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Castillo Grau & Asociados
ABOGADOS

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

Re.: Código 02-01-538
Expediente No. 00-26.419
Solicitud de Patente
BEECHAM PHARMACEUTICALS (PTE) LIMITED

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.oo, recibo No. 74.315/02

De Ustedes Atentamente,

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

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Industria y Comercio

SUPERINTENDENCIA

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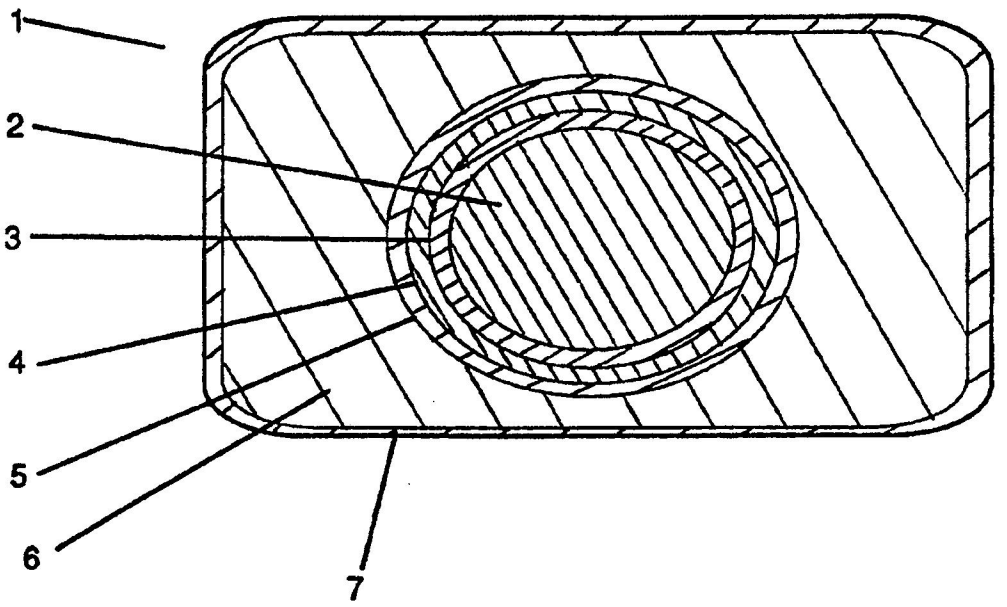
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(54) Title: PHARMACEUTICAL FORMULATION



(57) Abstract

A tablet formulation which comprises a core containing a pharmaceutically active material, coated with a release retarding coating, surrounded by a casing layer which includes a second pharmaceutically active material.

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Pharmaceutical Formulation

This invention relates to tablet formulations for oral administration, particularly to formulations, which comprise a β-lactam antibiotic, optionally together with a β-lactamase inhibitor.

Many known tablet formulations which include a β-lactam antibiotic are required to be taken orally three times a day. There is a need for oral formulations which need only be taken twice or less often per day. Methods of forming delayed or sustained release tablet formulations are known, for example coating the tablet with a release-retarding coating, or coating individual granules with such a coating, and compressing these coated granules into a tablet. "Release-retarding" as used herein, unless otherwise defined, refers both to release which is retarded so as to be sustained, i.e. active material is released gradually from the tablet, and to release which is retarded so as to be delayed, i.e. release begins or the rate of release increases after an initial delay.

Particular problems occur in the preparation of delayed or sustained release forms of the known antibacterial combination of the β-lactam antibiotic amoxycillin, in the form of its trihydrate, and the β-lactamase inhibitor clavulanic acid, in the form of an alkali metal salt, such as potassium clavulanate. This is because amoxycillin trihydrate is relatively insoluble in aqueous media, whereas potassium clavulanate is extremely soluble, hygroscopic and moisture-sensitive, and it is difficult to achieve sustained or delayed release of two such components at a compatible rate from a single formulation containing both.

According to this invention, a tablet formulation comprises a core which includes a first pharmaceutically active material, the core being coated with a release retarding coating, the coated core being itself surrounded by a casing layer which includes a second pharmaceutically active material.

The tablet formulation of the invention is suitable for oral administration, and provides a sustained and/or delayed release as a result of initial quick release of the second active material from the casing layer, and a sustained or delayed release of first active material from the coated core. Also the casing layer may serve to protect the core from the ingress of air and atmospheric moisture. Also coating of a single relatively large core in the tablet of the invention with a release-retarding coating requires less coating material than is required to coat a large number of smaller granules, and can therefore lead to a relatively low tablet weight.

The first and second pharmaceutically active materials in the tablet formulation may each individually, and/or together, comprise a β-lactam antibiotic optionally together with a β-lactamase inhibitor. Suitably the β-lactam antibiotic may be amoxycillin, e.g. in the form of its trihydrate, optionally together in

water and coated onto the core using a fluidised bed system. If water is used, preferably an anti-foaming agent such as activated polymethylsiloxane is also included.

It may be desirable, particularly in the case of cores which contain highly soluble or moisture sensitive active materials such as potassium clavulanate, to first apply one or more sub-coats to the core, before application of the release retarding coating layer, the sub-coat consequently lying beneath the release retarding coating. Suitable sub-coat materials include hydroxypropylmethyl cellulose, for example of the known types E5 and E15 (Trade Marks) in mixture. It may also be desirable to apply one or more over-coats after application of the release retarding coating layer, the over-coat consequently lying over the release retarding coating. Suitable over-coat materials include copolymers of methacrylic acid and methyl methacrylate, and hydroxypropylmethyl cellulose. The over-coat may be of the same material as the sub-coat. Typically such coatings may be applied by known techniques of aqueous film coating.

The casing layer may be applied to the coated core by a generally conventional process in which the coated core is encased in a mass of the powdered or granulated casing material components. The granules of such a casing material may be made by a conventional granulating process as known in the art, and as discussed above with reference to the manufacture of the core granules.

The casing layer itself may be coated with a final outer coating, for example of hydroxypropyl methyl cellulose, which may be applied by known film coating techniques in a similar manner to the way in which the sub-and over-coats may be applied to the core.

The tablet of the invention offers the advantages effect that the active material in the casing layer is released initially in the stomach, and the coated core releases its active material content more slowly. In this way as *in vivo* decay of the initially released material occurs, active material is subsequently released from the core to provide an extended blood level profile. If the release-retarding coating on the core is an enteric coating the release of active material from the core may occur in the intestine.

