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SUPERINTENDENCIA DE INDUST
Bogotá, D.C.

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Patente de Invención:
TABLETAS DE LIBERACIÓN MODIFICADA QUE INCLUYEN AMOXICILINA Y CLAVULANATO DE POTASIO
RECURSO DE REPOSICIÓN

En relación con el expediente de la referencia y actuando como apoderado de la sociedad BEECHAM PHARMACEUTICALS (PTE) LIMITED, legalmente constituida y domiciliada en Jurong, Singapur, manifiesto que de conformidad con lo dispuesto en los artículos 50 y 51 del Código Contencioso Administrativo, interpongo recurso de **REPOSICIÓN** contra la resolución N° 24080 dictada por el Superintendente de Industria y Comercio el 23 de Septiembre de 2005, notificada mediante memorial el día 29 de Septiembre de 2005, mediante la cual se negó el privilegio de patente de invención para la solicitud correspondiente a TABLETAS DE LIBERACIÓN MODIFICADA QUE INCLUYEN AMOXICILINA Y CLAVULANATO DE POTASIO.

I. OBJETO DEL RECURSO

Este recurso tiene como objeto que el Superintendente de Industria y Comercio revoque en su totalidad la resolución N° 24080 del 23 de Septiembre de 2005 y en su lugar dicte otra en la conceda el privilegio de patente de invención para la solicitud correspondiente a TABLETAS DE LIBERACIÓN MODIFICADA QUE INCLUYEN AMOXICILINA Y CLAVULANATO DE POTASIO por cumplir con los requisitos de novedad, altura inventiva y aplicación Industrial, exigidos por la normatividad Andina.

II. FUNDAMENTOS DE HECHO DEL RECURSO

1. El día 11 de Abril de 2000 actuando como representante legal y apoderado de la sociedad BEECHAM PHARMACEUTICALS (PTE)

" Que las nuevas reivindicaciones 1 a 21 contenidas en los folios 279 a 282 no cumplen con el requisito de nivel inventivo, y las reivindicaciones 22 y 23 contenidas en el folio 282 se refieren a usos"

Más adelante señala: " Visto lo anterior, se advierte que la invención en estudio no cumple el requisito de nivel inventivo, toda vez que para un experto medio en la materia se deriva de manera evidente del estado de la técnica, pues los conocimientos integrantes del estado del arte, anteriores a la fecha de la prioridad invocadas conducen de manera obvia a la invención propuesta hasta el punto de que la invención no se constituye en un paso más allá de lo existente."

Respecto a los argumentos de su Despacho me permito señalar lo siguiente:

1. En primer termino y siguiendo precisas instrucciones de mi cliente nos permitimos **desistir** las reivindicaciones 22 y 23.

2. Ahora bien, en relación con el **nivel inventivo** de las reivindicaciones 1 a 21 nos permitimos señalar lo siguiente:

   2.1. En relación con **D1,** el Examinador sostiene que liberación retardada y liberación lenta son lo mismo. No es así. Una formulación típica de liberación retardada tiene un recubrimiento entérico de modo que no se libere en el ambiente acídico del estómago sino que comience a liberarse a medida que la tableta va pasando a lo largo del tracto gastrointestinal, hacia regiones de pH más alto, por encima de 5. Una vez llegue a esta región, la liberación es inmediata. Por el contrario, en una formulación de liberación LENTA, la liberación comienza directamente en el estómago y continúa por un periodo prolongado. En la realización de la presente invención, el componente de liberación inmediata proviene de la capa convencional que comprende amoxicilina y clavulanato. Esto

es luego suplementado por una liberación más gradual de amoxicilina de la capa de liberación lenta. Como tal, no hay retardo en la liberación, ni siquiera en la amoxicilina de la capa de liberación lenta, es decir, pasa mas lentamente.

2.2. **D2** - Contrario a lo que el Examinador sostiene, no hay una descripción explícita de una formulación que tenga todo el ácido clavulánico y parte de la amoxicilina en una capa de liberación inmediata, la amoxicilina restante en una capa de liberación lenta y ninguna capa de barrera. Además, toda la fuerza de lo que enseña el D2 es modificar la liberación del componente de clavulanato, de modo que haya una liberación lenta en lugar de una liberación inmediata. Por ello, el único ejemplo de datos biológicos se provee en la tableta 6.1 la cual tiene clavulanato de liberación inmediata y de liberación lenta así como una capa de barrera, para modificar aún más el perfil de liberación (ver página 29 y Fig. 4). En comparación, en la presente formulación, los inventores han ido en contra de esta dirección, han echado un paso atrás y han rechazado la noción de modificar el perfil de liberación de clavulanato, regresando por el contrario a un perfil de liberación inmediata. Además, el D1 no contempla una tableta que tenga 1000 mg de amoxicilina – la cantidad más grande mencionada en la página 2, líneas 28 a 33 es de 875 mg. Nuevamente, los inventores han ido más allá del D2 y han especificado una dosis más alta de amoxicilina para la tableta, para una cantidad de dosis de 2000 mg. Esto supera la dosis más alta generalmente aceptada de amoxicilina en un producto de amoxicilina/clavulanato que era de 875 mg.

2.3. **D3**- Es anterior al D2 y mejora el enfoque de tableta bicapa ya conocido incorporando una capa de barrera para modificar aún más el perfil de liberación. Por ello, el Ejemplo 6 de la página 39, describe una tableta bicapa de amoxicilina con una capa de barrera. Los conceptos subyacentes del D3 son luego

III. FUNDAMENTOS DE DERECHO DEL RECURSO

El presente escrito de recurso se fundamenta en las siguientes disposiciones legales.

1. Artículos 49, 50, 51, 52, 56, 58 y 59 del Código Contenciosos Administrativo.
2. Artículo 16, 18, 19, 30 y 34 de la Decisión 486 de la Comisión de la Comunidad Andina de Naciones.
3. Demás normas concordantes y complementarias.

IV. NOTIFICACIONES

Recibiré notificaciones en la carrera 13 N° 37 – 43 piso 12, de Bogotá, D.C.

De usted atentamente,

GERMÁN CASTILLO GRAU
C.C.17.017.671 de Bogotá
TP 2978 del CSJ

BOGOTA A

El anterior memorial fué presentado personalmente por
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quien se identificó con la C. de C. No. 17.017.671
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(54) **NOVEL METHOD OF TREATMENT**

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(57) **ABSTRACT**

Bacterial infections may be treated using a high dosage regimen of amoxycillin and potassium clavulanate. Preferably, the dosage is provided by a bilayer tablet

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" modificata: immediata + lenta

than gum and one immediate release tablet comprising 875 mg amoxycillin trihydrate (formulation III);

[0179] (d) a dosage of 1500/125 mg amoxycillin/potassium clavulanate (made up of a modified release tablet comprising 500/125 mg crystallised sodium amoxycillin/potassium clavulanate and two immediate release tablet comprising 500 mg amoxycillin trihydrate (Amoxyl, SmithKline Beecham) (formulation IV); and

[0180] (e) a dosage of 1750/125 mg amoxycillin/potassium clavulanate, made up of a combination of one immediate release tablet comprising 875/125 mg amoxycillin trihydrate/clavulanate (Augmentin, SmithKline Beecham) and one immediate release tablet comprising 875 mg amoxycillin trihydrate (Amoxyl, SmithKline Beecham) (formulation V).

Results

Formulation	n	Cmax[1]	T>MIC[1,2]	AUC[1,3]
I	8	12.75 (4.96	4.5 (1.8)	47.83
II	8	18.56 (4.72	4.4 (1.0)	57.46
III	8	13.03 (2.34	5.73 (2.54)	54.93
IV	8	17.33 (4.66	4.8 (0.9)	56.71
V	40	20.21 (6.09	4.2 (0.9)	56.33

()standard deviation
[1]arithmetic mean value
[2]T>MIC is the time (h) above an amoxycillin concentration of 4 μg/ml
[3]Area under the curve (0 to 12 h, μg.h/mL)

[0181] The pharmacokinetic profile is shown in **FIG. 4**.

[0182] Study B

[0183] The second study investigated two different modified release dosages of 2000/125 mg (formulations VI and VII) against an immediate release dosage of 2000/125 mg (formulation VIII), as follows:

[0184] (a) a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of two bilayer tablets according to Example 1 (formulation VI);

[0185] (b) a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of two bilayer tablets according to Example 2 (formulation VII);

[0186] (c) a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of a combination of three tablets each comprising 500 mg amoxycillin (Amoxyl, SmithKline Beecham) and one tablet comprising 500 mg amoxycillin and 125 mg potassium clavulanate (Augmentin, SmithKline Beecham) (formulation VIII).

Results

Formulation	N	Cmax[1]	T > MIC[1,2]	T > MIC[1,3]	AUC[1,4]
VI	7	17.41 (1.93)	6.0 (1.3)	4.8 (1.2)	74.9
VII	8	17.46 (6.02)	5.9 (1.3)	4.0 (1.3)	71.5
VIII	12	23.75 (5.73)	4.9 (1.1)	3.5 (1.0)	69.2

() standard deviation
[1]arithmetic mean value
[2]T > MIC is the time (h) above an amoxycillin concentration of 4 μg/ml
[3]T > MIC is the time (h) above an amoxycillin concentration of 8 μg/ml
[4]Area under the curve (0 to 12 h, μg.h/mL).

[0187] Comparison of the AUC values for formulations VI and VII (bilayer tablets) against VIII (immediate release tablets) shows that the absorption of the amoxycillin component has not been compromised by formulating a part of it in a slow release layer. This means that there is no extra, unabsorbed amoxycillin which may otherwise cause problems further down in the GI tract, for instance due to a lack of absorption and destruction of symbiotic bacteria

[0188] It was also found that for formulation VI, there was less inter-subject variability in the amoxycillin plasma concentrations than for formulation VII. These formulations were the same, except that formulation VI also comprised xanthan gum (2%) in the slow release layer.

[0189] The pharmacokinetic profile for amoxycillin plasma concentration is shown in **FIG. 5** (in which A is formulation VI, B is formulation VII, D is formulation VIII).

[0190] The pharmacokinetic profile for the clavulanate component was substantially the same for the bilayer tablets and the immediate release tablets, showing that the bioavailability thereof was not compromised by incorporation into the immediate release layer of a bilayer tablet.

[0191] The present invention also extends to formulations which are bioequivalent to the tablets of formulations VI and VII, in terms of both rate and extent of absorption, for instance as defined by the US Food and Drug Administration and discussed in the so-called "Orange Book" (Approved Drug Products with Therapeutic Equivalence Evaluations, US Dept of Health and Human Services, 19th edn, 1999).

[0192] Reference Data

[0193] The existing Augmentin 875/125 mg tablet has a C_{max} value of 11.6±2.8 μg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802). The time above MIC was about 40% of the 12 hour dosing interval for an MIC of 2 μg/ml and about 30% for an MIC of 4 μg/ml (SmithKline Beecham data).

What is claimed is:

1. A method of treating a bacterial infection in a human in need thereof, which method comprises administering to said human a dosage of a therapeutically effective amount of amoxycillin and potassium clavulanate, such that the amount of amoxycillin is in the range of 1900 to 2600 mg and the amount of potassium clavulanate is such that the weight ratio of amoxycillin to potassium clavulanate is from about 2:1 to 20: 1, at a dosage regimen interval of about 12 hours.

2. The method according to claim 1 in which the weight ratio of amoxycillin to potassium clavulanate is from about 14:1 to 20: 1.

3. The method according to claim 1 in which the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 hours and a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 12 μg/mL.

4. The method according to claim 3 in which the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.8 hours and a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 16 μg/mL.

5. The method according to claim 1 in which the dosage regimen provides a mean plasma concentration of amoxycillin of 8 μg/mL for at least 4.4 hours.

6. The method according to claim 1 in which the dosage is delivered from an immediate release formulation.

7. The method according to claim 6 in which the dosage is provided as a single tablet, or as a number of smaller tablets, some of which may be the same and some of which may comprise amoxycillin only and no potassium clavulanate.

8. The method according to claim 7 in which the dosage is 2000/125, 2250/125 or 2500/125 mg of amoxycillin and potassium clavulanate, respectively.

9. The method according to claim 1 in which the dosage is delivered from a modified release formulation.

10. The method according to claim 9 in which the dosage is provided as a number of tablets, some of which may be the same and some of which may comprise amoxycillin only and no potassium clavulanate.

11. The method according to claim 9 in which the dosage is 2000/125, 2250/125 or 2500/125 mg of amoxycillin and potassium clavulanate.

12. The method according to claim 1 in which the infection is caused by the organism S. pneumoniae (including Drug Resistant and Penicillin Resistant S pneumoniae), H. influenzae or M. catarrhalis.

13. A method of treating a bacterial infection in a human in need thereof, which method comprises administering to said human a dosage of a therapeutically effective amount of amoxycillin and potassium clavulanate such that the amount of amoxycillin is in the range 1400 to 1900 mg, and an amount of potassium clavulanate such that the weight ratio of amoxycillin to potassium clavulanate is from 2:1 to 14:1, at a dosage regimen interval of about 12 hours, such that the regimen provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 h, and a mean maximum plasma concentration (Cmax) of amoxycillin of at least 12 μg/mL.

14. The method according to in claim 13 in which the weight ratio of amoxycillin to potassium clavulanate is from 12: 1 to 14:1.

15. The method according to claim 13 in which the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/ml for at least 4.8 hours and a mean maximum plasma concentration (Cmax) of amoxycillin of at least 16 μg/ml.

16. The method according to claim 13 in which the dosage is delivered from a modified release formulation.

17. The method according to claim 13 in which the dosage is 1500/125 or 1750/125 mg of amoxycillin and potassium clavulanate.

18. The method according to claim 13 in which the infection is caused by the organism S. pneumoniae (including Drug Resistant and Penicillin Resistant S pneumoniae), H. influenzae or M. catarrhalis.

19. An immediate release pharmaceutical formulation comprising from 950 to 1300 or 1900 to 2600 mg of amoxycillin and an amount of potassium clavulanate such that the weight ratio of amoxycillin to potassium clavulanate is from 14:1 to 20:1, in combination with a pharmaceutically acceptable carrier or excipient.

20. The immediate release pharmaceutical tablet formulation according to claim 19 comprising 1000 mg±5% amoxycillin and 62.5 mg±5% potassium clavulanate, in a nominal ratio of about 16:1, in combination with a pharmaceutically acceptable carrier or excipient.

21. The immediate release pharmaceutical formulation according to claim 19 in the form of a single dose sachet comprising 2000, 2250 or 2500 mg±5% amoxycillin and 125 mg±5% potassium clavulanate, in a nominal ratio of about 16:1, 18:1 or 20:1, respectively, or the corresponding half quantities thereof, in combination with a pharmaceutically acceptable carrier or excipient.

22. The immediate release formulation according to claim 19 in the form of a dispersible tablet, chewable tablet, effervescent dispersible or effervescent chewable tablet comprising 2000, 2250, or 2500 mg amoxycillin and 125 mg±5% potassium clavulanate, in a nominal ratio of about 16:1, 18:1 or 20: 1, respectively, or the corresponding half quantities thereof, in combination with a dispersible, or chewable base and, if effervescent, an effervescent coupling agent, and a pharmaceutically acceptable or carrier or excipient.

