

ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

Carrera 11A No. 94-76 Of. 305 - P.O. Box 94948, Bogotá, Colombia, S.A.
Tels: (571) 6162051 - 6162061 - 6161859 - 6161869
Fax: (571) 6161889

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As. 2462/P.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

SUPERINTENDENCIA Y COMERCIO
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Trámite: 002 PATENTES 9 1 REGISTRADO/ 530 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. 01-109.552
Solicitud de Patente a nombre de
McNEIL-PPC, INC.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad McNEIL-PPC, INC., domiciliada en Skillman, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 04 - 53,394 de julio 7, 2004, por la suma de \$353.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C. 39.779.452 de usaquén
T.P. 68.228
Cod. 5376
JEU/ra.

2462 \$52

NIT : 800176089-2

SUPERINTENDENCIA DE ECONOMIA
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 53,394
FECHA : JULIO 7 DE 2004

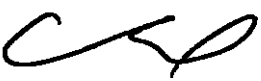
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4992977	06/07/2004	15,227,500.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	03 EXAMEN DE PATENTABILIDAD DE INVEN	353,000.00
		TOTAL :	\$ 353,000.00

SON: TRESCIENTOS CINCUENTA Y TRES MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Handwritten marks: a crossed-out 'S' and the number '3'

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 01-109552

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 539, DE
FECHA 30 DE ABRIL DE 2004, EL TERMINO HABIL SEÑALADO POR LA LEY
EXPIRA EL 02 DE AGOSTO DE 2004.**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud calga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI **X**

NO



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(12)

EUROPEAN PATENT APPLICATION

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(71) Applicant: WARNER-LAMBERT COMPANY
201 Taber Road
Morris Plains New Jersey 07960 (US)

(72) Inventor: Cherukuri, Subraman Rao
10 Jean Drive
Towaco, New Jersey 07082 (US)
Inventor: Chou, Tommy Linkwong
3 Dartmouth Avenue-2A
Bridgewater, New Jersey 08807 (US)

(74) Representative: Silliger, Jakob, Dr.
c/o CAPSUGEL AG Fabrikstrasseweg 2-4
CH-4144 Arlesheim (CH)

(84) Delivery system for cyclic amino acids with improved taste, texture and compressibility.

(87) A new delivery system for cyclic amino acid compounds and the process for its preparation is disclosed, which has use in a variety of products including conestibles such as chewing gum compositions, confections, and pharmaceutical such as chewable tablets. More particularly, this invention relates to a process for preparing a delivery system that provides enhanced masking of the bitter flavour characteristic of the active, reduced grittiness, retained stability at the elevated temperatures of product formulation, and improved compressibility for formation into tablets.

enmascara sabor amargo de cpo activo
reduce rugosidades
retiene estabilidad
mejora compresibilidad

EP 0 458 751 A1

Núcleo
1ª capa cubierta : + polímero formador de película (ver fls 162)
+ plastificante PG PEG

alginato

PVA

goma xantán

dextrina

pectina

gelatina

$\text{AcO}^- \text{C}$

$\text{AcO}^- - \text{flavono} - \text{C}$

2ª capa Grasas
Ácidos grasos
Ceras

Tableta masticable.

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ned to American Home Products Corporation discloses a preparation of spray dried acetaminophen prepared in a solution of a cationic copolymer based on dimethyl aminoethyl methacrylate and neutral methacrylic acid esters. The Blank et al. formulation is indicated to be "taste-neutral" and "fast dissolving." The specific copolymer is a member of a group of coating compositions that are sold under the name "EUDRAGIT" by Rohm Tech Incorporated, the United States representative of Rohm Pharma GmbH of West Germany. As mentioned, however, the use of this copolymer alone results in particles which will fracture under tableting compression owing to the hardness of the copolymer coating material.

European Patent Publication No. 0212841 based on Application No. 88111638.6 to Demari et al. and assigned to G. D. Searle & Co. relates to taste masking compositions wherein the active is incorporated into a copolymer having a plurality of carboxylic acid and ester groups. The formulation of the matrix of the active and the copolymer takes place with a solvent which is thereafter removed to yield a porous drugpolymer matrix. One of the features of this particular formulation is that the active will be released from the matrix at an acidic pH and, in particular, a pH of less than 4. In this instance, anionic copolymers are utilized and a variety of such copolymers including acrylic and substituted acrylic acids, cellulose esters, vinyl and substituted vinyl esters and polysulfonic acids and esters and amides are included. The polymers are particularly well-suited for actives having amido functional groups, such as alkaloids, amines, amides, and the like. One of the purported advantages of the formulations disclosed in this patent is indicated to be the taste masking abilities of the preparation.

European Patent Publication No. 0286228 based on Application No. 87308253.0 by Blank et al. and assigned to American Home Products Corporation discloses a preparation of a spray dried and neutral tasting acetaminophen powder using a solution of ethylcellulose with a suspension of colloidal silica in a lower alcohol solvent.

Lastly, PCT International Publication No. WO 88/03795 based upon Application No. PCT/US/87/03008 by Mehta, reveals a taste-masked composition coated with a combination of low temperature and high temperature film-forming materials such as, for example, cellulose esters, vinyl polymers, copolymers of methacrylic acid, and copolymers of methacrylic acid esters. The latter two mentioned polymeric materials are also members of the "EUDRAGIT" family of coating compositions.

All of the foregoing formulations, however, do not provide the desired level of taste masking and the combination of these qualities with compressibility in the instance where tablets are to be formed, particularly with respect to the cyclic amino acid actives that are presently of particular interest herein.

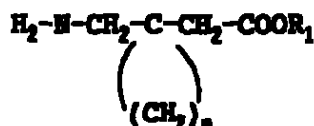
The above noted and other known techniques have heretofore provided no insight into the problem of concealing the bitter aftertaste of the present active, while at the same time permitting the active to exhibit improved compressibility in the instance where it is to be prepared in tablet form, as well as to function in a timely manner and with improved mouthfeel in the products to which it is desirably added. A need therefore exists for the development of a delivery system which remedies the aforementioned problems by preventing or at least minimizing the bitterness of the compound while at the same time permitting timely release of the active and promoting improved textural and mechanical properties.

According to the present invention there is provided a delivery system for a cyclic amino acid compound providing reduced bitterness with improved mouthfeel, compressibility, and high temperature stability, comprising:

- (a) a core material comprising a cyclic amino acid compound;
- (b) a first polymeric coating selected from water-insoluble and water-soluble polymeric film-forming materials, in an amount of from about 5% to about 100% by dry weight of the core material; and
- (c) a second hydrophilic coating selected from the group consisting of fats, fatty acids, waxes and mixtures thereof, present in an amount ranging from about 20% to about 400% by dry weight of the combination of said core material and said first hydrophilic coating.

The present invention provides a cyclic amino acid compound delivery system which comprises a composite having improved flavour masking and temperature stability characteristics, and smoother texture and mouthfeel when incorporated into lozenges, chewing gums and other products, and improved compressibility for preparation into products. The compound delivery system is prepared with a core material comprising a cyclic amino acid compound; a first coating selected from water-soluble or water-insoluble polymeric film-forming materials in an amount of from about 5% to about 100% by dry weight, and preferably from about 10% to about 25% by dry weight of the core material; and a second hydrophobic coating comprising a fat and/or wax component in an amount of from about 20% to about 400% by dry weight, and preferably from about 20% to about 100% by dry weight of the combined core material and first coating. In a particularly preferred embodiment, the first coating is present in an amount of about 25% by dry weight of the core material, and the second coating is present in an amount of 50% by dry weight of the combined core material and first coating.

Suitable cyclic amino acid compounds may be selected from the group consisting of compounds of the general formula:

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wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5 or 6; and the pharmacologically compatible salt thereof. The first coating includes both water-soluble and water-insoluble polymeric materials, with the water-insoluble materials including acrylic acid and substituted acrylic acid polymers and copolymers; vinyl and substituted vinyl ester polymers and copolymers; cellulose ethers, their polymers and copolymers; and polyelectrolytic acids, their esters and/or amides. The first coating may also be a water-soluble polymeric material such as a hydrocolloid. Hydrocolloid materials include pectins, alginates, cellulose and its derivatives, gelatin, gums, mucilages, and mixtures. The gelatin used herein possesses a bloom strength on the order of 250 or higher, which is desirable to form a strong and resilient coating on the active.

