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FORMULARIO UNICO DE OPOSICION
2000-12

1 OPOSICION A:

- [x] Patente de Invención
- [ ] Patente de Modelo de Utilidad
- [ ] Diseño Industrial
- [ ] Esquema de Trazado para Circuitos Integrados
- [ ] Marcas de Productos o Servicios
- [ ] Marca Colectiva
- [ ] Marca de Certificación
- [ ] Lema Comercial

2 SOLICITUD PUBLICADA

Número del expediente: 08 007.949
Solicitante: PANACEA BIOTEC LTD.
Apoderado: JUAN PABLO CADENA SARMIENTO.
Título de la nueva creación o denominación del signo:
COMPOSICIONES FARMACÉUTICAS DE LIBERACIÓN MODIFICADA Y SUS PROCESOS.
Gaceta 602 de 31 de Marzo de 2009, Nº de publicación 1441.

3 OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: **Lafrancol S.A.** Dirección: **Carrera 1 No. 46-84** Teléfono: **(092) 449.30.51** Fax: Domicilio: **Cali – Valle**	**IDENTIFICACION** C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: **890 301 463 -8**
REPRESENTANTE O APODERADO (74)	Nombre: **José Luis Reyes Villamizar** Dirección: **Cra. 17 No. 88-23, Of. 205** Teléfono: **621.26.31** E-mail: **info@reyes-abogados.com** Fax: **621.25.42** Domicilio: **Bogotá, D.C.**	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: **79'152.473 de Usaquén** **TP 44655**

4 FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser suceptibles de aplicación industrial), 16, y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) .

Justificación: VER ANEXO

5 **Comprobante de pago No.** 09-43,452 (Oposición) **Fecha** Junio 17 de 2009
_____ (Prórroga) Fecha _____

6 **Anexos:**

- [x] Comprobante de pago de la tasa
- [x] Poderes, si fuere el caso
- [x] Pruebas de los fundamentos de la oposición
- [x] Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso
- [x] Copia de la oposición para el traslado al solicitante.

7

NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: _____

C.C.No. 79.152.473 T.P. No. 44655

REYES & REYES
A B O G A D O S

S ñor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF: **Expediente 08 007.949**

TÍTULO SOLICITADO: **COMPOSICIONES FARMACÉUTICAS DE LIBERACIÓN MODIFICADA Y SUS PROCESOS.**

PUBLICACIÓN: **Gaceta 602 de 31 de Marzo de 2009, Nº d publicación 1441.**

PRIORIDAD: **IN 1681/DEI/2005 de 29/06/2005.**

SOLICITANTE: **PANACEA BIOTEC LTD.**

APODERADO: **JUAN PABLO CADENA SARMIENTO.**

TRÁMITE: **PRESENTACIÓN DE OPOSICION**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO COLOMBIANO S.A., LAFRANCOL S.A.,** en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **08 007.949,** por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LABORATORIO FRANCO COLOMBIANO S.A., LAFRANCOL S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTO DE LA OPOSICIÓN

La solicitud colombiana en trámite **08 007.949** que se refiere a una composición farmacéutica de liberación modificada comprendiendo por lo menos uno o unos agente(s) activo(s) o sus sales, ésteres, profármacos, solvatos, hidratos o derivados de los mismos farmacéuticamente aceptables; un sistema polimérico en una cantidad menor de alrededor de 80% en peso/peso de la composición comprendiendo por lo menos dos polímeros hinchables pH independientes y un polímero hidrófilo en una proporción de 1:20 hasta 20:1; opcionalmente otros excipientes farmacéuticamente aceptables; donde dicha composición proporciona un tiempo quieto inicial donde 5- 15% o menos del ingrediente(s) activo(s) se libera seguido de una liberación sostenida de ingrediente(s) activo(s), de tal manera que la composición dispone de unas concentraciones terapéuticas de agente(s) activo(s) durante unos periodos de tiempo prolongados; no reúne los requisitos necesarios para otorgársele el privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

En primer lugar, y ante la reivindicación textual de un "método de uso" de una composición de liberación modificada que comprende al menos un agente activo y un sistema polimérico, específicamente en su reivindicación 18, es relevante señalar que dicha pretensión resulta inaceptable a la luz de la Decisión 486, en tanto los "usos" son una categoría excluida del concepto de "Productos o Procedimientos" que establece el artículo 14 de la norma citada. Lo anterior,

además, en consonancia con reiteradas interpretaciones de la SIC sobre este punto.

Sin perjuicio de lo anterior me permito hacer notar que, aún si en gracia de discusión los usos o métodos terapéuticos fuesen permitidos en nuestro medio, éstos deberían cumplir necesariamente, y en forma simultánea, con los requisitos materiales de patentabilidad, es decir, novedad, nivel Inventivo y aplicación industrial. Además de anotar que respecto del pretendido "uso" el tercer requisito resulta de imposible cumplimiento, en tanto la reproducción industrial del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías sería del resorte de la profesión médica, y no, por supuesto, de las actividades industriales.

En otro aspecto, y esta vez refiriéndonos a la falta de nivel inventivo de la solicitud colombiana en tramite, cualquier persona medianamente versada en la materia reconoce que dentro del estado de la técnica, se reconocen dentro de la categoría de "comprimidos especiales" a aquellos comprimidos que presentan algunas características farmacocinéticas diferentes a las descritas para los comprimidos convencionales, y que dentro de esta categoría, los de mayor utilización son los sublinguales, bucales, masticables, efervescentes, multicapas, vaginales, de implantación, recubiertos y de liberación controlada[1]. A estos últimos en mención, corresponderían las características de la formulación que reivindica la solicitud colombiana en trámite. Específicamente, y dentro de las posibilidades de la liberación controlada que se reconocen en el estado de la técnica, las características de la formulación contenida en las reivindicaciones de la solicitud en cuestión, puede clasificarse como una formulación de liberación sostenida, en donde el principio activo se libera de forma continua cierta cantidad de fármaco durante un periodo de tiempo generalmente largo[2]. Como cualquier persona medianamente versada en la materia también debe reconocer, este tipo de formulaciones pueden obtenerse por distintos métodos, siendo el mas simple, la incorporación del principio activo en una matriz de naturaleza polimérica que forme una barrera lo suficientemente vizcosa que controle la difusión del principio activo o que se erosione lentamente permitiendo la liberación gradual del mismo[3]. Evidentemente la formulación descrita por la solicitud en cuestión, corresponde a

[1] Vila Jato. J.L. Tecnología Farmacéutica. Volumen II, página 142.
[2] Ibíd. Página 145.
[3] Ibíd. Página 145.

una formulación que obtiene sus características de liberación sostenida a través de la inserción del fármaco en un sistema polimérico dual hinchable, tal y como se expone claramente en la reivindicación 1. Además, y teniendo en cuenta que dentro de dichas características descritas para la formulación reivindicada por la solicitud en trámite, se hace mención del hinchamiento a través del uso de polímeros que atribuyan características hidrofílicas a dicha matriz polimérica, s relevante señalar que dichas características también son ampliamente reconocidas en el estado de la técnica, dentro de los mecanismos posibles para una liberación controlada, mecanismos tales como los descritos para los sistemas de liberación controlada tipo matrices hidrofílicas. Siendo mas especificos, los polímeros que se involucran para obtener la formulación reivindicada por la solicitud en cuestión, son polímeros claramente definidos y comúnmente utilizados en el estado de la técnica para la elaboración de este tipo de formulaciones, siendo estos polímeros correspondientes a polímeros naturales o semisintéticos, éteres de celulosa y polímeros de ácido acrílico[4].

En otras palabras, el tipo de formulaciones a las que se refiere la solicitud colombiana en tramite, corresponden a las características de la formulaciones de liberación controlada convencionales y ampliamente descritas en el estado de la técnica, y cualquier persona medianamente versada en la materia podría en principio involucrar cualquier fármaco en dicho tipo de formulaciones, aplicando adecuadamente los respectivos ensayos de preformulación y formulación.

Prueba de la versatilidad con que se pueden involucrar diversos tipos de fármacos en este tipo dem formulaciones, es lo contenido en los capítulos reivindicatorios de documentos publicados con anterioridad a la fecha de prioridad reivindicada por la solicitud en cuestión, tales como la patente Europea EP 0581676 publicada el 02 de febrero de 1994, la publicación internacional WO 99/18932 publicada el 22 de Abril de 1999, la publicación internacional WO 02/41876 publicada el 30 de Mayo de 2002 , la patente americana US 6 093420 publicada el 25 de Julio de 2000 y la publicación internacional WO 03/086353 publicada el 23 de Octubre de 2003 , en donde además es importante resaltar el uso de la misma clase de polímeros para la obtención del mecanismo de liberación controlada.

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[4] Ibíd. Página 399 a 402.

Para finalizar, y esta vez refiriéndonos a la falta de novedad de la invención, es importante resaltar que existen documentos que revelan con anterioridad la inclusión de algunos de los principios activos mencionados por la solicitud colombiana en tramite en el mismo tipo de formulaciones de liberación modificada, veamos:

La publicación internacional WO 2004/066910 publicada el 12 de Agosto de 2004 revela:

1. A solid oral controlled release pharmaceutical composition for administration to a subject in need thereof comprising:

(a) a therapeutically effective amount of a pharmaceutically active ingredient; and

(b) a controlled release modifying complex

wherein said complex comprises:

(i) a primary release modifying agent;

(ii) a secondary release modifying agent; and

(iii)an auxiliary release modifying agent wherein said primary, secondary and auxiliary release modifying agents are present in amounts that synergistically extend the release of the pharmaceutically active ingredient.

(...)

(i) a primary release modifying agent selected from low molecular weight hydrophilic polymers;

(ii) a secondary release modifying agent selected from high molecular weight hydrophilic polymers; and

(iii)an auxiliary release modifying agent selected from the starch derivatives

(...)

23. The pharmaceutical composition of claim 22, wherein the low soluble high dose API or a derivative is selected from Oxcarbazepine, Oxyphenbutazone, Paracetamol, Phenindione, Phenobarbitone, Phenylbutazone, Phenylsulphathiazole, Piperazine phosphate, Proguanil hydrochloride, Promethazine theoclate, Propylthiouracil, Quinidine sulphate, Quinine sulphate, Quinidochlor, Rifampicin, Simvastatin, Spironolactone,

(...)

26. The pharmaceutical composition of claim 25, wherein the low soluble low dose API or a derivative is selected from the group consisting of Alprazolam, Amiloride hydrochloride, Astemizole, Atorvastatin, Benzhexol hydrochloride,

(...)

29. The pharmaceutical composition of claim 1, wherein the primary release modifying agent is a low molecular weight polyethylene oxide.

(...)

37. The pharmaceutical composition of claim 1, wherein said composition further comprises at least one pharmaceutically acceptable additive selected from diluents, fillers, binders, glidants, and lubricants.

38. The pharmaceutical composition of claim 1, wherein said composition further comprises an optional coating which is designed for the modification of drug release.

(...)

La publicación internacional WO 2005/020993 publicada el 10 de Marzo de 2005 revela:

1. A solid pharmaceutical composition comprising an active ingredient selected among tacrolimus and analogues thereof, wherein less than 20% w/w of the active ingredient is released within 0.5 hours, when subjected to an in vitro dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium.

(...)

9. The composition according to claim 8, wherein less than 40 w/w% of the active pharmaceutical ingredient is released within 8 hours, preferably within 15 hours.

(...)

12. The composition according to claim 1 comprising a solid dispersion or solid solution of active ingredient in a hydrophilic or water-miscible vehicle and one or more modifying release agents.

(...)

17. The composition according to claim 12, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyethylene glycols, polyoxyethylene oxides, poloxamers, polyoxyethylene stearates, poly-epsilon caprolactone, polyglycolized glycerides such as Gelucire®, and mixtures thereof.

(...)

18. The composition according to claim 12, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyvinylpyrrolidones, polyvinyl-polyvinylacetate copolymers (PVP-PVA), polyvinyl alcohol (PVA), polymethacrylic polymers (Eudragit RS; Eudragit RL, Eudragit NE, Eudragit E), cellulose derivatives including hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, pectins, cyclodextrins, galactomannans, alginates, carragenates, xanthan gums and mixtures thereof.

(...)

50. Use of the solid composition according to claim 1 for the preparation of a controlled or modified release solid dosage form.

La publicación internacional WO 2004/026314 publicada el 01 de Abril de 2004 revela:

2. The oral dosage form comprising oxcarbazepine according to claim 1 which, when administered once a day, is released to produce constant MHD plasma levels over 24 hours.

3. The oral dosage form according to claim 1 or 2 consisting of a tablet core and a coating wherein the core comprises oxcarbazepine, optionally, a filler, and at least one further excipient selected from cellulose ethers, carboxyvinyl polymer of acrylic acid cross linked with alkyl ethers of sucrose or pentaerythritol and polymethacrylates.

(...)

9. The oral dosage form according to any one of claims 3 to 8 comprising as a filler microcrystalline cellulose.

(...)

Como se puede apreciar, en estas anterioridades se revela la inclusión de atorvastatina, oxcarbazepina, levetiracetam y simvastatina en matrices compuestas por compuestos del mismo tipo (poliméricas hidrofílicas) que permiten una liberación controlada de dicho principio activo. Específicamente se hace mención de compuestos tales como celulosa microcristalina, oxido de polialquilenos, gomas polisacáridas naturales, derivados de acido algínico, pectina, ácidos poliacrílicos entrecruzados, poliacrilatos, así como la presencia opcional de otros excipientes tales como diluentes, desintegrantes, rellenos, agentes de cubierta, entre otros.

En conclusión, la solicitud colombiana en tramite carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, en primer lugar porque incurre en una improcedencia directa de patentabilidad al reivindicar un método de uso de una formulación farmacéutica, y en segundo lugar porque carece tanto de novedad como de nivel inventivo al incluir principios activos en formulaciones farmacéuticas ampliamente descritas y convencionalmente usadas con anterioridad en el estado de la técnica.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16 y 18 de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- Capítulos reivindicatorios de todas las publicaciones mencionadas en el acápite dé Fundamentos de la Oposición.
- Vila Jato. J.L. Tecnología Farmacéutica. Volumen II, página 142, 145 y 399 a 402.

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de LAFRANCOL S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina. Lafrancol S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79'152.473 de Usaquén
T.P.A. 44.655 del C.S.J.

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

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(54) Agglomerated hydrophilic complexes with multi-phasic release characteristics.

(57) The present invention relates to a controlled release formulation which includes a therapeutically active medicament, a heterodisperse gum matrix, a pharmaceutically acceptable diluent, and an effective amount of a pharmaceutically acceptable surfactant and/or wetting agent to provide a multi-phasic controlled release of a therapeutically active medicament. The invention also relates to a method of preparing the same.

EP 0 581 676 A2

TABLE 20

EXAMPLE 21

Ingredient	mg/tab	%	G/350g
Excipient	750.0	88.64	487.50
PPA HCl	75.0	8.86	48.75
Lubritab™	16.92	2.00	11.00
Mag. Stear.	4.23	0.50	2.75
TOTAL	846.15	100%	550g

PPA HCl = Phenylpropanolamine Hydrogen Chloride

Mag. Stear. = Magnesium Stearate

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

Claims

1. A controlled-release oral solid dosage form for absorption of an active medicament in the gastro-intestinal tract, comprising

   an effective amount of a medicament to render a therapeutic effect;

   a controlled release excipient comprising a heterodisperse gum matrix comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum in the presence of aqueous solutions, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1; and

   an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said heterodisperse gum matrix being from about 3:7 to about 7:3;

   and an effective amount of a pharmaceutically acceptable surfactant or wetting agent to provide a multi-phasic release of said medicament when said dosage form is exposed to aqueous fluid.

2. A controlled release oral solid dosage form, comprising

   (i) a heterodisperse gum matrix comprising xanthan and locust bean gum in a ratio of about 1:1;

   (ii) an inert pharmaceutically acceptable diluent selected from the group consisting of a monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said diluent to said heterodisperse gum matrix being from about 3:7 to about 7:3;

   (iii) an effective amount of a medicament to render a therapeutic effect; and

   (iv) from about 1 to about 10 by weight of a pharmaceutically acceptable surfactant or wetting agent, said surfactant or wetting agent being selected from the group consisting of anionic surfactants, cationic surfactants, amphoteric surfactants, non-ionic surfactants, and mixtures of any of the foregoing, said medicament having a multi-phasic release of said medicament when exposed to aqueous fluid.

3. The oral solid dosage form of claims 1 or 2, wherein said a heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum.

4. The oral solid dosage form of claim 1, wherein said surfactant or wetting agent comprises from about 1 to about 10 percent of said formulation, by weight.

5. The oral solid dosage form of claims 1 or 2, which releases said medicament according to bi-phasic kinetics.

6. The oral solid dosage form of claims 1 or 2, wherein the ratio of said inert diluent to said heterodisperse gum matrix is about 1:1.

7. The oral solid dosage form of claims 1 or 2, wherein said surfactant or wetting agent is selected from the group consisting of pharmaceutically acceptable anionic surfactants, cationic surfactants, amphoteric (amphipathic/amphophilic) surfactants, non-ionic surfactants, and mixtures of any of the foregoing.

8. The oral solid dosage form of claim 7, wherein said surfactant or wetting agent is an anionic surfactant selected from the group consisting of monovalent alkyl carboxylates, acyl lactylates, alkyl ether carboxylates, N-acyl sarcosinates, polyvalent alkyl carbonates, N-acyl glutamates, fatty acid-polypeptide condensates, sulfuric acid esters, alkyl sulfates (including sodium lauryl sulfate (SLS)), ethoxylated alkyl sulfates, ester linked sulfonates (including docusate sodium or dioctyl sodium succinate (DSS)), alpha olefin sulfonates, phosphated ethoxylated alcohols; a cationic surfactant selected from the group consisting of monoalkyl quaternary ammonium salts, dialkyl quaternary ammonium compounds, amidoamines, aminimides; an amphoteric surfactant selected from the group consisting of N-substituted alkyl amides, N-alkyl betaines, sulfobetaines, N-alkyl β -aminoproprionates; a non-ionic surfactant selected from the group consisting of polyoxyethylene compounds, ethoxylated alcohols, ethoxylated esters, ethoxylated amides, polyoxypropylene compounds, propoxylated alcohols, ethoxylated/propoxylated block polymers, propoxylated esters, alkanolamides, amine oxides, fatty acid esters of polyhydric alcohols, ethylene glycol esters, diethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl fatty acid esters, sorbitan esters, sucrose esters, glucose (dextrose) esters; or mixtures of any of the foregoing.

9. The oral solid dosage form of claim 1, wherein said surfactant or wetting agent is a wetting agent selected from the group consisting of acacia, benzalkonium chloride, cholesterol, emulsifying wax, docusate sodium, glyceryl monostearate, lanolin alcohols, lecithin, poloxamer, poloxyethylene castor oil derivatives, poloxyethylene sorbitan fatty acid esters, poloxyethylene stearates, sodium lauryl sulfates, sorbitan esters, stearic acid, triethanolamine, and mixtures of any of the foregoing.

10. The oral solid dosage form of claim 7, wherein said surfactant or wetting agent is selected from the group consisting of sodium lauryl sulfate/polyethylene glycol (PEG) 6000 and sodium lauryl sulfate/PEG 6000/stearic acid.

11. The oral solid dosage form of claim 7, wherein said surfactant or wetting agent comprises sodium lauryl sulfate, docusate sodium, or a combination of sodium lauryl sulfate and docusate sodium.

12. The oral solid dosage form of claims 1-11, wherein said therapeutically active medicament is selected from the group consisting of antihistamines, analgesics, anti-inflammatory agents, gastro-intestinals, antiemetics, anti-epileptics, vasodilators, anti-tussive agents, expectorants, anti-asthmatics, antispasmodics, hormones, diuretics, anti-hypotensives, bronchodilators, anti-inflammatory steroids, antibiotics, antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, antacids, vitamins, and stimulants.

13. The oral solid dosage form of claims 1-12 which is a tablet.

14. A method of treating a human patient, comprising orally administering to the patient the oral solid dosage form of claims 1-13.

15. A method for preparing an oral solid dose formulation providing a multi-phasic release of a therapeutically active medicament when said dosage form is exposed to aqueous or gastric fluid, comprising

mixing a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum in the presence of aqueous solutions, such that the ratio of said heteropolysaccharide gum to said homopolysaccharide gum is from about 1:3 to about 3:1, to obtain a heterodisperse gum matrix;

adding an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, to said heterodisperse gum matrix such that the ratio of said inert diluent to said heterodisperse gum matrix is from about 3:7 to about 7:3;

adding an effective amount of a medicament to render a therapeutic effect, and

adding an effective amount of a pharmaceutically acceptable surfactant or wetting agent to provide a multi-phasic release of said medicament when said dosage form is exposed to aqueous fluid.

16. A method for preparing a controlled release dosage form which exhibits multi-phasic release of a medicament incorporated therein, comprising

preparing a controlled release multi-phasic excipient by mixing (i) a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum in the presence of aqueous solutions, such that the ratio of said heteropolysaccharide gum to said homopolysaccharide gum is from about 1:3 to about 3:1, with (ii) an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said heterodisperse gum matrix being from about 3:7 to about 7:3; and (iii) a pharmaceutically acceptable surfactant or wetting agent;

adding a therapeutically effective amount of a medicament to said controlled release multi-phasic excipient; and tableting said mixture of controlled release multi-phasic excipient and medicament, said surfactant or wetting agent being included in an amount sufficient to provide a multi-phasic release of said medicament from said tablet when said tablet is exposed to aqueous fluids.

17. The method of claims 15 or 16, further comprising compressing the final mixture into tablets.

18. The method of claims 15 or 16, wherein from about 1 to about 10 percent by weight surfactant or wetting agent is added.

19. The method of claims 15 or 16, wherein said surfactant or wetting agent is selected from the group consisting of anionic surfactants, cationic surfactants, amphoteric surfactants, non-ionic surfactants, and mixtures of any of the foregoing.