23. A modified release pharmaceutical formulation comprising amoxycillin and potassium clavulanate in a (w/w) ratio from about 2:1 to 20:1, comprising an immediate release phase and a slow release phase; the immediate release phase comprising all the potassium clavulanate and a first part of amoxycillin, with a pharmaceutically acceptable carrier or excipient; and the slow release phase comprising a second part of amoxycillin formulated with a release modifying pharmaceutically acceptable excipient.

24. The modified release formulation according to claim 23 in which the ratio of amoxycillin and potassium clavulanate is 14:1 to 16:1.

25. The modified release formulation according to claim 23 which has a biphasic profile with respect to amoxycillin.

26. The modified release formulation according to claim 23 which has an AUC value which is at least 80% of that of the corresponding dosage of amoxycillin taken as a conventional (immediate release) tablet(s), over the same dosage period.

27. The modified release formulation according claim 23 in which the ratio of amoxycillin in the immediate and slow release phases is from 3:1 to 1:3.

28. The modified release formulation according claim 23 comprising a unit dosage form in the range 700 to 1300 mg amoxycillin or 1400 to 2600 mg and a corresponding amount of potassium clavulanate.

29. The modified release formulation according to claim 28 in which the unit dosage is: 1000, 875 or 750 mg±5% amoxycillin and 62.5 mg±5% potassium clavulanate; or 2000, 1750 or 1500 mg±5% amoxycillin and 125 mg±5% potassium clavulanate; in a nominal ratio of about 16:1, 14:1 or 12:1, respectively, in combination with a pharmaceutically acceptable excipient or carrier.

30. The modified release formulation according to claim 29 in the form of a tablet.

31. The modified release formulation according to claim 30 comprising 1000 mg±5% amoxycillin and 62.5 mg±5% potassium clavulanate, in a nominal ratio of about 16:1; and in which the immediate release phase comprises about 563 mg±5% amoxycillin and about 62.5 mg±5% of potassium clavulanate, and the slow release phase comprises about 438 mg±5% of amoxycillin.

32. The modified release formulation according to claim 23 in which the amoxycillin of the slow release phase consists essentially of crystallised sodium amoxycillin.

33. The modified release formulation according to claim 23 which is a layered tablet and in which the immediate and slow release phases are provided for as separate layers of the layered tablet.

34. The layered tablet according to claim 33 in which the slow release layer further comprises a release retarding excipient which is selected from a pH sensitive polymer, a release-retarding polymer which has a high degree of swelling in contact with water or aqueous media, a polymeric material which forms a gel on contact with water or aqueous media, a polymeric material which has both swelling and gelling characteristics in contact with water or aqueous media, or mixtures thereof.

35. The layered tablet according to claim 34 in which the release retarding gellable polymer is selected from methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone, or xanthan gum.

36. The layered tablet according to claim 34 in which the release retarding excipient is xanthan gum.

37. The layered tablet according to claim 36 in which the xanthan gum is present in from 1 to 25% by weight of the layer.

38. The layered tablet according to claim 33 in which the slow release layer comprises from about 70 to 80% of amoxycillin, from about 1 to 25% of xanthan gum, from about 10 to 20% of fillers and/or compression agents, and a conventional quantity of a lubricant.

39. The layered tablet according to claim 33 in which the slow release phase comprises sodium amoxycillin and in which the slow release layer comprises a pharmaceutically acceptable organic acid present in a molar ratio of from 100:1 to 1:10 (amoxycillin salt to organic acid).

40. The layered tablet according to claim 39 in which the pharmaceutically acceptable acid is citric acid present in a molar ratio of about 50:1 to 1:2.

41. The layered tablet according to claim 40 further comprising a release retarding gellable polymer.

42. The layered tablet according to claim 41 in which the release retarding gellable polymer is xanthan gum.

43. The layered tablet according to claim 42 in which xanthan gum is present in from 0.5 to 8% by weight of the slow release layer.

44. The layered tablet according to claim 33 comprising in total about 700 to 1250 mg amoxycillin and a pro rata amount of potassium clavulanate, in a nominal ratio of about 16:1, 14:1 or 12: 1, respectively, in combination with a pharmaceutically acceptable excipient or carrier.

45. The layered tablet according to claim 39 which comprises in the immediate release layer about 1000 mg±5% of amoxycillin and 62.5 mg±5% of potassium clavulanate, and in the slow release layer about 438 mg±5% of crystallised sodium amoxycillin, about 78 mg±10% of citric acid and about 2% by weight of xanthan gum.

46. The modified release formulation according to claim 23 in which the immediate release phase is formed from immediate release granules comprising amoxycillin and potassium clavulanate; or immediate release granules comprising amoxycillin and potassium clavulanate admixed with a further immediate release granule comprising amoxycillin and the slow release phase is formed from slow release granules comprising amoxycillin.

47. The modified release formulation according to claim 46 which is formulated as a unit dose sachet, capsule, monolith tablet, dispersible tablet, chewable tablet, effervescent chewable tablet, or a effervescent dispersible tablet.

48. A pharmaceutical formulation comprising 1000 mg±5% amoxycillin and 62.5 mg±5% potassium clavulanic acid, in a nominal ratio of about 16: 1, in combination with a pharmaceutically acceptable excipient or carrier.

49. The pharmaceutical formulation according to claim 48 in which the amoxycillin is present as a mixture of amoxycillin trihydrate and sodium amoxycillin in a ratio of 3:1 to 1:3.

50. A pharmaceutical formulation comprising amoxycillin and potassium clavulanate in a ratio of from 1:1 to 30:1 in which amoxycillin is provided as a mixture of amoxycillin trihydrate and sodium amoxycillin in a ratio of from 3:1 to 1:3.

51. The pharmaceutical formulation according to claim 50 in which the ratio of amoxycillin trihydrate and sodium amoxycillin is from 3:2 to 2:3.

52. A pharmaceutical formulation comprising a pharmaceutically acceptable soluble salt of amoxycillin in a slow release phase which further comprises a release retarding excipient which is a pharmaceutically acceptable organic acid present in a molar ratio of from 100:1 to 1:10 (amoxycillin salt to organic acid).

53. The pharmaceutical formulation according to claim 52 in which the molar ratio is 50:1 to 1:5.

54. The pharmaceutical formulation according to claim 52 in which the organic acid is citric acid.

55. The pharmaceutical formulation according to claim 52 in which the soluble salt of amoxycillin is sodium amoxycillin.

56. A kit comprising an immediate release formulation comprising amoxycillin and potassium clavulanate, optionally with a conventional (immediate release) formulation comprising amoxycillin and a slow release formulation comprising amoxycillin (and no potassium clavulanate).

57. A slow release pharmaceutical formulation comprising amoxycillin (as the sole active ingredient) formulated with a release retarding excipient which causes a slow release of the amoxycillin from the formulation, and excluding tablets which comprise from 400 to 500 mg amoxycillin trihydrate or a mixture comprising at least 70% amoxycillin trihydrate and up to 30% sodium amoxycillin and hydroxypropylmethylcellulose.

58. The pharmaceutical formulation according to claim 57 which comprises 100 to 1250 mg amoxycillin.

59. A pharmaceutical formulation according to claim 57 in which the release retarding excipient is xanthan gum.

60. A pharmaceutical formulation according to claim 59 in which the xanthan gum is pharmaceutical grade xanthan gum, 200 mesh.

61. A pharmaceutical formulation according to claim 59 in which the xanthan gum is present in from about 0.5 to 25% by weight.

62. Compacted granules for use in a pharmaceutical formulation comprising amoxycillin a diluent or compression aid, and an organic acid (if amoxycillin is present as a soluble salt thereof), or release retarding polymer, or a mixture thereof.

63. Compacted granules for use in a pharmaceutical formulation comprising sodium amoxycillin, microcrystal-

line cellulose, and an organic acid or a release retarding polymer or a mixture thereof.

64. A process for preparing compacted granules according to 63 which process comprises the steps of blending together sodium amoxycillin, microcrystalline cellulose, and organic acid or release retarding polymer or mixture thereof, compacting the blend and then milling.

65. The pharmaceutical formulation according to claim 46 comprising slow release compacted granules comprising amoxycillin, a diluent/compression aid, and an organic acid (if amoxycillin is present as a soluble salt thereof) or a release retarding polymer or a mixture thereof, and immediate release compacted granules comprising amoxycillin and potassium clavulanate or immediate release compacted granules comprising amoxycillin and potassium clavulanate, and further immediate release compacted granules comprising amoxycillin.

66. A formulation according to claim 23 having an AUC, C_{max}, and t_{max} substantially according to **FIG. 5** (formulation VI or VII).

67. A formulation which is bioequivalent to the formulation of claim **66**.

* * * * *

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(54) Novel method of treatment using a high dosage regimen of amoxycillin and potassium clavulanate

Neue Behandlungsmethode unter Verwendung einer hochdosierten Form von Amoxycillin und Kaliumclavulanat

Nouvelle méthode de traitement à l'aide d'un fort régime de dosage d'Amoxycillin et de Clavulanate de Potassium

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EP 1 044 680 B1

Description

[0001] This invention relates to a novel method of treatment using amoxycillin and potassium clavulanate and for novel formulations, in particular tablet formulations, for use in such methods.

[0002] Amoxycillin and potassium clavulanate are respectively a known β-lactam antibiotic and a known β-lactamase inhibitor. Products comprising amoxycillin and potassium clavulanate are marketed under the trade name "Augmentin" by SmithKline Beecham. Such products are particularly effective for treatment of community acquired infections, in particular upper respiratory tract infections in adults and otitis media in children.

[0003] Various tablet formulations of amoxycillin and potassium clavulanate have been approved for marketing, comprising various different weights and ratios of amoxycillin and potassium clavulanate, for instance, conventional swallow tablets comprising 250/125, 500/125, 500/62.5, and 875/125 mg amoxycillin/clavulanic acid (in the form of potassium clavulanate). Such tablets comprise amoxycillin and clavulanic acid in the ratio 2:1, 4:1, 8:1 and 7:1, respectively . The 875/125 mg tablet was developed to provide a tablet formulation which could be administered in a bid (twice daily) dosage regimen It is also marketed for tid (three times daily) dosing, in Italy and Spain. The 500/62.5 mg tablet was also developed to provide a tablet formulation which could be administered in a bid dosage regimen, two such tablets being taken every 12h, in preference to a single 1000/125 mg tablet. A 1000/125mg single dosage is also available, in France, but as a single dosage sachet rather than a tablet. Typically, the approved regimens provides a single dosage of 125 mg of potassium clavulanate.

[0004] In addition, WO 97/09042 (SmithKline Beecham) describes tablet formulations comprising amoxycillin and clavulanic acid in a ratio in the range 12:1 to 20:1, preferably 14:1. Furthermore, it is suggested that the preferred dosage of 1750/125mg may be provided as two tablets, the first comprising 875/125mg amoxycillin and clavulanic acid and the second 875 mg amoxycillin. The 14:1 ratio is said to be useful for the empiric treatment of bacterial infection potentially caused by drug resistant *S pneumoniae* (DRSP). This patent application also describes paediatric formulations comprising amoxycillin and clavulanate in a 14:1 ratio, for administering amoxycillin dosages of 90 mg/kg/day. Data suggest that such a dosage may provide antibiotic concentrations sufficient to eradicate DRSP with amoxycillin +/- clavulanic acid MICs ≤ 4 μg/ml (Bottenfield et al, Pediatr Infect Dis J, 1998, 17, 963-8).

[0005] WO 94/16696 (SmithKline Beecham) discloses generally that clavulanic acid may unexpectedly enhance the efficacy of amoxycillin against microorganisms having a resistant mechanism which is not β-lactamase mediated.

[0006] Existing marketed tablet formulations of amoxycillin and potassium clavulanate are conventional in that they provide immediate release of the active ingredients once the tablet reaches the stomach. There has also been some interest in developing formulations in which the release profile is modified, to allow for a longer interval between dosages, for instances, every 12 hours (bid, q12h), rather than every 8 hours (tid, q8h).

[0007] Thus, for instance, WO 95/20946 (SmithKline Beecham) describes layered tablets comprising amoxycillin and, optionally, potassium clavulanate, having a first layer which is an immediate release layer and a second layer which is a slow release layer. The broadest ratio of amoxycillin to clavulanic acid is 30:1 to 1:1, with a preferred range of 8:1 to 1:1. Amoxycillin is suitably in the form of amoxycillin trihydrate. Examples provided of such bilayered tablets have amoxycillin trihydrate in the immediate release layer and amoxycillin plus clavulanate in the slow release layer. Multi-layered tablets are described more generically in WO 94/06416 (Jagotec AG). Further bilayered tablets comprising clavulanic acid and amoxycillin are described in WO 98/05305 (Quadrant Holdings Ltd). In such tablets, a first layer comprises amoxycillin and a second layer comprises clavulanate and the excipient trehalose, to stabilise the clavulanate component.

[0008] In addition, WO 95/28148 (SmithKline Beecham) describes amoxycillin / potassium clavulanate tablet formulations having a core containing amoxycillin and potassium clavulanate coated with a release retarding agent and surrounded by an outer casing layer of amoxycillin and potassium clavulanate. The release retarding agent is an enteric coating, so that there is an immediate release of the contents of the outer core, followed by a second phase from the core which is delayed until the core reaches the intestine. Furthermore, WO 96/04908 (SmithKline Beecham) describes amoxycillin/potassium clavulanate tablet formulations which comprise amoxycillin and potassium clavulanate in a matrix, for immediate release, and granules in a delayed release form comprising amoxycillin and potassium clavulanate. Such granules are coated with an enteric coating, so release is delayed until the granules reach the intestine. WO 96/04908 (SmithKline Beecham) describes amoxycillin/potassium clavulanate delayed or sustained release formulations formed from granules which have a core comprising amoxycillin and potassium clavulanate, surrounded by a layer comprising amoxycillin. WO 94/27557 (SmithKline Beecham) describes controlled release formulations of amoxycillin and clavulanic acid prepared using a hydrophobic waxy material which is then subjected to thermal infusion.

[0009] Controlled release formulations comprising amoxycillin have been described by several groups. Thus, Arancibia *et al* ((Int J of Clin Pharm, Ther and Tox, 1987, 25, 97-100) describe the pharmacokinetic properties and bioavailability of a controlled release formulation comprising 500 mg of amoxycillin. No further details of the formulation are provided. The formulation was however designed to release 21 to 35% during the first 60 minutes, 51 to 66% at 4 hours, 70 to 80% at 6 hours, 81 to 90% at 8 hours and more than 94% at 12 hours. They however found little, if any,

correlation between the *in vitro* dissolution rate and the pharmacokinetic behaviour in the body. Hilton *et al* (International Journal of Pharmaceutics, 1992, 86, 79-88) described an alternative controlled release tablet having a hydrophilic polymer matrix and a gas release system, to provide intragastric buoyancy, to enhance gastric retention time. This showed no advantage over a conventional capsule formulation, with bioavailability being diminished. In contrast, Hilton *et al* (Journal of Pharmaceutical Sciences, 1993, 82, 737-743) described a 750 mg controlled release tablet incorporating the enteric polymer hydroxypropylmethyl cellulose acetate succinate. This however failed to show any advantage over a conventional capsule. In particular, the bioavailability was reduced to 64.6% compared with the same dosage provided in a capsule. More recently, Hoffman *et al* (Journal of Controlled Release, 1998, 54, 29-37 and WO 98/22091) have described a tablet comprising 500 mg of amoxycillin in a matrix comprising hydroxypropyl methyl cellulose, designed to release 50% of its contents in the first three hours and complete the drug release process over eight hours. The time above MIC was found to be significantly extended, compared to a capsule formulation, but not enough for a 12 h dosing interval. The discussion is in the context of a theoretical MIC of 0.2 μg/ml.

