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Señores
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bogotá, D.C.

SUPERINDUSTRIA Y COMERCIO	
Radicación : 00030256 00000003	Folios: 2
Fecha (RAD): 2002-11-07 12:12:55	REGISTRO/ 538 PETICION
Trámite : DE PATENTES Y	
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES	
SUPERINDUSTRIA Y COMERCIO	

Re.: Código 02-01-538
Expediente No. 00-30.256
Solicitud de Patente
SMITHKLINE BEECHAM
CORPORATION

En relación con el Expediente de la referencia por medio del presente escrito muy respetuosamente me permito solicitarles se sirvan proceder a efectuar el EXAMEN DE PATENTABILIDAD de la solicitud aquí contenida.

Para tal efecto acompaño el comprobante de pago por concepto de \$ 318.000.00, recibo No. 74. 316/02

De Ustedes Atentamente,

GERMAN CASTILLO GRAU
T.P. # 2.978 del C.S.J.

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Industria y Comercio

SUPERINTENDENCIA

NIT : 800176089-2

Radicación : 00030256 00000003 Folios: 2
Fecha (AMD): 2002-11-07 16:34:55
Trámite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 02 - 74,316
FECHA : NOVIEMBRE 7 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CASTILLO BRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	6635317	06/11/2002	3,350,200.00

***** CONCEPTO *****

CANT. CONCEPTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
	TOTAL :	\$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Germán Castillo Grau
Apoderado

Oficio N° **05633**

REFERENCIA	Radicación	00 30256
	Trámite	002
	Evento	001
	Actuación	430
	Folios	009

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 30256, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 4-13
- . Ejemplos: folios 13-17
- . Capítulo reivindicatorio estudiado: folios 76-78
- . Se reivindica prioridad, presentada en Estados Unidos el 29.04.99, bajo el número 09/301838

Objeto de la invención

Según las reivindicaciones 1 a 22 de la presente solicitud, se refiere a un comprimido masticable que comprende trihidrato de amoxicilina en el que la base masticable comprende manitol al menos en un 25% en peso del contenido.

Clasificación internacional de patentes A 61 K 9/20, 31/545

Claridad de la solicitud

El art. 30 de la decisión 486 contempla que *“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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Teniendo en cuenta lo anterior, la reivindicación 15 es básicamente una repetición de la reivindicación 2.

La reivindicación 16 se refiere a un procedimiento según la reivindicación 14, y la reivindicación 14 se refiere a un comprimido masticable.

Favor hacer las aclaraciones y correcciones del caso

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 29.04.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	EP 0396335	"Formulación farmacéutica"	07.11.90
2	US 5498788	"Complejos de inclusión de ácido clavulánico y sus sales de potasio con derivados hidrofóbicos de beta-ciclodextrina y su proceso de preparación"	12.03.96

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 de la comisión de la comunidad andina, se procedió a evaluar 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.

Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 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"*

La publicación EP 0396335 se refiere a una tableta masticable que contiene un medicamento dispersado en una base masticable como el manitol. El ejemplo 1 describe tabletas masticables que contienen 33% de manitol y 41% de trihidrato de amoxicilina.

US 5498788 revela en su ejemplo 11 tabletas masticables que contienen 500 mg amoxicilina, 48% de manitol, crospovidona, y estearato de magnesio.

Teniendo en cuenta el objeto de la solicitud, el cual es proveer tabletas masticables de amoxicilina en una base de manitol, es una derivación evidente del estado de la técnica ya que las enseñanzas de los documentos citados enseñarían a una persona versada en la materia a fabricar las composiciones de la presente solicitud.

Finalmente no se demuestran propiedades sorprendentes o inesperadas de las tabletas de la presente solicitud en comparación con las del estado de la técnica.