The fat or wax component comprises fats, including fatty acids such as hydrogenated and partially hydrogenated oils; mono-, di- and triglycerides, polyglycerol esters and sorbitol esters. Waxes include natural and synthetic waxes, with representative waxes comprising polyolefin waxes, paraffin wax, beeswax, microcrystalline wax, and mixtures.

The cyclic amino acid compounds are prepared into the core material by standard processes such as spray drying and may optionally be prepared with additives such as excipients, including binding agents, fillers, and the like. Suitable excipients include sugar, mannitol, sorbitol and maltodextrin.

The present delivery system is produced by a process which comprises forming the cyclic amino acid compound and optionally one or more excipients into a first core material, applying the first coating to this core material preferably by fluidized bed coating, and then spray coating the second fat and/or wax coating over the particles thus formed.

The present delivery system may be incorporated into a variety of foods and confections, including chewing gums and hard candies, as well as pharmaceutical and preparations, such as chewable tablets. The present invention therefore includes chewing gums, hard candies and pharmaceutical products, all incorporating the present delivery system.

Accordingly, it is a principal object of the present invention to provide a cyclic amino acid compound delivery system that offers improved aftertaste masking characteristics.

It is a further object of the present invention to provide a cyclic amino acid compound delivery system as aforesaid which provides improved taste masking and mouthfeel in combination with temperature stability, and improved compressibility.

It is a still further object of the present invention to provide pharmaceutical products, nutritional supplements, personal hygiene, confectionery and comestible products, all having contained therein the cyclic amino acid compound delivery system of the present invention.

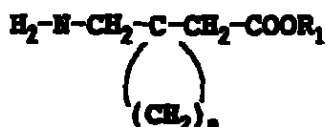
Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing description.

In accordance with the present invention, a delivery system for a cyclic amino acid compound is disclosed which offers reduced bitterness, and improved mouthfeel with desirable high temperature stability. The present delivery system accordingly comprises:

- (a) a core material comprising a cyclic amino acid compound;
- (b) a first polymeric coating selected from water-insoluble materials in an amount of from about 5% to about 100% by dry weight of the core material; and
- (c) a second hydrophobic coating selected from the group consisting of fats, waxes, and mixtures thereof, present in an amount of from about 20% to about 400% by dry weight of the combination of the core material and the first hydrophilic coating.

More particularly, the delivery system of the present invention comprises the core material with the first coating present in an amount of from about 10% to about 25% by dry weight of the core material, and the second coating present in an amount of from about 20% to about 100% by dry weight of the combination of the core material and the first coating. As indicated earlier herein, the preferred embodiment contemplates the presence of the first coating in an amount of 25% by dry weight of the core material, and the second coating in an amount of 50% by dry weight of the combination of the core material and the first coating.

The cyclic amino acid compounds in accordance with the present invention comprise those compounds having the following formula:



wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5 or 6; and the pharmacologically compatible salts thereof.

The preparation and utility of these compounds are set forth in commonly assigned U.S. Patent No. 4,024,178 to Sabzinger et al., and U.S. Patent No. 4,152,326 to Hartenstein et al. Both patent disclosures are incorporated herein by reference.

Particular cyclic amino acids include 1-aminomethyl-1-cyclohexane-acetic acid; ethyl-1-aminomethyl-1-cyclohexane-acetate; 1-aminomethyl-1-cycloheptane-acetic acid; 1-aminomethyl-1-cyclopentane-acetic acid; methyl 1-aminomethyl-1-cyclohexane-acetate; n-butyl 1-aminomethyl-1-cyclohexane-acetate; methyl 1-aminomethyl-1-cyclohexane-acetate; n-butyl 1-aminomethyl-1-cycloheptane acetate toluene sulfonate; 1-aminomethyl-1-cyclopentane-acetate benzene-sulfonate; and n-butyl 1-aminomethyl-1-cyclopentane-acetate. The foregoing list is not meant to be inclusive, and is merely representative of cyclic amino acid compounds that may be prepared into the delivery system of the present invention.

The cyclic amino acid compounds may optionally be formulated with one or more excipients. Such excipients may be selected from the group consisting of carbohydrate materials, polyhydric alcohols and mixtures thereof. Carbohydrates useful as excipients include traditional water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, lactose, mannose, galactose, fructose, dextrose, sucrose, sugar, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and the like, and mixtures thereof. The excipients are generally present in amounts of up to about 80% by dry weight of the core material and can be mixed in combination with each other or used individually.

Suitable water-insoluble film-forming polymeric materials are selected from the group consisting of acrylic acid and substituted acrylic acid polymers and copolymers; polysulfonic acid ester polymers; vinyl and substituted vinyl ester polymers and copolymers; cellulose ethers, their polymers and copolymers. Particular water-insoluble film-forming polymeric materials are selected from the group consisting of ethylcellulose; cellulose acetate; cellulose acetate phthalate; cellulose acetate butyrate; ethylene-vinyl acetates and/or phthalates; polyvinyl alcohol; polyvinyl acetates and/or phthalates; ethyl and/or methyl methacrylic acids, esters, and copolymers. Particularly preferred materials comprise ethylcellulose; the anionic copolymers based on polymethacrylic and acrylic acid esters; the neutral copolymer based on poly(meth)acrylic acid esters; and the cationic copolymer based on dimethylamino ethyl methacrylate and neutral methacrylic acid esters. The three acrylic-based polymers are sold under the trade name EUDRAGIT by Rohm Pharma of West Germany, and the ethylcellulose is sold as an aqueous suspension under the trade name AQUACOAT® by FMC, of Philadelphia, Pennsylvania.

Water-soluble polymeric materials suitable for preparation of the first coating broadly comprise hydrophilic materials and particularly, film forming hydrocolloids. The hydrocolloids may be generally selected from the group consisting of gums, pectins, alginates, mucilages, and mixtures thereof. Specifically, the hydrocolloid may be a material selected from the group consisting of gum arabic, tragacanth, karaya, ghatti, agar, alginates, carrageenans, fucellan, pectin, and mixtures thereof. The hydrocolloid may also be selected from polyvinyl pyrrolidone, gelatin, dextran, xanthan, curdan, cellulose, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carbomethyl cellulose, low methoxy pectin, propylene glycol alginate, and mixtures thereof. A preferred hydrocolloid comprises gelatin.

Materials suitable for the preparation of the second coating include the fats and/or waxes. Suitable fats include fatty acids such as hydrogenated or partially hydrogenated oils, with representative materials comprising palm oil, palm kernel oil, soybean oil, cottonseed oil, peanut oil, rapeseed oil, rice bran oil, sunflower oil, safflower oil, and mixtures thereof. Other materials also useful as fats herein may be selected from monoglycerides, diglycerides, triglycerides, polyglycerol esters, sorbitol esters, and mixtures thereof.

Suitable waxes include natural waxes, synthetic waxes, and mixtures thereof, and in particular, comprise materials selected from the group consisting of paraffin wax, beeswax, carnauba wax, candellilla wax, lanolin wax, bayberry wax, sugar cane wax, petrolatum, carbowax, spermaceti wax, rice bran wax, microcrystalline wax, and mixtures thereof. Naturally the foregoing is illustrative and not restrictive of suitable materials for inclusion in the delivery system of the invention, and the invention is considered to extend to unnamed equivalent materials within its scope.

The preparation of the present delivery system may be accomplished by a variety of agglomerative and/or

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HPHC
HEC
HPC
CHC
alginate
PVA
goma arabic
dextran (poly)
pectin
gelatin
+
PG

TABLE V

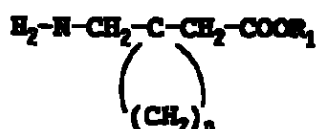
	Ingredient	Control (%)	Invention (%)
5	GABAPENTINE	6.26	--
	Aspartame	0.63	0.63
	Sugar	90.61	82.81
	Sodium Stearyl Fumarate	1.00	1.00
20	Spray Dried Cream Strawberry Flavour	1.00	1.00
	Dilute Monoammonium Glycyrrhizinate	0.50	0.50
	Encapsulation (AQUACOAT®/Fat)	--	14.06

The tablets were then subjected to taste panel testing and were evaluated for bitterness. The scale utilized extended from 0, reflecting no bitterness, to 100, indicating extreme bitterness. The control composition containing free GABAPENTIN® exhibited extreme bitterness, while the encapsulated composition prepared in accordance with the present invention had a rating of 40, indicating substantially reduced bitterness.

This invention may be embodied in other forms or carried out in other ways without departing from the spirit or essential characteristics thereof. The present disclosure is therefore to be considered as in all respects illustrative and not restrictive, the scope of the invention being indicated by the appended Claims, and all changes which come within the meaning and range of equivalency are intended to be embraced therein.