[0010] Part of the challenge in providing formulations of amoxycillin in which the drug release is effectively modified (and a ready explanation for the lack of success in the studies already referenced) is the relatively narrow window for absorption of the drug in the small intestine and the relatively short half life of the drug. Furthermore, the rapid elimination of amoxycillin (excretion half-life is 1.3 hours) makes it difficult to maintain serum levels as clearance from the body is very rapid.

[0011] In existing tablet formulations comprising amoxycillin and potassium clavulanate, amoxycillin is present in the form amoxycillin trihydrate, as the use of this form provides tablets with greater storage stability than those in which amoxycillin is present as sodium amoxycillin (see GB 2 005 538, Beecham Group Ltd). Sodium amoxycillin is however used as the amoxycillin component in existing formulations of amoxycillin and potassium clavulanate adapted for IV administration. The form of sodium amoxycillin used is a spray-dried form. In addition, EP 0 131 147-A1 (Beecham Group plc) describes a further form of sodium amoxycillin, so-called "crystalline sodium amoxycillin". A further process for preparing salts of amoxycillin, including sodium amoxycillin, is described in WO 99/62910 (SmithKline Beecham). Sodium amoxycillin is relatively water soluble in comparison to amoxycillin trihydrate.

[0012] Formulations comprising clavulanic acid and a pharmaceutically acceptable organic acid or a salt-like derivative thereof, for example calcium citrate, have been described in WO 96/07408 (SmithKline Beecham). In such formulations, it is postulated that the presence of the calcium citrate would help suppress the gastrointestinal intolerance associated with oral dosing of clavulanate-containing products.

[0013] Furthermore, US patent no. 5 051 262 (Elan Corp) describes the incorporation of an organic acid into a modified release formulation, to provide a microenvironment in which the locally modified pH helps to protect the active ingredient from degradation.

[0014] Of concern is the increasing resistance of pathogenic organisms, such as those found in respiratory tract infections, to anti-infective agents such as amoxycillin/potassium clavulanate, in particular drug resistant *S pneumoniae*. Increased resistance to penicillin of *S pneumoniae* (due to modified penicillin binding proteins) is developing around the world and is affecting clinical outcomes (see for instance Applebaum P C, Ped Inf Dis J, 1996, 15(10), 932-9). These penicillin resistant *S pneumoniae* (PRSP) have also been termed "DRSP" as they often exhibit decreased susceptibility not only to penicillin but also to a wider range of antimicrobial classes, including macrolides, azalides, beta-lactams, sulfonamides and tetracyclines. Amoxycillin (with or without clavulanate), along with some of the newer quinolones, has remained among the most active oral drugs against the increasingly resistant isolates of *S pneumoniae*, based on both MIC levels and pharmacokinetic properties of these compounds. Resistance rates (and MICs) have however continued to increase. Penicillin resistance in S. *pneumoniae* can be assessed according to criteria developed by the National Committee for Clinical Laboratory Standards (NCCLS), as follows: susceptible strains have MICs of ≤ 0.06 μg/ml, intermediate resistance is defined as an MIC in the range 0.12 to 1.0 μg/ml whilst penicillin resistance is defined as an MIC of ≥ 2 μg/ml. Furthermore, it is found that some 10% of pneumococci now have an amoxycillin MIC of 2 μg/ml.

[0015] There is consequently a need to provide new formulations of amoxycillin/clavulanate that combine the known safety profile and broad spectrum with improved activity against DRSP, including PRSP, with higher MICs in empiric treatment of respiratory infections where *S pneumoniae, H influenzae* and *M catarrhalis* are likely pathogens.

[0016] For β-lactams, including amoxycillin, it is recognised that the time above minimum inhibitory concentration (T > MIC) is the pharmacodynamic parameter most closely related to efficacy. For a variety of β-lactams, a bacteriological cure rate of 85 to 100% is achieved when serum concentrations exceed the MIC for more than about 40% of the dosing interval (Craig and Andes, Ped Inf Dis J, 1996, 15, 255-259). For a 12 hour dosing interval, this is about 4.8 hours.

[0017] A further parameter which may be of importance is the ratio of the maximum plasma concentration (Cmax) to the MIC value, as this may be related to the potential to select for resistance. Too low a ratio may encourage the development of resistant strains. Preferably, the plasma C_{max} value is well above the MIC value, for instance, at least two times, more preferably at least three times, most preferably at least four times, the MIC value.

[0018] In a clinical study using the existing Augmentin 875/125mg tablet, it was found that, when dosed at 12 hour

intervals, the time above MIC was about 40% for an MIC of 2 μg/ml but only about 30% for an MIC of 4 μg/ml. The existing Augmentin 875/125mg tablet has a C_{max} value of 11.6±2.8 μg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802).

[0019] Based on the foregoing considerations, there is a continuing need to provide new dosage regimens for amoxycillin/clavulanate giving optimised pharmacokinetic profiles for amoxycillin whilst not compromising the bioavailability of clavulanate, so that therapy is maximised, particularly against more resistant bacteria whilst the (further) development of resistance is minimised. It has now been found that such can be achieved using higher dosages of amoxycillin than previously contemplated.

[0020] Accordingly, the present invention provides for a modified release pharmaceutical formulation comprising amoxycillin and potassium clavulanate in the ratio from 14:1 to 20:1, more preferably 14:1 to 16:1 in which all of the potassium clavulanate and a first part of amoxycillin are formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and the first part of amoxycillin, to form an immediate release phase, and further comprising a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of the second part of amoxycillin, to form a slow release phase, and in which the ratio of amoxycillin in the immediate and slow release phases is from 3:1 to 1:3.

[0021] In a further aspect, the present invention provides for the use of amoxycillin and potassium clavulanate in the manufacture of a medicament as hereinbefore defined in claim 1 for treating bacterial infections in humans at dosage intervals of about 12 h.

[0022] Preferably, the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 h, preferably at least 4.6 h, more preferably at least 4.8 h, most preferably for about 6 h or longer.

[0023] More preferably, the dosage regimen provides a mean plasma concentration of amoxycillin of 8 μg/ml for at least 4.4 h, more preferably at least 4.6 h, most preferably at least 4.8 h.

[0024] Preferably, the dosage regimen provides a mean maximum plasma concentration (C_{max}) of amoxycillin which is at least 8 μg/mL, preferably at least 12 μg/mL, yet more preferably at least 14 μg/mL, most preferably at least 16 μg/mL.

[0025] Preferably, the mean plasma concentration of amoxycillin and the mean maximum plasma concentration of amoxycillin are measured after oral administration of a formulation comprising amoxycillin at the start of a light meal.

[0026] Bacterial infections amenable to the present invention include infections caused by the organisms *S pneumoniae* (including Drug Resistant *S pneumoniae* (DRSP), for instance Penicillin Resistant *S pneumoniae* (PRSP)), and/or the β-lactamase producing respiratory pathogens, most notably *H influenzae* and *M catarrhalis*, such as respiratory tract infections, including community acquired pneumoniae (CAP), acute exacerbations of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS), where the higher break points achievable through the improved pharmacokinetic profile will be especially advantageous compared to existing antibacterial agents. Most outpatient respiratory infections are caused by either *S pneumoniae* and/or the β-lactamase producing bacteria and are treated empirically so there is a continuing need for a method of treatment, such as the present invention, that provides a spectrum of activity that covers all such pathogens. The duration of therapy will generally between 7 and 14 days, typically 7 days for indications such as acute exacerbations of chronic bronchitis but 10 days for acute bacterial sinusitis. Typically, the dosages regimens are designed for adult patients, rather than paediatric patients.

[0027] The term "amoxycillin" is used generically to refer to amoxycillin or an alkaline salt thereof, in particular amoxycillin trihydrate and (crystallised) sodium amoxycillin, without distinction and unless otherwise indicated.

[0028] Unless otherwise indicated, weights of amoxycillin and (potassium) clavulanate refer to the equivalent weights of the corresponding free acids. In addition, it will be appreciated that in practice, weights of amoxycillin and clavulanate to be incorporated into a formulation will be further adjusted, in accord with conventional practice, to take account of the potency of the amoxycillin and clavulanate.

[0029] As used herein, the term "immediate release" refers to the release of the majority of the active material content within a relatively short time, for example within 1 hour, preferably within 30 minutes, after oral ingestion. Examples of such immediate release formulations include conventional swallow tablets, dispersible tablets, chewable tablets, single dose sachets and capsules.

[0030] As used herein, the term "modified release" refers to a release of drug substance from a pharmaceutical formulation which is at a slower rate than from an immediate release formulation such as a conventional swallow tablet or capsule and may include an immediate release phase and a slow release phase. Modified release formulations are well known in the art, see for instance Remington: The Science and Practice of Pharmacy, Nineteenth Edn, 1995, Mack Publishing Co, Pennsylvania, USA.

[0031] Preferably, the modified release formulations of the present invention are formulated such that the release of amoxycillin is effected predominantly through the stomach and small intestine, so that absorption through the specific amoxycillin absorption site in the small intestine is maximised. Preferably, the amoxycillin release profile is made up of a contribution from an immediate release component which is then complemented and extended by an on-going contribution from a slow release component Preferably, potassium clavulanate is released substantially immediately

from the formulation, when the formulation reaches the stomach and is absorbed therefrom, thereby minimising the risk of degradation from prolonged exposure to the stomach. Such formulations are preferably formulated such that the release of amoxycillin and potassium clavulanate occurs predominantly within 3 hours of ingestion of the formulation.

[0032] Typically, a dosage will provide 125 mg of potassium clavulanate, the amount approved in existing regimens where a lesser amount of amoxycillin is administered.

[0033] Representative modified release dosages include 1500/125, 1750/125 and 2000/125 mg of amoxycillin and potassium clavulanate, respectively. A preferred dosage is 2000/125 mg of amoxycillin and potassium clavulanate.

[0034] The dosage in a modified release formulation may conveniently be provided as a number of swallow tablets or capsules, for instance two, three or four, some of which may be the same and some of which may comprise amoxycillin only and no potassium clavulanate. Thus, for instance, a dosage of 2000 mg amoxycillin and 125 mg potassium clavulanate may be provided by two tablets each comprising 1000/62.5 mg amoxycillin/potassium clavulanate, one tablet comprising 1000 mg of amoxycillin and one tablet comprising 1000/125 mg amoxycillin/potassium clavulanate, two tablets each comprising 500 mg amoxycillin and one tablet comprising 1000/125 mg amoxycillin/potassium clavulanate or four tablets each comprising tablet 500/32.25 mg amoxycillin/potassium clavulanate. In addition, a dosage of 1750 mg amoxycillin and 125 mg potassium clavulanate may be provided by two tablets each comprising 875/62.5 mg amoxycillin/potassium clavulanate or one tablet comprising 875 mg of amoxycillin and one tablet comprising 875/125 mg amoxycillin/potassium clavulanate. A preferred tablet comprises 1000/62.5 mg amoxycillin/potassium clavulanate.

[0035] The dosage in an modified release formulation may be also provided as a single tablet. Because of the quantities of drug substance being used, this would preferably be other than a swallow tablet, for instance a dispersible tablet or a chewable tablet which may also be effervescent and/or dispersible or a dispersible tablet. A single unit dosage may also be conveniently provided as a single dosage sachet. It will be appreciated that the dosage may also be provided as a number of smaller non-swallow tablets or sachets, for instance 2 x 1000/62.5 mg or 4 x 500/32.25 mg amoxycillin/potassium clavulanate.

[0036] As used herein, the term "slow release" refers to the gradual but continuous or sustained release over a relatively extended period of the active material content (in this case amoxycillin) after oral ingestion and which starts when the formulation reaches the stomach and starts to disintegrate/dissolve. The release will continue over a period of time and may continue through until and after the formulation reaches the intestine. This can be contrasted with the term "delayed release" in which release of the active does not start immediately the formulation reaches the stomach but is delayed for a period of time, for instance until when the formulation reaches the intestine when the increasing pH is used to trigger release of the active from the formulation.

[0037] Preferably, the modified release formulation has an *in vitro* dissolution profile in which 45 to 65%, preferably 45 to 55% of the amoxycillin content is dissolved within 30 min; further in which 50 to 75%, preferably 55 to 65% of the amoxycillin content is dissolved within 60 min; further in which 55 to 85%, preferably 60 to 70% of the amoxycillin content is dissolved within 120 min; further in which 70 to 95%, preferably 75 to 85% of the amoxycillin content is dissolved within 180 min; and further in which 70 to 100%, preferably 75 to 100% of the amoxycillin content is dissolved within 240 min. In comparison, a conventional, immediate release amoxycillin tablet dissolves essentially completely within 30 minutes. The dissolution profile may be measured in a standard dissolution assay, for instance <711> Dissolution Test, Apparatus 2, provided in USP 23, 1995, at 37.0 ± 0.5°C, using deionised water (900 mL) and a paddle speed of 75 rpm.

[0038] Preferably, the modified release formulation has a biphasic profile *in vivo* with respect to amoxycillin, that is an initial burst from the immediate release phase to provide an acceptable C_{max} value, supplemented by a further contribution from the slow release phase, to extend the T>MIC parameter to an acceptable value.

[0039] Preferably, the modified formulation provides an "Area Under the Curve" (AUC) value which is substantially similar to, for instance at least 80%, preferably at least 90%, more preferably about 100%, of that of the corresponding dosage of amoxycillin taken as a conventional (immediate release) formulation, over the same dosage period, thereby maximising the absorption of the amoxycillin component from the slow release component.

[0040] The pharmcokinetic profile for a dosage of the present invention may be readily determined from a single dosage bioavailability study in human volunteers. Plasma concentrations of amoxycillin may then be readily determined in blood samples taken from patients according to procedures well known and documented in the art.

[0041] Representative modified release formulations include a tablet, including swallow tablets, dispersible tablets, chewable tablets which may also be effervescent and/or dispersible and, a capsule, granules or a sachet, typically a swallow tablet.

[0042] Representative modified release formulations having an immediate and a slow release phase provide a unit dosage in the range 700 to 1300 mg, preferably, 950 to 1300 mg, amoxycillin, for instance unit dosages of 1000, 875 and 750/62.5 mg amoxycillin/clavulanate. Alternatively, and where the physical size of the dosage form is not a problem, the unit dosage may provide the whole dosage, for instance a single dosage sachet, chewable tablet or dispersible

tablet may comprise 1400 to 2600 mg, preferably, 1900 to 2600 mg, amoxycillin, for instance unit dosages of 2000, 1750 and 1500/125 mg amoxycillin/clavulanate. It will be appreciated that such 1000, 875 and 750/62.5 mg formulations are novel.