The invention therefore also provides a method of preparing a pharmaceutical formulation as described herein, comprising the steps of forming a core which includes a first pharmaceutically active material, the core being coated with a release-retarding coating, then coating the core with a casing layer which includes a second pharmaceutically active material.

Clavulanic acid and its derivatives, e.g. salts such as potassium clavulanate are extremely moisture sensitive, and all operations carried out to prepare granules and formulations of this invention which contain clavulanate should be carried out

Claims:

1. A tablet formulation comprising a core which includes a first pharmaceutically active material, the core being coated with a release retarding coating, the coated core being itself surrounded by a casing layer which includes a second pharmaceutically active material.

2. A tablet formulation according to claim 1 characterised in that the first and second pharmaceutically active materials in the tablet formulation each individually, and/or together, comprise a β-lactam antibiotic optionally together with a β-lactamase inhibitor.

3. A tablet formulation according to claim 2 characterised in that the first and second active materials both comprise amoxycillin, optionally together in combination with clavulanate.

4. A tablet formulation according to claim 3 characterised in that both the core and the casing layer contain clavulanate and amoxycillin.

5. A tablet formulation according to claim 3 characterised in that all of the clavulanate is contained in the casing layer.

6. A tablet formulation according to claim 3 characterised in that all of the clavulanate is contained in the core.

7. A tablet formulation according to any one of the preceding claims characterised in that the core and the casing layer both comprise a compact of compressed ingredients including the respective active materials.

8. A tablet formulation according to any one of the preceding claims characterised in that the release-retarding coating is an enteric polymer.

9. A tablet formulation according to any one of the preceding claims having one or more sub-coats beneath the release retarding coating layer.

10. A tablet formulation according to any one of the preceding claims having one or more over-coats above the release retarding coating layer.

11. A tablet formulation according to any one of claims 1 to 10, substantially as

hereinbefore described with reference to the accompanying drawing.

12. A method of preparing a pharmaceutical formulation as claimed in any one of claims 1 to 11, characterised by the steps of forming a core which includes a first pharmaceutically active material, the core being coated with a release-retarding coating, then coating the core with a casing layer which includes a second pharmaceutically active material.

13. A pharmaceutical formulation as claimed in any one of claims 1 to 11 for use as an active therapeutic substance.

14. A pharmaceutical formulation as claimed in any one of claims 1 to 11 for use in the treatment of bacterial infections.

15. The use of a formulation as claimed in any one of claims 1 to 11 in the manufacture of a medicament for use in the treatment of bacterial infections.

16. A method of treatment of bacterial infections in humans or animals which comprises the administration of an effective amount of a pharmaceutical formulation as claimed in any one of claims 1 to 11.

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(54) Title: BILAYERED AMOXYCILLIN TABLETS

(57) Abstract

Tablet formulations for oral administration comprising a first layer which includes amoxycillin and/or clavulanate, and a second layer which includes amoxycillin and/or clavulanate. The overall tablet contains amoxycillin and the relative rate of release of amoxycillin and/or clavulanate from the first and second layers differs. The tablet formulations of the invention provide sustained release of amoxycillin and optionally also clavulanate.

BILAYERED AMOXICILLIN TABLETS

This invention relates to novel tablet formulations for oral administration of amoxycillin optionally together with clavulanic acid.

Amoxycillin and clavulanic acid are respectively a known β-lactam antibiotic and a known β-lactamase inhibitor. Their use together in antibiotic formulations is disclosed in for example GB 2005538, which discloses formulations comprising amoxycillin trihydrate and potassium clavulanate. In oral formulations amoxycillin is generally used in the form of its trihydrate, and clavulanic acid is generally used in the form of a pharmaceutically acceptable salt (hereinafter "clavulanate") in particular potassium clavulanate.

It is desirable to provide oral pharmaceutical formulations which release their active material content at a controlled rate after oral administration, so that for example release of the active material into the stomach or intestine occurs over a period of several hours after ingestion of the formulation. This can allow unit doses of the formulation to be taken at widely separated intervals, for example twice daily, whilst maintaining a therapeutically effective plasma level of the active material content, such as amoxycillin and clavulanate.

Among various ways of achieving a controlled rate of release are layered tablets. For example GB 1346609 discloses three layer tablets having two drug-containing layers located one on each side of an inert disintegrable intermediate layer. The only drug substance mentioned in GB 1346609 is Mepyrizole. US 4122157 discloses a controlled release nitrofurantoin tablet which comprises two adjacent layers, one being a rapid release layer, the other being a slow release layer. US 4,839,177 discloses controlled release tablets comprising a deposit-core containing an active drug substance, with a support platform applied to this deposit core.

Particular problems are encountered with making controlled-release formulations which include clavulanate in combination with antibiotics such as amoxycillin. Amoxycillin trihydrate and clavulanate differ substantially in their solubility in water. Potassium clavulanate is very water soluble and amoxycillin trihydrate is relatively insoluble, so it is difficult to avoid rapid leaching out of potassium clavulanate from formulations containing these two in admixture. Also clavulanate is relatively sensitive to hydrolysis, so degradation of clavulanate may occur on contact with aqueous gastrointestinal contents during the relatively long periods between oral administration of controlled-release formulations.

According to this invention a tablet formulation for oral administration comprises a first layer which includes amoxycillin and/or clavulanate, and a second

layer which includes amoxycillin and/or clavulanate, provided that the overall tablet contains amoxycillin, wherein the relative rate of release of amoxycillin and/or clavulanate from the first and second layers differs.

Amoxycillin may suitably be used in the form of amoxycillin trihydrate, and clavulanate may be used in the form of potassium clavulanate. The tablet formulation may contain other antibacterial agents in addition to amoxycillin and clavulanate. Amoxycillin, clavulanate and any such other antibacterial agents which may be present are herein singly and collectively referred to as "active material content" unless otherwise specifically identified.

Tablet formulations of this invention may provide extended plasma levels of their active material content, for example of amoxycillin and clavulanate after ingestion.

