



No. 11-096477- -00006-0000

Fecha: 2012-09-07 16:20:00 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 19

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 11-096-477

TÍTULO SOLICITADO: **SUSPENSIÓN FARMACÉUTICA DE LIBERACIÓN DOBLE.**

PUBLICACIÓN: Gaceta 640 de 15 de marzo de 2012, N° de publicación 182.

SOLICITANTE: PANACEA BIOTEC LTD.

APODERADO: DILIA MARIA RODRIGUEZ D` ALEMAN.

TRÁMITE: SUSTENTACIÓN DE OPOSICIÓN

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 **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 15 de junio de 2012, en los siguientes términos:

I. **RATIFICACIÓN.**

Comedidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- Atendiendo al concepto de unidad de invención revelado en el artículo 25 de la Decisión 486 - Artículo 25, nos referimos entonces al contenido de la reivindicación 1, en donde se revela una suspensión farmacéutica con ciertas características técnicas y en donde su parte final se revelan además “*sales farmacéuticamente aceptables, derivados, isómeros, polimorfos, solvatos, hidratos, análogos, enantiómeros, formas tautoméricas*”, es indispensable indicar que la obtención de este tipo de variaciones o derivaciones de una misma estructura química, en este caso del principio activo incluido en la suspensión, no conforman un único concepto inventivo, porque mientras la elaboración de una suspensión hace parte de las actividades de un formulador farmacéutico, la obtención de derivados, sales y variaciones de una misma estructura química hacen parte de las actividades netamente químicas y/o fisicoquímicas a través de las cuales se pueden descubrir o revelar estas características inherentes a toda sustancia. Lo anterior, complementado además con el no soporte de estas variaciones y derivaciones estructurales del mencionado principio activo, dado que en el capítulo descriptivo no se encuentra información que soporte la obtención de “*sales farmacéuticamente aceptables, derivados, isómeros, polimorfos, solvatos, hidratos, análogos, enantiómeros, formas tautoméricas*”, tal y como lo exige el artículo 30 de la Decisión 486.
- Las reivindicaciones 13 a 15, en donde se hace mención explícita al uso o al tratamiento terapéutico de trastornos tales como infecciones virales, infecciones bacterianas, hipertensión, insuficiencia cardíaca, entre otros, contravienen lo dispuesto en el artículo 20 literal d) la Decisión 486 de 2000.
- La selección de excipientes para la elaboración de productos farmacéuticos, de acuerdo con sus características fisicoquímicas, que se evalúan rutinariamente a través de los ensayos de preformulación y formulación; corresponde a las habilidades de una persona medianamente versada en la formulación de productos farmacéuticos, y por lo tanto, la elaboración de composiciones tales como suspensiones o el recubrimiento de partículas para conseguir un efecto diferente a la liberación inmediata, no pueden sustentar nivel inventivo alguno, más cuando dichas estrategias tecnológicas para la elaboración de

suspensiones¹ y recubrimientos para liberación modificada², se encuentran ampliamente descritos en el estado de la técnica. De especial atención resulta la inclusión de un polímero insoluble en agua y un agente lipídico en el núcleo del microgránulo que comprende el principio activo, dado que son esas inclusiones características de las matrices lipídicas³ y las matrices poliméricas⁴, reconocidas ampliamente en el estado de la técnica para obtener liberaciones modificadas.

- La solicitud colombiana en cuestión también menciona en su reivindicación 10 *“las formulaciones en polvo o gránulos se pueden fabricar al usar las técnicas de granulación de fusión en caliente”, por lo que cualquier persona medianamente versada en la formulación de productos farmacéuticos debe reconocer que dicha técnica (conocida también como melt granulation) es una estrategia tecnológica de formulación ampliamente reconocida. La producción de formulaciones farmacéuticas debe reconocer que la formación de dichas dispersiones del fármaco en el seno de un portador se puede realizar mediante técnicas de fusión, disolución-dsecación o una mezcla de ambas*⁵.
- En la granulación por fusión, generalmente el agente aglutinante puede añadirse ya fundido sobre la mezcla de polvos precalentada o en forma sólida junto con el resto de componentes de la mezcla, de tal forma que la granulación se desarrolla en “un solo paso” al fundir el aglutinante en el seno de la mezcla. Tras la fusión, el agente aglutinante actúa como líquido de unión de las partículas de polvo de forma similar al líquido adicionado en los procesos de vía húmeda. Dependiendo de la cantidad de aglutinante añadido, de los componentes que constituyen la mezcla y de la elección de las condiciones del proceso, es posible obtener gránulos o incluso pellets . Como se puede apreciar, estas mismas son las características técnicas esenciales del procedimiento reivindicado en la solicitud colombiana en trámite.
- Esta propiedad permite emplear esta técnica para la formulación de fármacos sensibles a la humedad, evitar el controvertido uso de solventes orgánicos y

¹ Vila Jato. J.L. Tecnología Farmacéutica. Volumen I. Páginas 299 a 316. Volumen II. Páginas 50 y 51.

² Vila Jato. J.L. Tecnología Farmacéutica Volumen II. Páginas 146 a 155.

³ Ibíd. Páginas 402 a 404.

⁴ Ibíd. Páginas 418 y 419.

