)_s-OW$ in which s is 2, 3, or 4 and W is hydrogen or C_{1-6} alkyl; hydroxyalkyl, aminoalkyl, mono-or di-alkylaminoalkyl, acylamino, alkylsulphonylamino, aminoacylamino, mono- or di-alkylaminoacylamino; with up to four R_3 substituents being present in the quinoline nucleus; or R_4 is a group $-(CH_2)_t-$ when cyclized onto R_5 as aryl, in which t is 1, 2, or 3;

R_5 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted aryl, wherein an optional substituent is hydroxy, halogen, C_{1-6} alkoxy or C_{1-6} alkyl, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

in which inter alia, Ar is phenyl, optionally substituted by C_{1-6} alkyl or halogen; thienyl or a C_{5-7} cycloalkdienyl group; R is C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyl or hydroxy C_{1-6} alkyl; R_1 and R_2 are each hydrogen or C_{1-6} alkyl; R_3 is hydrogen, hydroxy, halogen, C_{1-6} alkoxy or C_{1-6} alkyl; R_4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, anino, halogen, aminoalkoxy, mono- or di-alkylaminoalkoxy, mono- or di-alkylaminoalkyl, phthaloylalkoxy, mono- or di-alkylaminoacylarnino or acylamino; R_5 is phenyl, thienyl, furyl, pyrryl or thiazolyl, and X is oxygen.

X is O, S, or N—C≡N.

54 Claims, No Drawings

Compounds of formula (III), (IIId) and (IIIe) are commercially available compounds or can be prepared from known compounds by known methods (for example, compounds of formula (III) in which R' is alkoxycarbonyl, R'_1 and R'_2 are hydrogen and Ar' is as defined for the compounds of formula (I), are described in *Liebigs Ann. der Chemie*, 523, 199, 1936).

The activity of the compounds of formula (I) as NK_3 receptor antagonists in standard tests indicates that they are of potential therapeutic utility in the treatment of both the Primary and Secondary Disorders herein before referred to. The discovery that NK_3 receptor antagonists have potential therapeutic utility in treating the Secondary Disorders is new, and in a further aspect of the present invention there is provided the use of an NK_3 receptor antagonist for the treatment of the Secondary Disorders. There is also provided the use of an NK_3 receptor antagonist in the manufacture of a medicament for the treatment of any of the Secondary Disorders. The present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Disorders.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner. These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the

inflammation, inflammatory pain, eating disorders, allergic rhinitis, neurodegenerative disorders, psoriasis, Huntington's disease, and depression in mammals, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I), or a solvate or salt thereof, as defined in claim 23.

29. The method according to claim 28, wherein the pulmonary disorder is asthma.

30. The method according to claim 28, wherein the pulmonary disorder is chronic obstructive pulmonary disease.

31. The method according to claim 28, wherein the pulmonary disorder is airway hyperreactivity.

32. The method according to claim 28, wherein the pulmonary disorder is cough.

33. The method according to claim 28, wherein the skin disorder is atopic dermatitis.

34. The method according to claim 28, wherein the skin disorder is cutaneous wheal and flare.

35. The method according to claim 28, wherein the CNS disorder is Parkinson's disease.

36. The method according to claim 28, wherein the CNS disorder comprises movement disorders.

37. The method according to claim 28, wherein the CNS disorder is anxiety.

38. The method according to claim 28, wherein the eating disorder is food intake inhibition.

39. The method according to claim 28, wherein the neurodegenerative disorder is Alzheimer's disease.

40. (−)-(S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide or a salt or solvate thereof.

41. A pharmaceutical composition comprising a compound according to claim 40 or a pharmaceutically acceptable a salt or solvate thereof and a pharmaceutically acceptable carrier.

42. A method for the treatment and/or prophylaxis of pulmonary disorders, skin disorders and itch, neurogenic inflammation and CNS disorders, convulsive disorders, epilepsy, renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders, allergic rhinitis, neurodegenerative disorders, psoriasis, Huntington's disease, and depression in mammals, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, pharmaceutically acceptable, and non-toxic amount of a compound of formula (I), or a solvate or salt thereof, as defined in claim 40.

43. The method according to claim 42, wherein the pulmonary disorder is asthma.

44. The method according to claim 42, wherein the pulmonary disorder is chronic obstructive pulmonary disease.

45. The method according to claim 42, wherein the pulmonary disorder is airway hyperreactivity.

46. The method according to claim 42, wherein the pulmonary disorder is cough.

47. The method according to claim 42, wherein the skin disorder is atopic dermatitis.

48. The method according to claim 42, wherein the skin disorder is cutaneous wheal and flare.

49. The method according to claim 42, wherein the CNS disorder is Parkinson's disease.

50. The method according to claim 42, wherein the CNS disorder comprises movement disorders.

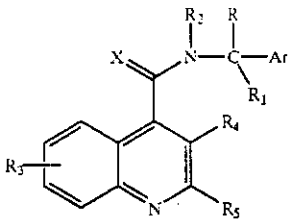
51. The method according to claim 42, wherein the CNS disorder is anxiety.

