

Bogotá, 26 de noviembre de 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Doctora
ALIX CESPEDES DE VERGEL
Jefe División Nuevas Creaciones
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Referencia: RAD. : 07-33189

Asunto: SUSTITUCIÓN DE PODER RESPECTO A LA SOLICITUD DE PATENTE DE INVENCION TITULADA "UNA PRESENTACION FARMACEUTICA EN FORMA DE CAPSULA BLANDA DE GELATINA QUE INCLUYE UN ANTAGONISTA DE LOS RECEPTORES DE ANGIOTENSINA II Y UN DIURETICO ASI COMO EL PROCESO PARA CONFORMAR DICHA PRESENTACION".

Solicitante: PROCAPS S.A.

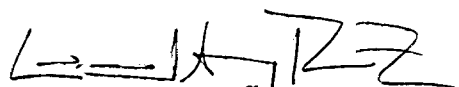
Cordial saludo,

De la manera más atenta solicito que se me reconozca como nuevo apoderado de la sociedad **PROCAPS S.A.** de acuerdo al poder anexo, para continuar el trámite de solicitud de patente de invención de la referencia.

Para tal efecto presento a usted el debido poder que me acredita en el presente asunto.

Favor tomar nota y proceder de conformidad

Cordialmente,


CIELO ANGELA PEÑA RODRIGUEZ
C.C. 51'940.252 de Bogotá
T.P.A. 82701 del C.S. de la J.

Doctora
ALIX CESPEDES DE VERGEL
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Referencia: SUSTITUCIÓN PODER
RAD. : 07-33189

Yo ELIANA ISAURA MORENO BOHÓRQUEZ, abogada en ejercicio, identificada como aparece al pie de mi firma, con tarjeta profesional No. 83823 del C.S. de la J., en mi calidad de APODERADA de PROCAPS S.A. en el trámite de la referencia, sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), manifiesto que en ejercicio de mis facultades, SUSTITUYO en los términos y condiciones el poder que me fue conferido, a la doctora CIELO ANGELA PEÑA RODRIGUEZ, abogada en ejercicio, con tarjeta profesional No. 82701 del C.S. de la J., para que continúe y lleve hasta su culminación el trámite de registro de **PATENTE DE INVENCION** radicado bajo el número de la referencia, denominado **"UNA PRESENTACION FARMACEUTICA EN FORMA DE CAPSULA BLANDA DE GELATINA QUE INCLUYE UN ANTAGONISTA DE LOS RECEPTORES DE ANGIOTENSINA II Y UN DIURETICO ASI COMO EL PROCESO PARA CONFORMAR DICHA PRESENTACION"**.

Dado y Firmado en Bogotá (Colombia) a los 9 días del mes de noviembre de 2009.

**NOTARIA PRIMERA DE CHIA
PRESENTACION PERSONAL**

Eliana Isaura Moreno Bohórquez

Este memorial dirigido a Superintendencia de Industria y Comercio,

ELIANA ISAURA MORENO BOHORQUEZ
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fué presentado personalmente ante el suscrito notario por
Eliana Isaura Moreno Bohórquez
Identificado C.C. 51'975.664 BA
T.P. de Abogado No. 83823. C.S.J.
Chía. 21 NOV. 2009

Acepto:

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US006197787B1

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

(10) **Patent No.:** US 6,197,787 B1

(45) **Date of Patent:** *Mar. 6, 2001

(54) **PHARMACEUTICAL FORMULATIONS
CONTAINING POORLY SOLUBLE DRUG
SUBSTANCES**

(75) **Inventors:** Nancy M. Franson, Collegeville;
Micael A. Guillot, Malvern; Sharon
M. Laughlin, Phoenixville; William L.
Rocco, Reading, all of PA (US)

(73) **Assignee:** Sanofi-Synthelabo, Paris (FR)

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

This patent is subject to a terminal dis-
claimer.

(21) **Appl. No.:** 09/410,600

(22) **Filed:** Oct. 1, 1999

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/028,504, filed on
Feb. 24, 1998, now abandoned, which is a continuation-in-
part of application No. 08/813,946, filed on Mar. 3, 1997,
now Pat. No. 5,837,714, which is a continuation-in-part of
application No. 08/808,761, filed on Mar. 3, 1997, now Pat.
No. 5,760,056, which is a continuation-in-part of application
No. 08/810,560, filed on Mar. 3, 1997, now Pat. No. 5,776,
987.