20. A controlled release multi-phasic pharmaceutical excipient, comprising:

a heterodisperse gum matrix comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum in the presence of aqueous solutions, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being form about 1:3 to about 3:1;

an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said heterodisperse gum matrix being from about 3:7 to about 7:3; and

from about 1 to about 20 percent by weight of a pharmaceutically acceptable surfactant or wetting agent.

21. The pharmaceutical excipient of claim 20, wherein said heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum, and said inert diluent comprises lactose, dextrose, sucrose, fructose, microcrystalline cellulose, xylitol, sorbitol or mixtures thereof.

22. The pharmaceutical excipient of claim 20, wherein said surfactant or wetting agent comprises from about 1 to about 10 percent of said formulation by weight.

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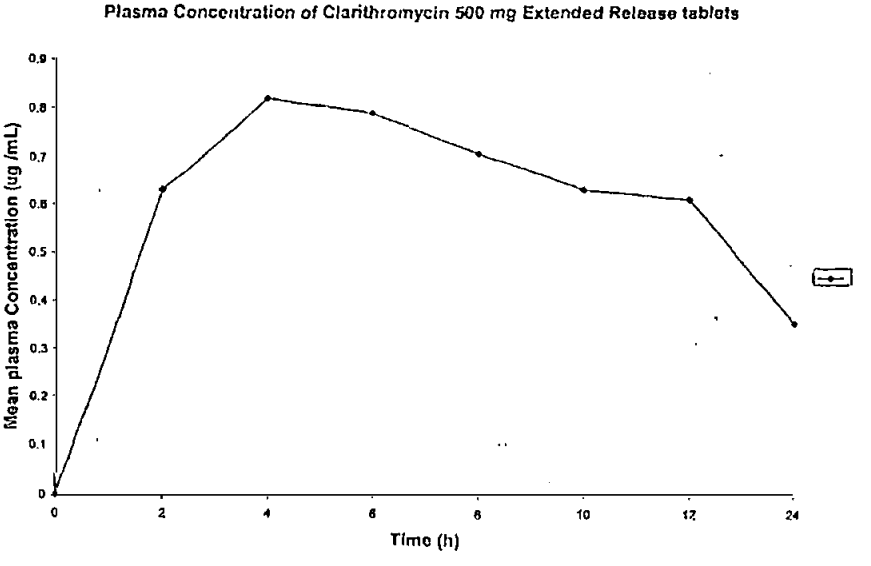
[Continued on next page]

(54) Title: CONTROLLED RELEASE MODIFYING COMPLEX AND PHARMACEUTICAL COMPOSITIONS THEREOF



(57) Abstract: Disclosed is a controlled release modifying complex for solid suitable comprises modifying excipients. The release modifying an auxiliary release thereof, wherein modifying agents effect and ingredient,oral controlled release pharmaceutical for an once-a-day administration. The active pharmaceutical ingredient, compositions composition a.release complex and other required pharmaceutically acceptable release modifying complex comprises a primary agent, a secondary release modifying agent and modifying agent or varying combinations said primary, secondary and auxiliary release are present in amounts that synergistically extend the release of active pharmaceutical ingredient.

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CLAIMS

1. A solid oral controlled release pharmaceutical composition for administration to a subject in need thereof comprising:

(a) a therapeutically effective amount of a pharmaceutically active ingredient; and

(b) a controlled release modifying complex

wherein said complex comprises:

(i) a primary release modifying agent;

(ii) a secondary release modifying agent; and

(iii)an auxiliary release modifying agent wherein said primary, secondary and auxiliary release modifying agents are present in amounts that synergistically extend the release of the pharmaceutically active ingredient.

2. A solid oral controlled release pharmaceutical composition for administration to a subject in need thereof comprising:

(a) a therapeutically effective amount of a pharmaceutically active ingredient; and

(b) a controlled release modifying complex

wherein said complex comprises:

(i) a primary release modifying agent; or

(ii) a secondary release modifying agent; and

(iii)an auxiliary release modifying agent wherein said primary, secondary and auxiliary release modifying agents are present in amounts that synergistically extend the release of the pharmaceutically active ingredient.

3. A solid oral controlled release pharmaceutical composition for administration to a subject in need thereof comprising:

(a) a therapeutically effective amount of a pharmaceutically active ingredient; and

(b) a controlled release modifying complex

wherein said complex comprises:

(i) a primary release modifying agent selected from low molecular weight hydrophilic polymers;

(ii) a secondary release modifying agent selected from high molecular weight hydrophilic polymers; and

(iii)an auxiliary release modifying agent selected from the starch derivatives

wherein said primary, secondary and auxiliary release modifying agents are present in amounts that synergistically extend the release of the pharmaceutically active ingredient.

4. A solid oral controlled release pharmaceutical composition for administration to a subject in need thereof comprising:

(a) a therapeutically effective amount of a pharmaceutically active ingredient; and

(b) a controlled release modifying complex

wherein said complex comprises:

(i) a primary release modifying agent selected from low molecular weight hydrophilic polymers; or

(ii) a secondary release modifying agent selected from high molecular weight hydrophilic polymers; and

(iii)an auxiliary release modifying agent selected from the starch derivatives

wherein said primary, secondary and auxiliary release modifying agents are present in amounts that synergistically extend the release of the pharmaceutically active ingredient.

5. The pharmaceutical composition of claim 1 wherein the dosage form is a tablet, caplet or capsule.

6. The pharmaceutical composition of claim 1, wherein the active pharmaceutical ingredient is a macrolide or azide antibiotic or a derivative thereof.

7. The pharmaceutical composition of claim 6, wherein the macrolide is an erythromycin derivative or its pharmaceutically acceptable hydrates, salts or esters.

8. The pharmaceutical composition of claim 6, wherein the azide is azithromycin, or its pharmaceutically acceptable hydrates, salts or esters.

9. The pharmaceutical composition of claim 7, wherein the erythromycin derivative is selected from the group consisting of clarithromycin, josamycin, midecamycin, kitamycin, roxithromycin, rokitamycin, oleandomycin, miocamycin, flurithromycin, and rosaramicin, and their pharmaceutically acceptable hydrates, salts and esters.

10. The pharmaceutical composition of claim 1, wherein the active pharmaceutical ingredient is a penicillin antibiotic or a derivative thereof.

11. The pharmaceutical composition of claim 10, wherein the penicillin derivative is selected from the group consisting of Amoxicillin, Ampicillin, Ampicillin Sodium, Apalcillin, Aspoxicillin, Azlocillin, Aztreonam, Bacampicillin, Cabenicillin, Carfecillin, Carindacillin, Ciclacillin, Cloxacillin, Dicloxacillin, and their pharmaceutically acceptable hydrates, salts and esters.

12. The pharmaceutical composition of claim 1, wherein the active pharmaceutical ingredient is a cephalosporin antibiotic or a derivative thereof.

13. The pharmaceutical composition of claim 12, wherein the cephalosporin derivative is selected from the group consisting of Cefacetrile, Cefadroxil, Cefaloridine, Cefalothin Sodium, Cefapirin, Cefazaflur, Cefazedone, Cefazolin, Cefradine, Ceftezole, Cefsulodin Sodium, Cefamandole, Cefonicid, Cefoperazone, Cefuroxime, Cefuzonam, Cefbuperazone, Cefoxitin, Cefminox, Cefmetazole, Cefotetan, Loracarbef, Cefmenoxime, Cefodizime Sodium, Cefotaxime, Cefpimizole, Cefpiramide, Ceftazidime, Ceftiolene, Ceftizoxime, Ceftriaxone, Cefepime, Cefetecol, Cefpirome, Cefquinome, Cefalosporin C, Cefozopran Hydrochloride, Cefaclor, Cefadroxil, Cefalexin, Cefaloglycine, Cefatrizine, Cefdinir, Cefetamet Pivoxil, Cefixime, Ceforanide, Cefotiam, Cefpodoxime, Cefpodoxime Proxetil, Cefprozil,

Cefradine, Cefroxadine, Cefteram Pivoxil, Ceftibuten, Cefuroxime Axetil, and their pharmaceutically acceptable hydrates, salts and esters.

14. The pharmaceutical composition of claim 1, wherein the active pharmaceutical ingredient is a quinolone antibiotic or a derivative thereof.

15. The pharmaceutical composition of claim 14, wherein the quinolone derivative is selected from the group consisting of Nalidixic Acid, Cinoxacin, Oxolinic Acid, Flumequine, Pipemidic Acid, Rosoxacin, Norfloxacin, Lomefloxacin, Ofloxacin, Enrofloxacin, Ciprofloxacin, Enoxacin, Amifloxacin, Fleroxacin, Gatifloxacin, Gemifloxacin, Pefloxacin, Rufloxacin, Sparfloxacin, Temafloxacin, Tosufloxacin, Grepafloxacin, Levofloxacin, Moxifloxacin, Trovafloxacin, and their pharmaceutically acceptable hydrates, salts and esters.

16. The pharmaceutical composition of claim 1, wherein the active pharmaceutical ingredient is a high soluble high dose API or a derivative thereof.

17. The pharmaceutical composition of claim 16, wherein the high soluble high dose API or a derivative is selected from the group consisting of Acebutolol hydrochloride, Amantadine hydrochloride, Aminocaproic acid, Aminophylline, Amodiaquine hydrochloride, Ascorbic acid, Bupropion hydrochloride, Carbenoxolone sodium, Cefuroxime sodium, Chloroquine phosphate, Chloroquine sulphate, Chlorpromazine hydrochloride, Ciprofloxacin hydrochloride, Cloxacillin sodium, Cycloserine, Diltiazem hydrochloride, Diethyl carbamazine citrate, Doxycycline hydrochloride, Ethosuximide, Ferrous gluconate, Isoniazid, Levamisole hydrochloride,Levetiracetam, Lincomycin hydrochloride, Mebeverine hydrochloride, Mepyramine maleate, Metformin hydrochloride, Metoprolol tartrate, Metoprolol succinate, Niacin, Nicotinamide, Nicotinic acid, Oxprenolol hydrochloride, Oxytetracycline hydrochloride, Penicillamine, Pentobarbitone sodium, Phenoxy Methyl Penicillin K, Phenytoin sodium, Piperazine adipate, Potassium chloride, Procainamide

hydrochloride, Propranolol hydrochloride, Pseudoephedrine hydrochloride, Quinalbarbitone sodium, Quinine bisulphate, Ranitidine hydrochloride, Sodium amino salicylate, Sodium fusidate, sodium valproate, Streptomycin sulphate, Tetracycline hydrochloride, Topiramate, Troxidone, Verapamil hydrochloride and the like and their pharmaceutically acceptable salts, ester and hydrates.

18. The pharmaceutical composition of claim 17, wherein the active ingredient is Nicotinic acid.

19. The pharmaceutical composition of claim 1, wherein the active pharmaceutical ingredient is a high soluble low dose API or a derivative thereof.

20. The pharmaceutical composition of claim 19, wherein the high soluble low dose API or a derivative is selected from the group consisting of Amitriptylline hydrochloride, captopril, Clonidine hydrochloride, Colchicin, Cyclophosphamide, Diphenhydramine hydrochloride, Dothiepen hydrochloride, Doxepin hydrochloride Ephedrine hydrochloride, Ergometrine maleate, Ergometrine tartrate, Fenfluramine hydrochloride, Folic acid, Glyceryl trinitrate, Hyoscine hydrobromide, Hyoscine buytlbromide, Imipramine hydrochloride, Isoprenaline sulphate, Isosorbide dinitrate, Isosorbide-5-mononitrate, Levocetrizine hydrochloride, Methadone hydrochloride, Methdilazine hydrochloride, Metoclopramide hydrochloride, Neostigmine bromide, Oxybutynin hydrochloride, Perindopril erbumine, Pethidine hydrochloride, Phenformin hydrochloride, Pheniramine maleate, Phenobarbitone sodium, Primaquine phosphate, Promethazine hydrochloride, Propantheline bromide, Propranolol hydrochloride, Pyridoxine hydrochloride, Salbutamol sulphate, Terbutaline sulphate, Thiamine hydrochloride, Timolol maleate, Tizanidine hydrochloride, Trifluoperazine hydrochloride, Triflupromazine hydrochloride, Triprolidine hydrochloride, Warfarin sodium and the like and their pharmaceutically acceptable salts, ester and hydrates.

21. The pharmaceutical composition of claim 20, wherein the active ingredient is Oxybutynin hydrochloride.

22. The pharmaceutical composition of claim 1, wherein the active pharmaceutical ingredient is a low soluble high dose API or a derivative thereof.

23. The pharmaceutical composition of claim 22, wherein the low soluble high dose API or a derivative is selected from the group consisting of Acetazolamide, Allopurinol, Atenolol, Carbamazepine, Cefadroxil, Cephalexin, Chloramphenicol, Cefuroxime Axetil, Chlorthalidone, Cilastozol, Cimetidine, Clarithromycin, Clofazemine, Dapsone, Diclofenac sodium, Diiodohydroxy quinolone, Diloxanide furoate, Disulfiram, Erythromycin, Erythromycin estolate, Erythromycin stearate, Ethacrynic cid, Ethionamide,, Ethopropazine hydrochloride, Ferrous fumarate, Fluconazole, Flurbiprofen, Furazolidone, Griseofulvin, Hydrochlorthiazide, Ibuprofen, Itraconazole, Ketoconazole, Ketoprofen, Labetalol hydrochloride, Levodopa, Linezolid, Lithium carbonate, Magaldrate, Mebendazole, Mefenamic acid, Megestrol acetate, Mercaptopurine, Mesalamimne, Nalidixic acid, Nateglinide, Niclosamide, Nitrofurantoin, Norfloxacin, Oxcarbazepine,. Oxyphenbutazone, Paracetamol, Phenindione, Phenobarbitone, Phenylbutazone, Phenylsulphathiazole, Piperazine phosphate, Proguanil hydrochloride, Promethazine theoclate, Propylthiouracil, Quinidine sulphate, Quinine sulphate, Quinidochlor, Rifampicin, Simvastatin, Spironolactone, Succinylsulphathiazole, Sulphadiazine, Sulphadimethoxine, Sulphadimidine, Sulphafurazole, Sulphaphenazole, Thiabendazole, Tinidazole, Tolbutamide, Triamterene, Sulphamethoxazole and the like and their pharmaceutically acceptable salts, ester and hydrates.

24. The pharmaceutical composition of claim 23, wherein the active ingredient is Clarithromycin.

25. The pharmaceutical composition of claim 1, wherein the active pharmaceutical ingredient is a low soluble low dose API or a derivative thereof.

26. The pharmaceutical composition of claim 25, wherein the low soluble low dose API or a derivative is selected from the group consisting of Alprazolam, Amiloride hydrochloride, Astemizole, Atorvastatin, Benzhexol hydrochloride, Betamethasone, Bromhexine hydrochloride, Bromocryptine mesylate, Buprenorphine hydrochloride, carbimazole, Chlordiazepoxide, Citalopram, Cortisone acetate, cyproheptadine hydrochloride, diazepam, Desloratadine, Dexamethasone hydrochloride, Dextromethorphan hydrochloride, dicyclomine hydrochloride, Dienoestrol, Digitoxin, Digoxin, Domperidone, Dydrogesterone, enalapril maleate, Esomeprazole, Ethinyloestradiol, Ethyloestrenol, Fludrocortisone acetate, Frusemide, glibenclamide, Glimepiride, haloperidol, Indomethacin, Isoxsuprine hydrochloride, Lanatoside C, Lercanidipine hydrochloride, Levonorgesrtel, Lomustine, Loratadine, Isoxuprine hydrochloride, methotrexate, Mecizine hydrochloride, Melphalan, Methotrexate, Methylergometrine maleate, Methylprednisolone, Mianserin hydrochloride, Mosapride, Nicoumalone, Nifedipine, Nitrazepam, Norethisterone, nortriptyline hydrochloride, Omeprazole, Ormeloxifene hydrochloride, Pentazocine hydrochloride, Phenindamine tartrate, piroxicam, prazosin hydrochloride, Prednisolone, Prednisone, Prochlorperazine maleate, Repaglinide, Riboflavinee, Rosuvastatin, Stilbostrol, Tamoxifen citrate, Thyroxine sodium, triamcinilone, Trimethoprim, Valdecoxib, Zolpidem tartrate and the like and their pharmaceutically acceptable salts, ester and hydrates.

27. The pharmaceutical composition of claim 26, wherein the active ingredient is Alprazolam.

28. The pharmaceutical composition of claim 26, wherein the active ingredient is Lercanidipine hydrochloride.

29. The pharmaceutical composition of claim 1, wherein the primary release modifying agent is a low molecular weight polyethylene oxide.

30. The pharmaceutical composition of claim 1, wherein the low molecular weight polyethylene oxide has a molecular weight of at least about 100,000.

31. The pharmaceutical composition of claim 1 wherein the low molecular weight polyethylene oxide has a molecular weight ranging from 100,000 to 900,000.

32. The pharmaceutical composition of claim 1, wherein the secondary release modifying agent is a high molecular weight polyethylene oxide.

33. The pharmaceutical composition of claim 1, wherein the high molecular weight polyethylene oxide has a molecular weight of at least about 1,000,000.

34. The pharmaceutical composition of claim 1, wherein the high molecular weight polyethylene oxide has a molecular weight ranging from 1,000,000 to 9,000,000.

35. The pharmaceutical composition of claim 1, wherein the auxiliary release modifying agent is a starch derivative selected from pregelatinized starch, partially pregelatinized starch, retrograded starch, or a combination thereof.

36. The pharmaceutical composition of claim 1, wherein the auxiliary release modifying agent is a retrograded starch.

37. The pharmaceutical composition of claim 1, wherein said composition further comprises at least one pharmaceutically acceptable additive selected from diluents, fillers, binders, glidants, and lubricants.

38. The pharmaceutical composition of claim 1, wherein said composition further comprises an optional coating which is designed for the modification of drug release.

39. The pharmaceutical composition of claim 38, wherein the coating composition is selected from the group consisting of cellulose ethers such as ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, and others such as polyvinyl alcohol, polyvinyl pyrrolidone, methacrylic acid derivatives, resins, clays, long chain hydrocarbons, long chain carboxylic

percent weight to about 80 percent weight of the release modifying complex.

49. The pharmaceutical composition of claim 48, wherein the primary release modifying agent comprises from about 5 percent weight to about 70 percent weight of the release modifying complex.

50. The pharmaceutical composition of claim 1, wherein the secondary release modifying agent comprises from about 1 percent weight to about 95 percent weight of the release modifying complex.

51. The pharmaceutical composition of claim 50, wherein the secondary release modifying agent comprises from about 5 percent weight to about 90 percent weight of the release modifying complex.

52. The pharmaceutical composition of claim 1, wherein the auxiliary release modifying agent comprises from about 1 percent weight to about 95 percent weight of the release modifying complex.

53. The pharmaceutical composition of claim 52, wherein the auxiliary release modifying agent comprises from about 5 percent weight to about 95 percent weight of the release modifying complex.

54. The pharmaceutical composition of claim 53, wherein the auxiliary release modifying agent comprises from about 10 percent weight to about 95 percent weight of the release modifying complex.

55. A controlled release pharmaceutical composition comprising a pharmaceutically active ingredient and a release modifying complex, wherein said release modifying complex comprises a synergistic combination of (a) a primary release modifying agent selected from a low molecular weight polyethylene oxide and (b) an auxiliary release modifying agent selected from a starch derivative, and said primary release modifying agent and auxiliary release modifying agent are

acids, long chain carboxylic acid esters, long chain alcohols and the like and mixtures thereof.

40. The pharmaceutical composition of claim 1, wherein said composition further comprises an optional coating which is not designed for the modification of drug release.

41. The pharmaceutical composition of claim 40, wherein the coating composition is selected from the group consisting of cellulose ethers such as ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, and others such as polyvinyl alcohol, polyvinyl pyrrolidone, methacrylic acid derivatives, resins, clays, long chain hydrocarbons, long chain carboxylic acids, long chain carboxylic acid esters, long chain alcohols and the like and mixtures thereof.

42. The pharmaceutical composition of claim 1, wherein said composition comprises from about 0.1 percent weight to about 90 percent weight of the active pharmaceutical ingredient.

43. The pharmaceutical composition of claim 42, wherein said composition comprises from about 0.1 percent weight to about 80 percent weight of the active pharmaceutical ingredient.

44. The pharmaceutical composition of claim 1, wherein the composition comprises from about 1 percent weight to about 90 percent weight of the release modifying complex.

45. The pharmaceutical composition of claim 44, wherein the composition comprises from about 5 percent weight to about 85 percent weight of the release modifying complex.

46. The pharmaceutical composition of claim 45, wherein the composition comprises from about 10 percent weight to about 80 percent weight of the release modifying complex.

47. The pharmaceutical composition of claim 1, wherein the primary release modifying agent comprises from about 1 percent weight to about 90 percent weight of the release modifying complex.

48. The pharmaceutical composition of claim 47, wherein the primary release modifying agent comprises from about 5

present in synergistic effective amounts to extend the release of the active pharmaceutical ingredient.

56. The pharmaceutical composition of claim 55, wherein the active pharmaceutical ingredient is a macrolide or azide antibiotic or a derivative thereof.

57. The pharmaceutical composition of claim 56, wherein the macrolide is an erythromycin derivative or its pharmaceutically acceptable hydrates, salts or esters.

58. The pharmaceutical composition of claim 56, wherein the azide is azithromycin, or its pharmaceutically acceptable hydrates, salts or esters.

59. The pharmaceutical composition of claim 57, wherein the erythromycin derivative is selected from the group consisting of clarithromycin, josamycin, midecamycin, kitamycin, roxithromycin, rokitamycin, oleandomycin, miocamycin, flurithromycin, and rosaramicin, and their pharmaceutically acceptable hydrates, salts and esters.

60. The pharmaceutical composition of claim 55, wherein the active pharmaceutical ingredient is a penicillin antibiotic or a derivative thereof.

61. The pharmaceutical composition of claim 60, wherein the penicillin derivative is selected from the group consisting of Amoxicillin, Ampicillin, Ampicillin Sodium, Apalcillin, Aspoxicillin, Azlocillin, Aztreonam, Bacampicillin, Cabenicillin, Carfecillin, Carindacillin, Ciclacillin, Cloxacillin, Dicloxacillin, and their pharmaceutically acceptable hydrates, salts and esters.