When the formulation of the invention contains amoxycillin and clavulanate the overall weight ratio of amoxycillin : clavulanate (expressed as the free acid equivalent) may vary between broad limits, for example between 30 : 1 to 1 : 1. Suitably the ratio may be between 8 : 1 to 1 : 1, for example between 7 : 1 to 1 : 1, typically around 4 : 1, eg between 3.5 : 1 and 4.5 : 1. When both of the layers comprise amoxycillin and clavulanate the amoxycillin : clavulanate ratio in each layer may be the same as the overall tablet ratio or there may be different ratios in each of the layers, making up the ratio in the overall tablet. For example one layer may contain amoxycillin without clavulanate and the other layer may contain amoxycillin plus clavulanate, making up the ratio in the overall tablet. For example one layer may contain clavulanate without amoxycillin and the other layer may contain amoxycillin plus clavulanate, making up the ratio in the overall tablet. For example one layer may contain amoxycillin without clavulanate and the other layer may contain clavulanate without amoxycillin, making up the ratio in the overall tablet.

Suitably the tablet formulations of the invention may contain up to the maximum permitted daily dose of amoxycillin and clavulanate per unit dose. The formulations may for example contain nominally around 875 mg of amoxycillin and around 250 mg of clavulanate. Suitably unit dose tablets of the invention may contain the following nominal weights (mg) of amoxycillin: clavulanate (expressed as free acid equivalent); 875 : 125, 500 : 250, 500 : 125; 250 : 125 and 250 : 62.5.

The differing relative rate of release of active material content from the first and second layers of the tablet may be achieved in various ways.

For example differing rates of release may be achieved by a first layer which is a rapid release layer, ie which releases the bulk of its active material content within a relatively short time, for example within 1 hour, eg within 30 minutes after

oral injestion, and a second layer which is a slow release layer, ie which releases the bulk of its active material content during a relatively long period after oral ingestion or is a delayed release layer which releases the bulk of its active material content after a period of delay after oral ingestion, either in the stomach or in the intestine.

Rapid release layers may for example be rapid disintegrating layers having a composition similar to that of known rapid-disintegrating tablets. For example, the composition may comprise principally active material content, binders such as plasdone K29-32 (trade mark), compression aids, fillers or diluents such as mannitol, microcrystalline cellulose, and silicon dioxide, eg Syloid (trade mark), disintegrants, eg Explotab (trade mark), Avicel (trade mark) lubricants such as talc, magnesium stearate etc. Suitably such a rapid release layer may comprise around 30 - 70 % (all percentages given herein are on a weight percentage basis unless otherwise stated) eg 50-60% of active material content, around 10 - 30% of fillers/compression aids, and conventional amounts of disintegrants and lubricants etc.

An alternative type of rapid-release layer may be a swellable layer having a composition which incorporates polymeric materials which swell rapidly and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass. Active material content may be rapidly leached out of this mass.

Slow release layers may have a composition which comprises active material content together with a release retarding material. Suitable release retarding materials include pH sensitive polymers, e.g. the known Eudragit (trade mark) polymers, for example Eudragit L (trade mark), i.e polymers based upon methacrylic acid copolymers, used either alone or with a plasticiser, release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents, polymeric materials which form a gel on contact with water or aqueous media, and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

Polymers which have a high degree of swelling include, inter alia, cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene co-polymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols etc. Gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone etc. Polymers

combined in various ways to form embodiments of tablet formulations of the present invention, as described below.

One embodiment comprises a tablet having a rapid disintegrating first layer which contains amoxycillin and/or clavulanate as active material, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release-retarding polymers such as Methocel E5, E50, E4M, K4M, K15M and K100M and mixtures thereof, with a barrier layer of either a substantially completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers, the overall tablet containing amoxycillin or amoxycillin plus clavulanate. Suitably the rapid disintegrating and slow release layers may both contain only amoxycillin as active material, or the rapid disintegrating and slow release layers may both contain amoxycillin plus clavulanate, or only the rapid disintegrating layer may contain clavulanate and the slow release layer may contain only amoxycillin as active material content.

Typically the first layer in such a tablet contains around 20-35%, eg around 25-30% of the overall tablet active material content. Suitably the first layer comprises 15-35%, the second layer comprises 50-70%, and the barrier layer comprises 5 - 30% of the overall tablet weight.

A further embodiment comprises a tablet having a rapid-disintegrating first layer which contains amoxycillin and/or clavulanate as active material, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers such as Methocel E5, E50, E4M, K4M, K15M or K100M or mixtures thereof, but without a barrier layer, the overall tablet (en conjunto) containing amoxycillin or amoxycillin plus clavulanate. Suitably the first layer in such a tablet contains some 20 - 35%, eg 25 - 30% of the overall (en conjunto) active material content.

A further embodiment comprises a slow-release first layer which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a second layer which is also a slow-release layer and which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers, the overall tablet containing amoxycillin or amoxycillin plus clavulanate.

Suitably in this embodiment the first layer may contain amoxycillin without clavulanate and the second layer may contain amoxycillin plus clavulanate, or the first and second layers may both contain amoxycillin plus clavulanate, or the first layer may contain amoxycillin without clavulanate and the second layer may contain clavulanate without amoxycillin. Suitable release-retarding polymers include

containing polymers which rapidly swell in contact with water or aqueous media so that the swollen mass is not rapidly discharged from the stomach containing amoxycillin or amoxycillin plus clavulanate as active material, and a second layer which is a slow release layer containing amoxycillin or amoxycillin plus clavulanate as active material, with a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers. The tablet of this embodiment may optionally be surrounded by a coating layer which is a rapidly disintegrating composition containing amoxycillin and clavulanate as active material.

A further embodiment is a tablet comprising three layers tablet in which all the three layers include an active material content. Suitably such a tablet may comprise a slow-or delayed-release first layer which comprises amoxycillin, optionally together with clavulanate, a rapid-release second layer which comprises amoxycillin, optionally together with clavulanate, and a third layer, sandwiched between the first and second layers, and being a slow- or delayed-release layer comprising calvulanate, optionally together with amoxycillin. Suitably in such a tablet the first layer may include amoxycillin without clavulanate, the second layer may comprise a mixture of amoxycillin plus clavulanate, and the third layer may comprise clavulanate or a mixture of clavulanate and amoxycillin. The first layer may suitably comprise amoxycillin and a release-retarding polymer such as Methocel E5 (trade mark) optionally together with a swellable material, the second layer may comprise a mixture of amoxycillin and clavulanate together with conventional fillers, binders, disintegrants etc, and the third, intermediate layer may comprise amoxycillin, clavulanate and a release retarding polymer such as Methocel K100M.

Each of the above-mentioned embodiments of the invention may be coated with a polymer layer, for example an enteric polymer such as the Eudragit (trade mark) polymers mentioned above, or a coating layer which contains active material content, such as a rapid-release layer which includes amoxycillin and/or clavulanate.