52. The method according to claim 42, wherein the eating disorder is food intake inhibition.

53. The method according to claim 42, wherein the neurodegenerative disorder is Alzheimer's disease.

54. A compound, or solvate or salt thereof, of formula (I):

(I)



in which:

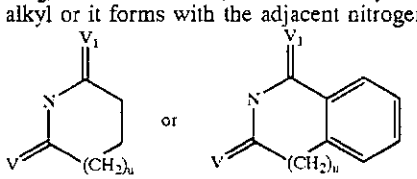
Ar is an optionally substituted phenyl group, or a naphthyl or C_{5-7} cycloalkdienyl group, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

R is linear or branched C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, an optionally substituted phenyl group or a phenyl C_{1-6} alkyl group, an optionally substituted five-membered heteroaromatic ring comprising up to four heteroatoms selected from O and N, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkylaminoalkyl, di C_{1-6} alkylaminoalkyl, C_{1-6} acylaminoalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylcarbonyl, carboxy, C_{1-6} alkoxyxcarbonyl, C_{1-6} alkoxycarbonyl C_{1-6} alkyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, halogeno C_{1-6} alkyl; or is a group $—(CH_2)_p—$ when cyclized onto Ar, where p is 2 or 3;

R_1 is hydrogen or C_{1-6} linear or branched alkyl, or together with R_2 form a $—(CH_2)n—$ group in which n represents 3, 4, or 5; R_1 together with R forms a group $—(CH_2)_q—$, in which q is 2, 3, 4 or 5;

R_2 is hydrogen;

R_3 is hydrogen, C_{1-6} linear or branched alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino, mono- and di-C_{1-6} alkylamino, $—O(CH_2)_r—NT_2$, in which r is 2, 3, or 4 and T is hydrogen or C_{1-6} alkyl or it forms with the adjacent nitrogen a group



in which V and V_1 are independently hydrogen or oxygen and u is 0,1 or 2; $—O(CH_2)_s—OW_2$ in which s is 2, 3, or 4 and W is hydrogen or C_{1-6} alkyl; hydroxyalkyl, aminoalkyl, mono-or di-alkylaminoalkyl, acylamino, alkylsulphonylamino, aminoacylamino, mono- or di-alkylaminoacylamino; with up to four R_3 substituents being present in the quinoline nucleus;

R_4 is hydroxy;

R_5 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted aryl, wherein an optional substituent is hydroxy, halogen, C_{1-6} alkoxy or C_{1-6} alkyl, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

X is O, S, or N—C≡N.

* * * * *

US006696084B2

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

(10) **Patent No.: US 6,696,084 B2**
(45) **Date of Patent: Feb. 24, 2004**

(54) **SPRAY DRYING PROCESS AND COMPOSITIONS OF FENOFIBRATE**

(75) Inventors: **Gary W. Pace**, Winchester, MA (US); **Awadesh K. Mishra**, Quebec (CA); **Robert A. Snow**, West Chester, PA (US); **Indu Parikh**, Durham, NC (US); **Pol-Henri W. Guivarc'h**, Quebec (CA)

(73) Assignee: **RTP Pharma Inc.**, Durham, NC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 144 days.

(21) Appl. No.: **09/838,593**

(22) Filed: **Apr. 20, 2001**

(65) **Prior Publication Data**

US 2002/0056206 A1 May 16, 2002

Related U.S. Application Data

(60) Provisional application No. 60/270,157, filed on Feb. 22, 2001, provisional application No. 60/241,761, filed on Oct. 20, 2000, and provisional application No. 60/234,186, filed on Sep. 20, 2000.