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En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	EP 0396335	1-22	Nivel Inventivo
2	US 5498788	1-22	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de 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 5 del título primero de la Circular Única Nº 10 de 2001


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 7 JUL 2005

CONCEPTO TÉCNICO Número 0947	EXAMINADOR TÉCNICO Código 202024
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Publication number: **0 396 335 A1**

EUROPEAN PATENT APPLICATION

Application number: 90304550.8

Int. Cl.⁵: **A61K 9/20, A61K 9/46**

Date of filing: 26.04.90

Priority: 28.04.89 GB 8909793

Date of publication of application:
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Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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Pharmaceutical formulation.

A chewable tablet comprises a medicament dispersed in a chewable base, such as mannitol, together with an effervescent couple, such as citric acid - sodium bicarbonate. The combination of effervescence and chewability with optional flavourings improves the taste characteristics of the medicament in oral administration. A disintegrant such as microcrystalline cellulose may be added to give the patient the option of dispersing the tablet in water.

EP 0 396 335 A1

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PHARMACEUTICAL FORMULATION

This invention relates to pharmaceutical compositions for oral administration of antibiotics and other medicaments with unpleasant taste characteristics, and particularly to compositions formulated as chewable tablets.

From the point of view of bioavailability, the preferred form of administration of sparingly soluble medicaments such as a β -lactam antibiotics is often an aqueous suspension. However, there are problems associated with this form of administration. For example, such preparations in multidose form may have a limited shelf life; and usual methods of dose measurement lack accuracy. The bitter taste of many such medicaments is also a drawback.

Solid dosage forms which are swallowed, such as tablets and capsules, provide accurate dosage and avoid taste problems; but since they have to disintegrate in the gastrointestinal tract and the medicament has then to dissolve before it can be absorbed, absorption tends to be slower than from a suspension, and may be less than complete. Also, some patients have difficulty swallowing tablets and capsules, and there is a practical limit to the size, and therefore the dose, that can be swallowed.

Single dose powders for reconstitution in sachet form, and dispersible tablets, offer the advantages of suspensions without the problems of instability, measurement inaccuracy, difficulty in swallowing, or size limitation. However, residues from the dispersed formulation may be another reason for incomplete doses being swallowed. This is a particular problem with dispersible tablets, since the component granules may disperse into particles which are too large to remain evenly suspended.

In general, chewable tablets are advantageous in that they combine the accuracy of dosage associated with tablets, with the optimum bioavailability of suspensions. They may also accommodate larger doses than swallow tablets or capsules. Their acceptability is, however, reduced for bitter tasting medicaments, such as antibiotics, especially at higher doses, for example 500 mg. and above.

The dispersion properties of dispersible tablets can be facilitated by the inclusion of an acid/base couple in which the base liberates carbon dioxide when the components of the couple are dissolved in water. Such an effervescent couple has also been included in tablets for swallowing, to aid their disintegration in the gastrointestinal tract. It is also known to provide effervescent formulations of medicaments in water-soluble form so as to provide clear solutions of the antibiotics.

It has now been found that the inclusion of an effervescent couple in chewable tablets of bitter-tasting medicaments has surprising advantages with respect to palatability, in addition to assisting the break-up of the tablets in the mouth when chewed or sucked. Such 'fizzy chewable' tablets are thus well-accepted by patients, especially small children, who would otherwise find the medicine difficult to take and who might therefore refuse treatment. This contribution to improved patient compliance is also important with other classes of patients, for example the elderly, and those with mental illness.

Accordingly in one aspect the present invention provides a chewable tablet comprising a chewable base, a medicament and an effervescent couple.

This chewable composition is especially suitable for improving the taste characteristics of a range of medicaments, particularly for improving the taste of bitter-tasting medicaments, but clearly also provides a pleasant mode of administering any medicament, particularly those with an unpleasant mouth-feel even in the absence of a bitter taste, for example antacids.

Typical bitter-tasting medicaments are β -lactam antibiotics including penicillins such as amoxycillin or ampicillin, optionally in admixture with a β -lactamase inhibitor especially when a high dose is needed. Other medicaments whose taste can be improved include antihistamine H_2 -receptor antagonists typically anti-ulcer compounds such as cimetidine, non-steroidal anti-inflammatory such as nabumetone, and bile acid sequestrants.