Suitably the tablet formulations of the invention may be formed by known compression tabletting techniques for example using a known multi-layer tabletting press. Suitably a dry densification process may be used, e.g. briquetting. Typically the active material content, pH modifiers, buffers, fillers and/or diluent, release retarding agents, disintegrants and binders, when used are mixed, then lubricants and compression aids are added. The complete mixture may then be compressed under high pressure in the tablet press. Roller compaction may be used to form granulates for compaction. Alternatively wet granulation may be used,

The test was performed according to USP XXXII <724>, apparatus 4.

Dissolution apparatus:

Dissolution apparatus:	SOTAX CE6 flow cell
	SOTAX CY7-50 pump

Test specifications:

Temperature:	37.0 ± 0.5°C
Test medium:	0 - 2h: HCl 0.01 M (pH 2.0)
	2 - 8h: phosphate buffer 0,05 M; pH = 6.6
Flow rate:	8.3 ml/min (500 ml/h)
Flow cell:	22.6 mm diameter

Solutions:

- 0.05 M phosphate buffer solution 3 (pH 6.6): Dissolve 544g potassium dihydrogenphosphate in 20.0L water and adjust to pH 6.6 with NaOH 40% (m/v).

- 0.05 M phosphate buffer solution 4 (pH 6.6): Dissolve 408g potassium dihydrogenphosphate and 39g sodium hydroxide pellets p.a. in 60L water.

Method:

Three tablets were tested each as follows. A 5 mm diameter ruby bead was placed at the bottom of the cone of the flow cell and the cone was filled with 1 mm diameter glass beads. A tablet was introduced into the cell and fixed vertically using a holder. The filter head was assembled and the parts fixed together by means of a clamping device. The dissolution medium warmed to 37.0 ± 0.5°C was introduced through the bottom of the cell at a flow rate of 8.3 ml/min. 0.01 M HCl from the beginning to 2 hours was used, then changed to buffer solution 4 until the end of the run.

The drug release after 30 min, 60 min 2 h 3 h, 4 h, 5 h, 6 h, 7 h and 8 h was determined.

As Potassium Clavulanate is very unstable at low pH values, the fractions for the time from 0 to 2 hours (medium 0.01 M HCL) were collected directly in a buffer solution and were mixed well with this buffer in a ratio of about 1:1.

Example 1

Tablets 1.1, 1.2 and 1.3, each having a structure as shown in Fig 1B were prepared using an oval biconvex punch 21 x 10 mm, having a rapid-disintegrating first layer and a slow-release second layer, with a barrier layer between. The composition of these tablets is as follows:

Example 2

Tablets 2.1 and 2.2 each having a structure as shown in Fig. 1B were prepared using an oval biconvex punch 21 x 10mm, having a first layer which is a rapid disintegrating layer, a second layer which is a slow-release layer, and a barrier layer sandwiched between them. These tablets had the following composition:

	Amounts in mg	
First Layer	**2.1**	**2.2**
AMX.$3H_2O$	118.7	118.7
(= AMX f.a.)	(102.6)	(102.6)
AMX.$3H_2O$: KCA 1:1*	83.4	83.4
(= AMX f.a.)	(35.1)	(35.1)
(= CA f.a.)	(36.3)	(36.3)
Avicel PH 102	45.1	45.1
Explotab	11.4	11.4
Talc	22.4	22.4
Mg-Stearate	8.4	8.4
Syloid 244	5.6	5.6
weight of layer	295.0	295.0
Barrier Layer	L1	L1
weight of layer	160.0	160.0
Second Layer		
AMX.$3H_2O$	305.27	305.27
(= AMX f.a.)	(263.75)	(263.75)
AMX.$3H_2O$: KCA 1:1*	214.40	214.40
(= AMX f.a.)	(90.26)	(90.26)
(= CA f.a.)	(93.26)	(93.26)
Methocel K4M	62.00	62.00
Methocel E5	62.00	62.00
Mannitol	46.00	-
KH_2PO_4	-	46.00

Polyvidon K30	10.03	10.03
Talc	5.00	5.00
Mg-Stearate	20.30	20.30
weight of layer	725.00	725.00

Total tablet weight	**1180.00**	**1180.00**
Total content AMX f.a.	491.7	491.7
Total content CA f.a.	129.6	129.6

* **Note:** Potassium clavulanate was used in the form of a commercially available 1 : 1 mixture of potassium clavulanate and amoxycillin trihydrate.

Example 3

Tablets 3.1 and 3.2 each having a structure as shown in Fig 1C were prepared, using respectively oval biconvex punch 18 x 8 mm and 21 x 10 mm, having a first layer which is a slow release layer, a second layer which is also a slow release layer and a barrier layer located on the end face of the second layer. These tablets had the following composition:

	Amounts in mg	
First Layer	**3.1**	**3.2**
AMX.$3H_2O$	305.27	327.52
(= AMX f.a.)	(263.75)	(282.98)
Methocel K4M	53.18	57.06
Methocel E5	53.18	57.06
Mannitol	53.18	57.06
Polyvidon K30	18.03	19.34
Talc	5.31	5.70
Mg-Stearate	5.85	6.26
weight of layer	494.00	530.00

	Amounts in mg		
	1.1	**1.2**	**1.3**
First Layer			
$AMX.3H_2O$	160.7	160.7	160.7
(= AMX f.a.)	(138.8)	(138.8)	(138.8)
Avicel PH 102	44.8	44.8	44.8
Explotab	11.2	11.2	11.2
Talc	22.3	22.3	22.3
Mg-Stearate	8.4	8.4	8.4
Syloid 244	5.6	5.6	5.6
weight of layer	253.0	253.0	253.0
Barrier Layer	L1	L1	S2
weight of layer	180.0	180.0	180.0
Second Layer			
$AMX.3H_2O$	413.3	413.3	413.3
(= AMX f.a.)	(357.1)	(357.1)	(357.1)
Methocel K4M	72.0	72.0	72.0
Methocel E5	72.0	72.0	72.0
Mannitol	72.0	26.0	72.0
KH_2PO_4	-	46.0	-
Polyvidon K30	28.6	28.6	28.6
Talc	7.2	7.2	7.2
Mg-Stearate	2.9	2.9	2.9
weight of layer	668.0	668.0	668.0
Total tablet weight	**1101.0**	**1101.0**	**1101.0**
Total content AMX f.a.	495.9	495.9	495.9

Second Layer 9.2	9.1	
AMX.3H$_2$O/K-CA 1:1	215.52	Barrier L1
(= AMX f.a.)	(90.73)	
(= CA f.a.)	(93.75)	
Methocel K4M	74.96	
Eudragit L*	56.22	
Dibutylphthalate*	5.62	
Polyvidon K30	13.12	
Talc	4.87	
Mg-Stearate	4.50	
weight of layer3	374.81	
Total tablet weight	1069.01	1069.01

* In these tablets the Eudragit L and plasticiser were coated directly onto the active material content by repeated steps of wet granulation. Two further examples of tablets (9.3 and 9.4) were prepared to the formula for 9.1 and 9.2 by first preparing a granulate of amoxycillin plus potassium clavulanate plus Methocel K4M, then coating the granulate with the Eudragit L.