(51) **Int. Cl.**[7] **A61K 9/14**; A61K 9/20; A61K 9/48

(52) **U.S. Cl.** **424/451**; 424/458; 424/464; 424/469; 424/470; 424/489; 424/490; 252/363.5

(58) **Field of Search** 424/489, 490, 424/493–498, 451, 458, 464, 469, 470; 252/303, 314, 363.5; 514/78

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,700,471	A		12/1997	End et al.
5,827,536	A	*	10/1998	Laruelle
5,922,355	A	*	7/1999	Parikh

FOREIGN PATENT DOCUMENTS

EP	0 807 431 A2	11/1997
WO	WO 00/30616	6/2000
WO	WO 00/37078	6/2000

* cited by examiner

Primary Examiner—Gollamudi S. Kishore
(74) *Attorney, Agent, or Firm*—Edwards & Angell, LLP

(57) **ABSTRACT**

The present invention relates to a novel spray drying process for the preparation of pharmaceutical compositions containing small particles of phospholipid-stabilized fenofibrate. This invention also relates to spray dried powdered compositions prepared according to this process, and to dosage forms of fenofibrate (capsules, tablets, powders, granules, and dispersions) prepared from these powdered compositions. The powdered compositions and dosage forms are useful in the treatment of dyslipidemia and dyslipoproteinemia and have the advantage that they provide reduced in vivo variability in the bioavailability of fenofibrate active species among fed and fasted patients when administered orally.

60 Claims, No Drawings

A spray-dried solid form of fenofibrate microparticles is useful in formation of drug delivery compositions including capsules, tablets, powders, granules, and formulations with additional excipients and drugs.

Compositions of microfluidized fenofibrate stabilized with a phospholipid surface active agent prepared according to this invention and formulated according to this invention provide substantial reduction to elimination of the food effect that is observed with other formulations of fenofibrate.

Examples of some suitable surface active substances that are useful in the microfluidization process of this invention include: (a) natural surfactants such as casein, gelatin, tragacanth, waxes, enteric resins, paraffin, acacia, gelatin, cholesterol esters and triglycerides, (b) nonionic surfactants such as polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, polyvinylpyrrolidone, and synthetic phospholipids, (c) anionic surfactants such as potassium laurate, triethanolamine stearate, sodium lauryl sulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, negatively charged phospholipids (phosphatidyl glycerol, phosphatidyl inosite, phosphatidylserine, phosphatidic acid and their salts), and negatively charged glyceryl esters, sodium carboxymethylcellulose, and calcium carboxymethylcellulose, (d) cationic surfactants such as quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride, (e) colloidal clays such as bentonite and veegum. A detailed description of these surfactants may be found in Remington's Pharmaceutical Sciences, and Theory and Practice of Industrial Pharmacy, Lachman et al, 1986.

More specifically, examples of suitable surface active substances in addition to a phospholipid useful in this invention include one or combination of the following: polaxomers, such as Pluronic™ F68, F108 and F127, which are block copolymers of ethylene oxide and propylene oxide available from BASF, and poloxamines, such as Tetronic™ 908 (T908), which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylene-diamine available from BASF, Triton™ X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas. Tween 20, 40, 60 and 80, which are polyoxyethylene sorbitan fatty acid esters, available from ICI Speciality Chemicals, Carbowax™ 3550 and 934, which are polyethylene glycols available from Union Carbide, hydroxy propylmethylcellulose, dimyristoyl phosphatidylglycerol sodium salt, sodium dodecylsulfate, sodium deoxycholate, and cetyltrimethylammonium bromide. These are all pharmaceutically acceptable surface active substances.

Preferred surface active substances are phospholipid surface active substances. By phospholipid surface active substances or phospholipid surface active agents is meant a single phospholipid or a mixture of two or more phospholipids, for example a mixture of two or three or four or five or from six to about ten phospholipids. Suitable phospholipids include animal and plant phospholipids; egg phospholipids; soya bean phospholipids; corn phospholipids; wheat germ, flax, cotton, and sunflower seed phospholipids; milk fat phospholipids; glycerophospholipids; sphingophospholipids; phosphatides; phospholipids containing fatty acid esters including palmitate, stearate, oleate, linoleate, and arachidonate which esters can be mixtures and mixtures of isomers in the phospholipids; phospholipids composed of fatty acids containing one or more than one double bonds such as dioleoyl phosphatidylcholine and egg phosphatidylcholine that are not stable as powders but are hygroscopic and can absorb moisture and become gummy; phospholipids composed of saturated fatty acids that are stable as powders and are less amenable to absorption of moisture; phosphatidylserines; phosphatidylcholines; phosphatidylethanolamines; phosphatidylinositols; phosphatidylglycerols such as dimyristoyl phosphatidylglycerol, L-alpha-dimyristoyl phosphatidylglycerol also known as 1,2-dimyristoyl-sn-glycero-3-phospho(rac-1-glycerol) and also known as DMPG; phosphatidic acid; hydrogenated natural phospholipids; and commercially available phospholipids such as those available from Avanti Polar Lipids, Inc. of Alabaster, Alabama, USA. In the absence of an internal counterion in the phospholipid, a preferred counterion is a monovalent cation such as sodium ion. The phospholipid may be salted or desalted, hydrogenated, partially hydrogenated, or unsaturated, natural, synthetic, or semisynthetic.