⁵ Vila Jato. J.L. Tecnología Farmacéutica. Volumen I. Páginas 201 a 202.

acortar el proceso de granulación en términos de tiempo y energía al eliminar la fase de secado. Asimismo, una adecuada selección del agente aglutinante y del resto de excipientes permitirá el desarrollo y elaboración de formas farmacéuticas tanto de liberación inmediata como de liberación controlada. Uno de los equipos más empleados en la granulación por fusión es el mezclador granulador de alta velocidad, que permite realizar esta técnica en un solo paso. Además, una vez optimizado el proceso, permite su aplicación a escala industrial⁶.

- Teniendo en cuenta que la solicitud colombiana en cuestión revela una mezcla en polvo de los ingredientes activos y los excipientes para formar un granulado que finalmente se formulara en tabletas y/o capsulas, es importante resaltar que precisamente en el estado de la técnica, la granulación por fusión es un proceso simplificado de aglomeración de partículas primarias de polvo para formar estructuras mayores denominadas gránulos. Generalmente, este granulado se utiliza como producto intermedio en la fabricación de comprimidos y cápsulas, aunque también puede ser empleado como producto final⁷.
- Las principales ventajas que conllevaría a cualquier persona medianamente versada en la formulación farmacéutica a escoger la granulación por fusión, son las siguientes: evita la formación de polvo, elimina la fase de secado haciendo el proceso de granulación más corto, y evita el uso de solventes y los posibles problemas que derivan de ello (hidrólisis de principio activo, empleo de equipos ignífugos etc.). Así mismo, para dicho formulador, escoger los principios activos que se pueden involucrar en un granulado a través de este proceso, parte del hecho (y mayor inconveniente de la técnica) que no se puede aplicar a sustancias termolábiles a las temperaturas habituales de trabajo⁸.
- En cuanto a la proporción del material aglutinante, en el estado de la técnica se ha reconocido que, en general, la granulación por fusión requiere aproximadamente entre un 10 y un 20 % en peso del agente aglutinante en la mezcla. Un exceso de aglutinante en la mezcla provocaría un sobre amasado,

⁶ Ibid.

⁷ Ibid.

⁸ Ibid.

mientras que si no se alcanza la proporción suficiente no tendrá lugar la formación del granulado⁹.

- la publicación WO 2007/143156 publicada el 13 de diciembre de 2007 revela todas las características técnicas esenciales que definen a las formulaciones tipo suspensión de liberación dual descritas en la solicitud colombiana en trámite; inclusive respecto a los excipientes utilizados, a los tamaños de partícula, al tipo de recubrimiento empleado en las micropartículas de liberación controlada, y si bien es cierto que la fenilefrina no hace parte de los ingredientes activos que menciona la solicitud colombiana en cuestión, el documento es a todas luces una guía para cualquier persona medianamente versada en la formulación de productos farmacéuticos que quieran formular cualquier otro principio activo en este mismo tipo de suspensiones duales.

II. COMPLEMENTO DE INFORMACIÓN.

Continuando con la demostración de falta de nivel inventivo podemos mencionar otros documentos que dejan en evidencia este hecho, veamos:

La patente americana US 2008/0026056 "Antibiotic-Based Pharmaceutical Formulation in Microcapsular Form" publicada el 31 de enero de 2008, revela:

1. Use of modified-release microcapsules, comprising a core that contains at least one active principle AP1 formed of at least one antibiotic, and a coating for said core that governs the modified release of said active principle, for the manufacture of a drinkable or orally dispersible antibiotic pharmaceutical formulation that makes it possible to limit the increase in the antibiotic resistance of the target germs.

(...)

3. Use according to claim 1, characterized in that the microcapsules have a particle size of between 50 nm and 800 µm.

(...)

⁹ Ibid.

8. Use according to claim 1, characterized in that the formulation comprises:

modified-release microcapsules whose core contains an active principle AP1 formed of an antibiotic,

and an active principle AP2 formed of an antibiotic or of an active principle other than an antibiotic, said AP2 being of the immediate-release type.

9. Use according to claim 1, characterized in that the core of the microcapsules comprises amoxicillin as active principle AP1.

(...)

11. Use according to claim 1, characterized in that the formulation is in the form of powders, tablets, granules, gelatin capsules, syrups or aqueous suspensions.

Por su parte la publicación internacional WO 2008/122993 "Controlled Release formulation of coated microparticles" publicada el 18 de octubre de 2008, revela:

In preferred embodiment, the active agent of the present invention is selected from but not limited to a group comprising paracetamol, ibuprofen, nimesulide, mycophenolate, carbamazepine, chlorpheniramine, phenylpropanolamine, amoxicillin, erythromycin, ciprofloxacin, tacrolimus, and the like or pharmaceutically acceptable salts, hydrates, polymorphs, esters, and derivatives thereof used either alone or in combination thereof. In an embodiment, the active agents useful for the present invention are preferably those which have a shorter to a medium duration of therapy such as analgesics, antibiotics, anti-inflammatory drugs, antipyretics, antihistamines, and the like. In another embodiment of the present invention, the compositions of the present invention may comprise of active agents which are useful for longer duration of therapy.

(...)

polyacrylic and polymethacrylic acids and polyacrylate and methacrylate based polymers, and mixtures thereof, such as Eudragit®, for example Eudragit® E100, Eudragit® EPO, Eudragit® L, Eudragit® S or the like (Rohm-Pharma, Darmstadt, Germany); reaction products such as hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose acetate succinate and the like, cellulose derivative such as an alkyl cellulose, a hydroxyalkyl cellulose, a hydroxyalkyl alkylcellulose or a cellulose ester with at least one

(...)

the core microparticles may range from about 0.5 μm to about 2000 μm preferably about 1 μm to about 1000 μm , more preferably from about 50 μm to about 500 μm . In an embodiment, the present invention provides liquid taste masked controlled release pharmaceutical formulations for oral administration of active agents which produces bad or bitter taste in mouth of a subject upon administration.