Example 10

Tablets 10.1 and 10.2 having a structure as shown in Fig. 1C were prepared

	Amounts in mg	
First Layer	**10.1**	**10.2**
AMX.3H$_2$O	438.68	438.68
(= AMX f.a.)	(379.0)	(379.0)
Methocel E5	53.00	53.00
Mannitol	6.52	6.52
Polyvidon K30	18.55	18.55
Talc	6.89	6.89
Mg-Stearate	6.36	6.36
weight of first layer 1	530.00	530.00

Claims:

1. A tablet formulation for oral administration, comprising a first layer which includes amoxycillin and/or clavulanate, and a second layer which includes amoxycillin and/or clavulanate, provided that the overall tablet contains amoxycillin, wherein the relative rate of release of amoxycillin and/or clavulanate from the first and second layers differs.

2. A tablet formulation according to claim 1 wherein the amoxycillin is in the form of amoxycillin trihydrate, and clavulanate is in the form of potassium clavulanate.

3. A tablet formulation according to claim 1 or 2 wherein one layer contains amoxycillin without clavulanate and the other layer contains amoxycillin plus clavulanate, making up the ratio in the overall tablet.

4. A tablet formulation according to claim 1 or 2 wherein one layer contains clavulanate without amoxycillin and the other layer contains amoxycillin plus clavulanate, making up the ratio in the overall tablet.

5. A tablet formulation according to claim 1 or 2 wherein one layer contains amoxycillin without clavulanate and the other layer contains clavulanate without amoxycillin, making up the ratio in the overall tablet.

6. A tablet formulation according to any one of the preceding claims wherein differing rates of release are achieved by a first layer which is a rapid release layer which releases the bulk of its active material content within a relatively short time, and a second layer which is a slow release layer which releases the bulk of its active material content during a relatively long period after oral ingestion or a delayed release layer which releases the bulk of its active material content after a period of delay after oral ingestion, either in the stomach or in the intestine.

7. A tablet formulation according to claim 6 wherein the rapid release layer is a rapid disintegrating layer.

8. A tablet formulation according to claim 6 wherein the rapid-release layer is a

swellable layer having a composition which incorporates polymeric materials which swell rapidly and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass.

9. A tablet formulation according to any one of the preceding claims wherein the slow release layer has a composition which comprises active material content together with a release retarding material.

10. A tablet formulation according to claim 9 wherein the release retarding material is selected from pH sensitive polymers, release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents, polymeric materials which form a gel on contact with water or aqueous media, and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

11. A tablet formulation according to claim 9 wherein the slow release layer contains polymers which rapidly swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not rapidly discharged from the stomach into the intestine.

12. A tablet formulation according to claim 9 wherein the slow- or delayed-release layer is a layer in which the active material content is mixed with, coated with, or embedded in a matrix of a poorly soluble or practically insoluble excipient, and/or a hydrophobic excipient.

13. A tablet formulation according to claim 9 wherein the delayed release layer uses the known properties of enteric polymers to delay release of active material content until the whole or part of the tablet is discharged by the stomach into the intestine after oral ingestion.

14. A tablet formulation according to any one of the preceding claims wherein differing rates of release are achieved by having a first layer which is a slow or delayed release layer, and a second layer which is also a slow or delayed release layer.

15. A tablet formulation according to claim 14 wherein one or both of the first

and second layers are slow release layers comprising active material together with release retarding materials.

16. A tablet formulation according to claim 14 wherein one or both of the first or second layers is a delayed release layer using enteric polymers.

17. A tablet formulation according to any one of the preceding claims wherein the tablet includes one or more barrier layers.

18. A tablet formulation according to claim 17 wherein the barrier layer is located between the respective first and second layers, and/or on one or more of the outer surfaces of the first and second layers.

19. A tablet formulation according to claim 17 or 18 wherein the barrier layer(s) is/are composed of polymers which are either substantially or completely impermeable to water or aqueous media, or are slowly erodable in water or aqueous media or biological liquids and/or which swell in contact with water or aqueous media.

20. A tablet formulation according to any one of the preceding claims wherein the tablet is wholly or partly covered by a coating layer.

21. A tablet formulation according to any one of the preceding claims which comprises a tablet having a rapid disintegrating first layer which contains amoxycillin and/or clavulanate as active material, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release-retarding polymers, with a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers, the overall tablet containing amoxycillin or amoxycillin plus clavulanate.

22. A tablet formulation according to any one of claims 1 - 20 which comprises a tablet having a rapid-disintegrating first layer which contains amoxycillin and/or clavulanate as active material, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, but without a barrier layer, the overall tablet containing

amoxycillin or amoxycillin plus clavulanate.

23. A tablet formulation according to any one of claims 1-20 which comprises a slow-release first layer which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a second layer which is also a slow-release layer and which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers, the overall tablet containing amoxycillin or amoxycillin plus clavulanate.

24. A tablet formulation according to any one of claims 1-20 which comprises a slow-release first layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a barrier layer of either a completely impermeable polymer or a slowly erodable polymer located on one of the end faces of the tablet.

25. A tablet formulation according to any one of claims 1-20 which comprises a rapid release first layer which is a swellable layer containing amoxycillin, and a slow-release or delayed release second layer as described above containing amoxycillin, or clavulanate, or amoxycillin plus clavulanate, having a barrier layer of either a substantially or completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers.