Preferred phospholipids include Lipoid E80, Lipoid EPC, Lipoid SPC, DMPG, Phospholipon 100H a hydrogenated soybean phosphatidylcholine, Phospholipon 90H, Lipoid SPC-3, and mixtures thereof. A currently most preferred phospholipid is Lipoid E80.

The concentration of surface active substance added to the formulations prepared according to this invention can be present in the range of 0.1 to 50%, preferably 0.2 to 20%, and more preferably 0.5 to 10%. A currently preferred level of Lipoid E80 is from about 0.5% to 15%, more preferably from about 0.5% to about 10%, and most preferably from 0.5 to 5%.

In a preferred aspect, a process is provided for the preparation of small particles or microparticles containing fenofibrate and a phospholipid surface stabilizing substance which comprises the steps of:

(a) mixing at high shear an admixture of fenofibrate and a phospholipid substance in an aqueous carrier in the absence of an organic solvent and optionally in the presence of one or more than one surface active substances within a first temperature range at or above the melting point of the drug to form a heated suspension containing the drug, then

(b) homogenizing said heated suspension in a first pressure range and within said first temperature range to form a heated homogenate containing the drug, then

(c) spray drying the heated homogenate to form dried small particles containing the drug wherein one or more bulking agents is added at any stage of either of steps (a) or (b) and wherein at least one surface active agent is a phospholipid.

In a specific aspect, the present invention is directed to a composition and a process for the preparation of microparticles of fenofibrate, which small particles are used to prepare an orally administered pharmaceutical composition comprising said microparticles of solid fenofibrate that are stabilized by a phospholipid surface active substance, wherein said microparticles are prepared in the presence of said phospholipid surface active substance, and wherein a therapeutically effective amount of said composition provides a quantity of fenofibrate active species to a fasted human patient in need of treatment by fenofibrate that is greater than 80% of the quantity of fenofibrate active species

For a combination comprising fenofibrate prepared according to this invention and atorvastatin, the amount of atorvastatin in a dosage form of this invention is in the range of 2 mg to 100 mg although preferably it will be from 5 to 80 mg, and more preferably from 5 to 20 mg.

For a combination comprising fenofibrate prepared according to this invention and rosuvastatin, the amount of rosuvastatin in a dosage form of this invention is in the range of 2 mg to about 80 mg although preferably it will be from 5 to 20 mg.

For a combination comprising fenofibrate prepared according to this invention and fluvastatin, the amount of fluvastatin in a dosage form of this invention is in the range of 2 mg to 50 mg although preferably it will be from 20 to 40 mg.

For a combination comprising fenofibrate prepared according to this invention and itavastatin, the amount of itavastatin in a dosage form of this invention is in the range of 0.1 to about 20 mg although preferably it will be from 2 to 10 mg.

For a combination comprising fenofibrate prepared according to this invention and cerivastatin, the amount of cerivastatin in a dosage form of this invention is in the range of 0.02 mg to 1.2 mg although preferably it will be from 0.2 to 0.8 mg.

An admixture of fenofibrate and a phospholipid surface active substance can be prepared by adding a phospholipid substance and fenofibrate to an aqueous carrier and then mixing at high shear for up to 30 minutes at a shear rate of up to 10,000 rpm. Preferably fenofibrate used to form the admixture is in the form of a powder or small crystals or small pieces that are less than about 5 mm in diameter to facilitate mixing. Larger sized crystals or masses of drug can be milled to about 5 mm or smaller before forming the admixture used in this invention to facilitate mixing.

Suitable aqueous carriers include water, sterile water, water for injection, and buffered water such as phosphate buffered water. The pH of the buffer can be in the range of from 4 to 10, preferably from 7 to 9, and most preferably from 7.5 to 8.5. A preferred aqueous carrier is 0.01 to 10 mM sodium phosphate buffer. The pH of the carrier is preferably established at room temperature before mixing with the phospholipid substance and the fenofibrate and before heating to a first temperature. The pH may be adjusted by addition of an acid or base such as HCl or NaOH to a solution of a phosphate salt. Preferably the aqueous carrier contains no dissolved oxygen. A currently most preferred aqueous carrier is 10 mM phosphate buffer.

In one aspect, the aqueous carrier can initially be at a temperature between about 1° C. to about 100° C., preferably between 20° C. and 90° C., and more preferably between 20° C. and 50° C. This is particularly useful for fenofibrate. The aqueous carrier can be heated to the desired first temperature range before or after the addition of the admixture.