62. The pharmaceutical composition of claim 55, wherein the active pharmaceutical ingredient is a cephalosporin antibiotic or a derivative thereof.

63. The pharmaceutical composition of claim 62, wherein the cephalosporin derivative is selected from the group consisting of Cefacetrile, Cefadroxil, Cefaloridine, Cefalothin Sodium, Cefapirin, Cefazaflur, Cefazedone, Cefazolin, Cefradine, Ceftezole, Cefsulodin Sodium, Cefamandole, Cefonicid,

Cefoperazone, Cefuroxime, Cefuzonam, Cefbuperazone, Cefoxitin, Cefminox, Cefmetazole, Cefotetan, Loracarbef, Cefmenoxime, Cefodizime Sodium, Cefotaxime, Cefpimizole, Cefpiramide, Ceftazidime, Ceftiolene, Ceftizoxime, Ceftriaxone, Cefepime, Cefetecol, Cefpirome, Cefquinome, Cefalosporin C, Cefozopran Hydrochloride, Cefaclor, Cefadroxil, Cefalexin, Cefaloglycine, Cefatrizine, Cefdinir, Cefetamet Pivoxil, Cefixime, Ceforanide, Cefotiam, Cefpodoxime, Cefpodoxime Proxetil, Cefprozil, Cefradine, Cefroxadine, Cefteram Pivoxil, Ceftibuten, Cefuroxime Axetil, and their pharmaceutically acceptable hydrates, salts and esters.

64. The pharmaceutical composition of claim 55, wherein the active pharmaceutical ingredient is a quinolone antibiotic or a derivative thereof.

65. The pharmaceutical composition of claim 64, wherein the quinolone derivative is selected from the group consisting of Nalidixic Acid, Cinoxacin, Oxolinic Acid, Flumequine, Pipemidic Acid, Rosoxacin, Norfloxacin, Lomefloxacin, Ofloxacin, Enrofloxacin, Ciprofloxacin, Enoxacin, Amifloxacin, Fleroxacin, Gatifloxacin, Gemifloxacin, Pefloxacin, Rufloxacin, Sparfloxacin, Temafloxacin, Tosufloxacin, Grepafloxacin, Levofloxacin, Moxifloxacin, Trovafloxacin, and their pharmaceutically acceptable hydrates, salts and esters.

66. The pharmaceutical composition of claim 55, wherein the active pharmaceutical ingredient is a high soluble high dose API or a derivative thereof.

67. The pharmaceutical composition of claim 66, wherein the high soluble high dose API or a derivative is selected from the group consisting of Acebutolol hydrochloride, Amantadine hydrochloride, Aminocaproic acid, Aminophylline, Amodiaquine hydrochloride, Ascorbic acid, Bupropion hydrochloride, Carbenoxolone sodium, Cefuroxime sodium, Chloroquine phosphate, Chloroquine sulphate, Chlorpromazine hydrochloride, Ciprofloxacin hydrochloride, Cloxacillin sodium, Cycloserine, Diltiazem hydrochloride, Diethyl carbamazine citrate,

Doxycycline hydrochloride, Ethosuximide, Ferrous gluconate, Isoniazid, Levamisole hydrochloride,Levetiracetam, Lincomycin hydrochloride, Mebeverine hydrochloride, Mepyramine maleate, Metformin hydrochloride, Metoprolol tartrate, Metoprolol succinate, Niacin, Nicotinamide, Nicotinic acid, Oxprenolol hydrochloride, Oxytetracycline hydrochloride, Penicillamine, Pentobarbitone sodium, Phenoxy Methyl Penicillin K, Phenytoin sodium, Piperazine adipate, Potassium chloride, Procainamide hydrochloride, Propranolol hydrochloride, Pseudoephedrine hydrochloride, Quinalbarbitone sodium, Quinine bisulphate, Ranitidine hydrochloride, Sodium amino salicylate, Sodium fusidate, sodium valproate, Streptomycin sulphate, Tetracycline hydrochloride, Topiramate, Troxidone, Verapamil hydrochloride and the like and their pharmaceutically acceptable salts, ester and hydrates.

68. The pharmaceutical composition of claim 67, wherein the active ingredient is Nicotinic acid.

69. The pharmaceutical composition of claim 55, wherein the active pharmaceutical ingredient is a high soluble low dose API or a derivative thereof.

70. The pharmaceutical composition of claim 69, wherein the high soluble low dose API or a derivative is selected from the group consisting of Amitriptylline hydrochloride, captopril, Clonidine hydrochloride, Colchicin, Cyclophosphamide, Diphenhydramine hydrochloride, Dothiepen hydrochloride, Doxepin hydrochloride Ephedrine hydrochloride, Ergometrine maleate, Ergometrine tartrate, Fenfluramine hydrochloride, Folic acid, Glyceryl trinitrate, Hyoscine hydrobromide, Hyoscine buytlbromide, Imipramine hydrochloride, Isoprenaline sulphate, Isosorbide dinitrate, Isosorbide-5-mononitrate, Levocetrizine hydrochloride, Methadone hydrochloride, Methdilazine hydrochloride, Metoclopramide hydrochloride, Neostigmine bromide, Oxybutynin hydrochloride, Perindopril erbumine, Pethidine hydrochloride, Phenformin hydrochloride, Pheniramine maleate, Phenobarbitone sodium, Primaquine phosphate,

Promethazine hydrochloride, Propantheline bromide, Propranolol hydrochloride, Pyridoxine hydrochloride, Salbutamol sulphate, Terbutaline sulphate, Thiamine hydrochloride, Timolol maleate, Tizanidine hydrochloride, Trifluoperazine hydrochloride, Triflupromazine hydrochloride, Triprolidine hydrochloride, Warfarin sodium and the like and their pharmaceutically acceptable salts, ester and hydrates.

71. The pharmaceutical composition of claim 70, wherein the active ingredient is Oxybutynin hydrochloride.

72. The pharmaceutical composition of claim 55, wherein the active pharmaceutical ingredient is a low soluble high dose API or a derivative thereof.

73. The pharmaceutical composition of claim 72, wherein the low soluble high dose API or a derivative is selected from the group consisting of Acetazolamide, Allopurinol, Atenolol, Carbamazepine, Cefadroxil, Cephalexin, Chloramphenicol, Cefuroxime Axetil, Chlorthalidone, Cilastozol, Cimetidine, Clarithromycin, Clofazemine, Dapsone, Diclofenac sodium, Diiodohydroxy quinolone, Diloxanide furoate, Disulfiram, Erythromycin, Erythromycin estolate, Erythromycin stearate, Ethacrynic cid, Ethionamide,, Ethopropazine hydrochloride, Ferrous fumarate, Fluconazole, Flurbiprofen, Furazolidone, Griseofulvin, Hydrochlorthiazide, Ibuprofen, Itraconazole, Ketoconazole, Ketoprofen, Labetalol hydrochloride, Levodopa, Linezolid, Lithium carbonate, Magaldrate, Mebendazole, Mefenamic acid, Megestrol acetate, Mercaptopurine, Mesalamimne, Nalidixic acid, Nateglinide, Niclosamide, Nitrofurantoin, Norfloxacin, Oxcarbazepine, Oxyphenbutazone, Paracetamol, Phenindione, Phenobarbitone, Phenylbutazone, Phenylsulphathiazole, Piperazine phosphate, Proguanil hydrochloride, Promethazine theoclate, Propylthiouracil, Quinidine sulphate, Quinine sulphate, Quinidochlor, Rifampicin, Simvastatin, Spironolactone, Succinylsulphathiazole, Sulphadiazine, Sulphadimethoxine, Sulphadimidine, Sulphafurazole, Sulphaphenazole, Thiabendazole, Tinidazole, Tolbutamide, Triamterene, Sulphamethoxazole and the

like and their pharmaceutically acceptable salts, ester and hydrates.

74. The pharmaceutical composition of claim 73, wherein the active ingredient is Clarithromycin.

75. The pharmaceutical composition of claim 55, wherein the active pharmaceutical ingredient is a low soluble low dose API or a derivative thereof.

76. The pharmaceutical composition of claim 75, wherein the low soluble low dose API or a derivative is selected from the group consisting of Alprazolam, Amiloride hydrochloride, Astemizole, Atorvastatin, Benzhexol hydrochloride, Betamethasone, Bromhexine hydrochloride, Bromocryptine mesylate, Buprenorphine hydrochloride, carbimazole, Chlordiazepoxide, Citalopram, Cortisone acetate, cyproheptadine hydrochloride, diazepam, Desloratadine, Dexamethasone hydrochloride, Dextromethorphan hydrochloride, dicyclomine hydrochloride, Dienoestrol, Digitoxin, Digoxin, Domperidone, Dydrogesterone, enalapril maleate, Esomeprazole, Ethinyloestradiol, Ethyloestrenol, Fludrocortisone acetate, Frusemide, Glibenclamide, Glimepiride, Haloperidol, Indomethacin, Isoxsuprine hydrochloride, Lanatoside C, Lercanidipine hydrochloride, Levonorgesrtel, Lomustine, Loratadine, Isoxuprine hydrochloride, methotrexate, Mecizine hydrochloride, Melphalan, Methotrexate, Methylergometrine maleate, Methylprednisolone, Mianserin hydrochloride, Mosapride, Nicoumalone, Nifedipine, Nitrazepam, Norethisterone, nortriptyline hydrochloride, Omeprazole, Ormeloxifene hydrochloride, Pentazocine hydrochloride, Phenindamine tartrate, piroxicam, prazosin hydrochloride, Prednisolone, Prednisone, Prochlorperazine maleate, Repaglinide, Riboflavinee, Rosuvastatin, Stilbostrol, Tamoxifen citrate, Thyroxine sodium, triamcinilone, Trimethoprim, Valdecoxib, Zolpidem tartrate and the like and their pharmaceutically acceptable salts, ester and hydrates.

77. The pharmaceutical composition of claim 76, wherein the active ingredient is Alprazolam.

78. The pharmaceutical composition of claim 76, wherein the active ingredient is Lercanidipine hydrochloride.

79. The pharmaceutical composition of claim 55, wherein the primary release modifying agent is a low molecular weight polyethylene oxide.

80. The pharmaceutical composition of claim 55, wherein the low molecular weight polyethylene oxide has a molecular weight of at least about 100,000.

81. The pharmaceutical composition of claim 55, wherein the low molecular weight polyethylene oxide has a molecular weight ranging from 100,000 to 900,000.

82. The pharmaceutical composition of claim 55, wherein the auxiliary release modifying agent is a starch derivative selected from pregelatinized starch, partially pregelatinized starch, retrograded starch, or a combination thereof.

83. The pharmaceutical composition of claim 55, wherein the auxiliary release modifying agent is a retrograded starch.

84. The pharmaceutical composition of claim 55, wherein said composition further comprises at least one pharmaceutically acceptable additive selected from diluents, fillers, binders, glidants, or lubricants.

85. The pharmaceutical composition of claim 55, wherein said composition further comprises an optional coating which is designed for the modification of drug release.

86. The pharmaceutical composition of claim 85, wherein the coating composition is selected from the group consisting of cellulose ethers such as ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, others such as polyvinyl alcohol, polyvinyl pyrrolidone, methacrylic acid derivatives, resins, clays, long chain hydrocarbons, long chain carboxylic acids, long chain carboxylic acid esters, long chain alcohols and the like or mixtures thereof.

87. The pharmaceutical composition of claim 55, wherein said composition further comprises an optional coating which is not designed for the modification of drug release.

88. The pharmaceutical composition of claim 87, wherein the coating composition is selected from the group consisting of cellulose ethers such as ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, and others such as polyvinyl alcohol, polyvinyl pyrrolidone, methacrylic acid derivatives, resins, clays, long chain hydrocarbons, long chain carboxylic acids, long chain carboxylic acid esters, long chain alcohols and the like and mixtures thereof.

89. The pharmaceutical composition of claim 55, wherein said composition comprises from about 0.1 percent weight to about 90 percent weight of the active pharmaceutical ingredient.

90. The pharmaceutical composition of claim 89, wherein said composition comprises from about 0.1 percent weight to about 80 percent weight of the active pharmaceutical ingredient.

91. The pharmaceutical composition of claim 55, wherein the composition comprises from about 1 percent weight to about 90 percent weight of the release modifying complex.

92. The pharmaceutical composition of claim 91, wherein the composition comprises from about 5 percent weight to about 85 percent weight of the release modifying complex.

93. The pharmaceutical composition of claim 92, wherein the composition comprises from about 10 percent weight to about 80 percent weight of the release modifying complex.

94. The pharmaceutical composition of claim 55, wherein the primary release modifying agent comprises from about 1 percent weight to about 90 percent weight of the release modifying complex.

95. The pharmaceutical composition of claim 94, wherein the primary release modifying agent comprises from about 5 percent weight to about 80 percent weight of the release modifying complex.

96. The pharmaceutical composition of claim 95, wherein the primary release modifying agent comprises from about 5 percent weight to about 70 percent weight of the release modifying complex.

97. The pharmaceutical composition of claim 55, wherein the auxiliary release modifying agent comprises from about 1 percent weight to about 95 percent weight of the release modifying complex.

98. The pharmaceutical composition of claim 97, wherein the auxiliary release modifying agent comprises from about 5 percent weight to about 95 percent weight of the release modifying complex.

99. The pharmaceutical composition of claim 98, wherein the auxiliary release modifying agent comprises from about 10 percent weight to about 95 percent weight of the release modifying complex.

100. A controlled release pharmaceutical composition comprising a pharmaceutically active ingredient and a release modifying complex, wherein said release modifying complex comprises a synergistic combination of (a) a secondary release modifying agent selected from a high molecular weight polyethylene oxide and (b) an auxiliary release modifying agent selected from a starch derivative, and said primary release modifying agent and auxiliary release modifying agent are present in synergistic effective amounts to extend the release of the active pharmaceutical ingredient.

101. The pharmaceutical composition of claim 100, wherein the active pharmaceutical ingredient is a macrolide or azide antibiotic or a derivative thereof.

102. The pharmaceutical composition of claim 101, wherein the macrolide is an erythromycin derivative or its pharmaceutically acceptable hydrates, salts or esters.

103. The pharmaceutical composition of claim 100, wherein the azide is azithromycin, or its pharmaceutically acceptable hydrates, salts or esters.

104. The pharmaceutical composition of claim 102, wherein the erythromycin derivative is selected from the group consisting of clarithromycin, josamycin, midecamycin, kitamycin, roxithromycin, rokitamycin, oleandomycin, miocamycin,

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flurithromycin, and rosaramicin, and their pharmaceutically acceptable hydrates, salts and esters.

105. The pharmaceutical composition of claim 100, wherein the active pharmaceutical ingredient is a penicillin antibiotic or a derivative thereof.

106. The pharmaceutical composition of claim 105, wherein the penicillin derivative is selected from the group consisting of Amoxicillin, Ampicillin, Ampicillin Sodium, Apalcillin, Aspoxicillin, Azlocillin, Aztreonam, Bacampicillin, Cabenicillin, Carfecillin, Carindacillin, Ciclacillin, Cloxacillin, Dicloxacillin, and their pharmaceutically acceptable hydrates, salts and esters.

107. The pharmaceutical composition of claim 100, wherein the active pharmaceutical ingredient is a cephalosporin antibiotic or a derivative thereof.

108. The pharmaceutical composition of claim 107, wherein the cephalosporin derivative is selected from the group consisting of Cefacetrile, Cefadroxil, Cefaloridine, Cefalothin Sodium, Cefapirin, Cefazaflur, Cefazedone, Cefazolin, Cefradine, Ceftezole, Cefsulodin Sodium, Cefamandole, Cefonicid, Cefoperazone, Cefuroxime, Cefuzonam, Cefbuperazone, Cefoxitin, Cefminox, Cefmetazole, Cefotetan, Loracarbef, Cefmenoxime, Cefodizime Sodium, Cefotaxime, Cefpimizole, Cefpiramide, Ceftazidime, Ceftiolene, Ceftizoxime, Ceftriaxone, Cefepime, Cefetecol, Cefpirome, Cefquinome, Cefalosporin C, Cefozopran Hydrochloride, Cefaclor, Cefadroxil, Cefalexin, Cefaloglycine, Cefatrizine, Cefdinir, Cefetamet Pivoxil, Cefixime, Ceforanide, Cefotiam, Cefpodoxime, Cefpodoxime Proxetil, Cefprozil, Cefradine, Cefroxadine, Cefteram Pivoxil, Ceftibuten, Cefuroxime Axetil, and their pharmaceutically acceptable hydrates, salts and esters.

109. The pharmaceutical composition of claim 100, wherein the active pharmaceutical ingredient is a quinolone antibiotic or a derivative thereof.

110. The pharmaceutical composition of claim 109, wherein the quinolone derivative is selected from the group consisting of Nalidixic Acid, Cinoxacin, Oxolinic Acid, Flumequine, Pipemidic Acid, Rosoxacin, Norfloxacin, Lomefloxacin, Ofloxacin, Enrofloxacin, Ciprofloxacin, Enoxacin, Amifloxacin, Fleroxacin, Gatifloxacin, Gemifloxacin, Pefloxacin, Rufloxacin, Sparfloxacin, Temafloxacin, Tosufloxacin, Grepafloxacin, Levofloxacin, Moxifloxacin, Trovafloxacin, and their pharmaceutically acceptable hydrates, salts and esters.

111. The pharmaceutical composition of claim 100, wherein the active pharmaceutical ingredient is a high soluble high dose API or a derivative thereof.

112. The pharmaceutical composition of claim 111, wherein the high soluble high dose API or a derivative is selected from the group consisting of Acebutolol hydrochloride, Amantadine hydrochloride, Aminocaproic acid, Aminophylline, Amodiaquine hydrochloride, Ascorbic acid, Bupropion hydrochloride, Carbenoxolone sodium, Cefuroxime sodium, Chloroquine phosphate, Chloroquine sulphate, Chlorpromazine hydrochloride, Ciprofloxacin hydrochloride, Cloxacillin sodium, Cycloserine, Diltiazem hydrochloride, Diethyl carbamazine citrate, Doxycycline hydrochloride, Ethosuximide, Ferrous gluconate, Isoniazid, Levamisole hydrochloride,Levetiracetam, Lincomycin hydrochloride, Mebeverine hydrochloride, Mepyramine maleate, Metformin hydrochloride, Metoprolol tartrate, Metoprolol succinate, Niacin, Nicotinamide, Nicotinic acid, Oxprenolol hydrochloride, Oxytetracycline hydrochloride, Penicillamine, Pentobarbitone sodium, Phenoxy Methyl Penicillin K, Phenytoin sodium, Piperazine adipate, Potassium chloride, Procainamide hydrochloride, Propranolol hydrochloride, Pseudoephedrine hydrochloride, Quinalbarbitone sodium, Quinine bisulphate, Ranitidine hydrochloride, Sodium amino salicylate, Sodium fusidate, sodium valproate, Streptomycin sulphate, Tetracycline hydrochloride, Topiramate, Troxidone, Verapamil hydrochloride

and the like and their pharmaceutically acceptable salts, ester and hydrates.

113. The pharmaceutical composition of claim 112, wherein the active ingredient is Nicotinic acid.

114. The pharmaceutical composition of claim 100, wherein the active pharmaceutical ingredient is a high soluble low dose API or a derivative thereof.

115. The pharmaceutical composition of claim 114, wherein the high soluble low dose API or a derivative is selected from the group consisting of Amitriptylline hydrochloride, captopril, Clonidine hydrochloride, Colchicin, Cyclophosphamide, Diphenhydramine hydrochloride, Dothiepen hydrochloride, Doxepin hydrochloride Ephedrine hydrochloride, Ergometrine maleate, Ergometrine tartrate, Fenfluramine hydrochloride, Folic acid, Glyceryl trinitrate, Hyoscine hydrobromide, Hyoscine buytlbromide, Imipramine hydrochloride, Isoprenaline sulphate, Isosorbide dinitrate, Isosorbide-5-mononitrate, Levocetrizine hydrochloride, Methadone hydrochloride, Methdilazine hydrochloride, Metoclopramide hydrochloride, Neostigmine bromide, Oxybutynin hydrochloride, Perindopril erbumine, Pethidine hydrochloride, Phenformin hydrochloride, Pheniramine maleate, Phenobarbitone sodium, Primaquine phosphate, Promethazine hydrochloride, Propantheline bromide, Propranolol hydrochloride, Pyridoxine hydrochloride, Salbutamol sulphate, Terbutaline sulphate, Thiamine hydrochloride, Timolol maleate, Tizanidine hydrochloride, Trifluoperazine hydrochloride, Triflupromazine hydrochloride, Triprolidine hydrochloride, Warfarin sodium and the like and their pharmaceutically acceptable salts, ester and hydrates.

116. The pharmaceutical composition of claim 115, wherein the active ingredient is Oxybutynin hydrochloride.

117. The pharmaceutical composition of claim 100, wherein the active pharmaceutical ingredient is a low soluble high dose API or a derivative thereof.

118. The pharmaceutical composition of claim 117, wherein the low soluble high dose API or a derivative is selected from the group consisting of Acetazolamide, Allopurinol, Atenolol, Carbamazepine, Cefadroxil, Cephalexin, Chloramphenicol, Cefuroxime Axetil, Chlorthalidone, Cilastozol, Cimetidine, Clarithromycin, Clofazemine, Dapsone, Diclofenac sodium, Diiodohydroxy quinolone, Diloxanide furoate, Disulfiram, Erythromycin, Erythromycin estolate, Erythromycin stearate, Ethacrynic cid, Ethionamide,, Ethopropazine hydrochloride, Ferrous fumarate, Fluconazole, Flurbiprofen, Furazolidone, Griseofulvin, Hydrochlorthiazide, Ibuprofen, Itraconazole, Ketoconazole, Ketoprofen, Labetalol hydrochloride, Levodopa, Linezolid, Lithium carbonate, Magaldrate, Mebendazole, Mefenamic acid, Megestrol acetate, Mercaptopurine, Mesalamimne, Nalidixic acid, Nateglinide, Niclosamide, Nitrofurantoin, Norfloxacin, Oxcarbazepine, Oxyphenbutazone, Paracetamol, Phenindione, Phenobarbitone, Phenylbutazone, Phenylsulphathiazole, Piperazine phosphate, Proguanil hydrochloride, Promethazine theoclate, Propylthiouracil, Quinidine sulphate, Quinine sulphate, Quinidochlor, Rifampicin, Simvastatin, Spironolactone, Succinylsulphathiazole, Sulphadiazine, Sulphadimethoxine, Sulphadimidine, Sulphafurazole, Sulphaphenazole, Thiabendazole, Tinidazole, Tolbutamide, Triamterene, Sulphamethoxazole and the like and their pharmaceutically acceptable salts, ester and hydrates.