The effervescent couple comprises a basic ingredient and an acidic ingredient, the basic ingredient liberating carbon dioxide when it and the acidic ingredient are contacted with saliva or added water.

The amount of the effervescent couple is selected at a level sufficient to counter the taste of the medicament without itself causing discomfort in the patients mouth. Normally the amount of effervescent couple will be less than that conventionally used in water-dispersible or solublizable tablets.

Preferred antibiotics are amoxycillin and ampicillin, preferably amoxycillin trihydrate. A preferred β -lactamase inhibitor is clavulanic acid, preferably as potassium clavulanate. Typically, the ratio of antibiotic to inhibitor is 4:1 or 2:1 by weight, but ratios of 12:1 to 1:1 may be used. The weight of antibiotic in a unit dose may range from 125mg to 1g, expressed in terms of the activity of the antibiotic. The weight of antibiotic in the composition calculated as the free acid, may range from 5% to 50% based on the weight of the tablet. The weight of the β -lactamase inhibitor in the composition, calculated as the acid, may range

from 0.4% to 30% based on the weight of the tablet.

Other medicaments used in the tablet of the invention will also typically comprise 5 to 50% of the tablet weight.

The effervescent couple typically comprises citric acid or sodium hydrogen citrate and sodium bicarbonate, but other physiologically acceptable acid/alkaline or alkaline earth metal carbonate mixtures may be used, for example tartaric, adipic, fumaric or malic acids, and sodium, potassium or calcium (bi)-carbonates or sodium glycine carbonate.

In general it has been found that preferred taste characteristics are exhibited when the relative proportions of the components of the effervescent couple on a chemical molecular equivalent basis are in the range of 4:3 to 1:3, more preferably about 2:3, expressed as the ratio of molecular equivalent of the acidic component to the basic component. In terms of a preferred combination of citric acid and sodium bicarbonate these values represent on a weight basis, a range from 1:1 to 0.3:1, preferably 0.5:1 expressed as the ratio of acidic to basic component.

However, in some formulations, the choice of flavouring agents may result in optimisation of taste characteristics when there is an excess of acidic component, for example, on a chemical molecular equivalent basis of from about 11:3 to 4:3 expressed as the ratio of acidic to basic component. For the combination of citric acid and sodium bicarbonate this represents 5:1 to 1:1 on a weight basis.

The weight of the acidic component may be in the range 0.5% to 20%, preferably 1.5% to 5%, of the weight of the tablet.

The weight of the basic component may be in the range 0.5% to 30%, preferably 1.5% to 10%, of the weight of the tablet.

In general, taste testing shows that acceptable taste characteristics are found with the effervescent couple representing 0.25% to 30% of the final tablet weight, with a preference for 10-15% in chewable antibiotics tablets but up to 20% for some other materials, such as nabumetone.

Preferred combinations comprise citric acid (or sodium hydrogen citrate) or malic acid with sodium carbonate in a weight ratio of 0.5:1 to 1:1.

The chewable base may be any of those conventionally employed in chewable tablets, for example mannitol, sorbitol, dextrose, fructose or lactose alone or combination. The tablets may also contain conventional lubricants such as magnesium stearate, sweetening agents such as sodium saccharin and aspartame, and flavouring and colouring agents.

In another aspect of this invention disintegrating agents are incorporated into the chewable tablet so as to give the patient the option of dispersing the tablet in a small amount of water prior to administration.

Suitable disintegrating agents are cellulose products such as microcrystalline cellulose, microfine cellulose or hydroxy propyl cellulose, and other materials such as cross-linked polyvinyl pyrrolidone (PVP) or sodium starch glycolate, used singly or in admixture. Hitherto in attempts to provide a dispersible tablet which can also be chewed containing conventional, especially cellulose - based disintegrants, the latter impart an unpleasant mouth-feel. However this is masked effectively when combined with an effervescent couple in the chewable tablets of this invention.

When using disintegrating agents to impart dispersibility to the chewable tablets, the amount of effervescent couple may be maintained at the levels indicated above relative to the weight of the final chewable, dispersible tablet. In view of the additional taste load, amounts of effervescent couple in the upper regions of the indicated ranges may be preferred.