After the fenofibrate and a phospholipid substance are added to the aqueous carrier, the admixture can then be heated if not already so, preferably in the absence of oxygen such as under a nitrogen or argon atmosphere, until the temperature rises to a first temperature range that is at or above the melting point of the drug. In the case of fenofibrate the admixture in the aqueous carrier can be heated to between 79° C. (the reported lowest melting point of fenofibrate) and 99° C., preferably between 79° C. and 95° C., and most preferably between 80° C. and 90° C. It is preferred that the temperature is at or up to about 20° C. above the melting point of the drug. Thus, the preferred first temperature range is in general from the melting point of the drug to about 20° C. above the melting point of the drug. The aqueous carrier can be heated to the first temperature range before or after the addition of the drug and the surface active substance. The admixture is maintained at the first temperature range while high shear mixing is applied. The admixture when thus prepared comprises a crude emulsion of melted drug and surface active substance in the heated aqueous carrier.

During the heating of the admixture, high shear mixing is applied. Suitable shear is derived for example from propeller-containing mixers, homogenizers, blenders, sonicators or other devices capable of producing a heated suspension. Suitable shear rates can range between 500 to 10,000 rpm, preferably 2,000 to 5,000 rpm. High shear mixing can be continued for up to 30 minutes or even longer if needed to form a heated suspension containing the drug. High shear mixing of the admixture when the temperature is below the melting point of the drug provides a suspension of the admixture in the aqueous carrier, and such suspension is useful as an antecedent to the heated suspension that is produced when the temperature is increased to or above the melting point of the drug. Continued application of high shear mixing or application of more vigorous or ultra-high shear mixing when the temperature is above the melting point of the drug can produce a heated homogenate of the admixture in the aqueous carrier. When the temperature is above the melting point of the drug, the heated suspension is a suspension of melted drug and surface active substance in the aqueous carrier. In one aspect, the heated suspension is an emulsion of melted drug and surface active substance in the aqueous carrier. High shear mixing and ultra-high shear mixing can be produced by the input of mechanical energy for example using a mechanical mixer or stirrer or mill configured with a mixing blade or propeller that can induce efficient mixing and particle size reduction through high shear turbulence, turbulent eddies, transfer of high fluid kinetic energy, high energy dissipation, pressure induced cavitation, and similar known mechanisms of homogenization.

In one aspect, devices useful in the preparation of a heated suspension of this invention can be employed in the preparation of the heated homogenate of this invention if sufficient energy is transferred to the particles of the heated suspension to produce a heated homogenate. In this case, heating of the admixture to form a heated suspension and then homogenization of the heated suspension to form a heated homogenate can be done as a continuous step combining step (a) and step (b) into a single step wherein a heated suspension is formed and then converted into a heated homogenate with out substantial change in apparatus or without substantial increase in energy applied to the heated admixture formulation.

Preferably one or more bulking agents is added during step (a) and/or during step (b).

As used herein, homogenization refers to the creation of a homogenate or uniform distribution of small particles containing drug in an aqueous carrier as a result of an energetic process being applied to an antecedent composition such as a mixture, admixture, blend, emulsion, suspension, dispersion or other composition of solids or solid particles or liquids or liquid particles or droplets comprising drug and one or more than one surface active substance in an aqueous carrier wherein the homogenate and the small particles produced are at least transiently stable toward phase separation into larger particles or droplets or non-uniform solid or liquid domains. Homogenization, par-

67 mg
100 mg
102 mg
104 mg
106 mg
134 mg
150 mg
153 mg
156 mg
159 mg
160 mg
200 mg
213 mg
250 mg
300 mg

EXAMPLE 6

The following formulations are prepared according to the method of example 1 leading to a heated homogenate before drying consisting of:

21-1) 9% fenofibrate, 3% Lipoid E80, 10% sucrose;
21-2) 10% fenofibrate, 3% Lipoid E80, 12% sucrose, 5% sorbitol;
21-3) 10% fenofibrate, 3.5% Lipoid E80, 12% sucrose, 1% sorbitol;
21-4) 9% fenofibrate, 2.7% Lipoid E80, 19% sucrose, 4.5% sorbitol.

The formulations are spray dried in a commercially available spray dryer consisting of a chamber with inside diameter of 1.22 meters and a cylindrical height of 1.14 meters with a 60° conical bottom. Electrically heated air is used as the process gas admitted via a ceiling disperser. Each spray dried formulation is isolated initially as a dried powder that can be handled in a dry atmosphere without caking.