26. A tablet formulation according to any one of claims 1-20 which comprises a slow-release first layer comprising amoxycillin optionally together with clavulanate as active material, and a second layer which is a delayed release layer comprising a disintegrable or soluble matrix within which are dispersed enteric polymer coated granules which comprise clavulanate, optionally together with amoxycillin, with a barrier layer sandwiched between the first and second layers.

27. A tablet formulation according to any one of claims 1-20 which comprises a first layer which is a slow release layer containing polymers which rapidly swell in contact with water or aqueous media so that the swollen mass is not rapidly

amoxycillin or amoxycillin plus clavulanate.

23. A tablet formulation according to any one of claims 1-20 which comprises a slow-release first layer which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a second layer which is also a slow-release layer and which contains amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers, the overall tablet containing amoxycillin or amoxycillin plus clavulanate.

24. A tablet formulation according to any one of claims 1-20 which comprises a slow-release first layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a slow-release second layer which comprises amoxycillin and/or clavulanate as active material together with one or more release retarding polymers, and a barrier layer of either a completely impermeable polymer or a slowly erodable polymer located on one of the end faces of the tablet.

25. A tablet formulation according to any one of claims 1-20 which comprises a rapid release first layer which is a swellable layer containing amoxycillin, and a slow-release or delayed release second layer as described above containing amoxycillin, or clavulanate, or amoxycillin plus clavulanate, having a barrier layer of either a substantially or completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers.

26. A tablet formulation according to any one of claims 1-20 which comprises a slow-release first layer comprising amoxycillin optionally together with clavulanate as active material, and a second layer which is a delayed release layer comprising a disintegrable or soluble matrix within which are dispersed enteric polymer coated granules which comprise clavulanate, optionally together with amoxycillin, with a barrier layer sandwiched between the first and second layers.

27. A tablet formulation according to any one of claims 1-20 which comprises a first layer which is a slow release layer containing polymers which rapidly swell in contact with water or aqueous media so that the swollen mass is not rapidly

discharged from the stomach containing amoxycillin or amoxycillin plus clavulanate as active material, and a second layer which is a slow release layer containing amoxycillin or amoxycillin plus clavulanate as active material, with a barrier layer of either a completely impermeable polymer or a slowly erodable polymer sandwiched between the first and second layers.

28. A tablet formulation according to any one of claims 1-20 which comprises a three-layer tablet in which all three of the layers include an active material content.

29. A tablet formulation according to claim 28 which comprises a slow-or delayed-release first layer which comprises amoxycillin, optionally together with clavulanate, a rapid-release second layer which comprises amoxycillin, optionally together with clavulanate, and a third layer, sandwiched between the first and second layers, and being a slow- or delayed-release layer comprising calvulanate, optionally together with amoxycillin.

30. A method for the manufacture of a tablet formulation according to any one of the preceding claims comprising the steps of forming said first and second layers, and any barrier layers and coating layer(s) which may be present.

31. A tablet formulation according to any one of claims 1-29 for use as a therapeutic substance for oral administration for the treatment of bacterial infections.

32. A method of use of a formulation as claimed in any one of claims 1-29, in the manufacture of a medicament for the treatment of bacterial infections.

33. A method of treatment of bacterial infections in humans or animals which comprises the administration thereto of a therapeutically effective amount of active material content included in a formulation as claimed in any one of claims 1-29.

34. A tablet formulation according to any one of claims 1-29 substantially as hereinbefore described with reference to the accompanying drawings.

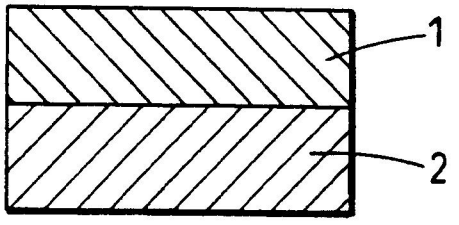


Fig. 1A

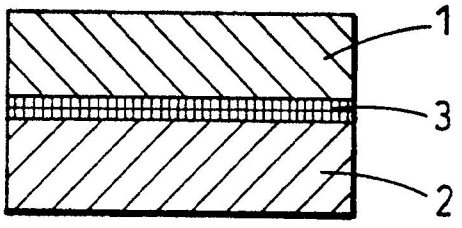


Fig. 1B

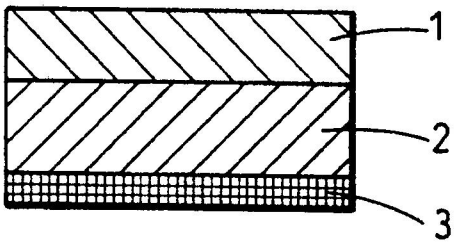


Fig. 1C

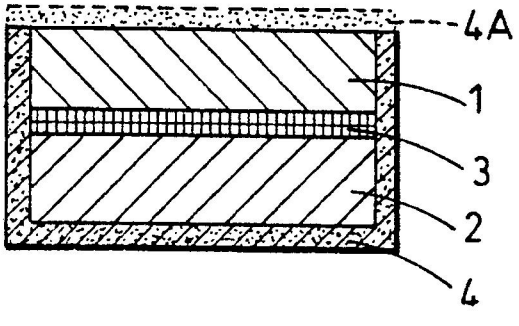


Fig. 1D

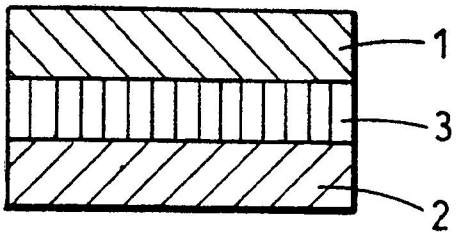


Fig. 1E

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(54) Title: PHARMACEUTICAL TABLET CAPABLE OF LIBERATING ONE OR MORE DRUGS AT DIFFERENT RELEASE RATES

(57) Abstract

Pharmaceutical tablet consisting of a first layer containing one or more drugs with immediate or controlled release formulation, a second layer containing one or more drugs, either equal to or different from the first layer, with slow release formulation, and a low-permeability barrier-type layer coating said second layer or, alternatively, placed between the first and second layer and, if necessary, containing a drug.

CLAIMS

1. Pharmaceutical compressed tablet capable of releasing one or more drugs at different rates, consisting of three layers, wherein

- a first layer contains one or more drugs with immediate or controlled release formulation, composed of rapidly swelling and/or soluble and/or erodible polymeric substances by contact with aqueous fluids, and adjuvants;
- a second layer contains one or more drugs, either equal to or different from those of the first layer, with slow release formulation, composed of swelling and/or gelable and/or erodible polymeric substances by contact with aqueous fluids, and adjuvants;
- a low-permeability barrier-type layer coating said second layer or, alternatively, placed between the first and second layer, consisting of (polymeric substances, adjuvants, plasticizing agents and, if necessary, a drug.)