(...)

6. The controlled release pharmaceutical composition according to claim 1, wherein the water insoluble polymer is selected from a group comprising pH independent or pH dependent polymer(s) or mixtures thereof

(...)

8. The controlled release pharmaceutical composition according to claim 7, wherein the pH independent polymer is water insoluble.

(...)

20. The controlled release pharmaceutical composition according to claim 19, wherein the composition is a liquid or semisolid oral dosage form such as suspension, paste, jelly, syrup or elixir.

(...)

21. The controlled release pharmaceutical composition according to claim 1 wherein composition may be formulated as fast melt formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, or a combination of immediate release and extended release formulations.

(...)

Como se puede apreciar claramente, en estos dos documentos se revelan las mismas características técnicas indispensables para obtener formulaciones del mismo tipo que las reivindicadas por la solicitud colombiana en trámite, en especial lo relacionado a la combinación de partículas de liberación controlada y de liberación inmediata en una misma formulación tipo suspensión. Inclusive se hace mención específica de los polímeros insolubles e independientes del pH, los intervalos de tamaño de partícula, los polímeros utilizados para el recubrimiento que aporta la liberación controlada y el mismo tipo de fármacos contenidos en la formulación. En otras palabras lo revelado en estas anterioridades afecta el nivel inventivo de las reivindicaciones 1 a 4 y 9 a 12.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados tanto en este complemento de información como en el escrito de oposición presentado en su momento, con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

V. ANEXOS.

- ❖ La patente americana US 2008/0026056 "Antibiotic-Based Pharmaceutical Formulation in Microcapsular Form" publicada el 31 de enero de 2008. Portada; Páginas 10 y 11.
- ❖ La publicación internacional WO 2008/122993 "Controlled Release formulation of coated microparticles" publicada el 18 de octubre de 2008. Portada; Pág 8, 10, 13, 28-31.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.



US 20080026056A1

(19) **United States**

(12) **Patent Application Publication**

Guimberteau et al.

(10) **Pub. No.: US 2008/0026056 A1**

(43) **Pub. Date: Jan. 31, 2008**

(54) **ANTIBIOTIC-BASED PHARMACEUTICAL FORMULATION IN MICROCAPSULAR FORM**

Publication Classification

- (51) **Int. Cl.**
A61K 9/50 (2006.01)
A61K 31/43 (2006.01)
A61P 31/04 (2006.01)
- (52) **U.S. Cl.** **424/464; 424/489; 424/490; 514/192**

(75) **Inventors:** Florence Guimberteau, Montussan (FR); Catherine Castan, Orlenas (FR); Remi Meyrueix, Lyon (FR); Gerard Soula, Meyzieu (FR)

Correspondence Address:
PATTON BOGGS LLP
8484 WESTPARK DRIVE
SUITE 900
MCLEAN, VA 22102 (US)

(57) **ABSTRACT**

The invention relates to oral antibiotic drugs. The object of the invention is to limit or even stop the increase in antibiotic resistance without sacrificing the requirements of (a) increased efficacy of oral antibiotics, particularly for pediatric applications, (b) tolerance, (c) broad spectra of activity, and (d) good patient compliance. This object is achieved by the invention, which proposes the use of modified-release microcapsules, comprising a core that contains at least one active principle API formed of at least one antibiotic, and a coating for said core that governs the modified release of said active principle, for the manufacture of a drinkable or orally dispersible antibiotic pharmaceutical formulation that makes it possible to limit the increase in the antibiotic resistance of the target germs, this formulation being: capable of administration in one or two, preferably two, intakes per day, and definable as follows, relative to an immediate-release oral formulation (IRF*) comprising at least one active principle API, and for the same dose D of API as IRF*:

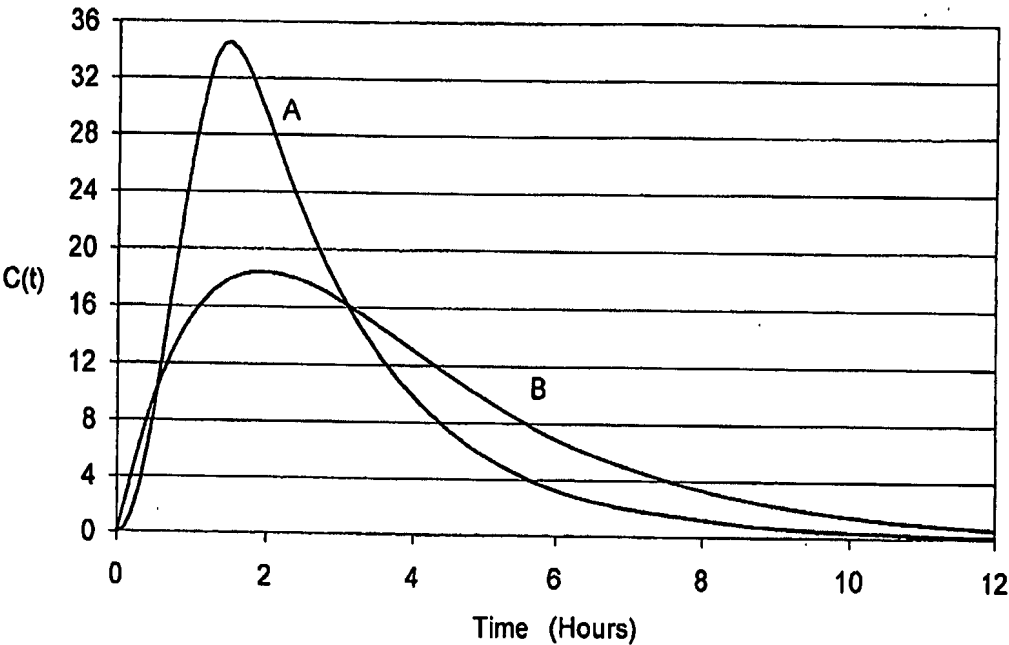
(73) **Assignee:** Flamel Technologies, Venissieux (FR)