EXAMPLE 7

A mixture of Lipoid E80 and fenofibrate is homogeneously dispersed in 10 mM pH 8.0+/−0.2 aqueous phosphate buffer using a ProScientific 400 high shear mixer at 2,000 to 3,600 rpm at ambient temperature for 30 minutes, and then heated to 95° C., 15° C. above the melting point of the drug, during continuous high shear mixing at 2,500 to 4,000 rpm. The heated suspension is then batchwise homogenized in 3 to 10 batch volume cycles using a Microfluidizer M110Y operated at 3,400 to 3,600 psig while maintained at 85° C. to 99° C. to form a heated homogenate containing the drug. The heated homogenate is then treated with bulking agents and excipients listed in the table below, mixed at the molten fenofibrate temperature, and then dried by spray drying in the molten state. The following compositions (in wt %) are prepared by this method.

Suspension No.	Fenofibrate	Lipoid E80	Sucrose	Mannitol	Ac-Di-Sol	Cab-O-Sil (colloidal silica)
7-a	10.0	0.5	17.5			
7-b	10.0	0.5	17.5		1.8	
7-c	10.0	0.5	17.5			0.5
7-d	10.0	0.5	7		3	0.5
7-e	10.0	0.5		7	3	0.5
7-f	10.0	0.5	17.5		1.8	0.5

Spray dried powders (100 parts) are blended with excipients Avicel-PH102 (18.5 parts), Ac-Di-Sol (3.95 parts), Cab-O-Sil (0.62 parts), and magnesium stearate (0.25 parts), processed into 1 mm granules or slugs by preliminary compression of the blend followed by crushing and sieving (USP Standard #14 sieve), blended with additional magnesium stearate, and then compressed into tablet dosage forms. Hardness of the tablets produced in different batches ranges from 2 to 9 KPa either in an automatic tableting machine or by manual compression using a CMS-15 tablet press (Cadmach Machinaries).

What is claimed is:

1. A process for the preparation of small particles or microparticles containing fenofibrate and a phospholipid surface stabilizing substance comprising the steps of:
   a) mixing at high shear an admixture of fenofibrate and a phospholipid in an aqueous carrier in the absence of an organic solvent and optionally in the presence of one or more than one surface active substances within a temperature range at or above the melting point of the fenofibrate to form a heated suspension containing the fenofibrate, then
   b) homogenizing said heated suspension in a pressure range and within said temperature range to form a heated homogenate containing the fenofibrate then
   c) spray drying the heated homogenate to form dried small particles containing the fenofibrate wherein one or more bulking agents is added at any stage of either of steps (a) or (b) and wherein at least one surface active agent is a phospholipid.

2. The process of claim 1 wherein the bulking agent is selected from the group consisting of a monosaccharide, a disaccharide, a trisaccharide, lactose, mannitol, sorbitol, trehalose, glycerol, dextrose, fructose, xylitol, and mixtures thereof.

3. The process of claim 1 wherein the bulking agent is selected from the group consisting of sucrose, lactose, mannitol, sorbitol, trehalose, and mixtures thereof.

4. The process of claim 1 wherein the surface active agent is a phospholipid selected from the group consisting of Lipoid E80, Lipoid EPC, Lipoid SPC, DMPG, Phospholipon 100H, Lipoid SPC-3, and mixtures thereof.

5. The process of claim 1 wherein the surface active agent is Lipoid E80.

6. The process of claim 1 wherein the temperature range is from the melting point of fenofibrate to 20° C. higher than the melting point of fenofibrate.

7. The process of claim 1 wherein the aqueous carrier is selected from the group consisting of water and buffered water wherein the pH of the buffer is from 4 to 10.

8. The process of claim 1 wherein the aqueous carrier is phosphate buffered water having a pH from 7 to 9.

9. The process of claim 1 wherein the aqueous carrier is phosphate buffered water having a pH from 7.5 to 8 5.

10. The process of claim 1 wherein the pressure range is from 2,000 to 30,000 psi.

11. The process of claim 1 wherein the small particles containing fenofibrate have an average size in the range from 0.1 to 10 micrometers.

12. The process of claim 1 wherein the small particles containing fenofibrate have an average size in the range from 0.1 to 5 micrometers.

13. The process of claim 1 wherein the small particles containing fenofibrate have an average size in the range from 0.1 to 2 micrometers.

14. A composition comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance that is prepared according to the process of claim 1 further containing from 0.1 to about 5% water.

15. An orally administered pharmaceutical composition comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance prepared according to the process of claim 1, wherein a therapeutically effective amount of said pharmaceutical composition provides a quantity of fenofibrate active species to a fasted human patient in need of treatment by said fenofibrate that is greater than 90% of the quantity of said fenofibrate active species provided by said amount to said patient when fed a high fat meal.

16. A capsule or tablet or powder or granular dosage form for oral administration comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance prepared according to the process of claim 1 wherein said amount of said dosage form provides a level of fibrate active species into the blood of a patient in a fasted state that differs by less than 25% of the level of said fibrate active species that said patient receives in a fed state.