[0043] Accordingly, in a further aspect, the present invention provides for a pharmaceutical formulation having an immediate release phase and a slow release phase and comprising:

(a) a unit dosage in the range 700 to 1300 mg, preferably, 950 to 1300 mg, amoxycillin, and a corresponding amount of potassium clavulanate, in a nominal ratio of about 16:1, 14;1 or 12:1, for instance unit dosages of 1000, 875 or 750 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, respectively, or

(b) a unit dosage in the range 1400 to 2600 mg, preferably, 1900 to 2600 mg, amoxycillin, and a corresponding amount of potassium clavulanate, in a nominal ratio of about 16:1, 14;1 or 12:1, for instance unit dosages of 2000, 1750 or 1500 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, respectively,

in combination with pharmaceutically acceptable excipients or carriers.

[0044] Preferably, the ratio of amoxycillin in the immediate and slow release phases is from 2:1 to 2:3, more preferably 3:2 to 1:1. Representative ratios include about 2:1, 9:7 or 1:1. It is found useful to employ an excess of amoxycillin in the immediate release phase, to ensure an adequate C_{max} value.

[0045] In the modified release formulations of the present invention, the portion of amoxycillin which is released immediately may be provided as amoxycillin trihydrate or an alkaline salt thereof, for instance potassium or sodium amoxycillin, preferably, (crystallised) sodium amoxycillin or a mixture thereof, preferably amoxycillin trihydrate; whilst the portion of amoxycillin which is released slowly is provided as amoxycillin trihydrate or an alkaline salt thereof, for instance potassium or (crystallised) sodium amoxycillin or a mixture thereof, preferably (crystallised) sodium amoxycillin.

[0046] Preferably, the modified release formulation is a tablet. In a preferred modified release tablet comprising 1000 mg amoxycillin and 62.5 mg potassium clavulanate, the immediate release phase comprises about 563 mg ±5% amoxycillin trihydrate and about 62.5 mg ±5% of potassium clavulanate and the slow release phase about 438 mg ±5% of amoxycillin, preferably as (crystallised) sodium amoxycillin.

[0047] In a representative modified release tablet of the present invention, the immediate release phase comprises about 438 mg amoxycillin, preferably amoxycillin trihydrate and about 62.5 mg of potassium clavulanate and the slow release phase about 438 mg of amoxycillin, preferably (crystallised) sodium amoxycillin, providing overall an 875/62.5 mg (14:1) tablet.

[0048] For a tablet formulation, the immediate and slow release phases may be provided in a number of different formats.

[0049] In a preferred aspect, the immediate and slow release phases are provided as separate layers of a layered tablet.

[0050] Accordingly, in a further aspect, the present invention provides for a layered tablet formulation comprising potassium clavulanate and amoxycillin in an immediate release layer phase and amoxycillin in a slow release layer. The layered tablet may have two layers, or two layers plus one or more barrier layer, as well as a coating layer. As used herein, the term "bilayer" tablet refers to a tablet consisting of an immediate release and a slow release layer, optionally with a coating layer.

[0051] An immediate release layer may be, for example, a layer which disintegrates immediately or rapidly and has a composition similar to that of known tablets which disintegrate immediately or rapidly. For example, the layer may comprise, in addition to the active material content, excipients including diluents such as microcrystalline cellulose; disintegrants such as cross-linked polyvinylpyrrolidone (CLPVP), sodium starch glycollate; compression aids such as colloidal silicon dioxide and microcrystalline cellulose; and lubricants such as magnesium stearate. Such an immediate release layer may comprise around 60 to 85 % (all percentages given herein are on a weight percentage basis unless otherwise stated), preferably 70 to 85 %, of active material content, around 10 to 30 %, preferably 10 to 20 % of fillers/compression aids, and conventional amounts of disintegrants and lubricants, typically about 0.5 to 3%, etc.

[0052] An alternative type of immediate release layer may be a swellable layer having a composition which incorporates polymeric materials which swell immediately and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass. Active material content may be immediately leached out of this mass.

[0053] Slow release layers have a composition which comprises amoxycillin together with a release retarding excipient which allows for slow release of amoxycillin. Suitable release retarding excipients include pH sensitive polymers, for instance polymers based upon methacrylic acid copolymers such as the Eudragit (trade mark) polymers, for example Eudragit L (trade mark) which may be 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.

[0054] Release retarding 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.

[0055] Release retarding gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone, xanthan gum etc.

[0056] Release retarding polymers simultaneously possessing swelling and gelling properties include medium-viscosity hydroxypropylmethylcellulose and medium-viscosity polyvinylalcohols.

[0057] A preferred release-retarding polymer is xanthan gum, in particular a fine mesh grade of xanthan gum, preferably pharmaceutical grade xanthan gum, 200 mesh, for instance the product Xantural 75 (also known as Keltrol CR, Trade Mark, Monsanto, 800 N Lindbergh Blvd, St Louis, MO 63167, USA). Xanthan gum is a polysaccharide which upon hydration forms a viscous gel layer around the tablet through which the active has to diffuse. It has been shown that the smaller the particle size, the slower the release rate. In addition, the rate of release of drug substance is dependent upon the amount of xanthan gum used and can be adjusted to give the desired profile. Controlled release formulations comprising from 7.5 to 25% xanthan gum are described in EP 0 234 670-A (Boots Co plc). The preferred embodiment is a tablet comprising ibuprofen as the drug substance and 15-20% xanthan gum, which is taken once daily.

[0058] Examples of other polymers which may be used include Methocel K4M (Trade Mark), Methocel E5 (Trade Mark), Methocel E5O (Trade Mark), Methocel E4M (Trade Mark), Methocel K15M (Trade Mark) and Methocel K100M (Trade Mark). An example of a suitable polymer mixture is a mixture of Methocel E5 and K4M, for example 1:1, w:w.

[0059] Other known release-retarding polymers which may be incorporated include hydrocolloids such as natural or synthetic gums, cellulose derivatives other than those listed above, carbohydrate-based substances such as acacia, gum tragacanth, locust bean gum, guar gum, agar, pectin, carageenin, soluble and insoluble alginates, carboxypolymethylene, casein, zein, and the like, and proteinaceous substances such as gelatin.

[0060] Such a slow release layer may contain polymers which immediately swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not immediately discharged from the stomach into the intestine.

[0061] The slow release layer may also include diluents such as lactose; compression aids such as microcrystalline cellulose; and lubricants such as magnesium stearate. The slow release layer may further comprise disintegrants, such as cross-linked polyvinylpyrrolidone (CLPVP) and sodium starch glycollate; binders such as povidone (polyvinylpyrrolidone); desiccants, such as silicon dioxide; and soluble excipients such as mannitol or other soluble sugars. Typically, the slow release layer comprises from about 60 to 80% by weight of amoxycillin; from 10 to 20 % by weight of diluent/compression aid and from 1 to 2.5 % by weight of lubricant.

[0062] When xanthan gum is used as release-retarding polymer, the layer contains from 60 to 80% of amoxycillin, from 1 to 25%, preferably 2 to 15%, more preferably 4 to 15% of xanthan gum, from 10 to 30%, preferably 10 to 20% of fillers/compression aids, and conventional quantities of lubricants, all % being by weight of the layer. In a preferred embodiment, the slow release layer comprises from 70 to 80% of amoxycillin, from 4 to 10%, of xanthan gum, from 10 to 20% of microcrystalline cellulose, and from 1 to 2.5 % of magnesium stearate, all % being by weight of the layer.

[0063] When release-retarding polymers other than xanthan gum are used, the slow release layer may contain around 30 to 70%, preferably from 40 to 60%, of amoxycillin, from 15 to 45% of release-retarding polymer, from 0 to 30% of fillers/compression aids, conventional quantities of lubricants, and from 5 to 20% of soluble excipients, all % being by weight of the layer.

[0064] It has also been surprisingly found that when the amoxycillin in the slow release layer is in the form of a soluble salt thereof, such as sodium amoxycillin, then the release thereof may be retarded by the inclusion of an organic acid.

[0065] Accordingly, the present invention further provides for a pharmaceutical formulation as hereinbefore defined and comprising a pharmaceutically acceptable soluble salt of amoxycillin, for instance sodium amoxycillin, in a slow release phase which further comprises a release retarding excipient which is a pharmaceutically acceptable organic acid present in a molar ratio of from 100:1 to 1:10, preferably 50:1 to 1:5, more preferably 20:1 to 1:2 (amoxycillin to organic acid).

[0066] It is believed that intimate contact between the organic acid and the salt of amoxycillin in the pharmaceutical formulation, for instance as a consequence of compacted granule formation or direct compression in a tablet, causes some form of interaction which modifies the release of the amoxycillin component from the formulation.

[0067] Soluble pharmaceutically acceptable salts of amoxycillin include alkali metal salts such as sodium and potassium; alkaline earth metal salts such as magnesium and calcium, and acid salts such as amoxycillin hydrochloride. Preferably, the salt is sodium amoxycillin, more preferably crystalline sodium amoxycillin.

[0068] As used herein, the term "pharmaceutically acceptable organic acid" refers to organic acids which are without pharmacological effect *per se,* have acceptable organoleptic properties, have acceptable density, do not have an extreme pH and are preferably solid. Examples thereof include mono-carboxylic acids and polycarboxylic acids having

from 2 to 25, preferably from 2 to 10, carbon atoms; monocyclic and polycyclic aryl acids such as benzoic acid; as well as monohydrogen, dihydrogen etc metal salts of multi-valent acids. A single pharmaceutically acceptable organic acid may be used, or two or more of such may be used in combination. Preferably, the organic acid is a $C_{(2-10)}$alkyl- or alkenyl- carboxylic acid having from one, two or three carboxylic acid groups, and optionally with one or more hydroxy substituents or an additional CO group in the carbon chain, for instance malonic acid, succinic acid, fumaric acid, maleic acid, adipic acid, lactic acid, levulinic acid, sorbic acid or a fruit acid such as tartaric acid, malic acid, ascorbic acid or citric acid, or an acidic salt thereof, more preferably citric acid, in particular anhydrous citric acid.

[0069] The organic acid may be used alone or in combination with a release retarding polymer as hereinbefore described. A preferred combination comprises citric acid and a release retarding gellable polymer, in particular xanthan gum. In the presence of the organic acid, for instance citric acid, xanthan gum may be used at a lower level then when included on its own, for instance, from 0.5 to 8%, preferably 1 to 5%, typically about 2%, by weight of the slow release layer.

[0070] When an organic acid is used as a release-retarding excipient, the slow release layer contains from 60 to 80% of a soluble salt of amoxycillin, from 10 to 30%, preferably 10 to 20% of fillers/compression aids, and conventional quantities of lubricants, all % being by weight of the layer. In a preferred embodiment, the slow release layer comprises from 60 to 70 % of a soluble salt of amoxycillin, from 10 to 20% of microcrystalline cellulose, and from 1 to 2.5 % of magnesium stearate, all % being by weight of the layer.

[0071] In a representative example, a layered tablet comprises in the slow release layer crystallised sodium amoxycillin and citric acid, in a molar ratio of about 50:1 to 1:2, preferably 20:1 to 1:2, more preferably 2:1 to 1:1.2, yet more preferably about 1:1. In a preferred embodiment, the slow release layer comprises about 438 mg ±5% crystallised sodium amoxycillin, about 78 mg ±10% citric acid and about 2% by weight of xanthan gum.

[0072] In a preferred layered tablet comprising 1000 mg amoxycillin and 62.5 mg potassium clavulanate, the immediate release layer comprises about 563 mg ±5% amoxycillin, preferably amoxycillin trihydrate, and about 62.5 mg ±5% of potassium clavulanate and the slow release layer about 438 mg ±5% of amoxycillin, preferably crystallised sodium amoxycillin, about 78 mg ±10% citric acid and about 2% by weight of xanthan gum.

[0073] The tablet formulations of the invention may also include one or more barrier layers, which may be located between the respective first and second layers, and/or on one or more of the outer surfaces of the first and second layers, for example the end faces of the layers of a substantially cylindrical tablet. Such barrier layers may, for example, be 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. Suitably the barrier layer should be such that it retains these characteristics at least until complete or substantially complete transfer of the active material content to the surrounding medium.

[0074] Suitable polymers for the barrier layer include acrylates, methacrylates, copolymers of acrylic acid, celluloses and derivatives thereof such as ethylcelluloses, cellulose acetate propionate, polyethylenes and polyvinyl alcohols etc. Barrier layers comprising polymers which swell in contact with water or aqueous media may swell to such an extent that the swollen layer forms a relatively large swollen mass, the size of which delays its immediate discharge from the stomach into the intestine. The barrier layer may itself contain active material content, for example the barrier layer may be a slow or delayed release layer. Barrier layers may typically have an individual thickness of 2 mm to 10 microns.

[0075] Suitable polymers for barrier layers which are relatively impermeable to water include the Methocel (trade mark) series of polymers mentioned above, for example Methocel K100M, Methocel K15M, Methocel E5 and Methocel E50, used singly or combined, or optionally combined with an Ethocel (trade mark) polymer. Such polymers may suitably be used in combination with a plasticiser such as hydrogenated castor oil. The barrier layer may also include conventional binders, fillers, lubricants and compression acids etc such as Polyvidon K30 (trade mark), magnesium stearate, and silicon dioxide, e.g. Syloid 244 (trade mark).

[0076] The tablet formulation of the invention may be wholly or partly covered by a coating layer, which may be a protective layer to prevent ingress of moisture or damage to the tablet. The coating layer may itself contain active material content, and may, for example, be an immediate release layer, which immediately disintegrates in contact with water or aqueous media to release its active material content, for example amoxycillin and potassium clavulanate. Preferred coating materials comprise hydroxypropylmethylcellulose and polyethylene glycol, with titanium dioxide as an opacifying agent, for instance as described in WO 95/28927 (SmithKline Beecham).

[0077] As well as active material content etc, the tablet of the invention may also include a pH modifying agent, such as a pH buffer, which may be contained in either the immediate-, or slow-release layers, or in a coating around all or part of the tablet. A suitable buffer is calcium hydrogen phosphate.

[0078] In a tablet without a barrier layer, the immediate release layer comprises from 50 to 60% and the slow release layer comprises from 40 to 50% of the overall tablet weight. When a barrier layer is present, the immediate release layer typically comprises from 40 to 50%, the slow release layer comprises from 35 to 45%, and the barrier layer comprises from 5 to 20% of the overall tablet weight.

[0079] It is found that a satisfactory pharmacokinetic profile may be obtained from a bilayered tablet of the present

invention without the need to include a barrier layer. Accordingly, a bi-layer tablet is preferred. This also reduces the complexity of the manufacturing process.

[0080] It will be appreciated that 1000, 875 /62.5 mg layered tablets having an immediate release layer and a slow release layer are novel. Accordingly, in a further aspect, the present invention provides for a pharmaceutical layered tablet formulation comprising an immediate release layer and a slow release layer and comprising from 700 to 1250 mg amoxycillin and a pro rata amount of potassium clavulanate, preferably 1000, or 875 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, or 14:1, respectively, in combination with pharmaceutically acceptable excipients or carriers. Preferably, the layered tablet is a bi-layered tablet.

[0081] Suitably the tablet formulations of the invention may be formed by known compression tabletting techniques, for example using a known multi-layer tabletting press. Preferably, in a preliminary step, slugging or roller compaction is used to form granulates. Lubricants and compression aids (if used) are then added, to form a compression blend for subsequent compaction.