- (21) **Appl. No.:** 11/631,030
- (22) **PCT Filed:** May 25, 2005
- (86) **PCT No.:** PCT/FR05/50366

§ 371(c)(1),
(2), (4) **Date:** Jun. 28, 2007

(30) **Foreign Application Priority Data**

Jun. 28, 2004 (FR) 0451353 $T_{mic} > T_{mic}^{*} of IRF^{*}$



[0151] Step 2: Coating

[0152] 450 g of granules obtained above are coated with 60 g of Eudragit RS100, 4 g of triethyl citrate and 16 g of PEG 35000, dissolved in isopropanol, in an Aeromatic-Fielder MP1 fluidized air bed apparatus.

Example 8

Preparation of Formulation 8 Comprising an Amoxicillin Fraction in the Form of Modified-Release (Sustained-Release) Microcapsules and an Amoxicillin Fraction in the Form of Immediate-Release Amoxicillin

[0153] 300 g of granules prepared in step 1 of Example 4 for the manufacture of micro-capsules are mixed with 700 g of microencapsulated amoxicillin corresponding to Formulation 4 of Example 4.

Example 9

Plasma Profiles of the Multimicrocapsular Amoxicillin Formulations According to the Invention

[0154] The plasma amoxicillin concentration profile after the administration of modified-release microcapsules according to the invention was simulated from the following data:

[0155] The dose administered is 43 mg/kg. The modified-release microcapsules release 39% of the dose in one hour and 50% of the dose in 1.4 hours. The plasma profile resulting from an IV injection ("response function IV") is a monoexponential function with an elimination half-life of 1.3 hours. Finally, the plasma profile is calculated by convolution of the amoxicillin release rate by the IV response function IV. The plasma profile obtained after administration of the modified-release microcapsules is compared in FIG. 1 with the profile resulting from the administration of the same dose of an immediate-release oral form IRF*. It is seen that the modified-release form according to the invention affords an increase in the time T_{mic} . For example, for MIC=4 µg/ml, T_{mic} is 5.3 hours for the immediate-release form and 7.3 hours for the form according to the invention. The modified-release microcapsular amoxicillin formulations according to the invention are therefore more effective, for the same dose, than the immediate-release amoxicillin formulations IRF*.

[0156] FIG. 1 attached shows two plasma amoxicillin concentration profiles A and B (µg/ml) resulting from the administration of 43 mg/kg, profile A being that of an immediate-release oral form (IRF*) and profile B being that of a modified-release microcapsular oral form of the type whose use is proposed according to the invention for the manufacture of an effective antibiotic drug.

1. Use of modified-release microcapsules, comprising a core that contains at least one active principle AP1 formed of at least one antibiotic, and a coating for said core that governs the modified release of said active principle, for the manufacture of a drinkable or orally dispersible antibiotic pharmaceutical formulation that makes it possible to limit the increase in the antibiotic resistance of the target germs.

2. Use according to claim 1, characterized in that this formulation can be defined as follows, relative to an imme-

diate-release oral formulation (IRF*) comprising at least one active principle AP1, and for the same dose D of AP1 as IRF*:

$$T_{mic} > T_{mic}^{*} \text{ of IRF}^{*}$$

preferably

$$T_{mic} > 1.1 \cdot T_{mic}^{*} \text{ of IRF}^{*}$$

and particularly preferably

$$3 \cdot T_{mic}^{*} \text{ of IRF}^{*} > T_{mic} > 1.1 \cdot T_{mic}^{*} \text{ of IRF}^{*}$$

where T_{mic} is the time for which the plasma concentration is greater than or equal to the minimum inhibitory concentration for a given antibiotic, and where T_{mic}^{*} is the T_{mic} of an immediate-release oral formulation (IRF*).

3. Use according to claim 1, characterized in that the microcapsules have a particle size of between 50 nm and 800 µm.

4. Use according to claim 1, characterized in that, in addition to the microcapsules, the formulation comprises at least one active principle AP1 formed of at least one immediate-release antibiotic.

5. Use according to claim 4, characterized in that the formulation comprises at least one immediate-release antibiotic AP1 in an amount less than or equal to 60% by weight, preferably less than or equal to 50% by weight and particularly preferably of between 0 and 40% by weight, based on the total amount of antibiotic AP1.