(51) **Int. Cl.** ⁷ A61K 31/70; A61K 31/4709;
A61K 31/1902; A61K 31/08

(52) **U.S. Cl.** 514/313; 514/23; 514/569;
514/723

(58) **Field of Search** 514/313, 569,
514/23, 723

(56) **References Cited**

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Primary Examiner—Phyllis G. Spivack

(74) *Attorney, Agent, or Firm*—Michael D. Alexander; Paul
E. Dupont

(57) **ABSTRACT**

A method for preparing pharmaceutical formulations of
poorly soluble drug substances in the form of concentrated
solutions for filling soft gelatin capsules and solid disper-
sions and suspensions for filling hard gelatin capsules and
compressing into tablets is provided. Pharmaceutical formu-
lations of poorly soluble drug substances are also disclosed.
The formulations include the sodium salt of the poorly
soluble drug substance, a conversion aid such as PEG,
polysorbate, a sugar alcohol (e.g. mannitol or xylitol),
propylene glycol or transcitol, and, in some cases an
excipient, such as dicalcium phosphate dihydrate, lactose
monohydrate, or microcrystalline cellulose.

50 Claims, No Drawings

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Ingredient	Composition mg/capsule
<u>SR48692 CAPSULE SOFT GELATIN 5MG</u> <u>SR48692 CAPSULE SOFT GELATIN 30MG</u>	
Polyethylene Glycol 400	1000
Sodium Hydroxide	2.50
Purified Water	96.4
SR48692	30
Soft Gelatin Capsule, White Opaque	
R.P. Scherer Capsule	
18 Oblong (Die Size W18BD)	
Gel Formula 005LSMH	
Color 911 P	1 Capsule
<u>SR48692 CAPSULE SOFT GELATIN 75MG</u>	
Polyethylene Glycol 400	969
Sodium Hydroxide	5.77
Purified Water	90.4
SR48692	75
Soft Gelatin Capsule, White Opaque	
R.P. Scherer Capsule	
18 Oblong (Die Size W18BD)	
Gel Formula 005LSMH	
Color 911 P	1 Capsule

IIb) In accordance with this embodiment of the present invention, the pharmaceutical formulations comprises a poorly soluble organic acid drug selected from the group consisting of: analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators and xanthines, propylene glycol; NaOH and water, wherein the mole equivalent of NaOH per mole equivalent of the poorly soluble drug is at least about 1.1.

Preferred drugs are SR48692 and Naproxyn.

The so-produced drugs are filled into soft gelatin capsules.

Example 9

<u>SR48692 CAPSULE SOFT GELATIN 5MG</u>	
Ingredient	Composition mg/capsule
Propylene Glycol	1020
Sodium Hydroxide	0.500
Purified Water	100
SR48692	5
Soft Gelatin Capsule, White Opaque	
R.P. Scherer Capsule	
18 Oblong (Die Size W18BD)	
Gel Formula 005LSMH	
Color 911 P	1 Capsule

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Example 10

<u>SR48692 CAPSULE SOFT GELATIN 30MG</u>	
Ingredient	Composition mg/capsule
Propylene Glycol	1000
Sodium Hydroxide	2.50
Purified Water	96.4
SR48692	30
Soft Gelatin Capsule, White Opaque	
R.P. Scherer Capsule	
18 Oblong (Die Size W18BD)	
Gel Formula 005LSMH	
Color 911 P	1 Capsule

Example 11

<u>SR48692 CAPSULE SOFT GELATIN 75MG</u>	
Ingredient	Composition mg/capsule
Propylene Glycol	969
Sodium Hydroxide	5.77
Purified Water	90.4
Soft Gelatin Capsule, White Opaque	
R.P. Scherer Capsule	
18 Oblong (Die Size W18BD)	
Gel Formula 005LSMH	
Color 911 P	1 Capsule

Suspensions IIIA and IIIB

IIIA) We have discovered a solvent system for SR48692 which produces a highly concentrated suspension of the active ingredient suitable for a hard gelatin capsule filling.

More specifically, there is provided a pharmaceutical formulation comprising:

0.1 to 40% by weight of SR48692;

0.1 to 40% by weight of Transcutol;

0.1 to 99% by weight starch;

NaOH; and

H₂O.

The SR48692 can be present in an amount up to 40%, preferably 0.1-35% and more preferably 0.5-30% by weight.

The Transcutol is present in an amount of 0.1 to 40%, preferably 0.5 to 35% and most preferably, 1 to 30% by weight of the solid dispersion. Transcutol is commercially available and/or can be prepared by techniques well known to those skilled in the art.

The starch can be present in an amount of 0.1-99% by weight. Starches which have previously been used in pharmaceutical formulations are preferred for use herein. The starch can be pre-gelatinized, i.e., chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. Suitable USP/NF starches are described in the Handbook of Pharmaceutical Excipients, Second Edition published jointly by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain, The Pharmaceutical Press, 1994. A preferred starch is Starch 1500, commercially available from Colorcon.

The suspension can comprise 0.1-20%, preferably 0.5-15% and more preferably 1-13% water. Higher amounts of water tend to soften and/or dissolve the gelatin capsules shells.