[0082] Preferred bilayer tablets of the present invention may be made by a process which comprises, as an early phase, the formation of slow release compacted granules, comprising the steps of milling sodium amoxycillin, a portion of the diluent/compression aid such as microcrystalline cellulose (typically about 30%), a portion of the lubricant (typically about 70%) and a pharmaceutically acceptable organic acid such as a fruit acid, for instance citric acid, and then blending with a release retarding polymer such as xanthan gum, if present, and a compression aid such as colloidal silicon dioxide, compacting the blend, for instance in a roller compactor or by slugging, and then milling, to form slow release granules. Preferably such granules have a size in the range 100 to 1000 microns. The incorporation of xanthan gum appears to also have an unexpected benefit on processibility.

[0083] Such slow release compacted granules may then be blended with other excipients such as the remaining magnesium stearate and microcrystalline cellulose, to form a slow release compression blend.

[0084] In addition, amoxycillin trihydrate, potassium clavulanate (preferably as as 1:1 blend with microcrystalline cellulose), microcrystalline cellulose (a portion of total used), are milled and blended with a lubricant such as magnesium stearate (preferably about 50% f total), and then compacted, for instance in a roller compactor or by slugging, and milled to form immediate release compacted granules. These immediate release compacted granules may then be blended with other excipients such as the remaining magnesium stearate and microcrystalline cellulose (about 13%), a compression aid such as colloidal silica, and a disintegrant such as sodium starch glycollate, to form an immediate release compression blend.

[0085] The immediate release and slow release compression blends may then be compressed as separate layers on a bilayer tablet press, to form bilayer tablets.

[0086] Alternatively, 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. A wet granulation process may be also be used, for instance with isopropanol as the solvent and Polyvidon K-30 (trade mark) as the wet granulating aid.

[0087] A barrier layer, if present, may typically be made up by a wet granulation technique, or by dry granulation techniques such as roller compaction. Typically the barrier material, e.g. Methocel (trade mark) is suspended in a solvent such as ethanol containing a granulation acid such as Ethocel or Polyvidon K-30 (trade mark), followed by mixing, sieving and granulation. Typically a first layer may be formed, then a barrier layer deposited upon it, e.g. by compression, spraying or immersion techniques, then the second layer may be formed so that the barrier layer is sandwiched between the first and second layers. Additionally, or alternatively, the first and second layers may be formed and a barrier layer may then be formed, for instance by compression, spraying or immersion, on one or more of the end faces of the tablet.

[0088] A process for the preparation of crystallised sodium amoxycillin is described in EP-A-0 131 147 (Beecham Group plc).

[0089] Potassium clavulanate is known to be extremely water sensitive. Therefore tablet formulations which contain potassium clavulanate should be made up in dry conditions, preferably at 30% relative humidity or less, and the ingredients of the formulation should be pre-dried where appropriate. Tablet formulations of the invention should be stored in containers which are sealed against the ingress of atmospheric moisture.

[0090] Tablet cores may then be coated with a coating layer which may be applied form an aqueous or an organic solvent system, preferably an aqueous solvent system, to provide film coated tablets.

[0091] The invention also provides a method for the manufacture of a tablet formulation as described above comprising the steps of forming said first and second layers, and any barrier layers and coating layer(s) which may be present.

[0092] In a further variant, a monolith modified release tablet may be prepared from slow release compacted granules comprising amoxycillin, a diluent/compression aid such as microcrystalline cellulose, and a pharmaceutically acceptable organic acid such as a fruit acid, for instance citric acid (if amoxycillin is present as a soluble salt thereof), or a

release retarding polymer such as xanthan gum or a mixture thereof, preferably a release retarding polymer (as hereinbefore described); and immediate release compacted granules comprising amoxycillin and potassium clavulanate (as hereinbefore described) or immediate release compacted granules comprising amoxycillin and potassium clavulanate, for instance in a 2:1 ratio, and further immediate release compacted granules comprising amoxycillin (as described in WO 98/35672, SmithKline Beecham Laboratoires Pharmaceutiques), the granules being combined with extragranular excipients to form tablets. Such granules may also be processed into other pharmaceutical formulations, for instance single dosage sachets, capsules or chewable tablets comprising a unit dosage as hereinbefore described.

[0093] Chewable tablets according to the present invention typically comprise a chewable base formed from, for instance, mannitol, sorbitol, dextrose, fructose or lactose alone or in combination. A chewable tablet may also comprise further excipients, for instance, disintegrants, lubricants, sweetening agents, colouring and flavouring agents. Such further excipients together will preferably comprise from 3 to 10%, more preferably 4 to 8%, yet more preferably 4 to 7% by weight of the tablet. Disintegrants may be present in from 1 to 4%, preferably from 1 to 3%, more preferably from 1 to 2% by weight of the tablet. Representative disintegrants include crospovidone, sodium starch glycollate, starches such as maize starch and rice strach, croscarmellose sodium and cellulose products such as microcrystalline cellulose, microfine cellulose, low substituted hydroxy propyl cellulose, either used singly or in admixture. Preferably, the disintegrant is crospovidone. Lubricants may be present in from 0.25 to 2.0%, preferably from 0.5 to 1.2% by weight of the tablet. Preferred lubricants include magnesium stearate. Preferably, the sweetening agent is an artificial sweetening agent such as sodium saccharin or aspartame, preferably aspartame, which may be present in from 0.5 to 1.5% by weight of the tablet. Preferably, a tablet of the present invention is substantially free of sugar (sucrose). Preferred flavouring agents include fruit flavours which may be natural or synthetic, for instance peppermint, cherry and banana, or a mixture thereof.

[0094] Single dose sachets according to the present invention comprise, in addition to the drug substance, excipients typically included in a sachet formulation, such as a sweetener, for instance aspartame, flavourings, for instance fruit flavours, optionally a suspending agent such as xanthan gum, as well as silica gel, to act as a desiccant

[0095] Capsules according to the present invention comprise, in addition to the drug substance, excipients typically included in a capsule, for instance starch, lactose, microcrystalline cellulose, magnesium stearate. It will be appreciated that due to the hygroscopic nature of clavulanate, the use of materials such as gelatin for forming the capsules should be avoided. Preferably, capsules are prepared from materials such as HPMC or a gelatin/PEG combination.

[0096] Preferably, the unit dosage forms of the present invention are packaged in containers that inhibit the ingress of atmospheric moisture, for instance blister packs, tightly closed bottles or desiccated pouch packs etc which are conventional in the art. Preferably, bottles also include a desiccating material, to preserve the clavulanate. Preferred bottles include HDPE bottles. Preferred blister packs include cold-formed blister packs in which each blister may contain one tablet, or two tablets,where the unit dosage is two tablets, for instance 2 x 1000/62.5 mg tablets, to improve patient compliance.

[0097] The invention will now be described by way of example only with reference to the accompanying drawings, in which:

Fig. 1 shows the structure of various types of layered tablets of the present invention, in particular the structure of substantially cylindrical compressed tablets are shown in longitudinal section. In Fig 1A, the tablet comprises a first layer (1) and a second layer (2), without any barrier layer or coating layer. In Fig 1B, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) sandwiched between the first and second layers (1) and (2). In Fig 1C, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) located on the end face of the second layer (2). In Fig 1D, the tablet comprises a first layer (1), a second layer (2), a barrier layer (3) sandwiched between the first and second layers (1) and (2), and a coating layer (4) which partly covers the tablet. The dotted line shows the possibility of the coating layer (4A) covering the entire tablet. In Fig. 1E, the tablet comprises a first layer (1) a second layer (2), and a third layer (3) intermediate between the first and second layers (1) and (2). All three of these layers (1), (2) and (3) include active material content.

Example 1 - 1000/62.5 mg modified release tablet

[0098]

Ingredient	mg/tabiet	% w/w
Immediate Release Layer		
Amoxycillin Trihydrate	654.1*	40.88

* Equivalent to 562.5 mg of amoxycillin based on an assay of 86.0%

(continued)

Ingredient	mg/tabiet	% w/w
Immediate Release Layer		
Potassium Clavulanate	76.2#	4.76
Microcrystalline Cellulose	136.4	8.52
Sodium Starch Glycollate	18.0	1.12
Colloidal Silicon Dioxide	6.3	0.39
Magnesium Stearate	9.0	0.56
Total (Immediate Release Layer)	900.0	56.23
Slow Release Layer		
Crystallised Sodium Amoxycillin	480.8**	30.05
Microcrystalline Cellulose	113.2	7.08
Xanthan Gurn	14.0	0.87
Anhydrous Citric Acid	78.0	4.87
Colloidal Silicon Dioxide	1.50	0.08
Magnesium Stearate	14.0	0.87
Total (Slow Release Layer)	700.0	43.74
Film coat		
Opadry YS-1-7700 - Composition:		
Hydroxypropylmethylcellulose 2910 6cp	11.6	
Hydroxypropylmethylcellulose 2910 15cp	3.9	
Titanium dioxide	15.1	
Polyethylene Glycol 3350	2.3	
Polyethylene Glycol 8000	2.3	
Total weight of coated tablet	1635.2	

Equivalent to 62.5 mg of clavulanic acid based on an assay of 82.0%

**Equivalent to 437.5 mg amoxycillin based on an assay of 91.0%

Example 2 - 1000/62.5 mg modified release tablet The immediate release layer and film coat are as for the tablet of Example 1

[0099]

Ingredient	mg/tablet	% w/w
Slow Release Layer		
Crystallised Sodium Amoxycillin	480.8**	30.05
Microcrystalline Cellulose	127.2	7.95
Anhydrous Citric Acid	78.0	4.87
Colloidal Silicon Dioxide	1.5	0.09
Magnesium Stearate	14.0	0.87
Total (Slow Release Layer)	700.0	43.74
Total Weight of coated tablet	1635.2	

**Equivalent to 437.5 mg amoxycillin based on an assay of 91.0%

Preparation of modified release tablets

[0100] Modified release tablets were prepared from immediate and slow release blends, in a batch process on a 900 and 700 kg scale respectively.. For the immediate release blend, containers were charged with dried microcrystalline

cellulose (1), amoxycillin trihydrate (2) and (5) (in 1:1 ratio), a potassium clavulanate/ dried microcrystalline cellulose blend (1:1) and magnesium stearate (about 50% of total) (4). The contents of containers (1) and (2) were passed through a mesh, milled in a "Fitzmill" operating at 1500 rpm and blended with the contents of container (3). The contents of container (4) were then screened and milled and blended with the initial blend and then blended with the contents of container (5) which had gone through a preliminary screening and milling step. This blend was then subjected to roller compaction using a Chilsonator operating at a pressure of 1000 psi ± 200psi and the product milled and screened through a vibratory screen with 14 and 80 meshes, to provide immediate release granules. The remaining excipients (colloidal silicon dioxide, magnesium stearate, dried microcrystalline cellulose and dried sodium starch glycollate) were then screened and milled and combined with a portion of the immediate release granules in a blender, blended and then combined with the remaining granules and blended, to form the IR blend.

[0101] For the slow release blend, containers were charged with dried microcrystalline cellulose (about 70%) and anhydrous citric acid (1), sodium amoxycillin (2) and (4) (in a 1:1 ratio), and magnesium stearate (about 70%), colloidal silicon dioxide and xanthan gum (3). The contents of containers (1) and (2) were screened and milled in a Fitzmill, and then blended with the contents of container (3), blended and then the contents of container (4) which had been milled and screened in a preliminary step. This blend was subjected to roller compaction on a chilsonator, operating at a pressure of 600 psi ± 100 psi, milled and screened, to provide slow release granules. The remaining excipients (magnesium stearate, dried microcrystalline cellulose) were screened and combined with a portion of the slow release granules, blend and then the remaining slow release granules added and blended, to provide the SR blend.

[0102] The IR and SR blends were then compressed as separate layers in a bilayer tablet press equipped with punches measuring 0.0406 inches by 0.8730 inches and having a modified capsule shape. For the first (immediate release) layer, there was no pre-compression, and the main compression was less than 10 KN. For the second layer, there was a pre-compression of less than 20 KN, and a main compression of less than 60 KN. The tablets thus produced had a total weight of 1600 mg ± 48 mg, a hardness in the range 8 to 18 SCU and a friability of less than 0.5%.

Finally, the tablet cores were coated with an aqueous film coating in a 60 inch coating pan, operating on a 300 kg sub-batch. The pan was equipped with 4 spray guns and rotated at 3 to 5 rpm. The inlet air was dehumidified with the temperature in the range 56 to 60°C whilst the exhaust air humidity was in the range 4 to 12% and the temperature in the range 43 to 50°C. The spray rate was 80 to 120 ml/min/spray gun.

Reference Example 3 - Slow release tablet (875 mg)

[0103]

(a) Sodium Amoxycillin Tablet		
	mg/tablet	%
Crystallised Sodium Amoxycillin 91%*	961.54	73.96
Dried Microcrystalline Cellulose	273.46	21.04
Magnesium Stearate	13.0	1.00
Xanthan gum 200 mesh**	52.0	4.00
Total	1300	100

(b) Sodium Amoxycillin Tablet with citric acid		
	mg/tablet	%
Crystallised Sodium Amoxycillin 91%*	961.54	66.31
Dried Microcrystalline Cellulose	288.96	19.92
Magnesium Stearate	14.50	1.00
Citric acid	156	10.75
Xanthan gum 200 mesh**	29.0	2.00
Total	1450	100

(c) Amoxycillin Trihydrate Tablet		
	mg/tablet	%
Amoxycillin Trihydrate 86%*	1017.4	78.26
Dried Microcrystalline Cellulose	217.6	16.74
Magnesium Stearate	13.0	1.00
Xanthan Gum, 200 mesh**	52.0	4.00
Total	1300	100

* adjusted for the potency of the amoxycillin component and corresponding to 875 mg amoxycillin,

** Xantural 75

Example 4 - 875/62.5 mg modified release tablet

Slow release layer

[0104] This may be formed using half the quantities given above, for a slow release layer comprising about 438 mg amoxycillin.

Immediate release layer - 1	
Amoxycillin trihydrate	507mg
(equiv to amoxycillin free acid)	(438)
Potassium clavulanate	71.8
(equivalent to clavulanic acid)	(62.5)
Microcrystalline cellulose (Avicel PH102)	125
Sodium starch glycollate (Explotab)	26
Magnesium stearate	6.5

[0105] The immediate release layer comprises nominally 438/62.5mg amoxycillin/clavulanate.

Immediate release layer - 2	
Amoxycillin trihydrate	507mg
(equiv to amoxycillin free acid)	(438)
Potassium clavulanate	71.8

(continued)

Immediate release layer - 2	
(equivalent to clavulanic acid)	(62.5)
Microcrystalline cellulose (Avicel PH102)	135
Sodium starch glycollate (Explotab)	34
Talc	67
Magnesium stearate	25
Silica (Syloid)	17

[0106] The immediate release layer comprises nominally 438/62.5mg amoxycillin/clavulanate.

Barrier Layers

[0107] Barrier layers and methods for their preparation are described in WO 95/20946 (SmithKline Beecham).

Preparation of Tablets

[0108] The active ingredients, fillers and diluents (microcrystalline cellulose), release controlling agents (if present), disintegrants (crospovidone, sodium starch glycollate) etc are mixed. Lubricants (talc, Mg-stearate) and colloidal silicon dioxide (Syloid 244) are added, and mixing is continued for another minute. The complete mixture is slugged on a tablet press or roller compacted (briquetting step), followed by size reduction (Apex, Fitzmill, Frewitt) and passage through an oscillatory sieve or particle size classifier (Kason, Sweco). If the flow properties are unsatisfactory, the briquetting step is repeated. Separate compressed blends are prepared for the immediate and slow release layers, and barrier layer, if present.