6. Use according to claim 1, characterized in that the core of the microcapsules comprises, as active principle AP1, an antibiotic selected from the following group: aminosalicic acid, nalidixic acid, amoxicillin, amoxicillin and potassium clavulanate, ampicillin, ampicillin and sulbactam, azithromycin, bacampicillin, carbenicillin indanyl sodium (and other carbenicillin salts), capreomycin, cefadroxil, cefazolin, cephalexin, cephalothin, cephalixin, cephaclor, cefprozil, cephadrine, cefamandole, cefonicid, ceforanide, cefuroxime, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, cefmetazole, cefotetan, ceftioxin, ciprofloxacin, clarithromycin, clindamycin, clofazimine, cloxacillin, cotrimoxazole, cycloserine, dicloxacillin, dirithromycin, erythromycin (and erythromycin salts such as estolate, ethylsuccinate, gluceptate, lactobionate, stearate), ethambutol-HCl and other salts, ethionamide, fosfomycin, imipenem, isoniazid, levofloxacin, lomefloxacin, loracarbef, methicillin, methenamine, metronidazole, mezlocillin, nafcillin, nitrofurantoin, norfloxacin, novobiocin, ofloxacin, oxacillin, penicillin V, penicillin salts, penicillin complexes, pentamidine, piperacillin, piperacillin and tazobactam, sparfloxacin, sulfacytine, sulfamerazine, sulfamethazine, sulfamethizole, sulfasalazine, sulfisoxazole, sulfapyrazine, sulfadiazine, sulfmethoxazole, sulfapyridine, ticarcillin, ticarcillin and potassium clavulanate, trimethoprim, trimetrexate, troleanomycin, vancomycin and mixtures thereof.

7. Use according to claim 1, characterized in that the formulation comprises:

modified-release microcapsules whose core contains an active principle AP1 formed of an antibiotic,

and modified-release microcapsules whose core contains an active principle AP2 formed of an antibiotic or of an active principle other than an antibiotic.

8. Use according to claim 1, characterized in that the formulation comprises:

modified-release microcapsules whose core contains an active principle AP1 formed of an antibiotic,
and an active principle AP2 formed of an antibiotic or of an active principle other than an antibiotic, said AP2 being of the immediate-release type.

9. Use according to claim 1, characterized in that the core of the microcapsules comprises amoxicillin as active principle AP1.

10. Use according to claim 1, characterized in that the formulation comprises at least one other antibiotic AP2 preferably formed of clavulanic acid and/or at least one of its salts (preferably potassium clavulanate), and even more preferably in an amoxicillin:clavulanate ratio of between 2:1 and 20:1, preferably of between 8:1 and 20:1 and particularly preferably of between 14:1 and 16:1.

11. Use according to claim 1, characterized in that the formulation is in the form of powders, tablets, granules, gelatin capsules, syrups or aqueous suspensions.

12. Use according to claim 10, characterized in that:

the formulation comprises:

micro capsules of amoxicillin,
optionally immediate-release amoxicillin,
immediate-release potassium clavulanate,
and optionally excipients,

and the formulation is designed for administration twice a day.

13. Use according to claim 1, characterized in that the microcapsule coating consists of a single layer.

* * * * *

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 October 2008 (16.10.2008)

PCT

(10) International Publication Number
WO 2008/122993 A1

- (51) International Patent Classification:
A61K 9/16 (2006.01) A61K 47/34 (2006.01)
A61K 9/50 (2006.01) A61K 47/38 (2006.01)

(21) International Application Number:
PCT/IN2008/000232

(22) International Filing Date: 8 April 2008 (08.04.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
783/DEL/2007 9 April 2007 (09.04.2007) IN

(71) Applicant (for all designated States except US):
PANACEA BIOTEC LIMITED [IN/IN]; B-1
Extn./A-27Mohan co-operative Industrial Estate, Mathura
Road, New Delhi 110 044 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): JAIN, Rajesh
[IN/IN]; Panacea Biotec Limited, B-1 Extn./A-27Mohan
co-operative Industrial Estate, Mathura Road, New Delhi
110 044 (IN). JINDAL, Kour Chand [IN/IN]; Panacea
Biotec Limited, B-1 Extn./A-27Mohan co-operative In-
dustrial Estate, Mathura Road, New Delhi 110 044 (IN).
BOLDHANE, Sanjay [IN/IN]; Panacea Biotec Limited,
B-1 Extn./A-27Mohan co-operative Industrial Estate,
Mathura Road, New Delhi 110 044 (IN).

(74) Agent: GUPTA, Bhartee; Panacea Biotec Limited, B-1
Extn./A-27Mohan co-operative Industrial Estate, Mathura
Road, New Delhi 110 044 (IN).
- (81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE,
EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID,
IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC,
LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN,
MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV,
SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL,
NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Declarations under Rule 4.17:**
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
 - of inventorship (Rule 4.17(iv))
- Published:**
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments



WO 2008/122993 A1

- (54) Title: CONTROLLED RELEASE FORMULATION OF COATED MICROPARTICLES
- (57) Abstract: Controlled release compositions comprising microparticles which comprise a core and at least one coat, wherein the core comprises at least one active agent(s), optionally at least one water soluble polymer(s) and optionally one or more pharmaceutically acceptable excipient(s); and at least one coat comprising at least one pH independent polymer(s) along with one or more pharmaceutically acceptable excipient(s) are provided. Preferably the controlled release pharmaceutical compositions comprise microparticles along with at least one in-situ gelling agent(s), at least one cross-linking agent(s) and optionally one or more pharmaceutically acceptable excipient(s), wherein the said compositions are formulated as oral reconstitutable pharmaceutical controlled release suspensions, which can be reconstituted using a suitable reconstituting medium such as water. Further, this invention provides process of preparation of such compositions and method of using them.

hypoglycemic; hypolipidemic; hypotensive; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; keratolytic; LHRH agonist; mood regulator; mucolytic; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective; NMDA antagonist; non-hormonal sterol derivative; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; psychotropic; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine A1 antagonist; serotonin antagonist; serotonin inhibitor; serotonin receptor antagonist; steroid; thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; amyotrophic lateral sclerosis agent; cerebral ischemia agent; vasoconstrictor; vasodilator; wound healing agent; xanthine oxidase inhibitor, or mixtures thereof.