119. The pharmaceutical composition of claim 118, wherein the active ingredient is Clarithromycin.

120. The pharmaceutical composition of claim 100, wherein the active pharmaceutical ingredient is a low soluble low dose API or a derivative thereof.

121. The pharmaceutical composition of claim 120, wherein the low soluble low dose API or a derivative is selected from the group consisting of Alprazolam, Amiloride hydrochloride, Astemizole, Atorvastatin, Benzhexol hydrochloride, Betamethasone, Bromhexine hydrochloride; Bromocryptine mesylate,

Buprenorphine hydrochloride, carbimazole, Chlordiazepoxide, Citalopram, Cortisone acetate, cyproheptadine hydrochloride, diazepam, Desloratadine, Dexamethasone hydrochloride, Dextromethorphan hydrochloride, dicyclomine hydrochloride, Dienoestrol, Digitoxin, Digoxin, Domperidone, Dydrogesterone, enalapril maleate, Esomeprazole, Ethinyloestradiol, Ethyloestrenol, Fludrocortisone acetate, Frusemide, glibenclamide, Glimepiride, haloperidol, Indomethacin, Isoxsuprine hydrochloride, Lanatoside C, Lercanidipine hydrochloride, Levonorgesrtel, Lomustine, Loratadine, Isoxuprine hydrochloride, methotrexate, Mecizine hydrochloride, Melphalan, Methotrexate, Methylergometrine maleate, Methylprednisolone, Mianserin hydrochloride, Mosapride, Nicoumalone, Nifedipine, Nitrazepam, Norethisterone, nortriptyline hydrochloride, Omeprazole, Ormeloxifene hydrochloride, Pentazocine hydrochloride, Phenindamine tartrate, piroxicam, prazosin hydrochloride, Prednisolone, Prednisone, Prochlorperazine maleate, Repaglinide, Riboflavinee, Rosuvastatin, Stilbostrol, Tamoxifen citrate, Thyroxine sodium, triamcinilone, Trimethoprim, Valdecoxib, Zolpidem tartrate and the like and their pharmaceutically acceptable salts, ester and hydrates.

122. The pharmaceutical composition of claim 121, wherein the active ingredient is Alprazolam.

123. The pharmaceutical composition of claim 121, wherein the active ingredient is Lercanidipine hydrochloride.

124. The pharmaceutical composition of claim 100, wherein the secondary release modifying agent is a high molecular weight polyethylene oxide.

125. The pharmaceutical composition of claim 100, wherein the high molecular weight polyethylene oxide has a molecular weight of at least about 1,000,000.

126. The pharmaceutical composition of claim 100, wherein the high molecular weight polyethylene oxide has a molecular weight ranging from 1,000,000 to 9,000,000.

127. The pharmaceutical composition of claim 100, wherein the auxiliary release modifying agent is a starch derivative selected from pregelatinized starch, partially pregelatinized starch, retrograded starch, or a combination thereof.

128. The pharmaceutical composition of claim 100, wherein the auxiliary release modifying agent is a retrograded starch.

129. The pharmaceutical composition of claim 100, wherein said composition further comprises at least one pharmaceutically acceptable additive selected from diluents, fillers, binders, glidants, and lubricants.

130. The pharmaceutical composition of claim 100, wherein said composition further comprises an optional coating which is designed for the modification of drug release.

131. The pharmaceutical composition of claim 130, wherein the coating composition is selected from the group consisting of cellulose ethers such as ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, others such as polyvinyl alcohol, polyvinyl pyrrolidone, methacrylic acid derivatives, resins, clays, long chain hydrocarbons, long chain carboxylic acids, long chain carboxylic acid esters, long chain alcohols and the like and mixtures thereof.

132. The pharmaceutical composition of claim 100, wherein said composition further comprises an optional coating which is not designed for the modification of drug release.

133. The pharmaceutical composition of claim 132, wherein the coating composition is selected from the group consisting of cellulose ethers such as ethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, and others such as polyvinyl alcohol, polyvinyl pyrrolidone, methacrylic acid derivatives, resins, clays, long chain hydrocarbons, long chain carboxylic acids, long chain carboxylic acid esters, long chain alcohols and the like and mixtures thereof.

134. The pharmaceutical composition of claim 100, wherein said composition comprises from about 0.1 percent weight to about 90 percent weight of the active pharmaceutical ingredient.

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135. The pharmaceutical composition of claim 134, wherein said composition comprises from about 0.1 percent weight to about 80 percent weight of the active pharmaceutical ingredient.

136. The pharmaceutical composition of claim 100, wherein the composition comprises from about 1 percent weight to about 90 percent weight of the release modifying complex.

137. The pharmaceutical composition of claim 136, wherein the composition comprises from about 5 percent weight to about 85 percent weight of the release modifying complex.

138. The pharmaceutical composition of claim 137, wherein the composition comprises from about 10 percent weight to about 80 percent weight of the release modifying complex.

139. The pharmaceutical composition of claim 100, wherein the secondary release modifying agent comprises from about 1 percent weight to about 95 percent weight of the release modifying complex.

140. The pharmaceutical composition of claim 139, wherein the secondary release modifying agent comprises from about 5 percent weight to about 90 percent weight of the release modifying complex.

141. The pharmaceutical composition of claim 100, wherein the auxiliary release modifying agent comprises from about 1 percent weight to about 95 percent weight of the release modifying complex.

142. The pharmaceutical composition of claim 141, wherein the auxiliary release modifying agent comprises from about 5 percent weight to about 95 percent weight of the release modifying complex.

143. The pharmaceutical composition of claim 142, wherein the auxiliary release modifying agent comprises from about 10 percent weight to about 95 percent weight of the release modifying complex.

144. A process for the preparation of controlled release pharmaceutical composition of the present invention.

145. A pharmaceutical composition which gives an improved method of extended release of the API from the dosage form, comprising of the API, the release retarding complex and the other required pharmaceutically acceptable additives; the improvements comprising the synergistic combination of release retardant complex in synergistic effective amounts to extend the release of the API.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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(54) Title: MODIFIED RELEASE COMPOSITIONS COMPRISING TACROLIMUS

(57) Abstract: A modified release composition comprising tacrolimus releases less than 20% w/w of the active ingredient within 0.5 hours when subjected to an in vitro dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium and has increased bioavailability by effectively reducing or even avoiding the effects of CYP3A4 metabolism. The modified composition may be coated with an enteric coating; and/or may comprise a solid dispersion or a solid solution of tacrolimus in a hydrophilic or water-miscible vehicle and one or more modifying release agents; and/or may comprise a solid dispersion or a solid solution of tacrolimus in an amphiphilic or hydrophobic vehicle and optionally one or more modifying release agents.

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CLAIMS

1. A solid pharmaceutical composition comprising an active ingredient selected among tacrolimus and analogues thereof, wherein less than 20% w/w of the active ingredient is released within 0.5 hours, when subjected to an in vitro dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium.

2. The solid pharmaceutical composition according to claim 1, wherein less than 20% w/w of the active ingredient is released within 3 hours.

3. The solid pharmaceutical composition according to claim 1, wherein less than 10% w/w of the active ingredient is released within 3 hours.

4. The solid pharmaceutical composition according to claim 1, wherein at least 50 % w/w of the active ingredient is released within 4 hours when subjected to an in vitro dissolution test using USP Paddle method and using 0.1N HCl as dissolution medium during the first 2 hours and then using a dissolution medium having a pH of 6.8.

5. The solid pharmaceutical composition according to claim 1, wherein at least 50 % w/w of the active ingredient is released within 2.5 hours when subjected to an in vitro dissolution test using USP Paddle method and using 0.1N HCl as dissolution medium during the first 2 hours and then using a dissolution medium having a pH of 6.8.

8. A solid pharmaceutical composition according to claim 1, wherein less than 50 w/w% of the active pharmaceutical ingredient is released within 8 hours, preferably within 15 hours, when subjected to an in vitro dissolution test using USP Paddle method and an aqueous dissolution medium adjusted to pH 4.5 with 0.005% hydroxypropylcellulose.

9. The composition according to claim 8, wherein less than 40 w/w% of the active pharmaceutical ingredient is released within 8 hours, preferably within 15 hours.

10. The composition according to claim 1, which is designed to substantially avoid CYP3A4 metabolism in the gastrointestinal tract upon oral administration.

11. The composition according to claim 10, wherein the composition is coated with an enteric coating.

12. The composition according to claim 1 comprising a solid dispersion or solid solution of active ingredient in a hydrophilic or water-miscible vehicle and one or more modifying release agents.

13. The composition according to claim 1, wherein the active ingredient is dispersed or dissolved in a hydrophobic vehicle.

14. The composition according to claim 13, wherein the hydrophobic vehicle is an oil, an oily material, a wax or a fatty acid derivative.

15. The composition according to claim 14, wherein the hydrophobic vehicle is selected from the group consisting of straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as stearic acid, myristic acid, palmitic acid, higher alcohols such as cetanol, stearyl alcohol, low melting point waxes such as glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, and mixtures thereof.

16. The composition according to claim 15, wherein the hydrophobic vehicle is glyceryl monostearate (GMS).

17. The composition according to claim 12, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyethylene glycols, polyoxyethylene oxides, poloxamers, polyoxyethylene stearates, poly-epsilon caprolactone, polyglycolized glycerides such as Gelucire®, and mixtures thereof.

18. The composition according to claim 12, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyvinylpyrrolidones, polyvinyl-polyvinylacetate copolymers (PVP-PVA), polyvinyl alcohol (PVA), polymethacrylic polymers (Eudragit RS; Eudragit RL, Eudragit NE, Eudragit E), cellulose derivatives including hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, pectins, cyclodextrins, galactomannans, alginates, carragenates, xanthan gums and mixtures thereof.

19. The composition according to claim 12, wherein the vehicle is a polyethylene glycol (PEG).

20. The composition according to claim 12, wherein the polyethylene glycol has an average molecular weight of at least 1500.

21. The composition according to claim 12comprising a mixture of two or more hydrophilic or water-miscible vehicles.

22. The composition according to claim 12, wherein the mixture comprises a polyethylene glycol and a poloxamer in a proportion of between 1:3 and 10:1, preferably between 1:1 and 5:1, more preferably between and 3:2 4:1, especially between 2:1 and 3:1, in particular about 7:3.

23. The composition according to claim 12, wherein the poloxamer is poloxamer 188.

24. The composition according to claim 12, wherein the polyethylene glycol has an average molecular weight of about 6000 (PEG6000).

25. The composition according to claim 1 which further comprises one or more modifying release agents selected from the group consisting of water-miscible polymers, water-insoluble polymers, oils and oily materials.

26. The composition according to claim 25, wherein the water-insoluble polymer is selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose nitrate, and mixtures thereof.

27. The composition according to claim 26, wherein the oil or oily material is hydrophilic and selected from the group consisting of polyether glycols such as polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers; polyglycolized glycerides such as Gelucire® and mixtures thereof.

28. The composition according to claim 27, wherein Gelucire® is selected among Gelucire® 50/13, Gelucire® 44/14, Gelucire® 50/10, Gelucire® 62/05 and mixtures thereof.

29. The composition according to claim 25, wherein the oil or oily material is hydrophobic and selected from the group consisting of straight chain saturated hydrocarbons, sorbitan esters,

paraffins; fats and oils such as cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as stearic acid, myristic acid, palmitic acid, higher alcohols such as cetanol, stearyl alcohol, low melting point waxes such as glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, and mixtures thereof.

30. The composition according to claim 25, wherein the oil or oily hydrophobic material has a melting point of at least about 20°C.

31. The composition according to claim 25, wherein the water-miscible polymer is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, poloxamers, polyoxyethylene stearates, poly -ε-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA, polymethacrylic polymers and polyvinyl alcohol (PVA), poly(ethylene oxide) (PEO) and mixtures thereof.

32. The composition according to claim 31, wherein the polymethacrylic polymers are selected among Eudragit® RS, Eudragit® RL, Eudragit® NE and Eudragit® E.

33. The composition according to claim 11, which is entero-coated using a water-miscible polymer having a pH-dependant solubility in water.

34. The composition according to claim 33, wherein the water-miscible polymer is selected from the group consisting of polyacrylamides; phthalate derivatives such as acid phthalates of carbohydrates including amylose acetate phthalate, cellulose acetate phthalate, cellulose acetate terephtahalate, cellulose acetate isophthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropyl cellulose phthalate, hydroxypropylcellulose acetate phthalate, hydroxypropyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate (HMPCP), methylcellulose phthalate, methyl cellulose acetate phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate; phthalates of other compounds including polyvinyl acetate phthalate (PVAP); other cellulose derivatives including hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethylcellulose, cellulose acetate trimellitate; alginates; carbomers;

polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, methacrylic acid copolymers (for example Eudragit® L and Eudragit® S); styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers; shellac, starch glycolate; polacrylin; vinyl acetate and crotonic acid copolymers and mixtures thereof.

35. The composition according to claim 1 which further comprises one or more pharmaceutically acceptable excipients.

36. The pharmaceutical composition according to claim 35, wherein the pharmaceutically acceptable excipients are selected from the group consisting of fillers, diluents, disintegrants, binders and lubricants.

37. The pharmaceutical composition according to claim 35 in particulate form, for example in powder form.

38. The pharmaceutical composition according to claim 35, wherein the particles have a geometric weight mean diameter d_{gw} from about 10 µm to about 2000 µm, preferably from about 20 µm to about 2000 µm, especially from about 50 µm to about 300 µm.

39. The pharmaceutical composition according to claim 35, wherein the particles have a geometric weight mean diameter d_{gw} from about 50 µm to about 300 µm.

40. A dosage form comprising the pharmaceutical composition according to claim 35, which is a solid oral dosage form.

41. The dosage form according to claim 40, which is a unit dosage form.

42. The dosage form according to claim 40, which further comprises a pharmaceutically acceptable additive selected from the group consisting of flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents and absorption enhancing agents.

43. The dosage form according to claim 40, wherein at least one pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt

thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

44. The dosage form according to claim 40, wherein at least one pharmaceutically acceptable excipient is a silica acid or a derivative or salt thereof.

45. The dosage form according to claim 40, wherein at least one pharmaceutically acceptable excipient is silicon dioxide or a polymer thereof.

46. The dosage form according to claim 45, wherein the silicon dioxide product has properties corresponding to Aeroperl® 300, (available from Degussa, Frankfurt, Germany).

47. Use of the oral pharmaceutical composition according to claim 1 to enhance the oral bioavailability of tacrolimus.

48. Use of the solid composition according to claim 1 for the preparation of an oral dosage form, preferably tablets, capsules or sachets.

49. Use of the solid composition according to claim 1 for the preparation of granules, pellets microspheres or nanoparticles.

50. Use of the solid composition according to claim 1 for the preparation of a controlled or modified release solid dosage form.

51. Use of the solid composition according to claim 1 for the preparation of a delayed release solid dosage form.

52. Use of the solid composition according to claim 1 for the preparation of a topical dosage form.

53. A method for the preparation of the composition according to claim 12, the method comprising the step of dissolving or dispersing tacrolimus or an analogue thereof in a hydrophilic vehicle to obtain a solid solution or dispersion at ambient temperature.

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(54) Title: MODIFIED RELEASE FORMULATIONS OF OXCARBAZEPINE AND DERIVATIVES THEREOF

(57) Abstract: Oral once a day dosage forms comprising oxcarbazepine are disclosed.

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Claims

1. An oral dosage form comprising oxcarbazepine adapted to be administered once a day.

2. The oral dosage form comprising oxcarbazepine according to claim 1 which, when administered once a day, is released to produce constant MHD plasma levels over 24 hours.

3. The oral dosage form according to claim 1 or 2 consisting of a tablet core and a coating wherein the core comprises oxcarbazepine, optionally, a filler, and at least one further excipient selected from cellulose ethers, carboxyvinyl polymer of acrylic acid cross linked with alkyl ethers of sucrose or pentaerythritol and polymethacrylates.

4. The oral dosage form according to claim 3 wherein a cellulose ether is employed which is hydroxypropyl methyl cellulose.

5. The oral dosage form according to claim 4 wherein the weight ratio of total hydroxypropyl-methyl cellulose to oxcarbazepine is from about 1:10 to about 1:20.

6. The oral dosage form according to claim 3 wherein a cellulose ether is employed which is ethyl cellulose.

7. The oral dosage form according to claim 6 wherein the weight ratio of total ethyl cellulose to oxcarbazepine is from about 1:10 to about 1:20.

8. The oral dosage form according to claim 3 comprising a polymethacrylate which is trimethylammonium methacrylate.

9. The oral dosage form according to any one of claims 3 to 8 comprising as a filler microcrystalline cellulose.

10. The oral dosage form according to any one of claims 1 to 9 having a 80% or greater release of the oxcarbazepine dose within 1 hour indicated in standard in vitro dissolution

tests at 37 degrees Celsius in water using sodium dodecyl sulphate as a solubilizing agent at a concentration of 1% for a 600 mg dosage form.

11. The oral dosage form according to any one of claims 1 to 10 releasing oxcarbazepine at a constant release rate for 4 hours or more as indicated in standard in vitro dissolution tests at 37 degrees Celsius in water using sodium dodecyl sulphate as a solubilizing agent at a concentration of 1% for a 600 mg dosage form.

12. The oral dosage form according to claim 11 releasing about 80 % of oxcarbazepine within 8 hours.

13. An oral dosage form comprising oxcarbazepine which, when administered once a day, is released to produce constant MHD plasma levels over 24 hours.

14. Use of oxcarbazepine for the manufacture of an oral dosage form medicament to be administered to a patient once a day wherein oxcarbazepine is released to produce a constant profile over 24 hours for the treatment of epilepsy.

15. Use of oxcarbazepine for the manufacture of an oral dosage form medicament according to any one of claims 1 to 13 for the treatment of epilepsy.

16. A method of orally administering oxcarbazepine, e.g., for the treatment of epilepsy, said method comprising orally administering to a patient in need of oxcarbazepine therapy once-a-day an oral dosage form of any one of claims 1 to 13.

17. A method of reducing the variability of bioavailability levels of cyclosporin A for patients during oxcarbazepine therapy, said method comprising orally administering to a patient in need of oxcarbazepine therapy an oral dosage form of any one of claims 1 to 13.

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(54) Title: NOVEL ONCE-A-DAY CONTROLLED RELEASE SULFONYLUREA FORMULATION

(57) Abstract

This invention is directed to a novel solid matrixed controlled release, oral dosage form where the dosage form contains a therapeutically effective amount of a sulfonylurea or a salt or derivative thereof in the matrix. Further, the use of an aqueous alkalizing medium affords substantially complete bioavailability of the drug from the matrix of the tablet. The core tablets may optionally be coated with a coating material in the range of 2 % to 10 % with an enteric material or with a water insoluble material like ethyl cellulose.

What is claimed is:

1. A controlled release dosage form for oral administration comprising

a) a therapeutically effective amount of glipizide or a pharmaceutically acceptable salt thereof; and,

b) a controlled release matrix comprising a gelling agent, an ionizable gel strength enhancing agent and an inert diluent;

wherein: the ratio of gelling agent to inert diluent is from about 1:8 to about 8:1; the gelling agent comprises xanthan gum and locust bean gum in a ratio of from about 3:1 to about 1:3; the ionizable gel strength enhancing agent increases the gel strength of the controlled release matrix; and, the glipizide is suspended or dissolved in a pharmaceutically acceptable wetting agent prior to incorporation with the remaing ingredients of the controlled release matrix.

2. The controlled release dosage form of claim 1 wherein said oral dosage form is effective for once a day oral administration.

3. The controlled release oral dosage form of claim 1 wherein the controlled release matrix comprises: xanthan gum; locust bean gum; and dextrose.

4. The controlled release oral dosage form of claim 3 wherein the controlled release matrix comprises: 12.0%w/w xanthan gum; 18%w/w locust bean gum; and, 65%w/w dextrose.

5. The controlled release oral dosage form of claim 4 wherein the controlled release matrix additionally comprises ethylcellulose.

6. The controlled release oral dosage form of claim 5 wherein the ethylcellulose is present in an amount of 5%w/w.

7. The controlled release oral dosage form of claim 1 wherein the inert diluent is selected from the group consisting of a monosaccharide, a disaccharide, a polyhydric alcohol, microcrystalline cellulose, starch and mixtures thereof.

8. The controlled release oral dosage form of claim 7 wherein the inert diluent is selected from the group consisting of sucrose, dextrose, lactose, fructose, xylitol, sorbitol and mixtures thereof.

9. The controlled release oral dosage form of claim 8 wherein the inert diluent is dextrose.

10. The controlled release oral dosage form of claim 1 wherein the controlled release matrix is wet granulated with a aqueous solution comprising an alkalizing excipient present in an amount effective to provide a pH ranging from about 7.0 to about 9.0.

11. The controlled release oral dosage form of claim 10, wherein said sulfonylurea is solubilized in said alkalized solution.

12. The controlled release oral dosage form of claim 11 wherein the alkalizing excipient is selected from the group consisting of a monovalent metal alkali and a divalent metal alkali.

13. The controlled release oral dosage form of claim 12 wherein the alkalizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, N-methylglucamine, or L-lysine and mixtures thereof.

14. The controlled release oral dosage form of claim 12 wherein the alkalizing agent is present in an amount ranging from about 0.001 percent through about 10 percent by weight of the formulation.

15. The controlled release oral dosage form of claim 1 in the form of a unit dosage selected from the group consisting of a tablet, a caplet and a soluble capsule comprising a plurality of beads or particles.