17. A capsule or tablet or powder or granular dosage form for oral administration comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance prepared according to the process of claim 1 wherein said amount of said dosage form provides a level of fibrate active species into the blood of a patient in a fasted state that differs by less than 20% of the level of said fibrate active species that said patient receives in a fed state.

18. A capsule or tablet or powder or granular dosage form for oral administration comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance prepared according to the process of claim 1 wherein said amount of said dosage form provides a level of fibrate active species into the blood of a patient in a fasted state that differs by less than 15% of the level of said fibrate active species that said patient receives in a fed state.

19. A capsule or tablet or powder or granular dosage form for oral administration comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance prepared according to the process of claim 1 wherein said amount of said dosage form provides a level of fibrate active species into the blood of a patient in a fasted state that differs by less than 10% of the level of said fibrate active species that said patient receives in a fed state.

20. A capsule or tablet or powder or granular dosage form for oral administration comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance prepared according to the process of claim 1 wherein said amount of said dosage form provides a level of fibrate active species into the blood of a patient in a fasted state that differs by less than 5% of the level of said fibrate active species that said patient receives in a fed state.

21. A tablet dosage form of claim 16 that further comprises a dried film-coating formed by application of a water based solution the dosage form.

22. A tablet dosage form of claim 16 that further comprises a pharmaceutically acceptable polymer in a coating.

23. A tablet dosage form claim 16 that further comprises a pharmaceutically acceptable carbohydrate in a coating.

24. The tablet dosage form of claim 23 where the carbohydrate in the coating is a sugar.

25. The dosage form of claim 16 further comprising one or more excipients selected from the group consisting of monosaccharides, disaccharides, disaccharides, raffinose, lactose, mannitol, sorbitol, trehalose, glycerol, dextrose, maltodextrose, fructose, xylitol, and mixtures thereof.

26. The dosage form of claim 16 wherein the phospholipid surface stabilizing substance comprises a mixture of phospholipids.

27. The dosage form of claim 16 wherein the phospholipid surface stabilizing substance is selected from the group consisting of egg phospholipid, Lipoid E80, Lipoid EPC, Lipoid SPC, DMPG, Phospholipon 100H, a hydrogenated soybean phosphatidylcholine, Phospholipon 90H, Lipoid SPC-3, and mixtures thereof.

28. The dosage form of claim 16 wherein the fenofibrate is crystalline.

29. The dosage form of claim 16 wherein the microparticles are smaller than 5 micrometers.

30. The dosage form of claim 16 wherein the microparticles are smaller than 4 micrometers.

31. The dosage form of claim 16 wherein the microparticles are smaller than 3 micrometers.

32. The dosage form of claim 16 wherein the microparticles are smaller than 2 micrometers.

33. The dosage form of claim 16 wherein the microparticles are smaller than 1 micrometers.

34. The dosage form of claim 16 to further containing from 0.1 to about 5% water.

35. The dosage form of claim 16 wherein the therapeutically effective amount is selected from the group consisting of 50 mg of fenofibrate, 51 mg of fenofibrate, 52 mg of fenofibrate, 53 mg of fenofibrate, 54 mg of fenofibrate, 67 mg of fenofibrate, 100 mg of fenofibrate, 102 mg of fenofibrate, 103 mg of fenofibrate, 104 mg of fenofibrate, 134 mg of fenofibrate, 150 mg of fenofibrate, 153 mg of fenofibrate, 156 mg of fenofibrate, 159 mg of fenofibrate, 160 mg of fenofibrate, 200 mg of fenofibrate, 213 mg of fenofibrate, 250 mg of fenofibrate, and 300 mg of fenofibrate.

36. An orally administered pharmaceutical composition comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance prepared according to the process of claim 1 wherein a therapeutically effective amount of said orally administered pharmaceutical composition provides a quantity of fenofibrate active species to a fasted human patient in need of treatment by fenofibrate that is greater than 85% of the quantity of fenofibrate active species provided by said amount to said patient when fed at least 1000 calories 50% of which are from fat.

37. An orally administered pharmaceutical composition comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance prepared according to the process of claim 1 wherein a therapeutically effective amount of said orally administered pharmaceutical composition provides a quantity of fenofibrate active species to a fasted human patient in need of treatment by fenofibrate that is greater than 90% of the quantity of fenofibrate active species provided by said amount to said patient when fed at least 1000 calories 50% of which are from fat.