2. The compressed tablet according to claim 1, wherein said polymeric substances of said first layer are selected from the group consisting of cross-linked polyvinylpyrrolidone, low- and medium-molecular-weight hydroxypropyl cellulose and hydroxypropyl methylcellulose, cross-linked sodium carboxymethylcellulose, carboxymethyl starch, potassium methacrylate-divinylbenzene copolymer, polyvinyl alcohols, starches, starch derivatives, microcrystalline cellulose and

cellulose derivatives, β-cyclodextrin and dextrin derivatives.

3. The compressed tablet according to claim 1, wherein said polymeric substances of said first layer equal 1.0 to 90% by wt. of said layer.

4. The compressed tablet according to claim 1, wherein said adjuvants of said first layer are selected from the group consisting of starch, pregelled starch, calcium phosphate, mannitol, lactose, saccharose, glucose, sorbitol, microcrystalline cellulose, gelatin, polyvinylpyrrolidone, methylcellulose, starch solution, ethylcellulose, arabic gum, tragacanth gum, magnesium stearate, stearic acid, colloidal silica, glyceryl monostearate, hydrogenated castor oil, waxes, and mono-, bi-, and trisubstituted glycerides.

5. The compressed tablet according to claim 1, wherein said polymeric substances of said second layer are selected from the group consisting of hydroxypropyl methylcellulose having molecular weight from 1,000 to 4,000,000, hydroxypropyl cellulose having molecular weight from 2,000 to 2,000,000, carboxyvinyl polymers, polyvinyl alcohols, glucans, scleroglucans, mannans, xanthans, alginic acid and derivatives thereof, carboxymethylcellulose and derivatives thereof, poly(methyl vinyl ethers/maleic anhydride), ethylcellulose, methylcellulose, and cellulose derivatives.

6. The compressed tablet according to claim 1, wherein said polymeric substances of said second layer equal 5 to 90% by wt. of said layer.

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2005-05-05

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Abril 12 de 2005

Doctor
GERMÁN CASTILLO GRAU

ASUNTO	Radicación No.	00 026 419
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	[illegible]
	Folios	0

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 4 - 64 y el nuevo capítulo reivindicatorio de los folios 229 - 236 de la solicitud en estudio.

2. Objeto de la Invención

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

Las reivindicaciones 1 a 58 se refieren a formulaciones en forma de tabletas que incluyen amoxicilina y clavulanato de potasio. Algunas son de liberación inmediata, otras de liberación modificada y otras tienen las dos capas: de liberación inmediata y de liberación lenta. El polímero de liberación retardada es metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP) ó goma xantan.

El problema planteado en esta solicitud es la necesidad de proporcionar un método para tratar infecciones bacterianas del tracto respiratorio.

Para resolver este problema técnico la solicitud en estudio proporciona formulaciones en forma de tabletas que incluyen amoxicilina y clavulanato de potasio. Algunas son de liberación inmediata, otras de liberación modificada y otras tienen las dos capas: de liberación inmediata y de liberación lenta.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/43 // 31/42.

También se reivindica prioridad de las Solicitudes de Patente de los Estados Unidos US 60 129 074 de abril 13 de 1999, US 60 150 727 de agosto 25 de 1999, US 60 159 813 de octubre 15 de 1999 con respecto a las cuales la fecha

de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Claridad de las reivindicaciones

Con referencia las reivindicaciones 3 - 5, 9, 18, 57 se aclara que las reivindicaciones deben definir la invención por sus características esenciales, estructurales o funcionales. No se admite que la reivindicación defina la invención por el resultado a alcanzar (del tipo: "cuya administración proporciona una concentración media..."), puesto que en realidad equivaldría a definir el problema técnico a resolver y el alcance de la reivindicación incluiría no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. El resultado a alcanzar no es una característica técnica de la invención. Hacer la corrección.

Con referencia la reivindicación 55 se observa que se define un producto por un procedimiento que no está reivindicado. Se aclara que las reivindicaciones de productos definidas en términos de un proceso de fabricación son admisibles solamente si los productos como tales cumplen los requisitos de patentabilidad, es decir, cuando entre otras cosas son nuevos e inventivos, y cuando no se pueden definir por sus características estructurales. Un producto no se convierte en nuevo simplemente por el hecho de que se produce mediante un procedimiento nuevo. Hacer la corrección.

Con referencia a la reivindicación 58 se observa que no es clara porque menciona una formulación pero esta no está definida, tal como se solicitó en el primer examen de forma, porque se pretenden proteger todas las nuevas formulaciones alternativas presentes o futuras que lleguen a ser equivalentes. Hacer la corrección.

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 publico 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 articulo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es abril 13 de 1999, 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	WO 95 28148	Formulación farmacéutica	Oct 26, 1995
D2	WO 95 20946	Tabletas de amoxicilina con dos capas	Ag 10, 1995

D3	WO 94 06416	Tabletas farmacéuticas capaces de liberar una o más drogas a diferentes velocidades de liberación	Mar 31, 1994

4. 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.

Evaluación de la Novedad

El Art. 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "*Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. 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 Art 40".

Las reivindicaciones 1 a 58 se refieren a formulaciones en forma de tabletas que incluyen amoxicilina y clavulanato de potasio. Algunas son de liberación inmediata, otras de liberación modificada y otras tienen las dos capas: de liberación inmediata y de liberación lenta. El polímero de liberación retardada es metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP) ó goma xantan.

D1 enseña una formulación de tableta que comprende un núcleo que contiene un compuesto activo recubierto con una cubierta de liberación retardada, rodeada de una capa exterior que contiene otro compuesto activo. La reivindicación 5 enseña una tableta en la cual todo el clavulanato está contenido en la capa exterior. La amoxicilina puede estar en el núcleo o en la cubierta. Enseña proporciones (amoxicilina:clavulanato) que varían dentro de límites tan amplios como 30:1 - 1:1.

D2 enseña un tabletas preparadas por granulación de una mezcla que comprende el compuesto activo, modificadores de pH, buffers, diluyentes, agentes de liberación retardada, desintegrantes y aglutinantes. Enseña polímeros de liberación retardada como metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico

(PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP).