16. The controlled release oral dosage form of claim 15 wherein the unit dosage form is further coated with a sustained release hydrophobic coating comprising a pharmaceutically acceptable hydrophobic polymer.

17. The controlled release oral dosage form of claim 16 wherein the hydrophobic coating is selected from the group consisting of ethyl cellulose, acrylic polymers, methacrylic polymers in an amount of from about 1 to about 30 percent, by weight of the total unit dosage form.

18. A method of manufacturing a controlled release oral dosage form suitable for once a day administration of a glipizide or a salt thereof comprising the steps of: a) granulating a controlled release matrix with an aqueous medium made alkaline by a pharmaceutically acceptable alkalizing agent present in an amount effective to provide a pH ranging from at least 7.0 to about 9.0 to produce a granulation;

b) suspending, dissolving or admixing a sulfonylurea compound in a pharmaceutically acceptable wetting agent to form an active agent composition;

c) mixing a suitable tableting lubricant, the active agent composition and said granulation to a lubricated granulation; and,

d) compressing said lubricated granulation into a solid dosage form; wherein the sulfonylurea is selected from the group consisting of tolbutamide, chlorpropamide, tolazamide, acetohexamide, glyburide, glibornuride, glisoxepide,

glipizide and gliclazide.

19. A method of treating type II diabetes comprising administering an at least once a day a solid controlled release oral dosage form comprising:

a) an effective amount of alkalized glipizide or a salt thereof,

b) a controlled release matrix which has been granulated with an aqueous medium made alkaline by pharmaceutically acceptable alkalizing agent present in an amount effective to provide a pH ranging from at least 7.0 to about 9.0,

wherein the controlled release oral dosage form provides a sustained release of glipizide over a period of 24 hours.

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(54) Title: PHARMACEUTICAL COMPOSITION FOR CONTROLLED RELEASE OF AN ACTIVE INGREDIENT

(57) Abstract: A pharmaceutical composition in the form of a tablet for controlled release of an active ingredient comprises a betalactam antibiotic such as cephalexin, cefaclor or their pharmaceutically acceptable hydrates, salts or esters as active ingredient, and a mixture of hydrophilic polymers selected from the group consisting of at least one sodium alginate and at least one xanthan gum as controlled release matrix; and optionally probenecid as an antibiotic adjuvant as either immediate release or controlled release part. The composition may also contain one or more of a water soluble and/or water dispersible diluent, wherein the quantities of the hydrophilic polymer matrix but still provides the desired once a day profile. The resulting modified release matrix formulation not containing probenecid may be administered once or twice daily. The resulting modified release matrix formulation containing probenecid may be administered once daily.

CLAIMS

1. A pharmaceutical composition for controlled release of an active ingredient, said composition comprising a controlled release matrix comprising a betalactam antibiotic or their pharmaceutically acceptable hydrates, salts or esters as the active ingredient, and a mixture of hydrophilic polymers, said hydrophilic polymers being selected from the group consisting of at least one sodium alginate and at least one xanthan gum; and optionally probenecid as either immediate release or controlled release part, wherein said composition comprises about 30 % to about 90 % by weight of active ingredient and about 1 % to about 25 % by weight of hydrophilic polymers comprising from about 0.1 % to about 20 % by weight of sodium alginate and about 0.1 % to about 20 % by weight of xanthan gum.
2. The composition as claimed in claim 1, wherein the betalactam antibiotic is selected from cephalexin, cefaclor or their pharmaceutically acceptable hydrates, salts or esters.
3. The composition as claimed in claim 1, wherein the active is released at a rate suitable for once daily or twice daily administration of the composition.
4. The composition as claimed in claim 1 in the form of a solid dosage.
5. The composition as claimed in claim 1, wherein the controlled release part of the pharmaceutical composition comprises from about 30 % to about 90 % by weight of active ingredient or their pharmaceutically acceptable hydrates, salts or esters and about 1 % to about 20 % by weight of hydrophilic polymers comprising of a low or a medium viscosity grade sodium alginate in an amount from about 0.1 % to about 15 % by weight and a medium or a high viscosity grade xanthan gum in an amount from about 0.1 % to about 15 % by weight.
6. The composition as claimed in claim 1, wherein the controlled release part of the pharmaceutical composition comprises from about 30 % to about 90 % by weight of active ingredient or their pharmaceutically acceptable hydrates, salts or esters and about 1 % to about 18 % by weight of hydrophilic polymers comprising of a low or a medium viscosity grade sodium alginate in an amount from about 1.0 % to about 10.0 % by weight and a medium or a high viscosity grade xanthan gum in an amount from about 1.0 % to about 10.0 % by weight.

7. The composition as claimed in claim 1, which further contains at least one water soluble or water dispersible diluent.
8. The composition as claimed in claim 7, wherein the water soluble or water dispersible diluent comprises about 1 % to about 30 % by weight of the composition.
9. The composition as claimed in claim 7, wherein the diluent is lactose.
10. The composition as claimed in claim 9, wherein the amount of lactose is from about 4 % to about 20 % by weight of the composition.
11. The composition as claimed in claim 7, wherein the diluent is microcrystalline cellulose.
12. The composition as claimed in claim 11, wherein the amount of microcrystalline cellulose is from about 4 % to about 15 % by weight of the composition.
13. The composition as claimed in claim 1 further comprising magnesium stearate, talc, colloidal silicon dioxide or mixtures thereof in amounts from about 0.2 % to about 5 % by weight each.
14. A composition as claimed in any preceding claim wherein a multidose contains 250 mg to 2 g active ingredient.
15. A composition as claimed in claims 1 to 13 in dosage unit form containing 100 to 1 g of active ingredient.
16. A process for the preparation of a pharmaceutical composition as claimed in claim 1, comprising mixing together the active ingredient and the hydrophilic polymers, and optionally probenecid together with at least one lubricant to form a blend, further compacting, sizing, blending and compressing into tablets.
17. A process for the preparation of a pharmaceutical composition as claimed in claim 1, comprising mixing together the active ingredient and the hydrophilic polymers together with at least one lubricant to form a blend, further compacting, sizing, blending and compressing into tablets along with immediate release probenecid part.
18. The composition as claimed in claim 1, wherein probenecid is present in an amount from about 250 mg to about 1000 mg.
19. The composition as claimed in claim 1, which further contains a disintegrating agent from about 2 % to about 9 % by weight of immediate release part.

20. The composition as claimed in claim 19 wherein disintegrating agent is sodium starch glycolate.

21. A process for the preparation of pharmaceutical composition as claimed in claim 1, comprising mixing together probenecid, diluent and disintegrating agent together, compacting, sizing and blending with lubricant and compressing the blend into tablets along with controlled release part of the active ingredient.

22. The composition as claimed in claim 1 wherein, the controlled release part in a hydrophilic matrix and immediate release probenecid part are compressed together into a tablet dosage form.

23. The composition as claimed in claim 1 wherein, the controlled release part in a hydrophilic matrix and immediate release probenecid part are compressed separately into tablets and packed in a way to be administered simultaneously.

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Baichwal

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[54] SUSTAINED RELEASE MATRIX FOR HIGH-DOSE INSOLUBLE DRUGS

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[58] Field of Search 424/468, 464; 426/481; 514/960

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[57] ABSTRACT

Sustained release dosage forms of high dose insoluble drugs such as ibuprofen and methods for their manufacture are disclosed.

46 Claims, 2 Drawing Sheets

TABLE 11

Dissolution Results					
Time (Hr)	Ex. 7	Ex. 8	Ex. 9	Ex. A	Ex. B
0	0	0	0	0	0
1	1.7	3.5	2.3	1.3	0.2
2	3.6	10.2	8.1	3.1	1.1
3	4.8	11.8	10.1	5.9	2.5
4	11.0	22.0	26.0	16.3	11.4
6	15.3	27.9	32.4	29.9	23.3
8	19.1	34.4	41.4	46.5	36.5
12	27.7	48.8	72.7	62.8	69.3
16	46.6	58.5	98.3	73.3	85.2
18	56.4	61.6	100.2	79.8	91.5
24	67.4	70.0	100.9	88.1	

The dissolution results are also graphically depicted in FIG. 2.

The results show that a suitable sustained release of ibuprofen is still obtained although the tablet formulations of Examples 7–9 contain 50% less sustained release excipient than Examples 4–6.

The Examples provided above are not meant to be exclusive. Many other variations of the present invention will be apparent to those skilled in the art, and are contemplated to be within the scope of the present invention.

What is claimed is:

1. A sustained release dosage form, comprising from about 500 mg to about 1000 mg of an insoluble NSAID and an effective amount of a sustained release carrier comprising xanthan gum, locust bean gum and a pharmaceutically acceptable inert diluent, wherein the total weight of said dosage form is from about 110 percent to about 140 percent by weight of said insoluble NSAID, said xanthan gum and said locust bean gum comprising from about 7 to about 40 percent by weight of the dosage form, said locust bean gum comprising from about 50% to about 95% of the sustained release carrier, said dosage form providing a dissolution of said NSAID in-vitro when measured by the USP Type II (Paddle) Method, of from about 6 percent by weight of said NSAID released after about 2 hours and a t_5 at about 12 to about 16 hours.

2. The dosage form of claim 1, wherein said NSAID is selected from the group consisting of ibuprofen, calcium fenoprofen, naproxen, etodolac, mefenamic acid, tolmetin, and mixtures thereof.

3. The dosage form of claim 1, wherein said NSAID is ibuprofen.

4. The sustained release dosage form of claim 1, wherein the dosage form is a tablet.

5. A sustained release dosage form, comprising from about 500 mg to about 1000 mg of an insoluble NSAID and an effective amount of a sustained release carrier comprising xanthan sum, locust bean (ium and a pharmaceutically acceptable inert diluent, wherein the total weight of said dosage form is from about 110 percent to about 140 percent by weight of said insoluble NSAID, said xanthan gum and said locust bean gum comprising, from about 7 to about 40 percent by weight of the dosage form, said locust bean gum comprising from about 50% to about 95% of the sustained release carrier, said dosage form providing a dissolution of said NSAID in-vitro when measured by the USP Type II (Paddle) Method, of from about 20 percent by weight of said NSAID released after about 4 hours and a t_{50} at about 12 to about 16 hours.

6. The dosage form of claim 5, wherein the said NSAID is selected from the group consisting of ibuprofen, calcium fenoprofen, naproxen, etodolac, mefenamic acid, tolmetin, and mixtures thereof.

7. The dosage form of claim 5, wherein the said NSAID is ibuprofen.

8. An oral sustained release dosage form, comprising a matrix comprising from about 500 to about 1000 mg of ibuprofen and a sustained release carrier comprising at least about 5% of xanthan gums about 50% to about 95% of a crosslinking agent comprising locust bean gum and a pharmaceutically accepable inert diluent; wherein the weight ratio of said ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.06 to about 1:0.4, said dosage form providing a dissolution of said ibuprofen in-vitro when measured by the USP Type II (Paddle) Method, of from about 6 percent by weight of said ibuprofen released after about 2 hours and a t_{50} at about 12 to about 16 hours.

9. The oral sustained release dosage form of claim 8, wherein the weight ratio of said ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.08 to about 1:0.25.

10. The oral sustained release dosage form of claim 8, comprising from about 800 to about 1000 mg ibuprofen.

11. A sustained release tablet comprising

from about 500 mg to about 1000 mg of an insoluble NSAID in a sustained release matrix comprising xanthan gum, locust bean gum and a pharmaceutically accepable inert diluent, wherein the total weight of said tablet is from about 110 percent to about 140 percent by weight of said insoluble NSAID, said xanthan gum and said locust bean gum comprising from about 7 to about 40 percent by weight of the tablet said locust bean gum comprising from about 50% to about 95% of the sustained release matrix, said tablet providing a dissolution of said NSAID in-vitro when measured by the USP Type II (Paddle) Method, of from about 6 percent by weight of said NSAID released after about 2 hours and from about 20 percent by weight of said NSAID released after about 4 hours and a t_{50} at about 12 to about 16 hours.

12. The sustained release tablet of claim 11, wherein said NSAID is ibuprofen and the total weight of said tablet is from about 119 percent to about 136 percent by weight of ibuprofen.

13. A sustained release ibuprofen tablet comprising

from about 500 to about 1000 mg ibuprofen uniformly dispersed in a sustained release carrier comprising

xanthan gum;

locust bean gum; and

an pharmaceutically acceptable inert diluent;

wherein the total weight of said xanthan gum and said locust bean gum is from about 7 to about 40 percent by weight of the final tablet weights the ratio of ibuprofen to the total weight of said xanthan gum and said locust bean gum is from about 1:0.06 to about 1 :0.4, and said locust bean gum comprising from about 50% to about 95% of the sustained release carrier, said tablet providing a dissolution of said ibuprofen in-vitro when measured by the USP Type II (Paddle) Method, of from about 6 percent by weight of said ibuprofen released after about 2 hours and a t_{50} at about 12 to about 16 hours.

14. A sustained release ibuprofen tablet of claim 13 wherein the ratio of ibuprofen to the total weight of said xanthan gum and said locust bean gum is from about 1:0.08 to about 1:0.25.

15. An oral sustained release dosage form, comprising

a matrix comprising from about 500 to about 1000 mg of ibuprofen and a sustained release carrier comprising at least about 5% of xanthan gum, about 50% to about 95% of a crosslinking agent comprising locust bean gum and a pharmaceutically acceptable inert diluent; wherein the weight ratio of said ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.06 to about 1:0.4, said dosage form providing a dissolution of said ibuprofen in-vitro when measured by the USP Type II (Paddle) Method, of from about 20 percent by weight of said ibuprofen released after about 4 hours and a t_{50} at about 12 to about 16 hours.

16. The oral sustained release dosage form of claim 15, wherein the weight ratio of said ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.08 to about 1:0.25.

17. The oral sustained release dosage form of claim 15, comprising from about 800 to about 1000 mg ibuprofen.

18. The sustained release dosage form of claim 5, wherein said NSAID is ibuprofen, and the total weight of said dosage form is from about 119 percent to about 136 percent by weight of ibuprofen.

19. A sustained release ibuprofen tablet comprising

from about 500 to about 1000 mg ibuprofen uniformly dispersed in a sustained release carrier comprising

xanthan gum;

locust bean gum; and

an pharmaceutically acceptable inert diluent;

wherein the total weight of said xanthan gum and said locust bean gum is from about 7 to about 40 percent by weight of the final tablet weight, and the ratio of ibuprofen to the total weight of said xanthan gum and said locust bean gum is from about 1:0.06 to about 1:0.4, and said locust bean gum comprising from about 50% to about 95% of the sustained release carrier, said tablet providing a dissolution of said ibuprofen in-vitro when measured by the USP Type II (Paddle) Method, of from about 20 percent by weight of said ibuprofen released after about 4 hours and a t_{50} at about 12 to about 16 hours.

20. The sustained release ibuprofen tablet of claim 19, wherein the ratio of ibuprofen to the total weight of said xanthan gum and said locust bean gum is from about 1:0.08 to about 1:0.25.

21. The sustained release dosage form of claim 1, comprising a matrix in which said NSAID is uniformly dispersed with said sustained release carrer.

22. The sustained release dosage form of claim 5, comprising a matrix in which said NSAID is uniformly dispersed with said sustained release carrier.

23. The sustained release dosage fonn of claim 5, wherein the dosage form is a tablet.

24. The oral sustained release dosage form of claim 8, wherein the dosage form is a tablet.

25. The oral sustained release dosage form of claim 15, wherein the dosage form is a tablet.

26. The sustained release dosage form of claim 1, wherein the sustained release carrier comprises wet granulated particles of xanthan gum, locust bean gum and pharmaceutically acceptable inert diluent.

27. The sustained release dosage form of claim 5, wherein the sustained release carrier comprises wet granulated particles of xanthan gum, locust bean gum and a pharmaceutically acceptable inert diluent.

28. The oral sustained release dosage fonn of claim 19, wherein the sustained release carrier comprises wet granulated particles of xanthan gum, locust bean gum and pharmaceutically acceptable inert diluent.

29. The sustained release tablet of claim 11, wherein the sustained release carrier comprises wet granulated particles of xanthan gum, locust bean gum and pharmaceutically acceptable inert diluent.

30. The sustained release ibuprofen tablet of claim 13, wherein the sustained release carrier comprises wet granulated particles of xanthan gum, locust bean gum and pharmaceutically acceptable inert diluent.

31. The oral sustained release dosage form of claim 15, wherein the sustained release carrier comprises wet granulated particles of xanthan gum, locust bean gum and pharmaceutically acceptable inert diluent.

32. The sustained release ibuprofen tablet of claim 19, wherein the sustained release carrier comprises wet granulated particles of xanthan gum, locust bean gum and pharmaceutically acceptable inert diluent.

33. The sustained release dosage form of claim 1, wherein the pharmaceutically acceptable inert diluent is selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, a cellulose, starches, pre-manufactured direct compression excipients and mixtures thereof.

34. The sustained release dosage form of claim 5, wherein the pharmaceutically acceptable inert diluent is selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, a cellulose, starches, pre-manufactured direct compression excipients and mixtures thereof.

35. The oral sustained release dosage form of claim 8, wherein the pharmaceutically acceptable inert diluent is selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, a cellulose, starches, pre-manufactured direct compression excipients and mixtures thereof.

36. The sustained release tablet of claim 11, wherein the pharmaceutically acceptable inert diluent is selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, a cellulose, starches, pre-manufactured direct compression excipients and mixtures thereof.

37. The sustained release ibuprofen tablet of claim 13, wherein the pharmaceutically acceptable inert diluent is selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, a cellulose, starches, pre-manufactured direct compression excipients and mixtures thereof.

38. The oral sustained release dosage form of claim 15, wherein the pharmaceutically acceptable inert diluent is selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, a cellulose, starches, pre-manufactured direct compression excipients and mixtures thereof.

39. The sustained release ibuprofen tablet of claim 19, wherein the pharmaceutically acceptable inert diluent is selected from the group consisting of a monosaccharide, a disaccharide, a polyhydric alcohol, a cellulose, starches, pre-manufactured direct compression excipients and mixtures thereof.

40. The sustained release dosage form of claim 1, wherein the ratio of locust bean gum to xanthan gum is 1:0.08.

41. The sustained release dosage form of claim 5, wherein the ratio of locust bean gum to xanthan gum is 1:0.08.

42. The oral sustained release dosage form of claim 8, wherein the ratio of locust bean gum to xanthan gum is 1:0.08.

43. The sustained release tablet of claim 11, wherein the ratio of locust bean gum to xanthan gum is 1:0.08.

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(54) Title: SUSTAINED RELEASE METOPROLOL FORMULATIONS

(57) Abstract: The present invention relates to a sustained release oral dosage forms containing a therapeutically effective amount of metoprolol tartrate, methods of preparing such formulations, and to methods of treatment utilizing such formulations.

What is claimed is:

1. A sustained release oral solid dosage form comprising:
a sustained release matrix comprising from about 12.5 to about 400 mg of metoprolol tartrate and a sustained release excipient;
said oral dosage form providing a mean Cmax of metoprolol from about 10 ng/ml to about 40 ng/ml when the dosage form contains 100 mg metoprolol tartrate; said dosage form providing a therapeutic effect for about 24 hours after oral administration.

2. The sustained release oral dosage form of claim 1, wherein said mean Cmax of metoprolol is from about 15 ng/ml to about 30 ng/ml when the dosage form contains 100 mg metoprolol tartrate.

3. The sustained release oral dosage form of claim 1, wherein said oral dosage form provides a mean C_{max} of metoprolol from about 40 ng/ml to about 90 ng/ml when the dosage form contains 200 mg metoprolol tartrate.

4. The sustained release oral dosage form of claim 1, wherein said oral dosage form provides a mean C_{max} of metoprolol from about 5 ng/ml to about 30 ng/ml when the dosage form contains 50 mg metoprolol tartrate.

5. The sustained release oral dosage form of claim 1, wherein said oral dosage form provides a mean C_{max} of metoprolol from about 2 ng/ml to about 15 ng/ml when the dosage form contains 25 mg metoprolol tartrate.

6. The sustained release oral dosage form of claim 1, wherein said oral dosage form is substantially dose proportional.

7. The sustained release oral dosage form of claim 1, wherein said sustained release excipient is pre-agglomerated prior to incorporation of the metoprolol tartrate.

8. The sustained release oral dosage form of claim 1, wherein said dosage form provides a mean Tmax at from about 2.5 to about 20 hours after oral administration.

9. The sustained release oral dosage form of claim 1, wherein said dosage form provides a mean Tmax at from about 6 to about 16 hours after oral administration.

10. The sustained release oral dosage form of claim 1, wherein said sustained release matrix comprises a plurality of matrix multiparticulates.

11. The sustained release oral dosage form of claim 10, wherein said matrix multiparticulates are overcoated with a coating comprising a hydrophobic material.

12. The sustained release oral dosage form of claim 11, wherein said hydrophobic material is selected from the group consisting a hydrophobic polymer, a cellulosic material, an acrylic polymer, a methacrylic acid polymer, a methacrylic copolymer, hydrogenated vegetable oils, zein, and mixtures thereof.

13. The sustained release oral dosage form of claim 11, wherein said hydrophobic material is ethylcellulose.

14. The sustained release oral dosage form of claim 11, wherein said hydrophobic material comprises one or more ammonio methacrylate copolymers.

15. The sustained release oral dosage form of claim 1, wherein said dosage form is a compressed tablet.

16. The sustained release oral dosage form of claim 15, further comprising a coating over said compressed tablet; said coating comprising a hydrophobic material.

17. The sustained release oral dosage form of claim 16, wherein said hydrophobic material is selected from the group consisting of a hydrophobic polymer, a cellulosic material, an acrylic polymer, a methacrylic acid polymer, a methacrylic acid copolymer, hydrogenated vegetable oils, zein, and mixtures thereof.

18. The sustained release oral dosage form of claim 1, wherein the sustained release excipient comprises a gelling agent selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

19. The sustained release oral dosage form of claim 1, wherein the sustained release excipient comprises a heteropolysaccharide gum and a homopolysaccharide gum.