The disintegrant is typically added at amounts of 5% to 30%, preferably from 15 to 20%, based on the final weight of the tablet.

The ingredients discussed above may be formed into tablets by conventional techniques, for example either by direct compression, or first slugging some of the ingredients, milling the slugs, blending with the remaining ingredients, and then compressing, as appropriate.

The chewable tablets are preferably packaged in sealed protective containers, such as screw cap bottles, plastic or metal tubes, aluminium foil sachets, aluminium-foil backed blister packs. It may be appropriate to incorporate a desiccant in the packaging. Alternatively, an edible desiccant may be incorporated in the composition as disclosed in EP-A-0 049 061 (Beecham).

Preferably the tablets are in unit-dose form. The amount of medicament in a unit-dose will depend on the condition to be treated and the assay of the medicament. The unit-dose will be repeated according to the usual regime for the medicament.

The invention is illustrated by the following Examples.

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Example 1		
250mg Dose Fizzy Chewable Tablet (β -lactam antibiotic)		
Ingredients	mg/tablet	(% w/w)
Amoxycillin Trihydrate equivalent to Amoxycillin free acid	250.00	41.667
Magnesium stearate	8.75	1.125
Citric acid	12.50	2.083
Sodium bicarbonate	25.00	4.167
Sodium saccharin	2.50	0.417
Lemon dry flavour	27.50	4.583
Lime dry flavour	1.38	0.230
Sorbitol B.P.	90.00	15.000
Mannitol U.S.P.	q.s.to 100%	
	600 mg	

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Example 2		
375mg Dose Fizzy Chewable Tablet (β -lactam antibiotic + β -lactamase inhibitor)		
Ingredient	mg/tablet	(% w/w)
Amoxycillin Trihydrate equivalent to Amoxycillin free acid	250.00	20.833
Potassium Clavulanate equivalent to clavulanic acid	125.00	10.417
Magnesium stearate	12.0	1.000
Citric acid	17.5	1.458
Sodium bicarbonate	35.0	2.917
Sodium saccharin	5.0	0.417
Lemon dry flavour	50.0	4.167
Lime dry flavour	2.5	0.208
Sorbitol B.P.	180.00	15.000
Silica gel dessicant	80.0	6.667
Mannitol U.S.P.	q.s to 100%	
	1200 mg	

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Manufacturing Procedure for Examples 1, 2 and 3

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All ingredients were reduced to the desired particle size by milling, then blended in a planetary mixer, to produce a compression mix. The compression mix was then tabletted on a rotary tableting press, to the desired tablet weight.

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US005498788A

United States Patent [19]

Žmitek et al.

[11] Patent Number: 5,498,788

[45] Date of Patent: Mar. 12, 1996

[54] INCLUSION COMPLEXES OF CLAVULANIC ACID AND OF POTASSIUM SALTS THEREOF WITH HYDROPHOBIC β -CYCLODEXTRIN DERIVATIVES A PROCESS FOR THE PREPARATION THEREOF

[75] Inventors: Janko Žmitek; Darja Ferčej-Temeljotov, both of Ljubljana; Katarina Verhnjak, Ptuj; Sonja Kotnik; Mateja Kovačič, both of Ljubljana, all of Slovenia

[73] Assignee: LEK, tovarna farmacevtskih, Slovenia

[21] Appl. No.: 369,301

[22] Filed: Jan. 6, 1995

Related U.S. Application Data

[63] Continuation of Ser. No. 84,951, Jul. 2, 1993, abandoned.

[30] Foreign Application Priority Data

Jul. 8, 1992 [SI] Slovenia P-9200139

[51] Int. Cl.⁶ C07D 487/04; A01K 9/26

[52] U.S. Cl. 540/349; 424/470; 536/103

[58] Field of Search 424/490; 540/349

[56] References Cited

U.S. PATENT DOCUMENTS

4,454,069	6/1984	Cook et al.	260/245.3
4,525,353	6/1985	Cole et al.	424/114
4,647,659	3/1987	Cook et al.	260/349
4,869,904	9/1989	Uekama et al.	424/400
5,310,898	5/1994	Copar	540/349

FOREIGN PATENT DOCUMENTS

1508977 4/1978 United Kingdom .