D3 enseña tabletas farmacéuticas capaces de liberar una o más drogas a diferentes velocidades de liberación. Las tabletas tienen una capa que contiene una o más drogas con formulación de liberación inmediata o controlada y otra capa, igual o diferente que la primera capa, que contiene una formulación de liberación controlada, y una capa de cubierta tipo barrera de baja permeabilidad que recubre la segunda capa ó esta colocada entre las primera y la segunda capa, y si es necesario, contiene una droga. Enseña polímeros de liberación retardada como metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP), goma xantan.

Se observa que las formulaciones en forma de tabletas que incluyen amoxicilina y clavulanato de potasio, algunas de liberación inmediata, otras de liberación modificada y otras tienen las dos capas: de liberación inmediata y de liberación lenta, donde el polímero de liberación retardada es metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP) ó goma xantan, de las reivindicaciones 1 a 58, ya habían sido enseñadas en D1, D2 y D3. De manera que no se pueden considerar nuevas.

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.*

Las reivindicaciones 1 a 58 se refieren a formulaciones en forma de tabletas que incluyen amoxicilina y clavulanato de potasio. Algunas son de liberación inmediata, otras de liberación modificada y otras tienen las dos capas: de liberación inmediata y de liberación lenta. El polímero de liberación retardada es metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP) ó goma xantan.

D1 enseña una formulación de tableta que comprende un núcleo que contiene un compuesto activo recubierto con una cubierta de liberación retardada, rodeada de una capa exterior que contiene otro compuesto activo. La reivindicación 5 enseña una tableta en la cual todo el clavulanato está contenido en la capa exterior. La amoxicilina puede estar en el núcleo o en la cubierta. Enseña proporciones (amoxicilina:clavulanato) que varían dentro de límites tan amplios como 30:1 - 1:1.

D2 enseña tabletas preparadas por granulación de una mezcla que comprende el compuesto activo, modificadores de pH, buffers, diluyentes, agentes de liberación retardada, desintegrantes y aglutinantes. Enseña polímeros de liberación retardada como metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP).

D3 enseña tabletas farmacéuticas capaces de liberar una o más drogas a diferentes velocidades de liberación. Las tabletas tienen una capa que

contiene una o más drogas con formulación de liberación inmediata o controlada y otra capa, igual o diferente que la primera capa, que contiene una formulación de liberación controlada, y una capa de cubierta tipo barrera de baja permeabilidad que recubre la segunda capa ó esta colocada entre las primera y la segunda capa, y si es necesario, contiene una droga. Enseña polímeros de liberación retardada como metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP), goma xantan.

~~, de las reivindicaciones 1 a 58,~~

Se observa que a partir de la combinación de las enseñanzas de estas anterioridades: D1 que enseña una formulación de tableta que comprende un núcleo que contiene un compuesto activo recubierto con una cubierta de liberación retardada, rodeada de una capa exterior que contiene otro compuesto activo. La reivindicación 5 enseña una tableta en la cual todo el clavulanato está contenido en la capa exterior. La amoxicilina puede estar en el núcleo o en la cubierta. Enseña proporciones (amoxicilina:clavulanato) que varían dentro de límites tan amplios como 30:1 - 1:1, D2 que enseña tabletas preparadas por granulación de una mezcla que comprende el compuesto activo, modificadores de pH, buffers, diluyentes, agentes de liberación retardada, desintegrantes y aglutinantes. Enseña polímeros de liberación retardada como metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP), D3 que enseña tabletas farmacéuticas capaces de liberar una o más drogas a diferentes velocidades de liberación. Las tabletas tienen una capa que contiene una o más drogas con formulación de liberación inmediata o controlada y otra capa, igual o diferente que la primera capa, que contiene una formulación de liberación controlada, y una capa de cubierta tipo barrera de baja permeabilidad que recubre la segunda capa ó esta colocada entre las primera y la segunda capa, y si es necesario, contiene una droga. Enseña polímeros de liberación retardada como metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP), goma xantan; se sugieren las formulaciones en forma de tabletas que incluyen amoxicilina y clavulanato de potasio, algunas de liberación inmediata, otras de liberación modificada y otras tienen las dos capas: de liberación inmediata y de liberación lenta, donde el polímero de liberación retardada es metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP) ó goma xantan, que son objeto de esta solicitud. Las reivindicaciones 1-58 no mencionan una característica que conceda un efecto diferente o especial a las formulaciones, así que estas son obvias y evidentes para una persona versada en la materia. Entonces debido a que: (a) la conformación de las formulaciones de esta solicitud, a partir de las anterioridades, es evidente para una persona conocedora de la materia; porque siendo bien conocidas las formulaciones en forma de tabletas que incluyen amoxicilina y clavulanato de potasio, de liberación inmediata, de liberación modificada y las de dos capas: de liberación inmediata y de liberación lenta (donde el polímero de liberación retardada es metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP) ó goma xantan), para una persona conocedora de la materia era evidente el elaborar las composiciones de esta solicitud de manera similar, teniendo en cuenta estos compuestos; (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a las

formulaciones, que pueda considerarse como un aporte a la técnica, porque las anterioridades ya enseñaban formulaciones en forma de tabletas que incluyen amoxicilina y clavulanato de potasio, de liberación inmediata, de liberación modificada y las de dos capas: de liberación inmediata y de liberación lenta (donde el polímero de liberación retardada es metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP) ó goma xantan) requeridas por estas, así que estas son obvias para una persona versada en la materia y (c) el problema planteado en esta solicitud era la necesidad de proporcionar un método para tratar infecciones bacterianas del tracto respiratorio y puesto que para resolver este problema técnico la solicitud proporciona formulaciones en forma de tabletas que incluyen amoxicilina y clavulanato de potasio, de liberación inmediata, de liberación modificada y las de dos capas: de liberación inmediata y de liberación lenta (donde el polímero de liberación retardada es metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP) ó goma xantan), es decir de manera similar a como se resolvía en las anterioridades D1, D2 y D3; entonces esta solicitud no tiene **nivel inventivo**.

5. Conclusión

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

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 95 28148	1 a 58	Novedad y nivel inventivo
D2	WO 95 20946	1 a 58	Novedad y nivel inventivo
D3	WO 94 06416	1 a 58	Novedad y 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 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 05 MAYO 2005

CONCEPTO TÉCNICO No. 509	EXAMINADOR TÉCNICO Código 202007