20. The sustained release oral dosage form of claim 19, wherein said heteropolysaccharide gum is xanthan gum and said homopolysaccharide gum is locust bean gum.

21. The sustained release oral dosage form of claim 1, wherein the sustained release excipient further comprises a ionizable gel strength-enhancing agent.

22. The sustained release oral dosage form of claim 21, wherein said ionizable gel strength-enhancing agent is selected from the group consisting of calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate, sodium fluoride, and mixtures thereof.

23. A sustained release oral solid dosage form comprising:
a sustained release matrix comprising from about 12.5 to about 400 mg metoprolol tartrate and a sustained release excipient;
said oral dosage form providing a mean Cmax at steady state of metoprolol from about 4 ng/ml to about 20 ng/ml when the dosage form contains 25 mg metoprolol tartrate; said dosage form providing a therapeutic effect for about 24 hours after oral administration.

24. The sustained release oral dosage form of claim 23, wherein the Cmax at steady state of metoprolol is from about 6 ng/ml to about 15 ng/ml when the dosage form contains 25 mg metoprolol tartrate.

25. The sustained release oral dosage form of claim 23, wherein said dosage form provides a mean Tmax at from about 2.5 to about 20 hours after oral administration.

26. The sustained release oral dosage form of claim 23, wherein said dosage form provides a mean Tmax at from about 6 to about 16 hours after oral administration.

27. The sustained release oral dosage form of claim 23, wherein said sustained release matrix comprises a plurality of matrix multiparticulates.

28. The sustained release oral dosage form of claim 27, wherein said matrix multiparticulates are overcoated with a coating comprising a hydrophobic material.

29. The sustained release oral dosage form of claim 28, wherein said hydrophobic material is selected from the group consisting a hydrophobic polymer, a cellulosic material, an acrylic polymer, a methacrylic acid polymer, a methacrylic copolymer, hydrogenated vegetable oils, zein, and mixtures thereof.

30. The sustained release oral dosage form of claim 28, wherein said hydrophobic material is ethylcellulose.

31. The sustained release oral dosage form of claim 28, wherein said hydrophobic material comprises one or more ammonio methacrylate copolymers.

32. The sustained release oral dosage form of claim 23, wherein said dosage form is a compressed tablet.

33. The sustained release oral dosage form of claim 32, further comprising a coating over said compressed tablet; said coating comprising a hydrophobic material.

34. The sustained release oral dosage form of claim 32, wherein said hydrophobic material is selected from the group consisting of a hydrophobic polymer, a cellulosic material, an acrylic polymer, a methacrylic acid polymer, a methacrylic acid copolymer, hydrogenated vegetable oils, zein, and mixtures thereof.

35. The sustained release oral dosage form of claim 23, wherein the sustained release excipient comprises a gelling agent selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

36. The sustained release oral dosage form of claim 23, wherein the sustained release excipient comprises a heteropolysaccharide gum and a homopolysaccharide gum.

37. The sustained release oral dosage form of claim 36, wherein said heteropolysaccharide gum is xanthan gum and said homopolysaccharide gum is locust bean gum.

38. The sustained release oral dosage form of claim 23, wherein the sustained release excipient further comprises a ionizable gel strength-enhancing agent.

39. The sustained release oral dosage form of claim 38, wherein said ionizable gel strength-enhancing agent is selected from the group consisting of calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate, sodium fluoride, and mixtures thereof.

40. A sustained release oral solid dosage form comprising:
a sustained release matrix comprising from about 12.5 mg to about 400 mg of metoprolol tartrate and a sustained release excipient; said oral dosage form providing a mean Cmax at steady state of metoprolol from about 5 ng/ml to about 30 ng/ml when the dosage form contains 50 mg metoprolol tartrate; said dosage form providing a therapeutic effect for about 24 hours after oral administration.

41. A sustained release oral dosage form comprising:
metoprolol tartrate in an amount of from about 12.5 mg to about 400 mg dispersed in a matrix comprising (i) a gelling agent said gelling agent in an amount of from about 10% to about 60% by weight of the dosage form, (ii) an inert pharmaceutical diluent in an amount of from about 5% to about 40% by weight of the dosage form, and (iii) an ionizable gel strength enhancing agent in an amount of from about 0.5% to about

16% by weight of the dosage form; a hydrophobic coating coated over said matrix in an amount of from about 1% to about 20% by weight of the dosage form; said dosage form providing for the sustained release of said metoprolol tartrate suitable for once a day administration.

42. The sustained release oral dosage form of claim 41, wherein said matrix is pre-agglomerated prior to incorporation of the metoprolol tartrate.

43. The sustained release oral dosage form of claim 41, wherein said gelling agent consists of a heteropolysaccharide gum and a homopolysaccharide gum.

44. The sustained release oral dosage form of claim 41, wherein said inert pharmaceutical diluent is mannitol.

45. A sustained release oral dosage form comprising:
a matrix comprising metoprolol tartrate in an amount of from about 12.5mg to about 400mg dispersed in a sustained release excipient comprising (i) locust bean gum in an amount of 5% to about 30% by weight of the oral dosage form and (ii) xanthan gum in an amount from about 5% to about 30% by weight of the oral dosage form, (iii) mannitol in an amount of from about 5 % to about 40% by weight of the oral dosage form, and (iv) calcium sulfate dihydrate in an amount of about 0.5% to about 16% by weight of the oral dosage form; and
a hydrophobic coating coated over said matrix in an amount of from about 1% to about 20% by weight of the oral dosage form;
said dosage form providing for the sustained release of said metoprolol tartrate suitable for once-a-day administration.

46. A sustained release tablet formulation comprising:
a matrix core composition comprising
(a) metoprolol tartrate in an amount of from about 12.5 mg to about 400 mg;
(b) a cellulose derivative selected from the group consisting of an alkylcellulose, hydroxyalkylcellulose, hydroxypropylalkylcellulose, or mixtures thereof; and
(c) a sustained release excipient comprising a gelling agent in an amount of about 10% to about 60% by weight of the formulation; an inert diluent in an amount of from

about 5% to about 40% by weight of the formulation; and an ionizable gel strength enhancing agent in an amount of from about 0.5% to about 16% by weight of the formulation; and

a coating over said core comprising

(a) a hydrophobic material in an amount of from about 2% to about 15% by weight of the formulation;

said formulation providing for the sustained release of said metoprolol tartrate suitable for once-a-day administration.

47. The sustained release tablet formulation of claim 46, wherein said hydrophobic material is selected from the group consisting of a hydrophobic polymer, a cellulosic material, an acrylic polymer, a methacrylic acid polymer, a methacrylic acid copolymer, hydrogenated vegetable oils, zein, and mixtures thereof

48. The sustained release tablet formulation of claim 46, wherein said hydrophobic material is ethylcellulose.

49. The sustained release tablet formulation of claim 46, wherein said hydrophobic material comprises one or more ammonio methacrylate copolymers.

50. The sustained release formulation of claim 46, wherein said coating further comprises hydroxypropylmethylcellulose.

51. A sustained release excipient for the sustained release of an active agent comprising from about 20% to about 60% of a gelling agent by weight of said sustained release excipient, said gelling agent consisting of a heteropolysaccharide gum and a homopolysaccharide gum; from about 1% to about 20% of an ionizable gel strength enhancing agent by weight of said sustained release excipient; and from about 6% to about 60% of mannitol by weight of the sustained release excipient.

52. The sustained release excipient of claim 51, further comprising a cellulosic material selected from the group consisting of alkylcellulose, hydroxyalkylcellulose, hydroxypropylalkylcellulose, or mixtures thereof.

53. The sustained release excipient of claim 51, wherein said heteropolysaccharide gum is xanthan gum.

54. The sustained release excipient of claim 51, wherein said homopolysaccharide gum is locust gum.

55. The sustained release excipient of claim 51, wherein said ionizable gel strength enhancing agent is selected from the group consisting of calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate, sodium fluoride, and mixtures thereof.

56. The sustained release excipient of claim 51, wherein said ionizable gel strength enhancing agent is calcium sulfate dihydrate.

57. A method of treating a patient with hypertension comprising:
administering to said patient a sustained release oral dosage form comprising a sustained release matrix comprising from about 12.5 to about 400 mg of metoprolol tartrate and a sustained release excipient; said oral dosage form providing a mean Cmax of metoprolol from about 10 ng/ml to about 40 ng/ml when the dosage form contains 100 mg metoprolol tartrate; said dosage form providing a therapeutic effect for about 24 hours after oral administration.

58. The method of claim 57, wherein said mean Cmax of metoprolol is from about 15 ng/ml to about 30 ng/ml when the dosage form contains 100 mg metoprolol tartrate.

59. A method of reducing blood pressure comprising
administering to a human patient a sustained release oral solid dosage form comprising a sustained release matrix comprising about 12.5 to about 400 mg of metoprolol tartrate and a sustained release excipient; said oral dosage form providing a mean Cmax of metoprolol from about 10 ng/ml to about 40 ng/ml when the dosage form contains 100 mg metoprolol tartrate, said dosage form providing a therapeutic effect for about 24 hours after oral administration.

60. A method of providing cardioselective antihypertensive therapy to a human patient comprising administering to said patient a sustained release oral dosage form comprising a sustained release matrix comprising about 12.5 to about 400 mg of metoprolol tartrate and a sustained release excipient; said oral dosage form providing a mean Cmax of metoprolol from about 10 ng/ml to about 40 ng/ml when the dosage form contains 100 mg metoprolol tartrate; said dosage form providing a therapeutic effect for about 24 hours after oral administration.

61. A method of preventing or reducing a mallaird-type reaction in a metoprolol tartrate sustained release oral dosage form comprising preparing said sustained release oral dosage form by combining a therapeutically effective amount of metoprolol tartrate with a sustained release excipient that provides for the sustained release of said metoprolol tartrate, and including in said dosage form an effective amount of mannitol to prevent or reduce the degradation of said metoprolol tartrate.

62. The method of claim 61, wherein said mannitol is included in said sustained release excipient prior to combining said excipient with said metoprolol tartrate.

63. The method of claim 61, wherein said mannitol is incorporated into said dosage when said metoprolol tartrate and said sustained release excipient are combined.

64. A method of preparing a sustained release tablet formulation of metoprolol tartrate for once-a-day administration comprising:
spray granulating a sustained release excipient and metoprolol tartrate with a suspension or solution comprising a cellulose derivative selected from the group consisting of an alkylcellulose, hydroxyalkylcellulose, hydroxyalkylalkylcellulose, or mixtures thereof; and tableting the resultant granulation such that each tablet provides a dose of metoprolol tartrate sufficient to provide a therapeutic effect for about 24 hours after oral administration.

65. The method of claim 64, further comprising overcoating the tablets with a coating comprising a hydrophobic material.

66. The method of claim 65, wherein the hydrophobic material is selected from the group consisting of hydrophobic polymer, a cellulosic material, an acrylic polymer, a methacrylic acid polymer, a methacrylic copolymer, hydrogenated vegetable oils, zein, and mixtures thereof.

67. A sustained release oral solid dosage form comprising:
a sustained release matrix comprising a therapeutically effective amount of metoprolol tartrate and a sustained release excipient;
said oral dosage form providing a mean Cmax of metoprolol from about 10 ng/ml to about 40 ng/ml per 100 mg metoprolol tartrate, said dosage form providing a therapeutic effect for about 24 hours after oral administration.

68. A method of treating a patient with hypertension comprising:
administering to said patient a sustained release oral dosage form comprising a sustained release matrix comprising a therapeutically effective amount of metoprolol tartrate and a sustained release excipient; said oral dosage form providing a mean Cmax of metoprolol from about 10 ng/ml to about 40 ng/ml per 100 mg metoprolol tartrate; said dosage form providing a therapeutic effect for about 24 hours after oral administration.

69. A method of reducing blood pressure comprising administering a sustained release oral dosage form of claim 67 to a human patient.

70. A method of reducing blood pressure comprising administering a sustained release oral dosage form of claim 67 to a human subject.

71. A method of providing cardioselective antihypertensive therapy to a human patient comprising administering a sustained release oral dosage form of claim 67 to a patient in need of said therapy.

72. A sustained release oral solid dosage form comprising:
a sustained release matrix comprising a therapeutically effective amount of metoprolol tartrate and a sustained release excipient; said oral dosage form providing

a mean Cmax at steady state of metoprolol from about 5 ng/ml to about 30 ng/ml per 50 mg metoprolol tartrate, said dosage form providing a therapeutic effect for about 24 hours after oral administration.

73. A sustained release oral solid dosage form comprising:
a sustained release matrix comprising a therapeutically effective amount of metoprolol tartrate and a sustained release excipient;
said oral dosage form providing a mean Cmax at steady state of metoprolol from about 4 ng/ml to about 20 ng/ml per 25 mg metoprolol tartrate, said dosage form providing a therapeutic effect for about 24 hours after oral administration.

74. A sustained release tablet formulation comprising:
about 31% by weight of metoprolol tartrate;
about 45% by weight of a sustained release excipient comprising xanthan gum, locust bean gum, calcium sulfate dihydrate, and mannitol;
about 3% by weight hydroxypropylmethylcellulose;
about 4% by weight talc;
about 2% by weight sodium stearyl fumarate;
about 9 to about 12% by weight hydrophobic coating material; and
about 3% by weight of a color coating material;
said formulation providing for the sustained release of said metoprolol tartrate.

75. The sustained release tablet formulation of claim 74, wherein said hydrophobic coating material comprises ethylcellulose in an amount of about 8% by weight of the formulation.

76. The sustained release tablet formulation of claim 74, wherein said sustained release excipient comprises about 20% by weight xanthan gum; about 30% by weight locust bean gum; about 10% by weight calcium sulfate dihydrate; and about 40% by weight mannitol.

77. A sustained release tablet formulation comprising:
about 32% by weight of metoprolol tartrate;

about 48% by weight of a sustained release excipient comprising xanthan gum, locust bean gum, calcium sulfate dihydrate, and mannitol;
about 4% by weight hydroxypropylmethylcellulose;
about 4% by weight talc;
about 2% by weight sodium stearyl fumarate;
about 8% by weight hydrophobic coating material; and
about 3% by weight of a color coating material;
said formulation providing for the sustained release of said metoprolol tartrate.

78. The sustained release tablet formulation of claim 77, wherein said hydrophobic coating material comprises a combination of two ammonio methacrylate copolymers in a combined amount of about 5% by weight of the formulation.

79. The sustained release tablet formulation of claim 77, wherein said sustained release excipient comprises about 20% by weight xanthan gum; about 30% by weight locust bean gum; about 10% by weight calcium sulfate dihydrate; and about 40% by weight mannitol.

80. The use of the oral solid dosage form or formulation of claims 1-56, 67, 72-78 or 79 in the preparation of a metoprolol tartrate formulation for treating hypertension, which provides a sustained release of said metoprolol tartrate after exposure of the dosage form or formulation to gastrointestinal fluid.

81. The use of the oral solid dosage form or formulation of claims 1-56, 67, 72-78 or 79 in the preparation of a metoprolol tartrate formulation for providing cardioselective anti-hypertension therapy, which provides a sustained release of said metoprolol tartrate after exposure of the dosage form or formulation to gastrointestinal fluid.

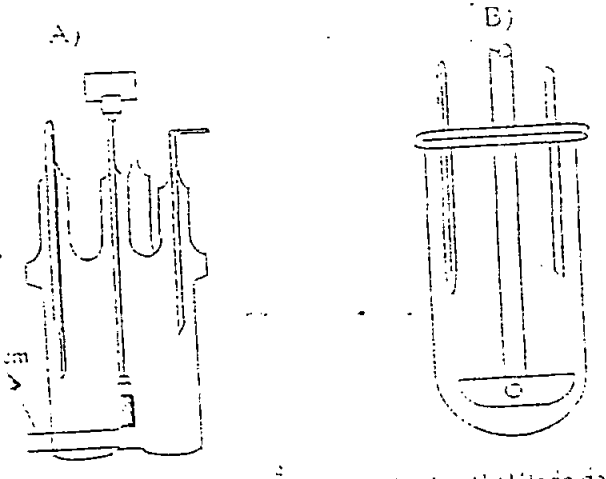
82. The use of the oral solid dosage form or formulation of claims 1-56, 67, 72-78 or 79 in the preparation of a metoprolol tartrate formulation for reducing blood pressure, which provides a sustained release of said metoprolol tartrate after exposure of the dosage form or formulation to gastrointestinal fluid.

75

conclusiones exclusivamente comparativas entre los distintos lotes. El c
nto de este test no garantiza la eficacia clínica; sin embargo, su incum
o hace, generalmente, que no se consiga una eficacia completa.

nsayo de disolución

e ha demostrado que el mismo principio activo, incorporado a comprimi
ulados de diferente forma, y que cumplen todos ellos los requerimientos
egación establecidos, no siempre presenta la misma actividad terapéutica. E
de manifiesto la necesidad de realizar estudios sobre la velocidad de diso
del principio activo, proceso condicionante de su absorción.
Aunque los ensayos de disolución son de gran importancia en el control de c
idos que contienen fármacos muy poco solubles, es preciso señalar que, po
s, no constituyen una medida de la biodisponibilidad, que debe ser evaluada s
n vivo. Si las correlaciones entre los resultados obtenidos *in vitro* e *in vivo*
stables, los ensayos de disolución pueden considerarse buenos indicadores d
lisponibilidad del fármaco en la formulación ensayada.
Se han propuesto diversos procedimientos para llevar a cabo este ensayo.
s habituales de los cuales son los métodos recogidos en la USP: *método del*
y método de la paleta, cuyos esquemas se presentan en la figura 2.55.



GURA 2.55. Aparatos USP para realizar ensayos de disolución. A) Método de cestillo. B) M
de la paleta

La composición del fluido de disolución para llevar a cabo el ensayo, junto
el método utilizado, se especifica en cada monografía de las farmacopeas, d
se incluye también la proporción de fármaco que debe disolverse en un perío
tiempo determinado. En general, los requerimientos de disolución de la USP

blecen que al menos un 75% del fármaco debe disolverse en 45 minutos. Con obje
to de reducir la variabilidad interlaboratorio en los test de disolución, la USP sugie
re el uso de discos estándares de ácido salicílico y prednisona como calibradores
del equipo de disolución.

2.2.11. Comprimidos especiales

Se incluye dentro de esta categoría a aquellos comprimidos que presentan algu
na característica farmacotécnica diferente de las descritas para los comprimidos
convencionales. Los comprimidos especiales de mayor utilización (sublinguales y
bucales, masticables, efervescentes, multicapa, vaginales, de implantación, de libe
ración sostenida y recubiertos) se describen a continuación.

A) Comprimidos sublinguales y bucales

Son comprimidos destinados a situarse bajo la lengua (sublinguales) o a man
tenerse en la cavidad oral (bucales), donde se disuelven lentamente liberando el
principio activo para producir un efecto local o ser absorbidos a través de la muco
sa y ejercer un efecto sistémico. En general, presentan pequeño tamaño y una for
ma plana u oval. Los comprimidos bucales deben disolverse con lentitud, para lo
cual en su formulación se evita la presencia de agentes disgregantes y se incorpo
ran aglutinantes enérgicos (gelatina, goma arábiga, carboximetilcelulosa...) y lubri
cantes de acción hidrofóbica, del tipo del estearato magnésico, que contribuyen a
aumentar el tiempo de disgregación. Además, se utilizan fuerzas elevadas de com
presión para obtener comprimidos duros. Se pueden administrar de esta forma hor
monas como la metiltestosterona, el citrato de oxitocina, la progesterona, antisép
ticos y antibióticos, etc.

Los comprimidos sublinguales suelen contener fármacos que serían destruidos o
inactivados a su paso por el tracto gastrointestinal. En general, están concebidos para
que el principio activo se ceda lentamente, de manera que la velocidad de liberación
sea del mismo orden de magnitud que la de absorción para asegurar el máximo apro
vechamiento de la dosis administrada. Si la liberación se produjera muy rápidamen
te, la mucosa no estaría en situación de absorber toda la cantidad de fármaco disuel
ta, por lo que una parte de éste sería deglutida junto con la saliva. Por el contrario, en
ciertos casos especiales, cuando se recurre a esta forma de administración para el tra
tamiento de situaciones urgentes, como la angina de pecho o el asma, los comprimi
dos sublinguales deben disolverse fácilmente, permitiendo una rápida absorción del
fármaco, por lo que para su obtención se emplean bajas fuerzas de compresión y se
les dota de una forma lenticular y de gran superficie. De este modo se administran
fármacos tales como la nitroglicerina, el clorhidrato de isoproterenol, el sulfato de iso
prenalina, el dinitrato de isosórbida, la ketanserina, etc.

F) *Comprimidos de implantación*

Los comprimidos de implantación están diseñados para ser depositados ba
la piel. Su objetivo es conseguir una acción prolongada (la duración del efecto os
la entre un mes y un año); deben, pues, presentar bajas velocidades de disgreg
ción y disolución en los fluidos tisulares. Ello se consigue utilizando una eleva
presión de compresión o recurriendo a la fusión conjunta del principio activo c
ciertos coadyuvantes grasos (grasas hidrogenadas o polietilenóxido 6000). En ge
ral, si es posible, se prefiere su fabricación sin la adición de excipientes; en el ca
de ser precisos, éstos deben ser totalmente solubles. Otros requisitos de los co
primidos de implantación son un reducido tamaño (2-3 mm de diámetro), la fab
cación en condiciones de asepsia y el envasado en recipientes estériles. La adm
nistración de este tipo de comprimidos debe realizarse mediante técnicas quirúrgi
o utilizando inyectores especiales (inyector de Kern). Su utilización en el hom
ha caído en desuso; han sido sustituidos por otras formas de dosificación, como
tubos de silicona de difusión controlada. No obstante, aunque su empleo está pr
ticamente restringido a la administración de hormonas estimulantes del crecimie
animal, un ejemplo característico del uso de este tipo de comprimidos en se
humanos lo constituye el disulfiram (Esperal R®, 100 mg), utilizado en el tra
miento crónico del alcoholismo.