Having been thus described, the present invention is summarized by the following clauses, numbered 1 - 28, and is defined by the claims appended thereafter.

1. A delivery system for a cyclic amino acid compound providing reduced bitterness with improved mouthfeel, compressibility, and high temperature stability, comprising:
- (a) a core material comprising a cyclic amino acid compound;
 - (b) a first polymeric coating selected from water-insoluble and water-soluble polymeric film-forming materials, in an amount of from about 8% to about 100% by dry weight of the core material; and
 - (c) a second hydrophilic coating selected from the group consisting of fats, fatty acids, waxes and mixtures thereof, present in an amount ranging from about 20% to about 400% by dry weight of the combination of said core material and said first hydrophilic coating.
2. The delivery system of 1 wherein said cyclic amino acid compound has the formula:



wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5 or 8; and the pharmacologically compatible salt thereof.

3. The delivery system of 1 wherein said cyclic amino acid compound is selected from the group consisting of 1-aminomethyl-1-cyclohexane-acetic acid; ethyl-1-aminomethyl-1-cyclohexane-acetate; 1-aminomethyl-1-cycloheptane-acetic acid; 1-aminomethyl-1-cyclopentane-acetic acid; methyl 1-aminomethyl-1-cyclohexane-acetate; n-butyl 1-aminomethyl-1-cyclohexane-acetate; methyl 1-aminomethyl-1-cyclohexane-acetate; n-butyl 1-aminomethyl-1-cycloheptane acetate toluene sulfonate; 1-aminomethyl-1-cyclopentane-acetate benzenesulfonate; and n-butyl 1-aminomethyl-1-cyclopentane-acetate.
4. The delivery system of 1-3 further including an excipient.
5. The delivery system of 4 wherein said excipient is selected from the group consisting of carbohydrate materials, polyhydric alcohols, and mixtures thereof.
6. The delivery system of 4 wherein said excipient is selected from the group consisting of monosaccharides, disaccharides, polysaccharides, partially hydrolyzed starch, corn syrup, sugar alcohols, and mixtures thereof.
7. The delivery system of 4 wherein said excipient is present in an amount of up to about 80% by dry weight of said core material.
8. The delivery system of 1 wherein said first coating comprises a water-insoluble film forming polymeric

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material.

9. The delivery system of 8 wherein said water-insoluble film forming polymeric material is selected from the group consisting of acrylic acid and substituted acrylic acid polymers and copolymers; polysulfonic acid ester polymers; vinyl and substituted vinyl ester polymers and copolymers; cellulose ethers, their polymers and copolymers.

10. The delivery system of 8 wherein said water-insoluble film-forming polymeric material is selected from the group consisting of ethylcellulose; cellulose acetate; cellulose acetate phthalate; cellulose acetate butyrate; ethylene-vinyl acetate and/or phthalate; polyvinyl alcohol; polyvinyl acetate and/or phthalate; and ethyl and/or methyl methacrylic acids, esters, and copolymers.

11. The delivery system of 8 wherein said water-insoluble film-forming polymeric material is selected from the group consisting of ethylcellulose; an anionic copolymer based on polymethacrylic and acrylic acid ester; a neutral copolymer based on poly(meth)acrylic acid ester; and, a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters; and mixtures thereof.

12. The delivery system of 1 wherein said first coating comprises a water-soluble film-forming polymeric material.

13. The delivery system of 1 wherein said first coating comprises a hydrocolloid.

14. The delivery system of 13 wherein said hydrocolloid is selected from the group consisting of gums, pectins, alginates, mucilages, and mixtures thereof.

15. The delivery system of 13 wherein said hydrocolloid is selected from the group consisting of gum arabic, tragacanth, karaya, ghatti, agar, alginates, carrageenans, fucan, pectin, and mixtures thereof.

16. The delivery system of 13 wherein said hydrocolloid is selected from the group consisting of polyvinyl pyrrolidone, gelatin, dextran, xanthan, curdian, cellulose, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, low methoxy pectin, propylene glycol alginate, and mixtures thereof.

17. The delivery system of 1 wherein said first coating is present in an amount of from about 10% to about 25% by dry weight.

18. The delivery system of 1 wherein said second coating is present in an amount of from about 20% to about 100% by dry weight.

19. The delivery system of 1 wherein said first coating is present in an amount of 25% by dry weight, and said second coating is present in an amount of 50% by dry weight.

20. The delivery system of 1 wherein the fat material is a fatty acid selected from the group consisting of hydrogenated or partially hydrogenated oils.

21. The delivery system of 20 wherein the hydrogenated or partially hydrogenated oils are selected from the group consisting of palm oil, palm kernel oil, soybean oil, rapeseed oil, rice bran oil, cottonseed oil, sunflower oil, safflower oil, and mixtures thereof.

22. The delivery system of 1 wherein the fat material is selected from the group consisting of mono-glycerides, diglycerides, triglycerides, polyglycerol esters, sorbitol esters, and mixtures thereof.

23. The delivery system of 1 wherein the wax material is selected from the group consisting of natural waxes, synthetic waxes and mixtures thereof.

24. The delivery system of 23 wherein the wax material is selected from the group consisting of paraffin wax, beeswax, carnauba wax, candelilla wax, lanolin wax, bayberry wax, sugar cane wax, petrolatum, carbowax, spermaceti wax, rice bran wax, microcrystalline wax, and mixtures thereof.

25. The delivery system of 1 incorporated into a chewing gum composition.

26. The delivery system of 1 incorporated into a confectionary composition.

27. The delivery system of 1 incorporated into a pharmaceutical composition.

28. The delivery system of 1 prepared into a chewable tablet.

Claims

1. A delivery system for a cyclic amino acid compound providing reduced bitterness with improved mouthfeel, compressibility, and high temperature stability, comprising:

(a) a core material comprising a cyclic amino acid compound;

(b) a first polymeric coating selected from water-insoluble and water-soluble polymeric film-forming materials, in an amount of from about 5% to about 100% by dry weight of the core material; and

(c) a second hydrophilic coating selected from the group consisting of fats, fatty acids, waxes and mixtures thereof, present in an amount ranging from about 20% to about 400% by dry weight of the combination of said core material and said first hydrophilic coating.

United States Patent [19]

Kotwal et al.

[11] Patent Number: 5,645,858

[45] Date of Patent: Jul. 8, 1997

[54] MULTILAYERED CONTROLLED RELEASE
PHARMACEUTICAL DOSAGE FORM[75] Inventors: Pramod M. Kotwal, Blue Bell, Pa.;
Stephen A. Howard, Flemington, N.J.[73] Assignee: Ortho Pharmaceutical Corporation,
Raritan, N.J.

[21] Appl. No.: 568,907

[22] Filed: Dec. 7, 1995

Related U.S. Application Data

[62] Division of Ser. No. 319,186, Oct. 6, 1994, Pat. No. 5,474,
786.[51] Int. Cl.⁶ A61K 9/36[52] U.S. Cl. 424/495; 424/490; 424/494;
424/497; 424/458; 424/461; 424/472[58] Field of Search 424/490, 494,
424/493, 497, 458, 461, 472