[0109] In some cases, where the bulk density is rather low, a densifying step (pre-tabletting and sieving as in the briquetting method) may be required in order to achieve the nominal weight of a particular layer.

[0110] The blends are then compressed as separate layers on a layer tablet press to form bilayered tablets. Tablets may then be coated with a white opaque coating, for instance the product Opadry, Opaspray (Colorcon).

Example 5 - Dissolution Testing Methods

[0111] The release of amoxycillin and clavulanate from tablets into static media was measured using the <711> Dissolution Test, Apparatus 2, provided in USP 23, 1995.

Test specifications:	
Temperature:	37.0 ± 0.5°C
Medium:	Deionized water, 900 mL
Paddle speed	75 rpm

Method

[0112] Aliquots of medium were removed for assay after 15, 30, 45, 60, 90, 120, 150, 180, 240, 300 360, 420 and 480 min, each aliquot being replaced simultaneously by an equal volume of medium to maintain constant volume. The amount of drug substance was determined by UV spectrometry, at 272nM. The resulting dissolution profile for the tablets of Example 1 and 2 are shown as Fig 2.

***in vivo* Pharmacokinetic evaluation of formulations**

[0113] The bioavailability of dosages according to the present invention were evaluated in two human volunteer studies, Study A and Study B. These were open, randomised, crossover studies in healthy volunteers. Each dosage was administered with the aid of approximately 200 mL water, at the start of a light breakfast and after an overnight fast. Blood samples were collected into tubes containing EDTA at nominal times of pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after start of dosing, for assay of plasma levels of amoxycillin and clavulanate. Samples were cooled in an ice-bath awaiting further processing. Plasma was separated by refrigerated centrifugation at 4°C and transferred to appropriately labelled polypropylene specimen containers and stored frozen at approximately -70°C until

assayed.

[0114] Samples were assayed for amoxycillin using a method based on protein precipitation with acetonitrile. Amoxycillin was extracted from human plasma (50 µL) by means of protein precipitation, using acetonitrile containing the internal standard and quantified by LC/MS/MS. Specifically, human plasma (50 µL) was pipetted into a 1.5 mL Eppendorf tube followed by the addition of acetonitrile containing the internal standard ([$^{13}C_6$]-amoxycillin, 200 µL). The tube was capped, vortex mixed and shaken for approximately 15 minutes. After centrifuging the sample (approximately 11,000 x g, for 15 minutes), the supernatant was transferred to a silanised 1.1 mL tapered autosampler vial containing 200 µL of 5mM ammonium acetate solution. An aliquot of extract was injected onto the HPLC/MS/MS system for analysis. The mass spectrometer was operated in positive ion mode, employing a Turbo IonSpray interface. Multiple reaction monitoring (MRM) was used to detect the components, amoxycillin and [$^{13}C_6$]-amoxycillin. The MRM procedure involves (1) mass selection of a characteristic ion of the required drug or internal standard in the first quadrupole mass analyser (2) fragmentation of the selected ion in the instrument's collision cell (3) detection of a fragment ion which is characteristic of the compound of interest. Quantification is performed by comparison of the chromatographic peak areas of the drug relative to the area of the internal standard. Linear responses in the analyte/internal standard peak area ratios were observed for analyte concentrations ranging from 0.05 µg/mL (lower limit of quantification; LLQ) to 10 µg/mL (upper limit of quantitication: ULQ).

[0115] Samples were assayed for clavulanate using a method based on protein precipitation with acetonitrile. Clavulanate was extracted from human plasma by means of liquid/liquid using internal standard and quantified by LC/MS/MS. Specifically, human plasma (50 µL) was pipetted into a 1.5 mL Eppendorf tube followed by 0.2mM ammonium acetate (200µL) before addition of acetonitrile containing the internal standard (6-aminopenicillanic acid, 400 µL). The tube was capped, vortex mixed and shaken for approximately 20 minutes. After centrifuging the sample (approximately 14,500 x g, for 15 minutes), the supernatant was transferred to a clean eppendorf tube and dichloromethane added. After further mixing and centrifugation (approximately 14, 500 x g for 10 minutes) supernatent (no more than 150uL) was transferred to a tapered 1.1mL autosampler vial and left uncapped for at least 20 minutes to allow any traces of dichloromethane to evaporate. An aliquot of the extract was injected onto the HPLC/MS/MS system for analysis. The mass spectrometer was operated in positive ion mode, employing a Turbo IonSpray interface. Multiple reaction monitoring (MRM) was used to detect the components, clavulanate and 6-aminopenicillanic acid. The MRM procedure involves (1) mass selection of a characteristic ion of the required drug or internal standard in the first quadrupole mass analyser (2) fragmentation of the selected ion in the instrument's collision cell (3) detection of a fragment ion which is characteristic of the compound of interest. Quantification is performed by comparison of the chromatographic peak areas of the drug relative to the area of the internal standard. Linear responses in the analyte/internal standard peak area ratios were observed for analyte concentrations ranging from 0.05 µg/mL (lower limit of quantification; LLQ) to 10 µg/mL (upper limit of quantitication: ULQ).

[0116] QC samples were assayed with each batch of samples against separately prepared calibration standards. The results of the QC samples were used to assess the day-to-day performance of the assay.

[0117] Plasma concentration-time data for each subject in each regimen were analysed by non-compartmental methods using the non-compartmental pharmacokinetic analysis program WinNonlin Professional Version 1.5. All calculations were based on actual sampling times. Pharmacokinetic parameters determined included maximum observed plasma concentration (Cmax) and time to reach maximum plasma concentration (Tmax). The apparent terminal elimination rate constant (lz) was derived from the log-linear disposition phase of the concentration-time curve using linear least-squares regression with visual inspection of the data to determine the appropriate number of points to calculate lz. The apparent terminal elimination half-life (T1/2) was calculated as ln(2)/lz.

[0118] Area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration [AUC(0-t)] was determined using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid [Chiou WL., J. Pharmacokinet. Biopharm., 1978,6,539-547]. The area under the plasma concentration-time curve extrapolated to infinity [AUC(0-inf)] was calculated as the sum of AUC(0-t) and C(t)/lz, where C(t) was the predicted concentration from the log-linear regression analysis at the last measurable time point.

[0119] The time above the minimum inhibitory plasma concentration (T>MIC) was calculated manually by graphical interpolation, where the minimum inhibitory plasma concentrations was defined as 4 ug/mL for amoxycillin.

[0120] The mean concentration-time profiles for amoxycillin and for clavulanate were derived at each nominal sampling time for each formulation. In cases where a post-dose value was not quantifiable, a value of 1/2 the LLQ (0.050 ug/mL) was assigned to determine the mean value. Where the calculated mean value was less than the LLQ or was based on greater than 50% NQ values, a value of NQ was assigned for that sampling time.

[0121] Log_e-transformed Cmax and untransformed T>MIC for each of the formulations were analysed using Analysis of Covariance (ANCOVA) fitting a single term for formulation and fitting the data from the reference formulation as a co-variate. The 95% confidence intervals for the means of each formulation were constructed using the residual variance from the model. For Cmax, the confidence interval estimates on the log scale were then back-transformed to obtain the 95% confidence intervals of the geometric mean. These results were displayed graphically.

[0122] Assumptions underlying the analyses were assessed by inspection of residual plots. Homogeneity of variance was assessed by plotting the studentised residuals against the predicted values from the model, whilst normality was assessed using normal probability plots. Particular attention was paid to any outlying values observed with the reference formulation.

Study A

[0123] The first study compared three modified release dosages of 1750/125 mg (formulations I to III) and a fourth modified release dosages not forming part of the present invention of 1500/125 mg (formulation IV) against an immediate release dosage of 1750/125 mg (formulation V), as follows:

(a) a dosage of 1750/125 mg amoxycillin/potassium clavulanate, made up of a combination of one modified release tablet comprising 875/125 mg amoxycillin trihydrate/clavulanate and 4% xanthan gum and one immediate release tablet comprising 875 mg amoxycillin trihydrate (formulation I);
(b) a dosage of 1750/125 mg amoxycillin/potassium clavulanate, made up of a combination of one modified release tablet comprising 875/125 mg crystallised sodium amoxycillin/clavulanate and 4% xanthan gum and one immediate release tablet comprising 875 mg amoxycillin trihydrate (formulation II);
(c) a dosage of 1750/125 mg amoxycillin/potassium clavulanate, made up of a combination of one modified release tablet comprising 875/125 mg crystallised sodium amoxycillin/clavulanate, citric acid (156 mg) and 2% xanthan gum and one immediate release tablet comprising 875 mg amoxycillin trihydrate (formulation III);
(d) a dosage of 1500/125 mg amoxycillin/potassium clavulanate (made up of a modified release tablet comprising 500/125 mg crystallised sodium amoxycillin/potassium clavulanate and two immediate release tablet comprising 500 mg amoxycillin trihydrate (Amoxyl, SmithKline Beecham) (formulation IV); and
(e) a dosage of 1750/125 mg amoxycillin/potassium clavulanate, made up of a combination of one immediate release tablet comprising 875/125 mg amoxycillin trihydrate/clavulanate (Augmentin, SmithKline Beecham) and one immediate release tablet comprising 875 mg amoxycillin trihydrate (Amoxyl, SmithKline Beecham) (formulation V).

Results

[0124]

Formulation	n	Cmax[1]	T>MIC[1,2]	AUC[1,3]
I	8	12.75 (4.96)	4.5 (1.8)	47.83
II	8	18.56 (4.72)	4.4 (1.0)	57.46
III	8	13.03 (2.34)	5.73 (2.54)	54.93
IV	8	17.33 (4.66)	4.8 (0.9)	56.71
V	40	20.21 (6.09)	4.2 (0.9)	56.33

() standard deviation
1 arithmetic mean value
2 T>MIC is the time (h) above an amoxycillin concentration of 4 µg/ml
3 Area under the curve (0 to 12 h, µg.h/mL)

[0125] The pharmacokinetic profile is shown in Figure 3.

Study B

[0126] The second study investigated two different modified release dosages of 2000/125 mg (formulations VI and VII) against an immediate release dosage of 2000/125 mg (formulation VIII), as follows:

(a) a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of two bilayer tablets according to Example 1 (formulation VI);
(b) a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of two bilayer tablets according to Example 2 (formulation VII);
(c) a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of a combination of three tablets each

comprising 500 mg amoxycillin (Amoxyl, SmithKline Beecham) and one tablet comprising 500 mg amoxycillin and 125 mg potassium clavulanate (Augmentin, SmithKline Beecham) (formulation VIII).

Results

[0127]

Formulation	N	Cmax[1]	T>MIC[1,2]	T>MIC[1,3]	AUC[1,4]
VI	7	17.41 (1.93)	6.0 (1.3)	4.8 (1.2)	74.9
VII	8	17.46 (6.02)	5.9 (1.3)	4.0 (1.3)	71.5
VIII	12	23.75 (5.73)	4.9 (1.1)	3.5 (1.0)	69.2

() standard deviation
[1] arithmetic mean value
[2] T>MIC is the time (h) above an amoxycillin concentration of 4 µg/ml
[3] T>MIC is the time (h) above an amoxycillin concentration of 8 µg/ml
[4] Area under the curve (0 to 12 h, µg.h/mL).

[0128] Comparison of the AUC values for formulations VI and VII (bilayer tablets) against VIII (immediate release tablets) shows that the absorption of the amoxycillin component has not been compromised by formulating a part of it in a slow release layer. This means that there is no extra, unabsorbed amoxycillin which may otherwise cause problems further down in the GI tract, for instance due to a lack of absorption and destruction of symbiotic bacteria

[0129] It was also found that for formulation VI, there was less inter-subject variability in the amoxycillin plasma concentrations than for formulation VII. These formulations were the same, except that formulation VI also comprised xanthan gum (2%) in the slow release layer.

[0130] The pharmacokinetic profile for amoxycillin plasma concentration is shown in Figure 4 (in which A is formulation VI, B is formulation VII, D is formulation VIII).

[0131] The pharmacokinetic profile for the clavulanate component was substantially the same for the bilayer tablets and the immediate release tablets, showing that the bioavailability thereof was not compromised by incorporation into the immediate release layer of a bilayer tablet.

[0132] The present invention also extends to formulations which are bioequivalent to the tablets of formulations VI and VII, in terms of both rate and extent of absorption, for instance as defined by the US Food and Drug Administration and discussed in the so-called "Orange Book" (Approved Drug Products with Therapeutic Equivalence Evaluations, US Dept of Health and Human Services, 19th edn, 1999).

Reference Data

[0133] The existing Augmentin 875/125mg tablet has a C_{max} value of 11.6±2.8 µg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802). The time above MIC was about 40% of the 12 hour dosing interval for an MIC of 2 µg/ml and about 30% for an MIC of 4 µg/ml (SmithKline Beecham data).

Claims

1. A modified release pharmaceutical formulation comprising amoxycillin and potassium clavulanate in a ratio from 14:1 to 20:1 in which all of the potassium clavulanate and a first part of amoxycillin are formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and the first part of amoxycillin, to form an immediate release phase, and further comprising a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of the second part of amoxycillin, to form a slow release phase, and in which the ratio of amoxycillin in the immediate and slow release phases is from 3:1 to 1:3.

2. A pharmaceutical formulation as claimed in claim 1 in which the ratio of amoxycillin and potassium clavulanate is 14:1 to 16:1.

3. A pharmaceutical formulation as claimed in claim 1 or 2 in which the ratio of amoxycillin and potassium clavulanate is 16:1.

4. A modified release pharmaceutical formulation as claimed in any one of claims 1 to 3 in which th in the immediate and slow release phases is from 3:1 to 2:3.

5. A pharmaceutical formulation as claimed in any one of claims 1 to 4 which has a biphasic pro amoxycillin.

6. A pharmaceutical formulation as claimed in any one of claims 1 to 5 which has an AUC value which is at 80% of that of the corresponding dosage of amoxycillin taken as a conventional, immediate release tablet(s), over the same dosage period.

7. A pharmaceutical formulation as claimed in any one of claims 1 to 6 in which the ratio of amoxycillin in the immediate and slow release phases is from 3:2 to 1:1.

8. A pharmaceutical formulation as claimed in any one of claims 1 to 7 comprising a unit dosage in the range 700 to 1300 mg or 1400 to 2600 mg amoxycillin and a corresponding amount of potassium clavulanate.

9. A pharmaceutical formulation as claimed in any one of claims 1 to 8 in which the unit dosage: is 1000 or 875 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate; or 2000 or 1750 mg ±5% amoxycillin and 125 mg ±5% potassium clavulanate; in a nominal ratio of about 16:1, or 14:1, respectively, in combination with pharmaceutically acceptable excipients or carriers.

10. A pharmaceutical formulation as claimed in any one of claims 1 to 9 which is a tablet formulation.

11. A pharmaceutical formulation as claimed in claim 10 comprising 1000 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1 in which the immediate release phase comprises about 563 mg ±5% amoxycillin and about 62.5 mg ±5% of potassium clavulanate and the slow release phase comprises about 438 mg ±5% of amoxycillin.