OTHER PUBLICATIONS

Lenga, Robert, The Sigma-Aldrich Library of Chemical Safety Data, Edition 1, 1985, p. 310.

Bekers, et al., Cyclodextrins in the Pharmaceutical Field,

Drug Development and Industrial Pharmacy, vol. 17, No. 11 (1991), pp. 1503-1549.

Chemical Abstracts, The American Chemical Society, vol. 101, No. 21 (1984), p. 808.

Hedges, Allan, Minutes of the Sixth International Symposium on Cyclodextrins, Symposium organized by American Maize-Products Company, (1992) pp. 1-8.

Matsubara, et al., Possible Use of Triacetylated Cyclodextrins in the Preparation of Sustained-Release Oily Injection of LHRH Agonist, Buserelin Acetate, pp. 547-550.

Karuzomi et al in Chem. Pharm. Bull vol. 23, pp. 3062-3068 (1975).

Primary Examiner—Iyothsna Venkat

Attorney, Agent, or Firm—Pollock, Vande Sande & Priddy

[57]

ABSTRACT

Described is a new process for the preparation of alkali clavulanate from an aqueous solution of pure clavulanic acid and of pharmaceutically acceptable potassium crude clavulanic acid, which is obtained in a conventional manner after the fermentation with a clavulanic-acid-producing microorganism, extracted with an ethyl acetate solution of a hydrophobic β -CD derivative such as heptakis-(2,3,6-tri-O-acetyl)- β -CD in equimolar amount or up to 10% excess with regard to clavulanic acid. The resulting novel inclusion complexes of clavulanic acid and hydrophobic β -CD derivative in a molar ratio about 1:1 are isolated, purified with water and then converted with potassium 2-ethyl hexanate to the potassium clavulanate, which is isolated. Furthermore, there are described new inclusion complexes of clavulanic acid and of its pharmaceutically acceptable potassium salt both with hydrophilic β -CD derivatives and with hydrophobic β -CD derivatives, processes for the preparation thereof and the use thereof for the preparation of galenic forms with immediate as well as with sustained action, in combination with amoxicillin trihydrate, which are valuable medicaments in the therapy of infectious diseases.

6 Claims, 9 Drawing Sheets

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The NMR spectrum corresponded to potassium clavulanate and triacetyl-β-CD.

EXAMPLE 10

Dispersion tablets containing clavulanic acid (125 mg) and amoxicillin (500 mg)

Ingredients	mg/tablet	%
inclusion complex of potassium clavulanate with Me-β-CD	833.3	27.78
amoxicillin trihydrate (corresponding to 500 mg of anhydrous amoxicillin)	574.0	19.13
croscopolidone (Kollidon CL)	50.0	1.67
saccharin	10.0	0.33
flavourings (fruit)	35.0	1.17
magnesium stearate	21.0	0.70
colloidal silica (Aerosil 200)	10.0	0.33
microcrystalline cellulose (Avicel pH 101)	ad 3000.0	ad 100.00

The equivalents of amoxicillin and clavulanic acid were mixed homogeneously and then briquetted with a part of the filler (microcrystalline cellulose). The briquettes were crushed and sieved through an oscillation sieve with a mesh size of 1.5 mm. The obtained granulate was mixed with the remaining adjuvants and tableted on a rotary tableting machine.

The tablets rapidly disintegrate in water giving a fine dispersion suitable for therapeutic application.