[56] References Cited

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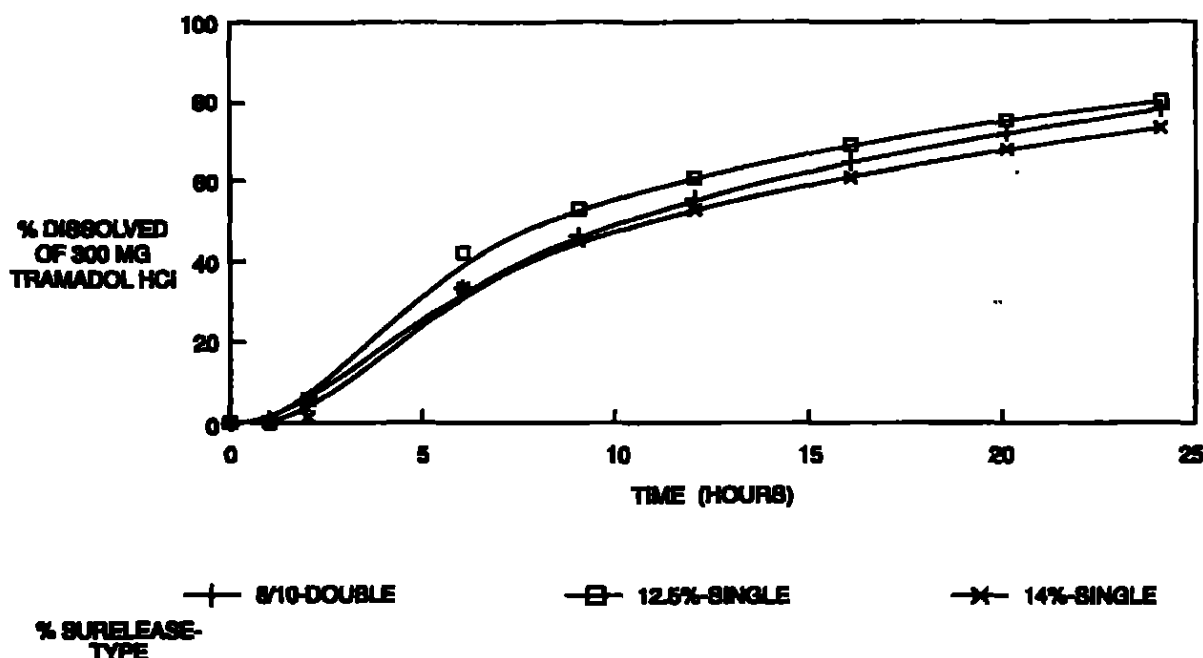
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5,395,626	3/1995	Kotwal et al.	424/472
5,407,686	4/1995	Patel et al.	424/468
5,474,786	12/1995	Kotwal et al.	424/472

Primary Examiner—Amy Hutina

[57] ABSTRACT

This invention is directed to a multilayered controlled release pharmaceutical dosage form. More particularly the dosage form is adapted for water soluble drugs and comprises a plurality of coated particles wherein each has multiple layers about a core containing a drug active whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer and preferably an outer layer of additional drug is adapted for immediate release to preferably provide one immediate releasing layer and at least two controlled releasing layers of a water soluble drug from the multilayered coated particle.

10 Claims, 1 Drawing Sheet

SINGLE VS DOUBLE LAYER BEADS
MEDIUM 7.4 pH

MULTILAYERED CONTROLLED RELEASE PHARMACEUTICAL DOSAGE FORM

This is a division of application Ser. No. 08/319,186, filed Oct. 6, 1994, which is hereby incorporated by reference, U.S. Pat. No. 5,474,786.

FIELD OF THE INVENTION

This invention is directed to a multilayered controlled release pharmaceutical dosage form. More particularly, the dosage form is adapted for controlled release of water soluble drugs and comprises a plurality of multilayered coated particles, wherein each particle has multiple layers about a core containing a drug active. The drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer and an outer layer of additional drug may be adapted for immediate release.

BACKGROUND OF THE INVENTION

Controlled release pharmaceutical dosage forms are well known and provide distinct advantages for delivery of certain chemotherapies. Controlled release dosage forms are particularly useful for drugs which act optimally at certain levels of plasma concentration over extended periods of time. Controlled release systems may also avoid the presence of ineffective or toxic levels of drugs which result from periodic administration of immediate release dosage forms which provide high initial levels of drug but may leave only ineffectively small amounts of drugs in the plasma near the end of the administration periods (i.e. cycles) prior to subsequent administration of drug. Controlled release dosage forms are also desirable for providing continuous chemotherapy for chronic conditions or those with a long duration of therapy by providing drugs in a sustained released manner that only requires administration either once or twice daily instead of every four to six hours as may be indicated for a particular drug.

The administration of highly water soluble drugs in a controlled release dosage form presents particular problems. The introduction of such highly water soluble drugs in controlled release dosage forms into a patient's digestive system has met with limited success due to the normally unpredictable leaching out of the very water soluble drug active into the digestive system when using conventional sustained release techniques. It is also challenging to provide a substantially zero or constant rate of release for drugs that are highly water soluble for extended periods of time.

It is therefore an object of the present invention to provide a multilayered controlled release pharmaceutical dosage form system, particularly for very water soluble drugs. This system provides desirable plasma levels of drugs with a substantially constant rate of release of the drugs from controlled release layers over a preselected period of time.

SUMMARY OF THE INVENTION

To achieve the objects and objectives in accordance with the invention the present invention provides a multilayered controlled release pharmaceutical dosage form, preferably for water soluble drugs, comprising a plurality of coated particles each comprising: a drug active core which is sequentially overcoated with a first controlled release barrier layer; at least one additional layer containing drug active which is overcoated with an additional controlled release layer; and preferably an outer layer containing drug active which is intended for immediate release; whereby, the

amount of drug active in the controlled release barrier material utilized in each coating layer thereof is provided in amounts effective to achieve a desirable plasma level of drug active in a patient over a preselected time period. In particularly preferred embodiments the time period is twelve or twenty-four hours (i.e. corresponding to once or twice daily administration).

In preferred embodiments of the invention the multilayered controlled release pharmaceutical dosage form for water soluble drugs comprises a plurality of coated particles each comprising:

- a core comprising an inert material which is coated or granulated with a water soluble drug active;
- a first coating layer over the drug containing core comprising a water soluble film forming polymer, preferably the film forming mixture additionally comprises a plasticizer;
- a second coating layer over the first coating layer comprising a film forming dispersion or solution which forms a controlled release layer over the coated drug core, preferably a water-based dispersion;
- a third coating layer comprising a water soluble film forming polymer and preferably a plasticizer;
- a fourth coating layer comprising additional water soluble drug active;
- a fifth coating layer comprising a water soluble film forming polymer and preferably a plasticizer;
- a sixth coating layer comprising a film forming dispersion or solution which forms a controlled release layer over the coated drug core, preferably a water-based dispersion; and
- a final coating layer of a water soluble film forming polymer and preferably a plasticizer.

In preferred embodiments of the invention the water soluble film forming polymer is hydroxypropyl methylcellulose and the plasticizer is polyethylene glycol.

Preferably the film forming polymer which forms the controlled release layer is provided as a water-based dispersion and comprises ethyl cellulose. Preferably the dispersion additionally comprises at least one of dibutyl sebacate, oleic acid, and sodium lauryl sulfate.

In preferred embodiments of the invention the water soluble drug active is selected from the group consisting of tramadol, pseudoephedrine and phenylpropanolamine and salts thereof. More preferably the drug active is very water soluble and is tramadol HCl or pseudoephedrine HCl. Most preferably the drug active is tramadol HCl. The invention is also intended to cover substantially pure active enantiomers of these drug actives.

In a particularly preferred embodiment of the invention the controlled release layers of the second and sixth coating layers are provided at levels to obtain a substantially constant release profile of the drug active over about a twenty-four hour period.

In other embodiments the invention provides a method of achieving a desirable plasma level of a water soluble drug over a twenty-four hour period in a patient comprising the steps of:

- preparing a multilayered controlled release dosage form by sequentially overcoating a drug active containing core with a first controlled release barrier layer;
- providing at least one additional layer containing drug active over said first controlled release barrier layer which in turn is overcoated by an additional controlled release layer; and
- providing an outer layer containing drug active which is intended for immediate release; whereby, the amount of drug

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SURELEASE and comprises ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water, and fused silica.

The multilayered controlled release pellets of the invention are preferably provided in a hard gelatin capsule but may also be provided in any other suitable oral dosage form such as a matrix comprising such pellets agglomerated with an appropriate and compatible binder to form a unitary solid dosage form which will release the intact pellets in the digestive tract after swallowing.

The film forming process of the invention can be carried out in conventional pans, preferably pans with one way air flow to provide more control over the pan environment. More preferably the coating is accomplished in a fluidized bed which is an air suspension technique known as "Wurster" coating. Most preferably the pellets are coated in a rotor granulator with a top fluid bed which provides rotation of the pellets during coating to ensure a more uniform coat of the pellets. Examples of a preferred coating apparatus of the invention is a GLATT GPCG-5 rotor granulator. Other coating materials and techniques can be applied such as those disclosed in *The Theory and Practice of Industrial Pharmacy*, Lachman et al., 3d edition, 1986.

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the invention and outline a process for preparing the compositions of the inventions and methods of practicing the invention.

EXAMPLES

The following ingredients, processes and procedures for preparing the compositions of the present invention correspond to that described above. The procedure below describes with particularity the various formulation ingredients and procedures utilized. Any methods, starting materials, reagents or excipients which are not particularly described will be generally known and available to those skilled in the pharmaceutical formulation arts. All formulation percentages are provided in percent by weight by total weight of the composition.