12. A pharmaceutical formulation as claimed in any one of claims 1 to 11 in which the amoxycillin of the slow release phase consists essentially of crystallised sodium amoxycillin.

13. A pharmaceutical formulation as claimed in any one of claims 1 to 12 which is a layered tablet comprising potassium clavulanate and amoxycillin in an immediate release layer and amoxycillin in a slow release layer.

14. A layered tablet as claimed in claim 13 in which the slow release layer comprises a release retarding excipient which is selected from a pH sensitive polymers; a release-retarding polymer which has a high degree of swelling in contact with water or aqueous media; a polymeric material which forms a gel on contact with water or aqueous media; and a polymeric material which have both swelling and gelling characteristics in contact with water or aqueous media, or a mixture thereof.

15. A layered tablet as claimed in claim 14 in which the release retarding gellable polymer is selected from methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, and non-cross linked polyvinylpyrrolidone, or xanthan gum.

16. A layered tablet as claimed in claim 14 or 15 in which the release retarding excipient is xanthan gum.

17. A layered tablet as claimed in claim 16 in which the xanthan gum is present in from 1 to 25% by weight of the layer.

18. A layered tablet as claimed in any one of claims 13 to 17 in which the slow release layer comprises from 70 to 80% of amoxycillin, from 1 to 25% of xanthan gum, from 10 to 20% of fillers/compression aids, and conventional quantities of lubricants.

19. A layered tablet as claimed in claim 13 in which the slow release phase comprises sodium amoxycillin and in which the slow release layer comprises a release retarding excipient which is a pharmaceutically acceptable organic acid present in a molar ratio of from 100:1 to 1:10, the ratio being amoxycillin salt to organic acid.

20. A layered tablet as claimed in claim 19 in which the pharmaceutically acceptable organic acid present in a molar ratio of from 50:1 to 1:5.

21. A layered tablet as claimed in claim 19 in which the pharmaceutically acceptable organic acid is present in a molar ratio of from 20:1 to 1:5.

22. A layered tablet as claimed in claim 19 in which the pharmaceutically acceptable organic acid is present in a molar ratio of from 20:1 to 1:2.

23. A layered tablet as claimed in any one of claims claim 19 to 22 in which the pharmaceutically acceptable acid is citric acid.

24. A layered tablet as claimed in claim 23 in which citric acid is present in a molar ratio of about 2:1 to 1:1.2.

25. A layered tablet as claimed in any one of claims 19 to 24 further comprising a release retarding gellable polymer.

26. A layered tablet as claimed in claim 25 in which the release retarding gellable polymer is xanthan gum.

27. A layered tablet as claimed in claim 21 in which xanthan gum is present in from 0.5 to 8% by weight of the slow release layer.

28. A pharmaceutical layered tablet formulation as claimed in any one of claims 19 to 27 comprising from 700 to 1250 mg amoxycillin and a pro rata amount of potassium clavulanate, in a nominal ratio of about 16:1 or 14:1, respectively, in combination with pharmaceutically acceptable excipients or carriers.

29. A layered tablet as claimed in claim 28 which comprises 1000 mg ±5% of amoxycillin and 62.5 mg ±5% of potassium clavulanate and which comprises in the slow release layer about 438 mg ±5% of crystallised sodium amoxycillin, about 78 mg ±10% of citric acid and optionally about 2% by weight of xanthan gum

30. A modified release pharmaceutical formulation as claimed in claim 1 in which the immediate release phase is formed from immediate release granules comprising amoxycillin and potassium clavulanate or immediate release granules comprising amoxycillin and potassium clavulanate and further immediate release granules comprising amoxycillin and the slow release phase is formed from slow release granules comprising amoxycillin.

31. A modified release pharmaceutical formulation as claimed in claim 30 which is a single dose sachet, a capsule, a monolith tablet, a dispersible tablet, or a chewable tablet which may be effervescent and/or dispersible.

32. A modified release pharmaceutical formulation as claimed in any one of claims 1 to 31 comprising 1000mg ±5% amoxycillin and 62.5mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, in combination with pharmaceutically acceptable excipients or carriers.

33. A modified release pharmaceutical formulation as claimed in any one of claims 1 to 32 which has an *in vitro* dissolution rate in which 45 to 65% of the amoxycillin content is dissolved within 30 min.

34. A modified release pharmaceutical formulation as claimed in any one of claims 1 to 33 which has an *in vitro* dissolution rate in which 50 to 75% of the amoxycillin content is dissolved within 60 min.

35. A modified release pharmaceutical formulation as claimed in any one claims 1 to 34 which has an *in vitro* dissolution rate in which 55 to 85% of the amoxycillin content is dissolved within 120 min.

36. A modified release pharmaceutical formulation as claimed in any one of claims 1 to 35 which has an *in vitro* dissolution rate in which 70 to 95% of the amoxycillin content is dissolved within 180 min.

37. A modified release pharmaceutical formulation as claimed in any one claims 1 to 36 which has an *in vitro* dissolution rate in which 70 to 100% of the amoxycillin content is dissolved within 240 min.

38. A pharmaceutical formulation as claimed in claim 31 comprising slow release compacted granules comprising amoxycillin, a diluent/compression aid, and a release retarding polymer which is xanthan gum, or a soluble salt of amoxycillin, a diluent/compression aid, and an organic acid or a release retarding polymer or a mixture thereof.

39. A formulation as claimed in any one of claims 1 to 38 having an AUC, C_{max}, and T>MIC substantially according

to Figure 4 (formulation VI or VII).

40. The use of amoxycillin and potassium clavulanate in the manufacture of a medicament as defined in claim 1 for treating bacterial infections in humans at dosage intervals of about 12 h.

41. The use as claimed in claim 40 in which the administration provides a mean plasma concentration of amoxycillin of 4 µg/mL for at least 4.4 h and a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 12 µg/mL.

42. The use as claimed in claim 40 in which the administration provides a mean plasma concentration of amoxycillin of 4 µg/mL for at least 4.8 h and a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 16 µg/mL.

43. The use as claimed in claim 40 in which the administration provides a mean plasma concentration of amoxycillin of 8 µg/mL for at least 4.4h.

44. The use as claimed in any one of claims 40 to 43 in which the infection is caused by the organisms *S pneumoniae*, including Drug Resistant and Penicillin Resistant *S pneumoniae, H influenzae* and/or *M catarrhalis.*

Patentansprüche

1. Pharmazeutische Formulierung mit modifizierter Freisetzung, die Amoxycillin und Kaliumclavulanat in einem Verhältnis von 14:1 bis 20:1 umfaßt, worin das gesamt Kaliumclavulanat und ein erster Teil von Amoxycillin mit pharmazeutisch akzeptablen Hilfsstoffen formuliert sind, die eine unmittelbare Freisetzung des Kaliumclavulanats und des ersten Teils von Amoxycillin erlauben, um eine Phase mit unmittelbarer Freisetzung zu bilden, und die ferner einen zweiten Teil von Amoxycillin umfaßt, der mit pharmazeutisch akzeptablen Hilfsstoffen formuliert ist, die eine langsame Freisetzung des zweiten Teils von Amoxycillin erlauben, um eine Phase mit langsamer Freisetzung zu bilden, und worin das Verhältnis von Amoxycillin in den Phasen mit unmittelbarer und langsamer Freisetzung 3:1 bis 1:3 ist.

2. Pharmazeutische Formulierung gemäß Anspruch 1, worin das Verhältnis von Amoxycillin und Kaliumclavulanat 14:1 bis 16:1 ist.

3. Pharmazeutische Formulierung gemäß Anspruch 1 oder 2, worin das Verhältnis von Amoxycillin und Kaliumclavulanat 16:1 ist.

4. Pharmazeutische Formulierung mit modifizierter Freisetzung gemäß einem der Ansprüche 1 bis 3, worin das Verhältnis von Amoxycillin in den Phasen mit unmittelbarer und langsamer Freisetzung 3:1 bis 2:3 ist.

5. Pharmazeutische Formulierung gemäß einem der Ansprüche 1 bis 4, die ein in bezug auf Amoxycillin zweiphasiges Profil hat.

6. Pharmazeutische Formulierung gemäß einem der Ansprüche 1 bis 5, die einen AUC-Wert hat, der wenigstens 80 % desjenigen der entsprechenden Dosierung von Amoxycillin ist, das als herkömmliche Tablette(n) mit unmittelbarer Freisetzung über den gleichen Dosierungszeitraum eingenommen wird.

7. Pharmazeutische Formulierung gemäß einem der Ansprüche 1 bis 6, worin das Verhältnis von Amoxycillin in den Phasen mit unmittelbarer und langsamer Freisetzung 3:2 bis 1:1 ist.

8. Pharmazeutische Formulierung gemäß einem der Ansprüche 1 bis 7, die eine Einheitsdosierung im Bereich von 700 bis 1300 mg oder 1400 bis 2600 mg Amoxycillin und eine entsprechende Menge Kaliumclavulanat umfaßt.

9. Pharmazeutische Formulierung gemäß einem der Ansprüche 1 bis 8, worin die Einheitsdosierung: 1000 oder 875 mg ± 5 % Amoxycillin und 62,5 mg ± 5 % Kaliumclavulanat; oder 2000 oder 1750 mg ± 5 % Amoxycillin und 125 mg ± 5 % Kaliumclavulanat; in einem Nennverhältnis von ca. 16:1. bzw. 14:1 ist, in Kombination mit pharmazeutisch akzeptablen Hilfsstoffen oder Trägern.

10. Pharmazeutische Formulierung gemäß einem der Ansprüche 1 bis 9, die eine Tablettenformulierung ist.

11. Pharmazeutische Formulierung gemäß Anspruch 10, die 1000 mg ± 5 % Amoxycillin und 62,5 mg ± 5 % Kaliumclavulanat in einem Nennverhältnis von ca. 16:1 umfaßt, wobei die Phase mit unmittelbarer Freisetzung ca. 563 mg ± 5 % Amoxycillin und ca. 62,5 mg ± 5 % Raliumclavulanat umfaßt und die Phase mit langsamer Freisetzung ca. 438 mg ± 5 % Amoxycillin umfaßt.

12. Pharmazeutische Formulierung gemäß einem der Ansprüche 1 bis. 11, worin das Amoxycillin der Phase mit langsamer Freisetzung im wesentlichen aus kristallisiertem Natriumamoxycillin besteht.

13. Pharmazeutische Formulierung gemäß einem der Ansprüche 1 bis 12, die eine Schichttablette ist, die Kaliumclavulanat und Amoxycillin in einer Schicht mit unmittelbarer Freisetzung und Amoxycillin in einer Schicht mit langsamer Freisetzung umfaßt.

14. Schichttablette gemäß Anspruch 13, worin die Schicht mit langsamer Freisetzung einen die Freisetzung retardierenden Hilfsstoff umfaßt, der aus einem pH-empfindlichen Polymer; einem die Freisetzung retardierenden Polymer, das einen hohen Quellgrad in Kontakt mit Wasser oder wäßrigen Medien hat; einem polymeren Material, das bei Kontakt mit Wasser oder wäßrigen Medien ein Gel bildet; und einem polymeren Material, das sowohl Quell- als auch Geliereigenschaften bei Kontakt mit Wasser oder wäßrigen Medien hat, oder aus einer Mischung daraus ausgewählt ist.

15. Schichttablette gemäß Anspruch 14, worin das die Freisetzung retardierende gelierbare Polymer aus Methylcellulose, Carboxymethylcellulose, Hydroxypropylmethylcellulose mit geringem Molekulargewicht, Polyvinylalkoholen mit geringem Molekulargewicht, Polyoxyethylenglykolen und nichtvernetztem Polyvinylpyrrolidon oder Xanthangummi ausgewählt ist.

16. Schichttablette gemäß Anspruch 14 oder 15, worin der die Freisetzung retardierende Hilfsstoff Xanthangummi ist.

17. Schichttablette gemäß Anspruch 16, worin das Xanthangummi mit 1 bis 25 Gew.-% der Schicht vorhanden ist.

18. Schichttablette gemäß einem der Ansprüche 13 bis 17, worin die Schicht mit langsamer Freisetzung 70 bis 80 % Amoxycillin, 1 bis 25 % Xanthangummi, 10 bis 20 % Füllstoffe/Preßhilfsstoffe und herkömmliche Mengen von Schmiermitteln umfaßt.

19. Schichttablette gemäß Anspruch 13, worin die Phase mit langsamer Freisetzung Natriumamoxycillin umfaßt, und worin die Schicht mit langsamer Freisetzung einen die Freisetzung retardierenden Hilfsstoff umfaßt, der eine pharmazeutisch akzeptable organische Säure ist, die in einem Molverhältnis von 100:1 bis 1:10 vorhanden ist, wobei das Verhältnis Amoxycillinsalz zu organische Säure ist.

20. Schichttablette gemäß Anspruch 19, worin die pharmazeutisch akzeptable organische Säure in einem Molverhältnis von 50:1 bis 1:5 vorhanden ist.

21. Schichttablette gemäß Anspruch 19, worin die pharmazeutisch akzeptable organische Säure in einem Molverhältnis von 20:1 bis 1:5 vorhanden.ist.

22. Schichttablette gemäß Anspruch 19, worin die pharmazeutisch akzeptable organische Säure in einem Molverhältnis von 20:1 bis 1:2 vorhanden ist.

23. Schichttablette gemäß einem der Ansprüche 19 bis 22, worin die pharmazeutisch akzeptable Säure Zitronensäure ist.

24. Schichttablette gemäß Anspruch 23, worin Zitronensäure in einem Molverhältnis von ca. 2:1 bis 1:1,2 vorhanden ist.

25. Schichttablette gemäß einem der Ansprüche 19 bis 24, die ferner ein die Freisetzung retardierendes gelierbares Polymer umfaßt.

26. Schichttablette gemäß Anspruch 25, worin das die Freisetzung retardierende gelierbare Polymer Xanthangummi ist.

27. Schichttablette gemäß Anspruch 21, worin Xanthangummi mit 0,5 bis 8 Gew.-% der Schicht mit langsamer Freisetzung vorhanden ist.

28. Pharmazeutische Schichttablettenforumlierung gemäß einem der Ansprüche 19 bis 27, die 700 bis 1250 mg Amoxycillin und eine anteilige Menge Raliumclavulanat in einem Nennverhältnis von ca. 16:1 oder respektive 14: 1 in Kombination mit pharmazeutisch akzeptablen Hilfsstoffen oder Trägern umfaßt.

29. Schichttablette gemäß Anspruch 28, die 1000 mg ± 5 % Amoxycillin und 62,5 mg ± 5 % Kaliumclavulanat umfaßt, und die in der Schicht mit langsamer Freisetzung ca. 438 mg ± 5 % kristallisiertes Natriumamoxicillin, ca. 78 mg ± 10 % Zitronensäure und gegebenenfalls ca. 2 Gew.-% Xanthangummi umfaßt.

30. Pharmazeutische Formulierung mit modifizierter Freisetzung gemäß Anspruch 1, worin die Phase mit. unmittelbarer Freisetzung aus Granalien mit unmittelbarer Freisetzung, die Amoxycillin und Kaliumclavulanat umfassen, oder aus Granalien mit unmittelbarer Freisetzung, die Amoxycillin und Kaliumciavulanat umfassen, und ferner Granalien mit unmittelbarer Freisetzung, die Amoxycillin umfassen, gebildet ist und die Phase mit langsamer Freisetzung aus Granalien mit langsamer Freisetzung gebildet ist, die Amoxycillin umfassen.