G) *Comprimidos de liberación controlada*

Los comprimidos se pueden formular para liberar el principio activo de ma
ra que se alcancen en el organismo concentraciones mantenidas, durante perío
prolongados de tiempo. Existen diversos tipos entre los que se incluyen los d
primidos de liberación retardada, en los que el principio activo no se libera h
un tiempo después de la administración o hasta que existan ciertas condicio
fisiológicas; los *de acción repetida*, que liberan periódicamente una dosis com
ta del fármaco en los líquidos gastrointestinales, y los *de liberación sostenida*,
liberan de forma continua una cantidad de fármaco. Estos comprimidos pue
obtenerse por distintos métodos. Uno de los más simples es la incorporación
principio activo en una matriz de naturaleza polimérica que forme una ban
mucilaginosa que controle la difusión del principio activo o que se erosione le
mente permitiendo la liberación gradual del mismo. Otra forma de control
liberación consiste en el recubrimiento de los comprimidos con cubiertas esp
les que permiten la cesión del fármaco por difusión, ósmosis, etc. Estos comp
dos requieren la realización de ensayos de disolución adecuadamente adapt
que permitan demostrar si la liberación del principio activo se realiza de ac
con la cinética prevista en su diseño. Este tipo de fármacos, dado su crecient
rés, será revisado en detalle en otro capítulo.

2.2.12. *Comprimidos recubiertos*

Aunque el recubrimiento de formas sólidas ya era practicado e
Egipto, una de las primeras referencias escritas a las formas recubier
en la literatura islámica y se debe a Rhaces (850-923). Tal como se cor
mente, el recubrimiento data de fines del siglo XIV, época en la que ya
ban "grageas". En Francia, en el siglo XVII, este método se utilizaba p
carar el sabor de algunos medicamentos; con este fin, Derenou revestía
y pastillas con metales (oro y plata); de aquí proviene el dicho castellan
píldora". Los recubrimientos azucarados se desarrollaron considerable
Francia a mediados del siglo XIX; en 1837 y 1840 se registraron dos paten
técnica. Sin embargo, los recubrimientos pelicular (el método más empl
actualidad) y por compresión son tecnologías relativamente nuevas, int
en la década de los años 50 del presente siglo.

El recubrimiento de comprimidos, paso adicional en el proceso de fab
aumenta el costo del producto; así, la decisión de recubrir un comprim
estar justificada por la consecución de uno o más de los siguientes objeti

- Enmascarar el color, sabor u olor desagradables.
- Facilitar la administración al presentar una superficie más suave y de
- Proporcionar una protección física y química de los componentes d
  mulación frente a agentes externos (humedad, oxígeno, luz...).
- Evitar incompatibilidades, incorporando por separado (cubierta y
  principios activos no compatibles entre sí.
- Conseguir una liberación controlada del fármaco mediante cubiert
  trorresistentes, que sólo permitan la liberación a nivel intestinal o cu
  especiales que regulen la velocidad de cesión.

Los comprimidos recubiertos, por sus especiales características, no debe
fraccionados, triturados o machacados, ya que puede comprometerse la est
dad del fármaco, su grado de absorción o la seguridad del tratamiento.

Los tipos de recubrimiento de comprimidos incluyen:

- Recubrimiento con azúcar o grageado.
- Recubrimiento pelicular.
- Recubrimiento por compresión.

De ellos, el menos empleado es el último. El grageado, por razones histór
sido el más empleado; sin embargo, en la actualidad, está siendo sustituido
recubrimiento pelicular. De hecho, la mayoría de los nuevos materiales de re
imiento se ha desarrollado para este tipo de cobertura que, además, es el m
ple y menos costoso.

3. Formulaciones pH-independientes

Puesto que el valor del pH varía de forma considerable a lo largo del tracto gastrointestinal, las formulaciones pH-independientes se presentan como una alternativa muy interesantes para su uso por vía oral. Estas formulaciones se obtienen mezclando un principio activo, ácido o base, con agentes *buffer* (sales de ácido cítrico) y excipientes que permiten obtener unos gránulos que se recubren con derivados de la celulosa que dan lugar a cubiertas semipermeables. Cuando los gránulos se encuentran en el aparato digestivo, penetra fluido a su interior y, por efecto del sistema *buffer*, el pH adquiere un valor adecuado, según el tipo de principio activo, se disuelve éste y difunde a través de la membrana polimérica a velocidad constante.

4. Matrices hidrofílicas

La formulación de principios activos en cápsulas gelatinosas o en comprimidos, utilizando polímeros hidrofílicos con elevada capacidad gelificante como excipientes base, representa una alternativa de indudable interés en el campo de la liberación controlada oral. Cuando estas formulaciones entran en contacto con un medio acuoso se produce una rápida hidratación de las macromoléculas situadas en la interfaz sólido-líquido, seguida de la formación de un lecho viscoso. Tal como se recoge en la figura 8.16, a medida que el agua va penetrando en el sistema con una velocidad que depende en gran medida de la naturaleza del polímero, la capa de gel experimenta una expansión progresiva que externamente se manifiesta en un incremento de su espesor. Al mismo tiempo, los estratos exteriores ya completamente hidratados se van dispersando en un proceso de erosión que lleva consigo la posibilidad de que el proceso de penetración de agua se prolongue hasta la total dispersión del sistema.

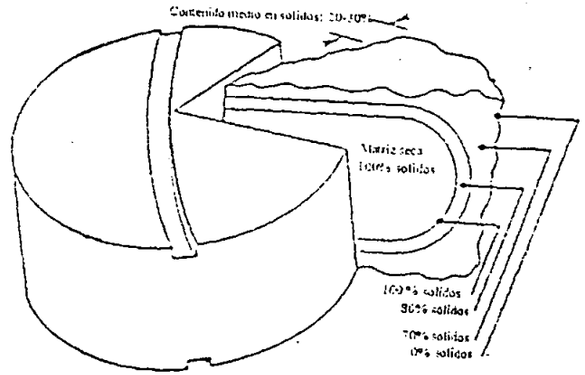


FIGURA 8.16. *Representación esquemática del proceso de hidratación de un comprimido de matriz hidrofílica.*

La liberación del principio activo a partir de un sistema matricial hidrofílico puede producirse por dos procesos simultáneos, tal como se recoge en la figura 8.17.

- Erosión o desgaste de las capas más externas y de menor consistencia del gel.
- Disolución del principio activo en el medio líquido y difusión a través del gel barrera, una vez que éste se ha formado.

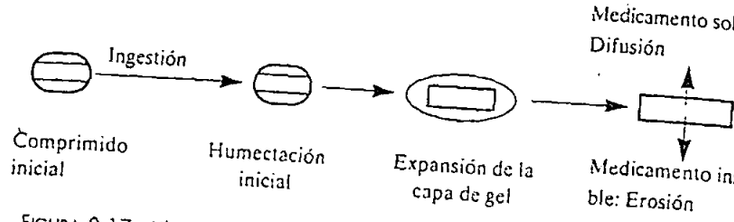


FIGURA 8.17. *Liberación de un principio activo a partir de una matriz hidrofílica.*

El predominio de uno u otro mecanismo está directamente relacionado con la hidrosolubilidad del principio activo. Si ésta es reducida, las posibilidades de cesión por difusión serán prácticamente nulas y la liberación se producirá casi exclusivamente por erosión superficial, con lo que se obtendrán perfiles característicos de la cinética de orden 0. En cambio, si el principio activo es moderada o marcadamente hidrosoluble, el mecanismo implicado en la liberación será la difusión; en este último caso, pueden distinguirse tres etapas en el proceso global de liberación:

- En la fase inicial el agua disuelve el principio activo que se encuentra en la superficie, lo que provoca su liberación inmediata. El agua penetra en la matriz a través de los poros y se produce la gelificación del polímero. En esta primera etapa la velocidad de penetración del líquido depende de la porosidad del sistema y la capa de gel no constituye necesariamente una capa de gel continua, especialmente cuando las partículas son relativamente grandes.
- En la segunda etapa o estacionaria, que abarca del 60 al 70% del proceso, el frente de agua penetra de forma continua en el sistema, al tiempo que se produce la expansión de la capa de gel. Durante la misma, la liberación del principio activo está controlada por el proceso de difusión y no por el de disolución del principio activo o por la velocidad de penetración del agua en el sistema.
- El período final o de agotamiento comienza cuando el frente ha alcanzado el centro del sistema y la concentración de principio activo ha caído por

debajo de su coeficiente de solubilidad. Esta etapa se caracteriza por una reducción gradual de la velocidad de liberación del principio activo.

Como polímeros que se pueden utilizar en la elaboración de matrices hidrofílicas se pueden considerar los siguientes:

— *Polímeros naturales o semisintéticos.* Son productos de origen vegetal (agar-agar, alginatos, etc.) o bien transformados mediante procesos físicos o de semisíntesis (chitosanos, almidones modificados, etc.).
— *Éteres de la celulosa.* Este grupo de derivados semisintéticos de la celulosa es el que ha encontrado mayor aplicación en el campo de las matrices hidrofílicas. Se obtienen substituyendo algunos átomos de hidrógeno de los grupos hidróxilo de la celulosa, de las unidades de glucosa, por grupos metilo, hidróxietilo, hidroxipropilo o carboximetilo. Las propiedades físicas y fisicoquímicas de los éteres de la celulosa están determinadas por el tipo, proporción y, en su caso, variedad de los grupos substituyentes. Esto sucede, por ejemplo, con la viscosidad de las dispersiones acuosas, aspecto de gran importancia en relación con muchas de las aplicaciones de estos excipientes.
— *Polímeros del ácido acrílico.* Integrados en el grupo de los carbomer y comercializados bajo el nombre de Carbopol®, constituyen actualmente unos polímeros con variedades que difieren en su peso molecular y en su capacidad viscosizante.

Los carbomer han encontrado interesantes aplicaciones en el campo de las formas orales de liberación controlada y con su empleo pueden conseguirse básicamente tres tipos de sistemas:

— *Sistemas de inclusión* en los que las moléculas se alojan en los espacios abiertos en la red molécular del polímero, tras provocar la floculación de éste en medio acuoso mediante una modificación controlada del pH. Finalmente, el aducto así formado se separa por filtración, se deseca y se comprime.
— *Sistemas megaloporosos.* Están constituidos por dos fases: una fase continua denominada "hospedadora", que controla la velocidad de penetración del líquido en el sistema, y otra en la que se encuentra el principio activo y que se encarga del control de su liberación durante un tiempo prolongado. Cuando uno de estos sistemas, obtenido por compresión de una mezcla de granulados de una y otra fase, se pone en contacto con un medio acuoso, el líquido penetra en la fase hospedadora debido a la presencia de cantidades importantes de componentes solubles, provocando la formación de grandes poros en el sistema. A medida que el líquido va penetrando en las partes internas del dispositivo, una parte cada vez mayor de la superficie de la fase responsable del control de la liberación se pone en disposición de ceder principio activo al líquido de los poros. Puesto que la velocidad con que aumenta la superficie útil para liberar principio activo a los megaloporos disminuye, mientras que aumenta la superficie total de los poros expuesta al líquido, los sistemas megaloporosos pueden proporcionar velocidades de liberación sensiblemente constantes.
— *Matrices hidrofílicas.* La capacidad gelificante de los carbomer los convierte en productos potencialmente útiles en la formulación de sistemas matriciales de carácter hidrofílico. La mayoría de las publicaciones se centran en la utilización de la variedad 934 y persiguen, como objetivo fundamental, la obtención de una formulación adecuada para el principio activo seleccionado en cada caso. Para ello se acude a modificaciones en las condiciones de elaboración y, en algunas ocasiones, a la incorporación de otros excipientes de diferente naturaleza.

5. Matrices lipídicas

Las matrices lipídicas constituyen una interesante alternativa para la obtención de niveles sostenidos en plasma de un principio activo administrado por vía oral. La base de estos sistemas matriciales está constituida por compuestos de tipo graso o lipídico que, en contacto con los fluidos gastrointestinales, sufren un gradual proceso de erosión, liberando lentamente el principio activo al medio. Sin embargo, las matrices lipídicas presentan generalmente problemas de estabilidad en las condiciones habituales de almacenamiento, ya que las grasas naturales y los compuestos lipídicos suelen sufrir con el tiempo transiciones polimórficas o amorfo-cristalinas que dan lugar a un endurecimiento y, en consecuencia, a una disminución de la velocidad de cesión del principio activo.

Entre los procedimientos utilizados para dispersar el principio activo en el material graso, se puede citar el consistente en adicionar una solución o dispersión del principio activo y aditivos en la grasa fundida y posteriormente eliminar el disolvente por evaporación. Otra alternativa consiste en incorporar directamente el principio activo y los aditivos a la matriz grasa, previamente fundida a una temperatura ligeramente superior a su punto de fusión.

La liberación de principios activos a partir de matrices lipídicas está controlada por los mecanismos de difusión y erosión, y prevalece uno u otro según las características del principio activo y del propio excipiente lipídico. Las matrices lipídicas presentan un cierto grado de porosidad que permite la penetración inicial del medio de disolución y, en consecuencia, la disolución y difusión del principio activo en el mismo. Paralelamente, se producirá una gradual erosión de la matriz por lipólisis enzimática, simple hidrólisis o solubilización por ionización. Así, la velocidad de liberación y, consecuentemente, la absorción de un principio activo a partir de una matriz lipídica dependen en gran medida de la composición de los fluidos digestivos. Las variaciones de pH y el contenido enzimático del tracto gas-

REYES & REYES
A B O G A D O S

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF: **Expediente 08 007.949**

TÍTULO SOLICITADO: **COMPOSICIONES FARMACÉUTICAS DE LIBERACIÓN MODIFICADA Y SUS PROCESOS.**

PUBLICACIÓN: **Gaceta 602 de 31 de Marzo de 2009, N° d publicación 1441.**

PRIORIDAD: **IN 1681/DEI/2005 de 29/06/2005.**

SOLICITANTE: **PANACEA BIOTEC LTD.**

APODERADO: **JUAN PABLO CADENA SARMIENTO.**

TRÁMITE: **PRESENTACIÓN DE OPOSICION**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO COLOMBIANO S.A., LAFRANCOL S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **08 007.949,** por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LABORATORIO FRANCO COLOMBIANO S.A., LAFRANCOL S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTO DE LA OPOSICIÓN

La solicitud colombiana en trámite **08 007.949** que se refiere a una composición farmacéutica de liberación modificada comprendiendo por lo menos uno o unos agente(s) activo(s) o sus sales, ésteres, profármacos, solvatos, hidratos o derivados de los mismos farmacéuticamente aceptables; un sistema polimérico en una cantidad menor de alrededor de 80% en peso/peso de la composición comprendiendo por lo menos dos polímeros hinchables pH independientes y un polímero hidrófilo en una proporción de 1:20 hasta 20:1; opcionalmente otros excipientes farmacéuticamente aceptables; donde dicha composición proporciona un tiempo quieto inicial donde 5- 15% o menos del ingrediente(s) activo(s) se libera seguido de una liberación sostenida de ingrediente(s) activo(s), de tal manera que la composición dispone de unas concentraciones terapéuticas de agente(s) activo(s) durante unos periodos de tiempo prolongados; no reúne los requisitos necesarios para otorgársele el privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

En primer lugar, y ante la reivindicación textual de un "método de uso" de una composición de liberación modificada que comprende al menos un agente activo y un sistema polimérico, específicamente en su reivindicación 18, es relevante señalar que dicha pretensión resulta inaceptable a la luz de la Decisión 486, en tanto los "usos" son una categoría excluida del concepto de "Productos o Procedimientos" que establece el artículo 14 de la norma citada. Lo anterior,

además, en consonancia con reiteradas interpretaciones de la SIC sobre este punto.

Sin perjuicio de lo anterior me permito hacer notar que, aún si en gracia de discusión los usos o métodos terapéuticos fuesen permitidos en nuestro medio, éstos deberían cumplir necesariamente, y en forma simultánea, con los requisitos materiales de patentabilidad, es decir, novedad, nivel Inventivo y aplicación industrial. Además de anotar que respecto del pretendido "uso" el tercer requisito resulta de imposible cumplimiento, en tanto la reproducción industrial del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías sería del resorte de la profesión médica, y no, por supuesto, de las actividades industriales.

En otro aspecto, y esta vez refiriéndonos a la falta de nivel inventivo de la solicitud colombiana en tramite, cualquier persona medianamente versada en la materia reconoce que dentro del estado de la técnica, se reconocen dentro de la categoría de "comprimidos especiales" a aquellos comprimidos que presentan algunas características farmacocinéticas diferentes a las descritas para los comprimidos convencionales, y que dentro de esta categoría, los de mayor utilización son los sublinguales, bucales, masticables, efervescentes, multicapas, vaginales, de implantación, recubiertos y de liberación controlada[1]. A estos últimos en mención, corresponderían las características de la formulación que reivindica la solicitud colombiana en trámite. Específicamente, y dentro de las posibilidades de la liberación controlada que se reconocen en el estado de la técnica, las características de la formulación contenida en las reivindicaciones de la solicitud en cuestión, puede clasificarse como una formulación de liberación sostenida, en donde el principio activo se libera de forma continua cierta cantidad de fármaco durante un periodo de tiempo generalmente largo[2]. Como cualquier persona medianamente versada en la materia también debe reconocer, este tipo de formulaciones pueden obtenerse por distintos métodos, siendo el mas simple, la incorporación del principio activo en una matriz de naturaleza polimérica que forme una barrera lo suficientemente vizcosa que controle la difusión del principio activo o que se erosione lentamente permitiendo la liberación gradual del mismo[3]. Evidentemente la formulación descrita por la solicitud en cuestión, corresponde a

[1] Vila Jato. J.L. Tecnología Farmacéutica. Volumen II, página 142.
[2] Ibíd. Página 145.
[3] Ibíd. Página 145.

una formulación que obtiene sus características de liberación sostenida a través de la inserción del fármaco en un sistema polimérico dual hinchable, tal y como se expone claramente en la reivindicación 1. Además, y teniendo en cuenta que dentro de dichas características descritas para la formulación reivindicada por la solicitud en trámite, se hace mención del hinchamiento a través del uso de polímeros que atribuyan características hidrofílicas a dicha matriz polimérica, es relevante señalar que dichas características también son ampliamente reconocidas en el estado de la técnica, dentro de los mecanismos posibles para una liberación controlada, mecanismos tales como los descritos para los sistemas de liberación controlada tipo matrices hidrofílicas. Siendo mas específicos, los polímeros que se involucran para obtener la formulación reivindicada por la solicitud en cuestión, son polímeros claramente definidos y comúnmente utilizados en el estado de la técnica para la elaboración de este tipo de formulaciones, siendo estos polímeros correspondientes a polímeros naturales o semisintéticos, éteres de celulosa y polímeros de ácido acrílico[4].

En otras palabras, el tipo de formulaciones a las que se refiere la solicitud colombiana en tramite, corresponden a las características de la formulaciones de liberación controlada convencionales y ampliamente descritas en el estado de la técnica, y cualquier persona medianamente versada en la materia podría en principio involucrar cualquier fármaco en dicho tipo de formulaciones, aplicando adecuadamente los respectivos ensayos de preformulación y formulación.

Prueba de la versatilidad con que se pueden involucrar diversos tipos de fármacos en este tipo dem formulaciones, es lo contenido en los capítulos reivindicatorios de documentos publicados con anterioridad a la fecha de prioridad reivindicada por la solicitud en cuestión, tales como la patente Europea EP 0581676 publicada el 02 de febrero de 1994, la publicación internacional WO 99/18932 publicada el 22 de Abril de 1999, la publicación internacional WO 02/41876 publicada el 30 de Mayo de 2002 , la patente americana US 6 093420 publicada el 25 de Julio de 2000 y la publicación internacional WO 03/086353 publicada el 23 de Octubre de 2003 , en donde además es importante resaltar el uso de la misma clase de polímeros para la obtención del mecanismo de liberación controlada.

[4] Ibíd. Página 399 a 402.

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Para finalizar, y esta vez refiriéndonos a la falta de novedad de la invención, es importante resaltar que existen documentos que revelan con anterioridad la inclusión de algunos de los principios activos mencionados por la solicitud colombiana en tramite en el mismo tipo de formulaciones de liberación modificada, veamos:

La publicación internacional WO 2004/066910 publicada el 12 de Agosto de 2004 revela:

1. A solid oral controlled release pharmaceutical composition for administration to a subject in need thereof comprising:

(a) a therapeutically effective amount of a pharmaceutically active ingredient; and

(b) a controlled release modifying complex

wherein said complex comprises:

(i) a primary release modifying agent;

(ii) a secondary release modifying agent; and

(iii)an auxiliary release modifying agent wherein said primary, secondary and auxiliary release modifying agents are present in amounts that synergistically extend the release of the pharmaceutically active ingredient.

(...)

(i) a primary release modifying agent selected from low molecular weight hydrophilic polymers;

(ii) a secondary release modifying agent selected from high molecular weight hydrophilic polymers; and

(iii)an auxiliary release modifying agent selected from the starch derivatives

(...)

23. The pharmaceutical composition of claim 22, wherein the low soluble high dose API or a derivative is selected from Oxcarbazepine, Oxyphenbutazone, Paracetamol, Phenindione, Phenobarbitone, Phenylbutazone, Phenylsulphathiazole, Piperazine phosphate, Proguanil hydrochloride, Promethazine theoclate, Propylthiouracil, Quinidine sulphate, Quinine sulphate, Quinidochlor, Rifampicin, Simvastatin, Spironolactone,

(...)

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26. The pharmaceutical composition of claim 25, wherein the low soluble low dose API or a derivative is selected from the group consisting of Alprazolam, Amiloride hydrochloride, Astemizole, Atorvastatin, Benzhexol hydrochloride,

(...)

29. The pharmaceutical composition of claim 1, wherein the primary release modifying agent is a low molecular weight polyethylene oxide.

(...)

37. The pharmaceutical composition of claim 1, wherein said composition further comprises at least one pharmaceutically acceptable additive selected from diluents, fillers, binders, glidants, and lubricants.

38. The pharmaceutical composition of claim 1, wherein said composition further comprises an optional coating which is designed for the modification of drug release.

(...)