Example 1

300 mg. tramadol sustained release capsules

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for tramadol HCl 300 mg sustained release capsules is provided below:

Components	% weight/weight (theoretical)	mg/Capsule (theoretical)
Tramadol HCl (ORADRY® Clear YS-3-7011) ¹	68.34	300
Purified Water, USP ²	1.14	5.01
Sugar Spherns, NF	—	—
ORADRY® Clear YS-1-7006 ³	12.5	54.87
SURELEASE® E-7-7030 ⁴ Capsules ⁵	4.48	19.66
	13.54	59.44
Total	100.00%	438.98mg ⁶

-continued

Components	% weight/weight (theoretical)	mg/Capsule (theoretical)
¹ A mixture of hydroxypropyl methylcellulose, polyethylene glycol and polyurethane glycol.		
² Purified Water, USP is evaporated during processing.		
³ A mixture of hydroxypropyl methylcellulose and polyethylene glycol.		
⁴ Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fused silica.		
⁵ The water in the dispersion is evaporated during processing.		
⁶ White, opaque, hard gelatin capsule, size 00.		
⁷ Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 300 mg tramadol hydrochloride per capsule.		

The quantitative batch composition for tramadol hydrochloride 300 mg sustained release capsule is shown below (Theoretical batch quantity 25,741 capsules):

Components	Weight
Step 1: Preparation of Tramadol Hydrochloride Beads (Bead Build-up #1)	
Opadry® Clear YS-3-7011	12.000
Purified Water, USP	0.200
Sugar Spherns, NF	5.454
	4.000
Total Weight Tramadol Hydrochloride Beads (Bead Build-up #1)	16.200 kg
Step 2: Clear & Sustained Release Bead coating #1	
Tramadol Hydrochloride Beads (derived from Step 1)	8.000
Opadry® Clear YS-1-7006	0.360
Purified Water, USP	5.928
Surelease® E-7-7030	0.672
Total Weight Clear Coated Sustained Release Beads	9.062 kg
Step 3: Tramadol Hydrochloride Beads (Build-up #2)	
Sustained Release Beads (derived from Step 2)	8.000
Tramadol Hydrochloride	4.320
Opadry® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Tramadol Hydrochloride Beads (Build-up #2)	12.352 kg
Step 4: Clear & Sustained Release Bead Coating #2	
Tramadol Hydrochloride Beads (derived from Step 3)	10.000
Opadry® Clear YS-1-7006	0.230
Purified Water, USP	6.430
Surelease® E-7-7030	1.080
Total Weight Tramadol Hydrochloride Sustained Release Beads	11.300 kg
Step 5: Capsule Filling	—

B. Methods of Manufacturing and Packaging

NOTE: The drug substance and excipients may be deagglomerated, if needed, by milling or screening.

Step 1: Preparation of Tramadol Hydrochloride Beads (Bead Build-up #1)

a. Preparation of Tramadol Hydrochloride Build-up Solution

I. Admix the batch quantity of Purified Water, USP and the batch quantity of Opadry® Clear YS-3-7011.

II. Add the batch quantity of tramadol hydrochloride and mix for approximately 1.5 hours.

b. Preparation of Tramadol Hydrochloride Beads

I. Load the bowl of a suitable bead coater such as the Glatt GPCG 5 Rotor-Granulator with the batch quantity of sugar spheres, NF and heat until the bed reaches approximately 40° C.-60° C.

ii. While maintaining the bed temperature at approximately 40°-60° C., spray the entire tramadol hydrochloride/Opadry® Clear YS-3-7011 solution prepared in Step 1.a. onto the sugar spheres.

iii. Remove the tramadol hydrochloride beads from the granulator and screen to remove any agglomerates and any fine powder.

Step 2: Clear and Sustained Release Bead Coating #1

a. Preparation of Clear Coat #1

Add 54.7% of the batch quantity of Purified Water, USP (3.240 kg) and the batch quantity of Opadry® Clear YS-1-7006 (0.360 kg) and mix for approximately 1-2 hours.

b. Preparation of Sustained Release Dispersion #1

Add 11.3% of the batch quantity of Purified Water, USP (0.672 kg) and 2.688 kg of Surelease® E-7-7050 dispersion and mix for approximately 1-2 hours.

c. Preparation of Coated Beads

i. Transfer the batch quantity of the tramadol hydrochloride beads prepared in Step 1. (8.0 kg) into a suitable bead coater such as the Glatt GPCG 5 Rotor-Granulator and heat until the bed reaches approximately 40° C.-60° C.

ii. Maintain the bed temperature at the following conditions and spray:

40° C.-60° C. 88.9% of the Opadry® Clear YS-1-7006 solution prepared in Step 2.a.

42° C.-50° C. the batch quantity of the Surelease® E-7-7050 dispersion prepared in Step 2.b.

40° C.-60° C. the remaining batch quantity (11.1%) of the Opadry® Clear YS-1-7006 solution prepared in Step 2.a.

iii. Remove the tramadol sustained release beads derived in Step 2.c.ii. from the granulator and screen the beads to remove any agglomerates and any remaining fine powder.

Step 3: Tramadol Hydrochloride Beads (Build-up #2)

a. Preparation of the Tramadol Hydrochloride Build-up Solution

i. Add the batch quantity of Purified Water, USP and the batch quantity of Opadry® Clear YS-3-7011.

ii. Add the batch quantity of tramadol hydrochloride and mix for approximately 1-2 hours.

b. Preparation of the Tramadol Hydrochloride Beads

i. Load the bowl of a suitable bead coater such as the Glatt GPCG 5 Rotor-Granulator with the batch quantity of sustained release beads from Step 2. (8.0 kg) and heat until the bed reaches approximately 40° C.-60° C.

ii. Spray on the entire tramadol hydrochloride/Opadry® Clear YS-3-7011 solution prepared in Step 3.a. onto the heated sustained release beads, while maintaining the bed temperature at approximately 40° C.-60° C.

iii. Remove the tramadol hydrochloride beads from the granulator and screen the beads to remove any agglomerates and any fine powder.

Step 4: Clear and Sustained Release Bead Coating #2

a. Preparation of Clear Coat

Add 34.9% of the respective batch quantity of Purified Water, USP (2.250 kg) and the respective batch quantity of Opadry® Clear YS-1-7006 (0.250 kg) and mix for approximately 1-2 hours.

b. Preparation of Sustained Release Dispersion #2

Add to a suitable stainless steel mixing tank 16.3% of the batch quantity of Purified Water, USP (1.050 kg) and 4.200 kg of Surelease® E-7-7050 dispersion and mix for approximately 1-2 hours.

c. Preparation of Coated Beads

i. Transfer the batch quantity of the tramadol hydrochloride beads prepared in Step 3. (10.0 kg) into a suitable granulator such as the Glatt GPCG 5 Rotor-Granulator and heat until the bed reaches approximately 40° C.-60° C.

ii. Maintain the bed temperature at the following conditions and sprays:

40° C.-60° C. 80% of the Opadry® Clear YS-1-7006 solution prepared in Step 4.a.

42° C.-50° C. the batch quantity of the Surelease® E-7-7050 dispersion prepared in Step 4.b.

40° C.-60° C. the remaining batch quantity (20.0%) of the Opadry® Clear YS-1-7006 solution prepared in Step 4.a.

iii. Remove the tramadol sustained release beads derived in Step 4.c.ii. from the granulator and screen the beads to remove any agglomerates and any remaining fine powder.

iv. Dry the beads in a 45° C.-55° C. dry heat oven for approximately 24 hours.

Step 5: Capsule Filling

a. Based on the in-process assay results, calculate the fill weight of the tramadol hydrochloride sustained release beads.

b. On a suitable filling machine or by hand, fill the calculated amount of tramadol hydrochloride sustained release beads into white, opaque, hard gelatin capsules (size 00).

Example 2

Preparation of Pseudoephedrine sustained Release Capsules

Follow the procedure of Example 1 but replace the tramadol HCl with pseudoephedrine HCl and reduce all of the ingredients to two-thirds to produce 200 mg pseudoephedrine sustained release capsules.

The present invention provides for a heretofore unrealized consistent drug release pattern for very water soluble drugs such as tramadol HCl and pseudoephedrine HCl from a sustained released pellet system. The advantages obtained by the multilayered pellets of the invention are indicated in the appended graph of FIG. 1 for comparing formulations for tramadol. The graph shows that the double layer bead of the invention (i.e. two controlled release layers, i.e. 8% and 10% controlled release layer amounts, by weight of the total weight of the beads) provides a more linear (i.e., more constant or uniform) release rate as compared to single layered beads with a single controlled release layer (i.e., 12.5% and 14% controlled release layer amounts by weight of the total weight of the beads).