In preferred embodiment, the active agent of the present invention is selected from but not limited to a group comprising paracetamol, ibuprofen, nimesulide, mycophenolate, carbamazepine, chlorpheniramine, phenylpropanolamine, amoxicillin, erythromycin, ciprofloxacin, tacrolimus, and the like or pharmaceutically acceptable salts, hydrates, polymorphs, esters, and derivatives thereof used either alone or in combination thereof. In an embodiment, the active agents useful for the present invention are preferably those which have a shorter to a medium duration of therapy such as analgesics, antibiotics, anti-inflammatory drugs, antipyretics, antihistamines, and the like. In another embodiment of the present invention, the compositions of the present invention may comprise of active agents which are useful for longer duration of therapy.

The compositions of the present invention are useful in masking the taste of bitter drugs intended for oral administration. Further, the controlled release pharmaceutical compositions of the present invention upon reconstitution remains stable for a prolonged period of time at least for the entire duration of therapy and also provide a controlled release of the active agent(s). The reconstituted suspension compositions do not form any substantial sedimentation of the dispersed particles or a hard cake during storage; instead the particles forming any loose deposits can be easily resuspended upon shaking prior to use.

In an embodiment of the present invention, the water insoluble polymer(s) present in the core composition of the microparticle is selected from but not limited to a group comprising pH independent or pH dependent polymer(s) or mixtures thereof as described hereinafter.

In another embodiment of the present invention, the first coating composition is formulated as a release controlling system that aids in providing controlled release of the active agent(s).

polyacrylic and polymethacrylic acids and polyacrylate and methacrylate based polymers, and mixtures thereof, such as Eudragit®, for example Eudragit® E100, Eudragit® EPO, Eudragit® L, Eudragit® S or the like (Rohm-Pharma, Darmstadt, Germany); reaction products such as hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose acetate succinate and the like, cellulose derivative such as an alkyl cellulose, a hydroxyalkyl cellulose, a hydroxyalkyl alkylcellulose or a cellulose ester with at least one polybasic acid such as succinic acid, maleic acid, phthalic acid, tetrahydrophthalic acid, hexahydrophthalic acid, trimellitic acid or pyromellitic acid; polyvinyl acetate phthalate (PVAP), polyvinyl acetaldiethylamino acetate, shellac, or mixtures thereof. Preferably the pH dependent polymer used is polymethacrylate polymer such as Eudragit® E100 or Eudragit® EPO. More preferably the pH dependent polymer used is Eudragit® EPO.

In an embodiment of the present invention, the active agent(s) comprises from about 1% to about 90% by weight of dry weight of dry formulation before reconstitution. The first coating composition may constitute about 1% to about 90%, preferably about 10% to about 50% by weight of the total microparticle weight. The additional second coating composition may constitute about 1% to about 90%, preferably about 10% to about 50% by weight of total microparticle weight.

In an embodiment of the present invention, the reconstituted suspension composition comprising paracetamol as an active agent provides a release of at least about 30% of the active agent in about 6 hours, about 35%-75% in about 10 hours and not less than about 75% of the active agent after 20 hours when tested in vitro in 500 ml 0.1 N HCl as dissolution media using the USP Apparatus Type-II (paddle) at 50 RPM. Further, no significant difference in the release profile of active agent was found even when the composition was stored upto 7 days after reconstitution. The composition of the present invention is capable of releasing the active agent(s) along the gastrointestinal tract and independent of pH conditions of gastrointestinal tract to achieve and maintain therapeutic concentrations of the active agent(s) for prolonged periods of time.

In an embodiment of the present invention, the in-situ gelling agent present in the controlled release pharmaceutical composition is selected from but not limited to a group comprising alginates such as sodium alginate; or gums such as locust bean gum, xanthan gum, tragacanth, xylan, arabinogalactan, agar, gellan gum, scleroglucan, guar gum, apricot gum (Prunus armeniaca, L.), carrageenan, pectin, acacia gum, dragon gum, hog gum, talha, dextran, and gum arabic and the like, or mixtures thereof. In a preferred embodiment, the in-situ gelling agent is sodium alginate. In an embodiment of the present invention, the cross-linking agent

composition of the present invention is preferably a liquid or semisolid oral dosage form such as suspension, paste, jelly, syrup or elixir. The granulation technique is either aqueous or non-aqueous, more preferably wet granulation. In preferred embodiment, powder or granular formulations may be manufactured using techniques which are generally conventional in the field of manufacture of pharmaceutical formulations and in the manufacture of dry formulations for reconstitution into such formulations. For example a suitable technique of manufacture comprises mixing dry powdered or granulated ingredients with suitable excipient(s) and compressing to form solid dosage forms like tablets or dispersing in a suitable medium to form liquid dosage composition. In preferred embodiment, the present invention relates to liquid pharmaceutical formulations like suspensions for oral administration of active agent(s) wherein the composition releases the active agent(s) in a controlled manner such that the release profile of the active agent does not change during the storage of the liquid formulation.