EXAMPLE 11

Chewing tablets containing clavulanic acid (125 mg) and amoxicillin (500 mg)

Ingredients	mg/tablet	%
inclusion complex of potassium clavulanate with Me-β-CD	833.3	27.78
amoxicillin trihydrate (corresponding to 500 mg of anhydrous amoxicillin)	574.0	19.13
croscopolidone (Kollidon CL)	5.0	0.17
polyvinyl pyrrolidone	60.0	2.00
colloidal silica (Aerosil 200)	10.0	0.33
saccharin	10.0	0.33
flavourings (fruit)	35.0	1.17
magnesium stearate	15.0	0.50
microcrystalline cellulose (Avicel pH 101)	60.0	2.00
mannitol	ad 3000.0	ad 100.00

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The equivalents of amoxicillin and clavulanic acid were homogeneously mixed together with a part of the fillers (microcrystalline cellulose and mannitol) and the obtained mixture of powders was briquetted. The briquettes were crushed and sieved through an oscillation sieve with a mesh size of 1.5 mm. The obtained granulate was mixed with the remaining adjuvants and tableted.

Tablets were suitable for chewing.
We claim:

1. A process for the preparation of clavulanic acid or of potassium salt thereof from a concentrate of a clear aqueous solution of crude clavulanic acid in the form of a sodium salt obtained after the fermentation with a clavulanic-acid-producing microorganism, which is acidified with sulfuric acid to a pH value between 1 and 3, wherein acidified solution of crude clavulanic acid is immediately extracted with a solution of a hydrophobic β-cyclodextrin derivative selected from the group consisting of heptakis-(2,3,6-tri-O-acetyl)-β-cyclodextrin, heptakis-(2,6-di-O-ethyl)-β-cyclodextrin, heptakis-(2,3-di-O-ethyl)-β-cyclodextrin and heptakis-(2,3,6-tri-O-ethyl)-β-cyclodextrin in an inert organic solvent, the so formed crude intermediate inclusion complex of clavulanic acid with said hydrophobic β-cyclodextrin is isolated from the organic phase, subsequently purified with water and the purified said inclusion complex is then converted with potassium 2-ethyl hexanoate to potassium clavulanate, which is then isolated.

2. A process for the preparation of clavulanic acid or of potassium salt thereof according to claim 1, wherein acidified solution of crude clavulanic acid is extracted with a solution of heptakis-(2,3,6-tri-O-acetyl)-β-CD in ethyl acetate as the inert organic solvent to form an inclusion complex of clavulanic acid with heptakis-(2,3,6-tri-O-acetyl)-β-CD.

3. A process for the preparation of clavulanic acid or of potassium salt thereof according to claim 1, wherein the intermediate inclusion complex of clavulanic acid with heptakis-(2,3,6-tri-O-acetyl)-β-CD is converted with potassium 2-ethyl hexanoate to potassium clavulanate.

4. A process for the preparation of clavulanic acid or of potassium salt thereof according to claim 1, the intermediate inclusion complex of clavulanic acid with said hydrophobic β-cyclodextrin is formed in a molar ratio of about 1:1.

5. A process for the preparation of clavulanic acid or of potassium salt thereof according to claim 1, wherein the intermediate inclusion complex of clavulanic acid with heptakis-(2,3,6-tri-O-acetyl)-β-cyclodextrin is formed in a molar ratio of about 1:1.

6. A process for the preparation of the potassium salt of clavulanic acid according to claim 1 wherein said inclusion complex is converted with potassium 2-ethyl hexanoate.

* * * * *

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-30256

EDICTO No. 15361

**LA SECRETARÍA GENERAL AD-HOC
HACE SABER:**

Que esta Superintendencia profirió Resolución No. 27774 de 24-OCT-2005. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

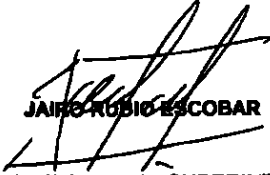
ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "FORMULACIONES FARMACEUTICAS MASTICABLES QUE COMPRENDEN COMPUESTOS DE AMOXICILINA".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Germán Castillo Grau, o a quien haga sus veces, en su calidad de apoderado de Smithkline Beecham Corporation., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFIQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 24 OCT. 2005

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIME RUBIO ESCOBAR

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 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 04-NOV-2005 Este edicto se desfija hoy 21-NOV-2005 a las cinco (5:00 p.m.)

Secretaría General Ad-Hoc

EDICTO No. 15361