The scope of the present invention is not limited by the description, examples or suggested uses herein and modifications can be made without departing from the spirit of the invention. The multilayered dosage forms of the invention may, for example, have other applications and uses in addition to those described herein, e.g. for vitamin supplements or for controlled delivery of diagnostic agents.

Applications of the compositions and methods of the present invention for medical or pharmaceutical uses can be accomplished by any clinical, medical, and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. Thus it is intended that the invention cover any modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

What is claimed is:

1. A multilayered controlled release pharmaceutical dosage form for water soluble drugs comprising a plurality of coated particles each comprising: a drug active core comprising a mixture of hydroxypropyl methylcellulose, polyethylene glycol and propylene glycol which is sequentially

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overcoated with a first controlled release barrier layer comprising ethyl cellulose; and at least one additional layer containing drug active comprising a mixture of hydroxypropyl methylcellulose, polyethylene glycol and propylene glycol which is overcoated with an additional controlled release layer comprising ethyl cellulose; whereby, the amount of drug active and the controlled release barrier material utilized in each coating layer thereof is provided in amounts effective to achieve a desirable plasma level of drug active in a patient over a preselected twelve to twenty-four hour period.

2. The multilayer dosage form of claim 1 additionally comprising an outer layer containing drug active which is intended for immediate release.

3. The multilayer dosage form of claim 1 comprising at least one additional coating layer of a water soluble film forming polymer interposed between one or more of the controlled release layers and the adjoining layer containing drug active.

4. A method of achieving a desired plasma level of a water soluble drug over a desired time period in a patient comprising the steps of:

preparing a multilayered controlled release dosage form by sequentially overcoating a drug active containing core comprising a mixture of hydroxypropyl methylcellulose, polyethylene glycol and propylene glycol with a first controlled release barrier layer comprising ethyl cellulose; and

providing at least one additional layer containing drug active comprising a mixture of hydroxypropyl methylcellulose, polyethylene glycol and propylene glycol over said first controlled release barrier layer which is overcoated by an additional controlled release layer comprising ethyl cellulose; whereby, the amount of drug active and the controlled release barrier material utilized in each coating layer thereof is provided in an amount effective to achieve a desirable plasma level of drug active in a patient over a desired period of time.

5. The method of claim 4 additionally comprising an outer layer containing drug active which is intended for immediate release.

6. The method of claim 4 wherein the desired time period is about twelve or twenty-four hours.

7. The method of claim 4 wherein the drug is tamadol HCl or pseudoephedrine HCl.

8. The method of claim 4 wherein the sequential coatings are all applied in aqueous systems.

9. The method of claim 4 wherein the multilayered dosage form comprises at least one additional coating layer of a water soluble film forming polymer interposed between one or more of the controlled release layers and the adjoining layer containing drug active.

10. The method of claim 4 wherein two or more different drug actives are provided in the dosage form.

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- Dolan, Thomas Francis
Sandwich, Kent CT13 9NJ (GB)
- Haueberger, Angela Carol Gatlin
East Lyme, Connecticut 06333-1238 (US)

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(71) Applicant: PFIZER INC.
New York, N.Y. 10017 (US)

(74) Representative: Moore, James William
Pfizer Limited,
European Patent Department,
Ramsgate Road
Sandwich, Kent CT13 9NJ (GB)

(72) Inventors:
• Bell-Huff, Cristl
West Bloomfield, Michigan 48322 (US)

(54) Pharmaceutical formulations comprising sildenafil

(57) Pharmaceutical formulations of the compound sildenafil.

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down movement is repeated at a rate equivalent to thirty times a minute. The dosage form is disintegrated when no particles remain above the gauze.

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Claims

1. An orally disintegrating pharmaceutical preparation which comprises sildenafil free base together with a pharmaceutically acceptable carrier. 10
2. An orally disintegrating pharmaceutical preparation as claimed in claim 1 which comprises sildenafil free base together with a pharmaceutical carrier, which rapidly disintegrates in the mouth. 15
3. A preparation as claimed in claim 2, wherein said preparation is prepared by a method which comprises the steps of 20
 - (a) combining and compressing a water soluble meltable binder, at least one excipient and sildenafil free base into a tablet,
 - (b) melting said binder in said tablet and
 - (c) solidifying said binder. 25
4. A preparation as claimed in claim 3 wherein said binder is a polyethylene glycol, a sucrose ester, an ethoxylated fatty acid or an ethoxylated alcohol. 30
5. A preparation as claimed in claim 3 wherein step (a) includes combining with a volatilizable material which is removed after the compression step.
6. A preparation as claimed in claim 5 wherein the volatilizable material is ammonium bicarbonate. 35
7. A method of treating human sexual dysfunction which comprises administering an orally disintegrating pharmaceutical preparation as claimed in claim 1, and allowing said preparation to disintegrate in the mouth. 40
8. A method as claimed in claim 7 wherein the pharmaceutical preparation is administered to an impotent male. 45
9. A method as claimed in claim 7 where the pharmaceutical preparation is administered to a female. 50

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DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

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(21) Numéro de la demande internationale: PCT/FR99/01811 (22) Date de dépôt international: 23 juillet 1999 (23.07.99) (30) Données relatives à la priorité: 98/10091 3 août 1998 (03.08.98) FR (71) Déposant (pour tous les Etats désignés sauf US): LABORATOIRES PROGRAPHARM [FR/FR]; Zone Industrielle, F-28170 Châteauneuf en Thymerais (FR). (72) Inventeurs; et (73) Inventeurs/Déposants (US seulement): BRUNA, Brionne [FR/FR]; 13, rue des Parigaudes, F-28300 Jouy (FR). GENDROT, Edouard [FR/FR]; 24, rue de Dreux, F-28500 Gernay (FR). CHAUVEAU, Charles [FR/FR]; 2, ruelle des Bruyères, F-06560 Valbonne (FR). DEMICHELIS, Alain-Gilles [FR/FR]; 77, chemin de la Tête de Lion, F-06130 Grasse (FR). (74) Mandataires: VUILLERMOZ, Bruno etc.; Cabinet Laurent & Charra, 20, rue Louis Chirpaz, Boîte postale 32, F-69131 Ecully (FR).		(81) Etats désignés: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, brevet ARIPO (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Publiée Avec rapport de recherche internationale.
(54) Titre: METHOD FOR MAKING COATED GABAPENTINE OR PREGABALINE PARTICLES (54) Titre: PROCEDE DE FABRICATION DE PARTICULES DE GABAPENTINE OU DE PREGABALINE ENROBÉES (57) Abstract The invention concerns a method for making coated particles of γ-aminobutyric acid analogue whereof the lactam content by weight relative to the weight of γ-aminobutyric acid analogue is less than 0.5 %. The invention is characterised in that it consists in spraying a coating solution comprising at least a polymer in an organic solvent on said γ-aminobutyric acid analogue particles. (57) Abrégé Procédé pour la fabrication de particules d'analogue d'acide γ-aminobutyrique enrobées dont la teneur en lactame en poids par rapport au poids d'analogue d'acide γ-aminobutyrique est inférieure à 0,5 %, caractérisé en ce que l'on pulvérise une solution d'enrobage comprenant au moins un polymère dans un solvant organique sur lesdites particules d'analogue d'acide γ-aminobutyrique.		

REVENDICATIONSx43
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- 1/ Procédé pour la fabrication de particules d'analogue d'acide γ -aminobutyrique enrobées dont la teneur en lactame en poids par rapport au poids d'analogue d'acide γ -aminobutyrique est inférieure à 0,5%, caractérisé en ce que l'on pulvérise une solution d'enrobage comprenant au moins un polymère dans au moins un solvant organique sur lesdites particules d'analogue d'acide γ -aminobutyrique.
- 10 2/ Procédé selon la revendication 1, caractérisé en ce que l'analogue d'acide γ -aminobutyrique est la gabapentine.
- 3/ Procédé selon la revendication 1, caractérisé en ce que l'analogue d'acide γ -aminobutyrique est la prégabaline.
- 15 4/ Procédé selon la revendication 2, caractérisé en ce que le polymère représente entre 60 et 80 % en poids de la gabapentine.
- 5/ Procédé selon la revendication 3, caractérisé en ce que le polymère
- 20 représente entre 15 et 30 % en poids de la prégabaline.
- 6/ Procédé selon l'une des revendications 1 à 5, caractérisé en ce que les particules d'analogue d'acide γ -aminobutyrique sont préalablement uniformisées en taille, par pulvérisation sur lesdites particules d'une solution d'un agent liant
- 25 hydrosoluble dans un solvant organique, puis tamisage et calibrage des particules agglomérées obtenues.
- 7/ Procédé selon l'une des revendications 1 à 6, caractérisé en ce que la pulvérisation de la solution d'enrobage est effectué en lit fluidisé.
- 30 8/ Procédé selon l'une des revendications 1 à 7, caractérisé en ce que le solvant organique est choisi dans le groupe comprenant l'acétone, l'éthanol, l'isopropanol, seul ou en mélange.