La publicación internacional WO 2005/020993 publicada el 10 de Marzo de 2005 revela:

1. A solid pharmaceutical composition comprising an active ingredient selected among tacrolimus and analogues thereof, wherein less than 20% w/w of the active ingredient is released within 0.5 hours, when subjected to an *in vitro* dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium.

(...)

9. The composition according to claim 8, wherein less than 40 w/w% of the active pharmaceutical ingredient is released within 8 hours, preferably within 15 hours.

(...)

12. The composition according to claim 1 comprising a solid dispersion or solid solution of active ingredient in a hydrophilic or water-miscible vehicle and one or more modifying release agents.

(...)

17. The composition according to claim 12, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyethylene glycols, polyoxyethylene oxides, poloxamers, polyoxyethylene stearates, poly-epsilon caprolactone, polyglycolized glycerides such as Gelucire®, and mixtures thereof.

(...)

18. The composition according to claim 12, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyvinylpyrrolidones, polyvinyl-polyvinylacetate copolymers (PVP-PVA), polyvinyl alcohol (PVA), polymethacrylic polymers (Eudragit RS; Eudragit RL, Eudragit NE, Eudragit E), cellulose derivatives including hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, pectins, cyclodextrins, galactomannans, alginates, carragenates, xanthan gums and mixtures thereof.

(...)

50. Use of the solid composition according to claim 1 for the preparation of a controlled or modified release solid dosage form.

La publicación internacional WO 2004/026314 publicada el 01 de Abril de 2004 revela:

2. The oral dosage form comprising oxcarbazepine according to claim 1 which, when administered once a day, is released to produce constant MHD plasma levels over 24 hours.

3. The oral dosage form according to claim 1 or 2 consisting of a tablet core and a coating wherein the core comprises oxcarbazepine, optionally, a filler, and at least one further excipient selected from cellulose ethers, carboxyvinyl polymer of acrylic acid cross linked with alkyl ethers of sucrose or pentaerythritol and polymethacrylates.

(...)

9. The oral dosage form according to any one of claims 3 to 8 comprising as a filler microcrystalline cellulose.

(...)

Como se puede apreciar, en estas anterioridades se revela la inclusión de atorvastatina, oxcarbazepina, levetiracetam y simvastatina en matrices compuestas por compuestos del mismo tipo (poliméricas hidrofílicas) que permiten una liberación controlada de dicho principio activo. Específicamente se hace mención de compuestos tales como celulosa microcristalina, oxido de polialquilenos, gomas polisacáridas naturales, derivados de acido algínico, pectina, ácidos poliacrílicos entrecruzados, poliacrilatos, así como la presencia opcional de otros excipientes tales como diluentes, desintegrantes, rellenos, agentes de cubierta, entre otros.

TO

En conclusión, la solicitud colombiana en tramite carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, en primer lugar porque incurre en una improcedencia directa de patentabilidad al reivindicar un método de uso de una formulación farmacéutica, y en segundo lugar porque carece tanto de novedad como de nivel inventivo al incluir principios activos en formulaciones farmacéuticas ampliamente descritas y convencionalmente usadas con anterioridad en el estado de la técnica.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16 y 18 de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- Capítulos reivindicatorios de todas las publicaciones mencionadas en el acápite de Fundamentos de la Oposición.
- Vila Jato. J.L. Tecnología Farmacéutica. Volumen II, página 142, 145 y 399 a 402.

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de LAFRANCOL S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina. Lafrancol S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79'152.473 de Usaquén
T.P.A. 44.655 del C.S.J.

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REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE JULIO - - - - - - -

DEL AÑO DOS MIL DOS (2002). ----------

ACTO: ----------

1.- PODER ESPECIAL.----------

OTORGADO POR: LAFRANCOL S.A., con Nit. No. - - -

890.301.463-8 - - - - - -

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No. 79.152.473 de Usaquén - Bogotá.---------

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL, DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA, ANTE MI, DIANA BEATRIZ LOPEZ, - - - - - -

NOTARIA TREINTA Y TRES (33) - - - - -

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE SE CONSIGNA EN LOS SIGUIENTES TERMINOS:----------

COMPARECIO: JUAN MARIA RENDON, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 17.125.100 - - -

Expedida en Bogotá - - - - - -

Y manifestó:----------

PRIMERO: Que obra en su carácter de Representante Legal de en nombre y representación de LAFRANCOL S.A., sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Cali - Valle, constituida mediante escritura pública número

REPUBLICA DE COLOMBIA
Notaría Treinta y Tres
Bogotá D.C.
Notario Encargado
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confrontación auténtica con el original que se tuvo a la vista

De la Notaría

De fecha

Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.----------

SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a **JOSE LUIS REYES VILLAMIZAR**, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C, República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo, contencioso, administrativo y judicial, en todo lo concerniente a los siguientes asuntos:----------

a.- Obtención, formulación de oberservaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos.----------

b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- administrativos relacionados con estos derechosa u otros de diferente naturaleza, acciones y procesos que

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Como NOTARIO NOVENO DE BOGOTA D.C. cotejé esta copia con el original que tuve a la vista y encontré que es fiel y auténtica del mismo. 16 ABR. 2008

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AA 8567152

promueva Lafrancol S.A., o se promuevan contra esta y.---------

c.- Para que en todos los asuntos arriba determinados, tanto en los términos señalados por los artículos 42 y complementarios de la decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C. pueda sustituir este mandato, transigir, conciliar,admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.----------

Manifestamos que de la veracidad de las declaraciones del contenido y autenticidad de los documentos anexos en éste instrumento público sólo responden los comparecientes.

HASTA AQUI LA MINUTA PRESENTADA

OTORGAMIENTO Y AUTORIZACION: Leído el presente instrumento Público por los comparecientes y advertidos de la formalidad de su contenido dentro del término legal, lo hallaron conforme con sus intenciones y lo aprobaron en todas sus partes y firmaron junto con la Suscrita Notaria quien da fe y lo autoriza. -----

Se utilizaron las hojas de papel Notarial Números: AA 8567146, 8567152.

REPUBLICA DE COLOMBIA
Notaría Treinta
Bogotá, D.C.
Notario Encargado
EL NOTARIO TREINTA
DEL CIRCULO DE BOGOTA, D.C.
DA FE que esta reproducción
fotostática corresponde con OTRA
AUTENTICADA que tuve a la vista
12 JUN 2009
Bogotá, D.C.

COPIA NOTARIO NOVENO DE BOGOTÁ, D.C. después de la debida confrontación, auténtico esta copia por corresponder a la copia auténtica del documento, de la cual se ha tomado y que se ha tenido a la vista
Bogotá, D.C. 12 JUN 2009

DERECHOS NOTARIALES: $ 49.600.oo

RESOLUCION No. 4188 del 28 de Diciembre del 2001

JUAN MARIA RENDON

C.C.No. 17.125.10c de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

JOSE LUIS REYES VILLAMIZAR

C.C. No. 79.152.473

TEL: 621-2631

DIANA BEATRIZ LOPEZ

DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

n.c.a.

En Segunda COPIA (FOTOCOPIA)
tomada de su original que se expide conforme al
Artículo 79 del Decreto 960 de 1978 en 06
hojas útiles con destino a Jose Luis Reyes
Villamizar.
Santafé de Bogotá D.C. 05 JUL. 2002

NOTARIO TREINTA DEL CIRCULO DE BOGOTÁ D.C.
LA PRESENTE FOTOCOPIA CORresponde con OTRA QUE ESTA reproducción QUE TUVE A LA VISTA
Bogotá D.C.
2 JUN. 2009
REPUBLICA DE COLOMBIA
Notaría Treinta
33 Bogotá D.C.
Notario Encargado
Secretario Notaría 33
BOGOTA, D. C.

CAMARA DE COMERCIO DE BOGOTA

01

82968014

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/06/12 HORA: 12:09:24

OPERACION: 02C030612058 PAGINA: 1

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CERTIFICA:

NOMBRE:LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL :---K 1 46 84
DIRECCION NOTIFICACION JUDICIAL:---K 1 46 84
CIUDAD:CALI
MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTUBRE DE 1958
DIRECCION ELECTRONICA : lafrancolsa@lafrancol.co
DIRECCION WEB : www.lafrancol.com
AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO. INS LIBRO
E.P. 1104	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	19467
E.P. 2309	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	20089
E.P. 1725	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	24528
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	26360
E.P. 2422	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963	26717
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964	28406
E.P. 101	31/01/1966	NOTARIA CUARTA DE CALI	01/02/1966	31039

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IMPRESO POR BARRAMO S.A. NIT 860.013.711-5 (0664 01-2009

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E.P. 552 21/03/1968 NOTARIA CUARTA DE CALI 01/04/1968
35711

E.P. 4964 12/12/1972 NOTARIA CUARTA DE CALI 16/01/1973
2975 IX

E.P. 1956 30/05/1973 NOTARIA CUARTA DE CALI 13/06/1973
4337 IX

E.P. 4964 12/12/1972 NOTARIA CUARTA DE CALI 28/11/1973
5994 IX

E.P. 5579 12/11/1973 NOTARIA CUARTA DE CALI 28/11/1973
5995 IX

E.P. 4406 30/09/1974 NOTARIA CUARTA DE CALI 28/11/1974
10887 IX

E.P. 192 03/02/1978 NOTARIA CUARTA DE CALI 14/02/1978
25355 IX

E.P. 3479 07/09/1979 NOTARIA CUARTA DE CALI 19/09/1979
34204 IX

E.P. 4274 12/12/1984 NOTARIA NOVENA DE CALI 19/12/1984
73088 IX

E.P. 1155 21/05/1985 NOTARIA SEPTIMA DE CALI 03/06/1985
76917 IX

E.P. 1553 20/06/1986 NOTARIA SEPTIMA DE CALI 08/07/1986
85997 IX

E.P. 1458 09/06/1987 NOTARIA SEPTIMA DE CALI 24/12/1987
3508 IX

E.P. 7222 14/12/1988 NOTARIA TERCERA DE CALI 19/12/1988
13847 IX

E.P. 4530 04/09/1989 NOTARIA TERCERA DE CALI 07/09/1989
21508 IX

E.P. 3865 02/08/1990 NOTARIA TERCERA DE CALI 13/08/1990
31708 IX

E.P. 8305 13/12/1995 NOTARIA TERCERA DE CALI 23/01/1996
557 IX

E.P. 4559 16/11/1999 NOTARIA TERCERA DE CALI 26/11/1999
7911 IX

E.P. 6.004 02/12/2004 NOTARIA TERCERA DE CALI 14/12/2004

*** CONTINUA ***

CAMARA DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/06/12 HORA: 12:09:24

OPERACION: 02C030612058 PAGINA: 3

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13371 IX
E.P. 6241 27/12/2006 NOTARIA TERCERA DE CALI 19/01/2007
625 IX
E.P. 389 07/02/2008 NOTARIA TERCERA DE CALI 19/02/2008
1880 IX
E.P. 1907 11/05/2009 NOTARIA TERCERA DE CALI 26/05/2009
5950 IX

CERTIFICA:

VIGENCIA: 29 DE SEPTIEMBRE DEL AÑO 2057

CERTIFICA:

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.
ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) AÑOS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.
PARAGRAFO PRIMERO. SUPLENTES: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTES: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS

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IMPRESO POR GABRIELONI S.A. NIT 860.013.741-5 | 0004-01-2009

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CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMMLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS.

EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS,

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CAMARA DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/06/12 HORA: 12:09:24

OPERACION: 02C030612058 PAGINA: 5

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COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX
FUE(RON) NOMBRADO(S):
GERENTE GENERAL Y REPRESENTANTE LEGAL
JUAN MARIA RENDON GUTIERREZ
C.C.17125100
PRIMER SUPLENTE DEL GERENTE
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831
SEGUNDO SUPLENTE DEL GERENTE
ROBERTO M. VENTURA CRISPINO
C.C.9086003

CERTIFICA:

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2032 DEL LIBRO IX
FUE(RON) NOMBRADO(S):
TERCER SUPLENTE DEL GERENTE
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

CERTIFICA:

DOCUMENTO: ACTA No. 112 DEL 25 DE MARZO DE 2008
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 03 DE MARZO DE 2009 No. 2453 DEL LIBRO IX
FUE(RON) NOMBRADO(S)
JUNTA DIRECTIVA
PRINCIPALES
PRIMER RENGLON
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831
SEGUNDO RENGLON
ROSA VICTORIA VENTURA DE VISBAL

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IMPRESO POR: BARRAMEDIA S.A. NIT 860.013.711-5 10534 01 2009

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C.C.38992048
TERCER RENGLON
CARLOS ANTONIO ESPINOSA PEREZ
C.C.16684716
SUPLENTES
PRIMER RENGLON
JUAN MARIA RENDON GUTIERREZ
C.C.17125100
SEGUNDO RENGLON
ROBERTO M. VENTURA CRISPINO
C.C.9086003
TERCER RENGLON
ISABEL CRISPINO DE VENTURA
C.C.29402071

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX
FUE(RON) NOMBRADO(S):
REVISOR FISCAL
ALFREDO LOPEZ & CIA. LTDA
NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 08 DE MAYO DE 2008
ORIGEN: ALFREDO LOPEZ & CIA LTDA
INSCRIPCION: 23 DE MAYO DE 2008 No. 5771 DEL LIBRO IX
FUE(RON) NOMBRADO(S):
REVISOR FISCAL PRINCIPAL
ALFREDO LOPEZ CAMPO
C.C.8241912
REVISOR FISCAL SUPLENTE
ANDERSON DAVID RODRIGUEZ REYES
C.C.16916373

CERTIFICA:

CAPITAL AUTORIZADO: $10,000,000,000

*** CONTINUA ***

CAMARA DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/06/12 HORA: 12:09:24

OPERACION: 02C030612058 PAGINA: 7

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NUMERO DE ACCIONES: 1,000,000,000
VALOR NOMINAL: $10
CAPITAL SUSCRITO: $7,500,000,000
NUMERO DE ACCIONES: 750,000,000
VALOR NOMINAL: $10
CAPITAL PAGADO: $7,500,000,000
NUMERO DE ACCIONES: 750,000,000
VALOR NOMINAL: $10

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 30 DE ABRIL DE 2004
INSCRIPCION: 03 DE MAYO DE 2004 No. 4859 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 29 DE ABRIL DE 2005
INSCRIPCION: 06 DE MAYO DE 2005 No. 4983 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 15 DE JUNIO DE 2006
INSCRIPCION: 21 DE JUNIO DE 2006 No. 7526 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 01 DE NOVIEMBRE DE 2006
INSCRIPCION: 28 DE NOVIEMBRE DE 2006 No. 13380 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE DICIEMBRE DE 2006
INSCRIPCION: 21 DE DICIEMBRE DE 2006 No. 14301 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE DICIEMBRE DE 2007
INSCRIPCION: 21 DE DICIEMBRE DE 2007 No. 13604 DEL LIBRO IX
CONSTA EL GRUPO EMPRESARIAL:
CONTROLANTE
LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
NIT. 890301463-8
DOMICILIO:CALI VALLE
NACIONALIDAD:COLOMBIA

ACTIVIDAD: A) LA FABRICACION, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACIÓN DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACIÓN, DISTRIBUCIÓN Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACIÓN DE TODOS LOS ACTOS, CONTRATOS,

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IMPRESO POR BANCARIANO S.A. NIT 860.013.715-5 10:09:01 2009

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CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PUEDE LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAÍCES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAÍCES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD, DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

SUBORDINADA

AMERICAN GENERICS S A

NIT. 800223214-9

DOMICILIO:CALI VALLE

NACIONALIDAD:COLOMBIA

PRESUPUESTO DE CONTROL:NUMERAL 3, ARTÍCULO 27 DE LA LEY 222.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LAFRANCOL INTERNACIONAL S.A.

NIT. 815003912

DOMICILIO:PALMIRA VALLE

NACIONALIDAD:COLOMBIA

PRESUPUESTO DE CONTROL: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. POSEE EL 40% Y LABORATORIOS PAULY PHARMACEUTICAL S.A. POSEE EL 40% Y AMERICAN GENERICS S.A POSEE EL 19.97%

ACTIVIDAD: REALIZACIÓN DE ACTIVIDADES DESDE LA ZONA FRANCA, LAS CUALES CONSISTEN EN LA PRESTACIÓN DE TODO TIPO DE SERVICIOS ASÍ COMO DISTRIBUIR, VENDER, COMPRAR, IMPORTAR, EXPORTAR Y ALMACENAR TODO TIPO DE MATERIAS PRIMAS, PRODUCTOS TERMINADOS Y SEMITERMINADOS RELACIONADOS CON LA INDUSTRIA DE ALIMENTOS, COSMÉTICA Y FARMACÉUTICA.

SUBORDINADA

LAFRANCOL PERÚ S.A

DOMICILIO:LIMA LIMA

NACIONALIDAD:PERU

PRESUPUESTO DE CONTROL: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. POSEE EL 93.0%

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACEUTICOS DE USO

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/06/12 HORA: 12:09:24

OPERACION: 02C030612058 PAGINA: 9

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HUMANO.
SUBORDINADA
LABORATORIOS PAULY PHARMACEUTICAL S A
NIT. 800097402-6
DOMICILIO:CALI VALLE
NACIONALIDAD:COLOMBIA
PRESUPUESTO DE CONTROL:NUMERAL 3, ARTÍCULO 27 DE LA LEY 222.
ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO
SUBORDINADA
LAFRANCOL (USA) CORP
DOMICILIO:ESTADOS UNIDOS
NACIONALIDAD:ESTADOS UNIDOS
PRESUPUESTO DE CONTROL: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. POSEE EL 65.25%
ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.
SUBORDINADA
GAMAR SOCIEDAD LIMITADA
NIT. 890312050-7
DOMICILIO:CALI VALLE
NACIONALIDAD:COLOMBIA
PRESUPUESTO DE CONTROL:NUMERAL E, ARTICULO 27 DE LA LEY 222.
ACTIVIDAD:TODAS LAS ACTIVIDADES RELACIONADAS CON LAS ARTES GRAFICAS.
SUBORDINADA
LAFRANCOL GUATEMALA S.A.
NIT. 4088707
DOMICILIO:GUATEMALA
NACIONALIDAD:GUATEMALA
PRESUPUESTO DE CONTROL:NUMERAL 3, ARTÍCULO 27 DE LA LEY 222
ACTIVIDAD: PRODUCCIÓN, FABRICACIÓN, EXPORTACIÓN Y DISTRIBUCIÓN DE PRODUCTOS FARMACÉUTICOS Y/O ALIMENTICIOS Y NATURALES DE CONSUMO HUMANO Y LA COMERCIALIZACIÓN DE TODA CLASE DE MERCANCÍAS POR CUENTA PROPIA O EN NOMBRE DE TERCEROS.
SUBORDINADA

*** CONTINUA ***

IMPRESO POR RAMASAMAO S.A. NIT 860.012.711-5 10/04/01:2009

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/06/12 HORA: 12:09:24

OPERACION: 02C030612058 PAGINA: 10

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DISTRIBUCIONES UQUIFA LTDA
NIT. 800182021-7
DOMICILIO:CALI VALLE
NACIONALIDAD:COLOMBIA
PRESUPUESTO DE CONTROL:NUMERAL 3, ARTÍCULO 27 DE LA LEY 222
ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS Y ALIMENTOS FUNCIONALES DE CONSUMO HUMANO
SUBORDINADA
LABORATORIOS NATURMEDIK S A
NIT. 800226363-1
DOMICILIO:CALI VALLE
NACIONALIDAD:COLOMBIA
PRESUPUESTO DE CONTROL:NUMERAL 3, ARTÍCULO 27 DE LA LEY 222.
ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE CONSUMO HUMANO.
SUBORDINADA
FOCUS PHARMACEUTICAL
NIT. 900104555
DOMICILIO:BOGOTA DISTRITO CAPITAL
NACIONALIDAD:COLOMBIA
PRESUPUESTO DE CONTROL:NUMERAL 3, ARTÍCULO 27 DE LA LEY 222.
ACTIVIDAD: DESARROLLO, FABRICACIÓN O PRODUCCIÓN, DIRECTAMENTE O A TRAVÉS DE TERCEROS EN CUALQUIER MODALIDAD NEGOCIAL, LA COMERCIALIZACIÓN Y DISTRIBUCIÓN NACIONAL O INTERNACIONAL, DE TODA CLASE DE ARTÍCULOS DE GÉNERO FARMACÉUTICO, ESPECÍFICAMENTE DE MEDICAMENTOS.
SUBORDINADA
LAFRANCOL DOMINICANA S.A.
DOMICILIO:SANTO DOMINGO REPUBLICA DOMINICANA
NACIONALIDAD:REPUBLICA DOMINICANA
PRESUPUESTO DE CONTROL:NUMERAL 3, ARTÍCULO 27 DE LA LEY 222.
ACTIVIDAD: FABRICACIÓN DE PRODUCTOS FARMACÉUTICOS.

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734908- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/06/12 HORA: 12:09:24

OPERACION: 02C030612058 PAGINA: 11

****

UBICADO EN: CRA. 1A NRO. 46A 28 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734911- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A
UBICADO EN: CRA. 1B NRO. 46A 121 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734913- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A
UBICADO EN: CRA. 3 NRO. 47 25 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL
UBICADO EN: ---K 1 46 84 DE CALI
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S A
UBICADO EN: ---K 1A 46 A 32 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S A
UBICADO EN: --K 1 46A 70 DE CALI

*** CONTINUA ***

IMPRESO POR SAMARANO S.A. NIT 800.513.711-5 2006-07-2006

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2009/06/12 HORA: 12:09:24

OPERACION: 02C030612058 PAGINA: 12

****

FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL AÑO 2009

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 25 DE MARZO DE 2009 .

CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 12 DIAS DEL MES DE JUNIO DEL AÑO 2009 HORA: 12:09:30

100

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

ERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-007949- -00005-0000
ha: 2009-06-17 17:07:23 Dep. 2020 NUECREACIONES
11 PATENTEIYII Eve: 379 FASENACIONALII
400 OPOSIOBSERVTER Folios: 100

RECIBO OFICIAL DE CAJA : 09 - 43,452
FECHA : JUNIO 12 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	111083615	11/06/2009	1,726,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	287,000.00
		TOTAL :	$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____