SR48692 was added slowly to allow wetting, but during last quarter of addition of SR48692 the mixture became very doughy, so 0.83 g of water was added to make mixture more "liquid" state. Mixed for 30 minutes (alternated between hand kneading with spatula and mixing with Lightnn' mixer. The speed was adjusted depending on how much was needed to mix the mixture, and the mixer was raised and lowered while mixing. The reaction was very difficult to mix, and the mixer was unable to readily mix the reaction. After refrigeration at 5° C. for 10 minutes, the mixture was broken into pieces, ground in a coffee grinder and mixed to powder. FTIR confirmed Na salt conversion, but mixing remained a serious obstacle in terms of processing.

Having described the invention with reference to its preferred embodiments, it is to be understood that modifications within the scope of the invention will be apparent to those skilled in the art

What is claimed is:

1. A pharmaceutical formulation in the form of a solid dispersion comprising:

a) a poorly soluble organic acid drug substance selected from the group consisting of: analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators and xanthines;

b) propylene glycol;

c) a sufficient quantity of a solid diluent selected from the group consisting of xylitol, dicalcium phosphate dihydrate, and lactose monohydrate/microcrystalline cellulose to provide a solid dispersion.

2. The pharmaceutical formulation of claim 1 wherein said drug substance is SR48692.

3. The pharmaceutical formulation of claim 1 further comprising a base.

4. The pharmaceutical formulation of claim 1 wherein said drug substance is Naproxyn.

5. The pharmaceutical formulation of claim 4 further comprising a base.

6. The pharmaceutical formulation of claim 1 further comprising a base.

7. A process of preparing a pharmaceutical formulation in the form of a solid dispersion comprising the steps of:

a) dissolving a poorly soluble organic acid drug substance in aqueous sodium hydroxide propylene glycol mixture to form a solution wherein said poorly soluble drug substance is selected from the group consisting of: analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral

agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators and xanthines; and

b) adding the solution to a sufficient quantity of a solid diluent selected from the group consisting of xylitol, dicalcium phosphate dihydrate, and lactose monohydrate and/or microcrystalline cellulose to provide a solid dispersion.

8. The process of claim 7 further comprises adding water or aqueous xylitol to said sodium hydroxide propylene glycol mixture in step (a).

9. The process of claim 7 wherein said drug substance is SR48692.

10. The process of claim 7 wherein said drug substance is Naproxyn.

11. A concentrated drug solution for soft gelatin capsule filling consisting essentially of:

a) a poorly soluble organic acid drug selected from the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators and xanthines;

b) propylene glycol;

c) sodium hydroxide; and

d) water;

wherein the mole equivalent of sodium hydroxide per mole equivalent of the poorly soluble drug is at least 1.1.

12. The concentrated drug solution of claim 11 wherein said poorly soluble drug is SR48692.

13. The concentrated drug solution of claim 12 wherein the ratio of mole equivalents of sodium hydroxide per mole equivalent of SR48692 is at least 1.2.

14. The concentrated drug solution of claim 11 wherein said poorly soluble drug is Naproxyn.

15. The concentrated drug solution of claim 14 wherein the ratio of mole equivalents of sodium hydroxide per mole equivalent of Naproxyn is at least 1.2.

16. The concentrated drug solution of claim 11 wherein the ratio of mole equivalents of sodium hydroxide per mole equivalent of said poorly soluble drug is at least 1.2.

17. A pharmaceutical formulation in a highly concentrated suspension form for a hard gelatin capsule filling comprising:

0.1 to 40% by weight of SR48692;

0.1 to 40% by weight propylene glycol;



US005219856A

United States Patent [19]
Olson

[11] **Patent Number:** **5,219,856**
[45] **Date of Patent:** **Jun. 15, 1993**

[54] **ANGIOTENSIN-II RECEPTOR BLOCKING,
HETEROCYCLE SUBSTITUTED
IMIDAZOLES**

[75] **Inventor:** **Richard E. Olson, Wilmington, Del.**

[73] **Assignee:** **E. I. du Pont de Nemours and
Company, Wilmington, Del.**

[21] **Appl. No.:** **863,881**

[22] **Filed:** **Apr. 6, 1992**

[51] **Int. Cl.⁵** **C07D 401/14; C07D 403/14;
A61K 31/495; A61K 31/535**

[52] **U.S. Cl.** **514/252; 544/364;
544/370; 544/337; 544/121; 514/85; 514/235.8**

[58] **Field of Search** **544/364, 370, 337, 121;
514/252, 85, 235.8**

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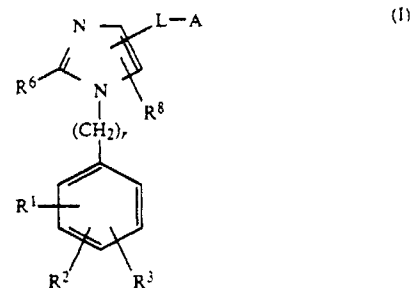
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Primary Examiner—Mary C. Lee
Assistant Examiner—Lenora A. Miltenberger

[57] ABSTRACT

Novel heterocycle substituted imidazoles of Formula (I), which are useful as angiotensin-II antagonists, are disclosed:



11 Claims, No Drawings