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9/ Procédé selon la revendication 8, caractérisé en ce que le solvant organique comprend 50 parties d'acétone et 50 parties d'éthanol pour 100 parties en masse/masse.

5 10/ Procédé selon la revendication 6, caractérisé en ce que l'agent liant est mis en solution dans de l'éthanol.

11/ Procédé selon l'une des revendications 1 à 10, caractérisé en ce que le polymère est choisi dans le groupe comprenant le polyméthacrylate, les
10 copolymères d'amino éthylméthacrylate, les polymères cellulose, seuls ou en mélange.

12/ Procédé selon l'une des revendications 1 à 11, caractérisé en ce que la solution d'enrobage contient en outre un agent édulcorant choisi dans le groupe
15 comprenant l'aspartam, l'acésulfam de potassium, le monoammonium glycyrrhizinate, le saccharinate de sodium, les sucres et dérivés, les polyols et dérivés, seuls ou en mélange.

13/ Procédé selon l'une des revendications 1 à 12, caractérisé en ce que la
20 solution d'enrobage contient en outre un agent antistatique choisi dans le groupe comprenant la silice colloïdale, la silice précipitée et le talc.

14/ Procédé selon l'une des revendications 1 à 13, caractérisé en ce que l'on mélange à sec les particules enrobées obtenues avec des excipients de compression
25 avant de les soumettre à une étape de compression pour obtenir des comprimés.

15/ Procédé selon la revendication 14, caractérisé en ce que les excipients de compression sont choisis dans le groupe comprenant les agents diluants, les agents lubrifiants, les agents aromatisants, les agents édulcorants, seuls ou en mélange.

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16/ Procédé selon la revendication 15, caractérisé en ce que les excipients de compression comprennent en outre au moins un agent désintégrant choisi dans le groupe comprenant la carboxyméthylcellulose sodique, la crospovidone et le carboxyméthylamidon.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Octubre 4 de 2006

Abogada
JIMENA ESCOBAR URIBE

ASUNTO	Radicación No.	01 109 552
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	Evento	001
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	Folios	0

Título de la solicitud: "Partículas de encubrimiento de Textura que contienen un Ingrediente Activo".

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 6 – 32, el capítulo reivindicatorio de los folios 33 – 46 y la oposición de los folios 110-115 y 152-155 de la solicitud.

2. Objeto de la invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 – 13, 37-44, 64, 67-71 se refieren a una partícula en la que la textura está recubierta, que comprende:

- (a) un núcleo que contiene un ingrediente activo (antiinflamatorio no esteroideo, acetaminofeno, pseudoefedrina, meclizina, famotidina, loperamida, ranitidina, cimetidina, astemizol, loratadina, desloratadina, fexofenadina, cetirizina, antácidos);
- b) una capa de recubrimiento de sabor conformada por un polímero entérico (ftalato de HPMC, acetato succinato de HPMC, acetato ftalato de celulosa) y un polímero formador de película insoluble (acetato de celulosa, EC) y
- (c) otra capa de recubrimiento conformada por: un polímero formador de película (HPMC, HPC, HEC, CMC sódico, almidones, alginatos, PVAs, gomas xantan, guar, polisacáridos, pectinas, gelatinas) y un agente antigranuloso (PEO, PEG).

Las reivindicaciones 14-22, 45-51, 65 se refieren a tabletas masticables que

constan de partículas de la reivindicación 1 ó 37.

Las reivindicaciones 23-30, 52-57 se refieren a tabletas de desintegración rápida que constan de partículas de la reivindicación 1.

Las reivindicaciones 31-36, 58-63, 66, 72 se refieren a un método para encubrir la textura de partículas, que consiste en aplicar la capa de revestimiento de un polímero formador de película (HPMC) y un agente antigranuloso (PE, PEG).

El problema planteado en esta solicitud es la necesidad de una forma de dosificación oral en la cual las partículas de ingrediente activo están recubiertas para encubrir el sabor y la textura y no requiere de agua para su consumo.

Para resolver este problema técnico la solicitud en estudio proporciona composiciones farmacéuticas masticables compuestas por partículas de ingrediente activo recubiertas por una película formada por un polímero formador de película (HPMC, HPC, HEC, CMC sódico, almidones, alginatos, PVAs, gomas xantan, guar, polisacáridos, pectinas, gelatinas) y un agente antigranuloso (PE, PEG).

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 9 /00 // 9/14 // 9/16 // 9/28.

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 09 745 243 de diciembre 21 de 2000, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Con respecto a los Art. 28 y 30 de la D 486

El artículo 28 de la Decisión 486 establece: *"La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información:*

- a) el sector tecnológico al que se refiere o al cual se aplica la invención;*
- b) la tecnología anterior conocida por el solicitante que fuese útil para la comprensión y el examen de la invención, y las referencias a los documentos y publicaciones anteriores relativas a dicha tecnología;*
- c) una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior;*
- d) una reseña sobre los dibujos, cuando los hubiera;*
- e) una descripción de la mejor manera conocida por el solicitante para ejecutar o llevar a la práctica la invención, utilizando ejemplos y referencias a los dibujos, de ser éstos pertinentes; y,*
- f) una indicación de la manera en que la invención satisface la condición de ser susceptible de aplicación industrial, si ello no fuese evidente de la descripción o de la naturaleza de la invención.*

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

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Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple".

La descripción divulga la invención de manera suficientemente clara y completa para su comprensión, tal como lo establece el Art 28 de la decisión 486 de la Comisión Andina. Menciona el sector tecnológico al que pertenece, los antecedentes de la técnica, la divulgación del problema técnico, la solución propuesta y la ventaja frente a la tecnología anterior.

Pero en cuanto a la reivindicación 8 se observa que esta no define el objeto porque que no menciona en forma clara y ordenada los compuestos que lo caracterizan; pero menciona que "cumple con la especificación de disolución de USP", lo cual no lo caracteriza. Se recuerda que el resultado a alcanzar no es una característica técnica de la invención. Las reivindicaciones deben definir la invención por sus características esenciales, en este caso por medio de los compuestos que lo conforman. La invención no queda definida por el resultado a alcanzar (tal como "cumple con la especificación de disolución de USP"), puesto que la reivindicación incluiría no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Debe hacerse la corrección necesaria.

4. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es diciembre 21 de 2000, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	EP 0 458 751	Delivery system for cyclic amino acids with improved taste, texture and compressibility.	Nov 27, 1991
D2	US 5 645 858	Formas de dosis farmacéuticas de liberación controlada multicapa	Jul 8, 1997

5. Argumentos de la Oposición

Dice el oponente que EP 0 458 751 y EP 0 608 850 afectan la novedad de esta solicitud.

Agrega que las solicitudes colombianas 99 048 774 (WO 00 07568) y 99 030 493 (EP 0 960 621) afectan la novedad.

6. Respuesta a los argumentos de la Oposición

Se aclara que EP 0 458 751 es la misma anterioridad considerada en esta solicitud como D1. Y tal como se explica en la "Evaluación de Nivel Inventivo", la anterioridad sugiere al técnico con conocimientos medios el utilizar dos capas de recubrimiento, por lo cual es claro que **está afectado el nivel inventivo**, dado el tipo de compuestos que conforman la primera capa, que son los que se mencionan en la segunda capa de esta solicitud. Ahora bien, la solicitud en estudio no tiene el mismo tipo de componentes de la segunda capa que se enseñan en esta anterioridad (grasas, ácidos grasos, ceras). De manera que no está afectada la novedad.

Con respecto a EP 0 608 850 se observa que esta anterioridad también enseña dos capas de recubrimiento, lo cual sugiere al técnico con conocimientos medios, la utilización de dos capas, tal como se menciona ahora en esta solicitud; por lo cual **está afectado el nivel inventivo**. Pero, como se observa, aunque el tipo de polímeros de la anterioridad es el mismo tipo de polímeros que se utilizan en esta solicitud; la primera capa de esta solicitud se forma con dos polímeros y la segunda con un polímero y un plastificante, mientras que en la anterioridad la primera capa se forma con un polímero y un plastificante y la segunda con un polímero. De manera que no son iguales y no está afectada la novedad.