In another embodiment of the present invention, the suspension may be provided in the form of a dry powder or granular substance comprising the active agent(s) and one or more excipient(s), which may be freshly prepared into the liquid suspension form by simply adding water and mixing so as to obtain a homogeneous and stable formulation. The dry suspension may be prepared by mixing the active agent(s) in the form of powder or granules alongwith one or more suspension adjuvant(s). The granulations may be prepared according to various conventional granulation techniques well known to person skilled in the art; more preferably by wet granulation or may result from simple physical mixing of the various components. More preferably granules are coated with polymer system to provide formulation of drug with controlled release profile that does not change during the storage of the liquid formulation.

In another embodiment, the composition of the present invention can be formulated as fast melt formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, or a combination of immediate release and extended release formulations. In another embodiment of the present invention, the size of the core microparticles may range from about 0.5 μm to about 2000 μm preferably about 1 μm to about 1000 μm , more preferably from about 50 μm to about 500 μm . In an embodiment, the present invention provides liquid taste masked controlled release pharmaceutical formulations for oral administration of active agents which produces bad or bitter taste in mouth of a subject upon administration.

In an embodiment, the appropriate amount of any pharmaceutically active agent(s) in the dosage form will depend on the particular agent and/or the intended daily dose

Claims

1. The controlled release pharmaceutical compositions comprising microparticles which comprise a core and at least one first coat, wherein the core comprises at least one active agent(s) or its pharmaceutically acceptable salts, derivatives, isomers, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof; optionally at least one water insoluble polymer(s), and optionally one or more pharmaceutically acceptable excipient(s); wherein at least one first coat comprises at least one pH independent polymer(s) alongwith one or more pharmaceutically acceptable excipient(s).
2. The controlled release pharmaceutical composition comprising microparticles according to claim 1 wherein the said composition comprises at least one additional second coating layer comprising at least one pH dependent polymer(s) optionally one or more pharmaceutically acceptable excipient(s).
3. The controlled release pharmaceutical composition according to claim 1 which comprises of microparticles alongwith at least one in-situ gelling agent(s), at least one cross-linking agent(s) and optionally one or more pharmaceutically acceptable excipient(s) wherein the said compositions are preferably formulated as oral reconstitutable controlled release suspension, which can be reconstituted using a suitable reconstituting medium such as water.
4. The controlled release pharmaceutical composition according to claim 1, wherein the active agent is selected from a group comprising adrenergic agent; adrenocortical steroid; adrenocortical suppressant; aldosterone antagonist; amino acid; anabolic; analeptic; analgesic; anesthetic; anorectic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-anemic; anti-anginal; anti-arthritis; anti-asthmatic; anti-atherosclerotic; antibacterial; anticholinergic; anticoagulant; anticonvulsant; antidepressant; antidiabetic; antidiarrheal; antidiuretic; anti-emetic; anti-epileptic; antifibrinolytic; antifungal; antihemorrhagic; antihistamine; antihyperlipidemia; antihypertensive; antihypotensive; anti-infective; anti-inflammatory; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiparasitic; antiproliferative; antipsychotic; antirheumatic; antiseborrheic; antisecretory; antispasmodic; antithrombotic; anti-ulcerative; antiviral; appetite suppressant; blood glucose regulator; bone resorption inhibitor; bronchodilator; cardiovascular agent; cholinergic; depressant; diagnostic aid; diuretic; dopaminergic agent; estrogen receptor agonist; fibrinolytic; fluorescent agent; free oxygen radical scavenger; gastric acid suppressant; gastrointestinal motility effector; glucocorticoid; hair growth stimulant; hemostatic; histamine H2 receptor antagonists; hormone;

- hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; keratolytic; LHRH agonist; mood regulator; mucolytic; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective;
- 5 NMDA antagonist; non-hormonal sterol derivative; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; psychotropic; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine A₁ antagonist; serotonin antagonist; serotonin inhibitor; serotonin receptor antagonist; steroid; thyroid hormone; thyroid inhibitor; thyromimetic;
- 10 tranquilizer; amyotrophic lateral sclerosis agent; cerebral ischemia agent; vasoconstrictor; vasodilator; wound healing agent; xanthine oxidase inhibitor, or mixtures thereof.
5. The controlled release pharmaceutical composition according to claim 4, wherein
- 15 the active agent is selected from a group comprising paracetamol, ibuprofen, nimesulide, mycophenolate, carbamazepine, chlorpheniramine, phenylpropanolamine, amoxicillin, erythromycin, ciprofloxacin, metformin, tacrolimus, and the like or pharmaceutically acceptable salts, hydrates, polymorphs, esters, and derivatives thereof used either alone or in combination thereof.
- 20 6. The controlled release pharmaceutical composition according to claim 1, wherein the water insoluble polymer is selected from a group comprising pH independent or pH dependent polymer(s) or mixtures thereof
- 25 7. The controlled release pharmaceutical composition according to claim 1 or 6, wherein the pH independent polymer is selected from a group comprising alkyl celluloses such as methyl cellulose, hydroxyalkyl celluloses such as hydroxypropyl cellulose and hydroxyethyl cellulose, high molecular weight polyethylene glycols, gelatin, polyvinylimidazoles, polyvinylpyridine N-oxides,
- 30 copolymers of vinylpyrrolidone with long-chained alpha-olefins, copolymers of vinylpyrrolidone with vinylimidazole, poly(vinylpyrrolidone/dimethylaminoethyl methacrylates), polyacrylate polymers, copolymers of vinylpyrrolidone/dimethylaminopropyl methacrylamides, copolymers of vinylpyrrolidone/ dimethylaminopropyl acrylamides, quaternised copolymers of
- 35 vinylpyrrolidones and dimethylaminoethyl methacrylates, terpolymers of vinylcaprolactam/ vinylpyrrolidone/ dimethylaminoethyl methacrylates, copolymers of vinylpyrrolidone and methacrylamidopropyl-trimethylammonium chloride, terpolymers of caprolactam/vinylpyrrolidone/dimethylaminoethyl methacrylates, copolymers of styrene and acrylic acid, polyacrylamides,
- 40 copolymers of ethyl acrylate with methacrylate and methacrylic acid, copolymers