38. An orally administered pharmaceutical composition comprising microparticles containing fenofibrate and a phospholipid surface stabilizing substance prepared according to the process of claim 1 wherein a therapeutically

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE
Apoderado

ASUNTO

Radicación	06-096376
Trámite	002
Evento	001
Actuación	430
Oficio	3070
Folios	11

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap.I ☒ Cap. II ☐

No. Sol. Internacional PCT/US2005/010350
Fecha de Presentación Internal. 28/03/2005

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: 28 a 44 y 174 como se radicó inicialmente

Reivindicaciones: Folios 45 a 48 como se radicó inicialmente

Prioridad: Folios: 01
30/03/2004, US, 60/557.571

2. Objeto de la Invención

Titulo de la invención: Composiciones farmacéuticas secadas por atomización

Problema Técnico Planteado: cómo obtener composiciones farmacéuticas de talnentanto por atomización con la recuperación completa del tamaño de partículas

Solución: Un proceso de preparación de una composición de talnentanto por atomización

IPC: A61K 9/16, 31/47

3. De la solicitud de Patente

Reivindicaciones *(artículo 30 D 486)*
La reivindicación 1 no se encuentra de forma clara, puesto que se encuentran los elementos de la composición con los del proceso, sin tener concisión con el título de la solicitud.

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La reivindicación 19 se encuentra de forma independiente con respecto a la reivindicación 1.
La reivindicación 30 de formas de dosificación se encuentra caracterizada por la composición.
Las reivindicaciones 31 a 32 se encuentran caracterizadas por la forma de administración.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de presentación de la solicitud prioritaria: 30 de Marzo de 2004

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 30/03/2004 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

N°	Documento	Título	Fecha de publicación
D1	US 6,608,083	Quinoline derivatives (2)	19/08/2003
D2	US 6,696,084	Spray drying process compositions of fenofibrate	24/02/2004

7. Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en:

Un proceso para la preparación de una composición secada por atomización, la composición comprende i) partículas de talnentanto con un D_v90 en el rango entre 0.1 y 2.0µm, ii) uno o más surfactantes iónicos y iii) uno o más vehículos solubles, el proceso comprende a) la trituración en húmedo de una dispersión de partículas de talnentanto sólidas hasta Dv90 entre el rango entre 0.1 y 2.0µm, cuya dispersión comprende uno o más surfactantes iónicos y uno o más vehículos solubles, luego b) secado por atomización o granulación por atomización de la dispersión resultante.

El Estado de la Técnica más cercano es **D1**, que da a conocer composiciones del compuesto talnentanto (Ver columna 113, líneas 30-31) en formulaciones en spray que comprenden partículas micronizadas en combinación con un surfactante, solvente o un agente dispersante para prevenir la sedimentación de las partículas. Preferiblemente el tamaño de partícula, es cerca de de 2 a 10 micrones

La composición objeto de esta solicitud se diferencia de las composiciones de **D1**, en que el proceso de preparación no se encuentra descrito, y que las formulaciones objeto de invención poseen un D_v90 en el rango entre 0.1 y 2.0µm

El hecho de incluir el proceso de preparación para formulaciones de talnentanto que poseen un D_v90 en el rango entre 0.1 y 2.0µm por atomización que se daban a conocer en **D1**, causa la recuperación completa del tamaño de partículas.

El Problema Técnico Objetivo era "cómo obtener composiciones farmacéuticas de talnentanto por atomización con la recuperación completa del tamaño de partículas"

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D2 describe una manera de solucionar el problema técnico, un procedimiento de preparación para partículas entre el rango de 0.1 y 2.0µm (Ver columna 45, reivindicación 13), mediante molienda húmeda del fármaco en medio acuoso (Ver columna 26, líneas 60-66; ver columna 44, reivindicación 1; página 16, [0165] con el empleo de surfactantes iónicos (Ver columna 21, líneas 10-35) y un soporte en la composición y donde dicho proceso comprende la atomización de las partículas (spray-drying) (Ver columna 44, reivindicación 1)

La reivindicación es obvia, porque el Experto en la Materia enfrentado al problema de "obtener composiciones farmacéuticas de talnentanto por atomización con la recuperación completa del tamaño de partícula", incluiría "la molienda húmeda del fármaco en medio acuoso y su posterior atomización" cómo se revela en **D2**, con el fin de obtener el proceso de preparación de las composiciones que se enseñan en **D1**, logrando de esta forma el proceso y la composición objeto de esta solicitud. Por tanto, la reivindicación 1 no tiene Nivel Inventivo. Las reivindicaciones dependientes 2-32, no mencionan alguna característica que haga inventiva a la composición de la reivindicación 1, por lo cual se considera que no tienen nivel inventivo.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 6,608,083	1-32	Nivel Inventivo
D2	US 6,696,084	1-32	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
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 05 MAR. 2010

CONCEPTO TÉCNICO No. 0774	**EXAMINADOR TÉCNICO** Código No. 202070