Con respecto a que las solicitudes colombianas 99 048 774 (WO 00 07568) y 99 030 493 (EP 0 960 621) afectan la novedad, se observa (folios 170-174) que ninguna menciona las dos capas de recubrimiento que caracterizan a las partículas de esta solicitud, aunque mencionan algunos de los polímeros utilizados. De manera que no afectan la novedad ni el nivel inventivo.

7. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

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

Las reivindicaciones 1 – 13, 37-44, 64, 67-71 se refieren a una partícula en la que la textura está recubierta, que comprende:

- (a) un núcleo que contiene un ingrediente activo;
- b) una capa de recubrimiento de un polímero entérico (ftalato de HPMC, acetato succinato de HPMC, acetato ftalato de celulosa) y un polímero formador de película insoluble (acetato de celulosa, EC) y
- (c) otra capa de recubrimiento conformada por: un polímero formador de película (HPMC, HPC, HEC, CMC sódico, almidones, alginatos, PVAs, gomas xantan, guar, polisacáridos, pectinas, gelatinas) y un agente antigranuloso (PEO, PEG).

Las reivindicaciones 14-22, 45-51, 65 se refieren a tabletas masticables que constan de partículas de la reivindicación 1 ó 37.

Las reivindicaciones 23-30, 52-57 se refieren a tabletas de desintegración rápida que

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constan de partículas de la reivindicación 1.

Las reivindicaciones 31-36, 58-63, 66, 72 se refieren a un método para encubrir la textura de partículas, que consista en aplicar la capa de revestimiento de un polímero formador de película (HPMC) y un agente antigranuloso (PEO, PEG).

D1 enseña partículas que tienen (a) un núcleo que contiene un ingrediente activo; (b) una capa de recubrimiento de un polímero formador de película (HPMC, HPC, HEC, CMC, alginato, PVA, goma xantan, guar, dextrán (polisacárido), pectina, gelatina) y PG, acetato ftalato de celulosa y acetato ftalato de celulosa (c) otra capa de recubrimiento formada por grasas, ácidos grasos, ceras. Enseña además (ver pág. 11), las tabletas masticables preparadas con este material. El objeto logrado en esta anterioridad era enmascarar el sabor amargo de los compuestos activos y la superficie rugosa, además de proveer más estabilidad y mejorar la compresibilidad.

D2 enseña una forma de dosificación de liberación controlada. Las partículas están recubiertas secuencialmente con una película de liberación controlada y al menos otra película hecha de una mezcla de HPMC y plastificantes PEG y PG. Agrega (columna 5) que los pellets de liberación controlada preferiblemente se proveen en una cápsula de gelatina dura ó cualquier otra forma de dosis oral apropiada tal como una matriz que comprende los pellets aglomerados con un aglutinante apropiado y compatible para formar una forma de dosis sólida unitaria.

Evaluación del Nivel Inventivo

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

Se observa que:

- (a) debido a que los elementos característicos de la partícula reivindicada, es decir: (a) núcleo que contiene un ingrediente activo; b) capa de recubrimiento de un polímero entérico (ftalato de HPMC, acetato succinato de HPMC, acetato ftalato de celulosa) y un polímero formador de película insoluble (acetato de celulosa, EC) y (c) otra capa de recubrimiento conformada por un polímero formador de película (HPMC, HPC, HEC, CMC sódico, almidones, alginatos, PVAs, gomas xantan, guar, polisacáridos, pectinas, gelatinas) y un agente antigranuloso (PEG); eran conocidos en las anterioridades D1 y D2, una persona de habilidades ordinarias en el arte adaptaría fácilmente estos elementos a la partícula de esta solicitud. Aunque se observa que los componentes que conforman la primera cubierta de la anterioridad D1 son los que se mencionan en la segunda de esta solicitud, estas enseñanzas, junto con lo enseñado en D1 donde las partículas están recubiertas secuencialmente con una película de liberación controlada y al menos otra película hecha de una mezcla de HPMC y plastificantes PEG y PG, una persona normalmente conocedora del arte hubiera llegado de manera lógica a las partículas aquí reivindicadas;
- (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a las partículas reivindicadas conformadas por núcleo que contiene un ingrediente activo; capa de

+80
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recubrimiento de un polímero entérico y un polímero formador de película insoluble y (c) otra capa de recubrimiento conformada por un polímero formador de película y un agente antigranuloso, porque el aquí llamado "agente antigranuloso", que puede ser PEG, siempre se ha utilizado, como se observa en las dos anterioridades; solo que se conocen con el nombre de "plastificantes"; pero es obvio que ya entonces ejercían la misma función de homogenizar la superficie evitando rugosidades y mejorando la textura. Así que no se puede considerar como un aporte a la técnica y son obvios para una persona versada en la materia;

- (c) el problema planteado en esta solicitud que era la necesidad de una forma de dosificación oral en la cual las partículas de ingrediente activo están recubiertas para encubrir el sabor y la textura y no requiere de agua para su consumo se resuelve proporcionando composiciones farmacéuticas masticables compuestas por partículas de ingrediente activo recubiertas por una película formada por un polímero formador de película y un agente antigranuloso (PEO, PEG), es decir de la misma manera como se resolvía en las anterioridades, tal como explica D1, donde se logró el objeto de enmascarar el sabor amargo de los compuestos activos y la superficie rugosa, además de proveer más estabilidad y mejorar la compresibilidad; Además en D1 no se necesitaba de agua para su consumo porque estas tabletas son masticables;
- (d) el resultado obtenido: es decir composiciones farmacéuticas masticables compuestas por partículas de ingrediente activo recubiertas por una película formada por un polímero formador de película y un agente antigranuloso (PEO, PEG) no es inesperado;
- (e) no parece haberse superado un prejuicio técnico anterior, con las composiciones farmacéuticas masticables compuestas por partículas de ingrediente activo recubiertas por una película formada por un polímero formador de película y un agente antigranuloso (PEO, PEG) propuestas de manera que el objeto de las reivindicaciones 1 – 13, 37-44, 64, 67-71 no tiene nivel inventivo.

Se observa también que, puesto que las partículas que caracterizan a las tabletas masticables de las reivindicaciones 14-22, 45-51, 65 y a las tabletas de desintegración rápida de las reivindicaciones 23-30, 52-57, no tienen nivel inventivo, tampoco lo tienen las tabletas.

Con respecto a las reivindicaciones 31-36, 58-63, 66, 72 que se refieren a un método para encubrir la textura de partículas, que consiste en aplicar la capa de revestimiento de un polímero formador de película (HPMC) y un agente antigranuloso (PEO, PEG), se observa que D2 enseñaba previamente (ver columnas 9 y 10) la preparación de partículas cubiertas con varias capas: primero se aplica una primera capa de liberación controlada y luego se aplica otra de HPMC, PG y PEG. Lo cual sugiere el método mencionado en esta solicitud, por lo que no hay nivel inventivo.

8. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	EP 0 458 751	1 – 72	Nivel inventivo
D2	US 5 645 858	1 – 72	Nivel inventivo

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

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


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha
12 OCT. 2006

CONCEPTO TÉCNICO No. 1585	EXAMINADOR TÉCNICO Código 202007
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 1-109552

EDICTO No. 4521

LA SECRETARÍA GENERAL AD-HOC HACE SABER:

Que esta Superintendencia profirió Resolución No. 4910 de 28-FEB-2007. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud

correspondiente a "PARTICULAS DE ENCUBRIMIENTO DE TEXTURA QUE CONTIENEN UN INGREDIENTE ACTIVO".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Jimena Escobar Uribe, o a quien haga sus veces, en su calidad de apoderada de McNeil-Ppc, Inc., y al doctor José Luis Reyes Villamizar en su calidad de apoderado de la sociedad opositora Tecnoquímicas S.A., entregándoles copia de la misma, advirtiéndoles que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, del cual podrán hacer uso al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CÚPLASE

Dada en Bogotá, D.C., a los 26 FEB. 2007

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:00 a.m. de hoy.

Secretaría General Ad-Hoc 13-MAR-2007
Secretaría General Ad-Hoc
EDICTO No. 4521

Este edicto se desfija hoy 27-MAR-2007 a las 4:30 p.m.