- of maleic acid with unsaturated hydrocarbons and mixed polymerisation products of the said polymers, polysaccharide gums, both natural and modified (semi-synthetic), including but not limited to veegum, agar, guar gum, locust bean gum, gum arabic, okra gum, bentonite, arabinoglactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, and the like or mixtures thereof.
- 5
8. The controlled release pharmaceutical composition according to claim 7, wherein the pH independent polymer is water insoluble.
- 10
9. The controlled release pharmaceutical composition according to claim 8, wherein the water insoluble pH independent polymer is selected from a group comprising polyacrylate polymers such as Eudragit® NE 30D, Eudragit® RS, Eudragit® RS 30D, Eudragit® RL or a cellulosic polymer such as ethylcellulose (Ethocel std 10 cps) or mixtures thereof.
- 15
10. The controlled release pharmaceutical composition according to claim 2 or claim 6, wherein the pH dependent polymer is selected from a group comprising polyacrylic and polymethacrylic acids and polyacrylate and methacrylate based polymers, and mixtures thereof, such as Eudragit® E100, Eudragit® EPO, Eudragit® L, Eudragit® S; reaction products such as hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), cellulose acetate trimillitate (CAT), hydroxypropyl methylcellulose acetate succinate and the like, cellulose derivative such as an alkyl cellulose, a hydroxyalkyl cellulose, a hydroxyalkyl alkylcellulose or a cellulose ester with at least one polybasic acid such as succinic acid, maleic acid, phthalic acid, tetrahydrophthalic acid, hexahydrophthalic acid, trimellitic acid or pyromellitic acid; polyvinyl acetate phthalate (PVAP), polyvinyl acetaldiethylamino acetate, shellac, or mixtures thereof.
- 20
- 25
- 30
11. The controlled release pharmaceutical composition according to claim 10, wherein the pH dependent polymer is polymethacrylate polymer such as Eudragit® E100 or Eudragit® EPO.
- 35
12. The controlled release pharmaceutical composition according to claim 1, wherein the active agent(s) comprises from about 1% to about 90% by weight of dry weight of dry formulation before reconstitution.
- 40
13. The controlled release pharmaceutical composition according to claim 3, wherein the reconstituted suspension composition comprising paracetamol as an active agent provides a release of at least about 30% of the active agent in about 6 hours, about 35%-75% in about 10 hours and not less than about 75% of the active agent

after 20 hours when tested in vitro in 500 ml 0.1 N HCl as dissolution media using the USP Apparatus Type-II (paddle) at 50 RPM.

14. The controlled release pharmaceutical composition according to claim 3, wherein
5 the in-situ gelling agent is selected from a group comprising alginates such as sodium alginate; or gums such as locust bean gum, xanthan gum, tragacanth, xylan, arabinogalactan, agar, gellan gum, scleroglucan, guar gum, apricot gum, carrageenan, pectin, acacia gum, dragon gum, hog gum, talha, dextran, and gum arabic and the like, or mixtures thereof.
15. The controlled release pharmaceutical composition according to claim 14,
10 wherein the in-situ gelling agent is sodium alginate.
16. The controlled release pharmaceutical composition according to claim 3, wherein
15 the cross-linking agent is selected from a group comprising calcium carbonate, calcium sulfate, calcium chloride, aluminium chloride, magnesium chloride, calcium lactate, magnesium sulfate, and the like or mixtures thereof.
17. The controlled release pharmaceutical composition according to claim 16,
20 wherein the cross-linking agent is a divalent or trivalent metal cation salt.
18. The controlled release pharmaceutical composition according to claim 1, wherein
25 the pharmaceutically acceptable excipient(s) are selected from a group comprising diluents, lubricants, binders, fillers, viscosity modifiers, surfactants, anti-caking agents, thixotropic agents, anti-oxidants, colorants, flavoring agents, sweeteners, preservatives, glidants, chelating agents, plasticizers, vehicles, wetting agents, complexing agents, buffering agents, preservatives, suspending agents, release modifiers, viscosity enhancing agents, and the like known to the art used either alone or in combination thereof.
19. The controlled release pharmaceutical composition according to claim 1, wherein
30 the composition may be formulated as an oral dosage form either as a solid, semi-solid, or a liquid preparation such as tablets, capsules, patches, powders, granules, dry syrup, suspension, gels, jelly, syrup, elixir, solutions, emulsions, and the like.
20. The controlled release pharmaceutical composition according to claim 19,
35 wherein the composition is a liquid or semisolid oral dosage form such as suspension, paste, jelly, syrup or elixir.
21. The controlled release pharmaceutical composition according to claim 1 wherein
40 composition may be formulated as fast melt formulations, lyophilized formulations,