31. Pharmazeutische Formulierung mit modifizierter Freisetzung gemäß Anspruch 30, die eine Einzeldosispackung, eine Kapsel, eine Monolith-Tablette, eine dispergierbare Tablette oder eine kaubare Tablette ist, die sprudelnd und/oder dispergierbar sein kann.

32. Pharmazeutische Formulierung mit modifizierter Freisetzung gemäß einem der Ansprüche 1 bis 31, die 1000 mg ± 5 % Amoxycillin und 62,5 mg ± 5 % Kaliumclavulanat in einem Nennverhältnis von ca. 16:1 in Kombination mit pharmazeutisch akzeptablen Hilfsstoffen oder Trägern umfaßt.

33. Pharmazeutische Formulierung mit modifizierter Freisetzung gemäß einem der Ansprüche 1 bis 32, die eine Auflösungsgeschwindigkeit in vitro hat, in der 45 bis 65 % des Amoxycillin-Gehalts innerhalb von 30 min aufgelöst werden.

34. Pharmazeutische Formulierung mit modifizierter Freisetzung gemäß einem der Ansprüche 1 bis 33, die eine Auflösungsgeschwindigkeit in vitro hat, in der 50 bis 75 % des Amoxycillin-Gehalts innerhalb von 60 min aufgelöst werden.

35. Pharmazeutische Formulierung mit modifizierter Freisetzung gemäß einem der Ansprüche 1 bis 34, die eine Auflösungsgeschwindigkeit in vitro hat, in der 55 bis 55 % des Amoxycillin-Gehalts innerhalb von 120 min aufgelöst werden.

36. Pharmazeutische Formulierung mit modifizierter Freisetzung gemäß einem der Ansprüche 1 bis 35, die eine Auflösungsgeschwindigkeit in vitro hat, in der 70 bis 95 % des Amoxycillin-Gehalts innerhalb von 180 min aufgelöst werden.

37. Pharmazeutische Formulierung mit modifizierter Freisetzung gemäß einem der Ansprüche 1 bis 36, die eine Auflösungsgeschwindigkeit in vitro hat, in der 70 bis 100 % des Amoxycillin-Gehalts innerhalb von 240 min aufgelöst werden.

38. Pharmazeutische Formulierung gemäß Anspruch 31, die kompaktierte Granalien mit langsamer Freisetzung umfaßt, die Amoxycillin, ein Verdünnungsmittel/einen Preßhilfsstoff und ein die Freisetzung retardierendes Polymer, das Xanthangummi ist, oder ein lösliches Salz von Amoxycillin, ein Verdünnungsmittel/einen Preßhilfsstoff und eine organische Säure oder ein die Freisetzung retardierendes Polymer oder eine Mischung daraus umfassen.

39. Formulierung gemäß einem der Ansprüche 1 bis 38 mit einem AUC, C_{max} und T>MHK im wesentlichen gemäß Figur 4 (Formulierung VI oder VII).

40. Verwendung von Amoxycillin und Kahumdavulanat in der Herstellung eines Medikaments wie in Anspruch 1 definiert zur Behandlung von bakteriellen Infektionen bei Menschen und mit Dosierungsintervallen von ca. 12 h.

41. Verwendung gemäß Anspruch 40, worin die Verabreichung eine mittlere Plasmakonzentration von Amoxycillin von 4 µg/ml für wenigstens 4,4 h und eine mittlere maximale Plasmakonzentration (C_{max}) von Amoxycillin von

wenigstens 12 µg/ml bereitstellt.

42. Verwendung gemäß Anspruch 40, worin die Verabreichung eine mittlere Plasmakonzentration von Amoxycillin von 4 µg/ml für wenigstens 4,8 h und eine mittlere maximale Plasmakonzentration (C_{max}) von Amoxycillin von wenigstens 16 µg/ml bereitstellt.

43. Verwendung gemäß Anspruch 40, worin die Verabreichung eine mittlere Plasmakonzentration von Amoxycillin von 8 µg/ml für wenigstens 4,4 h bereitstellt.

44. Verwendung gemäß einem der Ansprüche 40 bis 43, worin die Infektion durch die Organismen S. pneumoniae verursacht wird, einschließlich arzneistoffresistenten und penicillinresistenten S. pneumoniae, H. influenzae und/oder M. catarrhalis.

Revendications

1. Formulation pharmaceutique à libération modifiée comprenant de l'amoxycilline et du clavulanate de potassium selon un rapport de 14:1 à 20:1 dans laquelle l'intégralité du clavulanate de potassium et une première partie d'amoxycilline sont formulés à l'aide d'excipients pharmaceutiquement acceptables qui permettent une libération immédiate du clavulanate de potassium et de la première partie de l'amoxycilline afin de former une phase de libération immédiate et comprenant par ailleurs une seconde partie d'amoxycilline formulée avec des excipients pharmaceutiquement acceptables qui permet une libération lente de la seconde partie d'amoxycilline, de façon à former une phase de libération lente et dans laquelle le rapport d'amoxycilline lors des phases de libération immédiate et lente est de 3:1 à 1:3.

2. Formulation pharmaceutique selon la revendication 1, dans laquelle le rapport d'amoxycilline et de clavulanate de potassium est de 14:1 à 16:1.

3. Formulation pharmaceutique selon la revendication 1 ou 2, dans laquelle le rapport d'amoxycilline et de clavulanate de potassium est de 16:1.

4. Formulation pharmaceutique à libération modifiée selon l'une quelconque des revendications 1 à 3, dans laquelle le rapport d'amoxycilline lors des phases de libération immédiate et lente est de 3:1 à 2:3.

5. Formulation pharmaceutique selon l'une quelconque des revendications 1 à 4, laquelle a un profil biphasique en ce qui concerne l'amoxycilline.

6. Formulation pharmaceutique selon l'une quelconque des revendications 1 à 5, laquelle a une valeur AUC qui est au moins de 80 % de celle du dosage correspondant d'amoxycilline, considérée comme comprimé (s) à libération immédiate traditionnelle, sur la même période de dosage.

7. Formulation pharmaceutique, selon l'une quelconque des revendications 1 à 6, dans laquelle le rapport d'amoxycilline lors des phases de libération immédiate et lente est de 3:2 à 1:1.

8. Formulation pharmaceutique selon l'une quelconque des revendications 1 à 7, comprenant un dosage unitaire inscrit dans une plage de 700 à 1300 mg ou 1400 à 2600 mg d'amoxycilline et d'une quantité correspondante de clavulanate de potassium.

9. Formulation pharmaceutique selon l'une quelconque des revendications 1 à 8, dans laquelle le dosage unitaire est de 1000 ou 875 mg ± 5 % d'amoxycilline et 62,5 mg ± 5 % de clavulanate de potassium ; ou de 2000 ou 1750 mg ± 5 % d'amoxycilline et 125 mg ± 5 % de clavulanate de potassium ; dans un rapport nominal d'environ 16:1 ou 14:1, respectivement, en combinaison avec les excipients ou véhicules pharmaceutiquement acceptables.

10. Formulation pharmaceutique selon l'une quelconque des revendications 1 à 9 qui est une formulation de comprimés.

11. Formulation pharmaceutique selon la revendication 10, comprenant 1000 mg ± 5 % d'amoxycilline et 62,5 mg ± 5 % de clavulanate de potassium, dans un rapport nominal d'environ 16:1 dans laquelle la phase de libération

immédiate comprend environ 563 mg ± 5 % d'amoxycilline et environ 62,5 mg ± 5 % de clavulanate de potassium et la phase de libération lente comprend environ 438 mg ± 5 % d'amoxycilline.

12. Formulation pharmaceutique selon l'une quelconque des revendications 1 à 11, dans laquelle l'amoxycilline de la phase de libération lente consiste essentiellement en de l'amoxycilline de sodium cristallisée.

13. Formulation pharmaceutique selon l'une des revendications 1 à 12 qui est en comprimé multicouches comprenant du clavulanate de potassium et de l'amoxycilline dans une couche à libération immédiate et de l'amoxycilline dans une couche à libération lente.

14. Comprimé multicouches selon la revendication 13, dans lequel la couche à libération lente comprend un excipient retardant la libération qui est sélectionné à partir des polymères sensibles au pH ; un polymère retardant la libération qui a un haut degré de gonflement au contact de l'eau ou d'un milieu aqueux ; un matériau polymère qui forme un gel au contact de l'eau ou d'un milieu aqueux ; et un matériau polymère qui a à la fois des propriétés de gonflement et de gélification au contact de l'eau ou d'un milieux aqueux, ou un mélange de ceux-ci.

15. Comprimé multicouches selon la revendication 14, dans lequel le polymère gélifiable retardant la libération est sélectionné parmi la méthyle cellulose, la carboxyméthylecellulose, l'hydroxypropyleméthylecellulose de faible poids moléculaire, les alcools polyvinyliques de faible poids moléculaire, les polyoxyéthylèneglycoles et la pyrrolidone polyvinylique non réticulée ou la gomme de xanthane.

16. Comprimé multicouches selon la revendication 14 ou 15, dans lequel l'excipient retardant la libération est la gomme de xanthane.

17. Comprimé multicouches selon la revendication 16, dans lequel la gomme de xanthane est présente dans 1 à 25 % en poids de la couche.

18. Comprimé multicouches selon l'une quelconque des revendications 13 à 17, dans lequel la couche à libération lente comprend de 70 à 80 % d'amoxycilline, de 1 à 25 % de gomme de xanthane, de 10 à 20 % d'agents de remplissage/compression, et des proportions traditionnelles de lubrifiants.

19. Comprimé multicouches selon la revendication 13, dans lequel la phase de libération lente comprend de l'amoxycilline de sodium et dans lequel la couche à libération lente comprend un excipient retardant la libération qui est un acide organique pharmaceutiquement acceptable présent dans un rapport molaire de 100:1 à 1:10, le rapport étant un sel d'amoxycilline par rapport à l'acide organique.

20. Comprimé multicouches selon la revendication 19, dans lequel l'acide organique pharmaceutiquement acceptable est présent dans un rapport molaire allant de 50:1 à 1:5.

21. Comprimé multicouches selon la revendication 19, dans lequel l'acide organique pharmaceutiquement acceptable est présent dans un rapport molaire allant de 20:1 à 1:5.

22. Comprimé multicouches selon la revendication 19, dans lequel l'acide organique pharmaceutiquement acceptable est présent dans un rapport molaire allant de 20:1 à 1:2.

23. Comprimé multicouches selon l'une quelconque des revendications 19 à 22, dans lequel l'acide pharmaceutiquement acceptable est de l'acide citrique.

24. Comprimé multicouches selon la revendication 24, dans lequel l'acide citrique est présent dans un rapport molaire allant 2:1 à 1:1,2.

25. Comprimé multicouches selon l'une quelconque des revendications 19 à 24 comprenant par ailleurs un polymère gélifiable retardant la libération.

26. Comprimé multicouches selon la revendication 25, dans lequel le polymère gélifiable retardant la libération est la gomme de xanthane.

27. Comprimé multicouches selon la revendication 21, dans lequel la gomme de xanthane est présente dans une

plage allant de 0,5 à 8 % en poids de la couche à libération lente.

28. Formulation pharmaceutique de comprimé multicouches selon l'une quelconque des revendications 19 à 27, comprenant de 700 g à 1250 mg d'amoxycilline et une proportion de clavulanate de potassium au pro rata, dans un rapport nominal d'environ 16:1 ou 14:1, respectivement, en combinaison avec des excipients ou des véhicules pharmaceutiquement acceptables.

29. Comprimé multicouches selon la revendication 28, qui comprend 1000 mg ± 5 % d'amoxycilline et 62,5 mg ± 5 % de clavulanate de potassium, et qui comprend dans une couche à libération lente environ 438 mg ± 5 % d'amoxycilline de sodium cristallisée, environ 78 mg ± 10 % d'acide citrique et éventuellement environ 2 % en poids de gomme de xanthane.

30. Formulation pharmaceutique à libération modifiée selon la revendication 1, dans laquelle la phase de libération immédiate est formée à partir de granules à libération immédiate, comprenant de l'amoxycilline et du clavulanate de potassium ou des granules à libération immédiate comprenant de l'amoxycilline et du clavulanate de potassium et par ailleurs des granules à libération immédiate comprenant de l'amoxycilline et la phase de libération lente est formée à partir de granules à libération lente comprenant de l'amoxycilline.

31. Formulation pharmaceutique à libération modifiée selon la revendication 30 qui est un sachet à dose unique, une capsule, un comprimé monolithe, un comprimé soluble ou un comprimé à mâcher, lequel comprimé peut être effervescent et/ou soluble.

32. Formulation pharmaceutique à libération modifiée selon l'une quelconque des revendications 1 à 31, comprenant 1000 mg ± 5 % d'amoxycilline et 62,5 mg ± 5 % d'acide clavulanique de potassium, dans un rapport nominal d'environ 16:1, en combinaison avec des excipients ou véhicules pharmaceutiquement acceptables.

33. Formulation pharmaceutique à libération modifiée selon l'une quelconque des revendications 1 à 32, qui a un taux de dissolution *in vitro* dans lequel 45 à 65 % du contenu en amoxycilline est dissout dans les 30 minutes.

34. Formulation pharmaceutique à libération modifiée selon l'une quelconque des revendications 1 à 33, qui a un taux de dissolution in *vitro* dans lequel 50 à 75 % du contenu en amoxycilline est dissout dans les 60 minutes.

35. Formulation pharmaceutique à libération modifiée selon l'une quelconque des revendications 1 à 34, qui a un taux de dissolution *in vitro* dans lequel 55 à 85 % du contenu en amoxycilline est dissout dans les 120 minutes.

36. Formulation pharmaceutique à libération modifiée selon l'une quelconque des revendications 1 à 35, qui a un taux de dissolution *in vitro* dans lequel 70 à 95 % du contenu en amoxycilline est dissout dans les 180 minutes.

37. Formulation pharmaceutique à libération modifiée selon l'une quelconque des revendications 1 à 36, qui a un taux de dissolution *in vitro* dans lequel 70 à 100 % du contenu en amoxycilline est dissout dans les 240 minutes.

38. Formulation pharmaceutique à libération modifiée selon la revendication 31 comprenant des granules compactées à libération lente comprenant de l'amoxycilline, un agent de dilution/compression et un polymère retardant la libération, lequel s'avère être de la gomme de xanthane, ou un sel soluble d'amoxycilline, un agent de dilution/compression et un acide organique ou un polymère retardant la libération ou un mélange de ceux-ci.

39. Formulation selon l'une quelconque des revendications de 1 à 38 ayant une valeur AUC, C_{max} et T > MIC substantiellement selon la figure 4 (formulation VI ou VII).

40. Utilisation d'amoxycilline et de clavulanate de potassium dans la fabrication d'un médicament défini selon la revendication 1 destiné à traiter les infections bactériennes chez l'homm à des intervalles posologiques d'environ 12 h

41. Utilisation selon la revendication 40, dans laquelle l'administration fournit une concentration plasmatique moyenne d'amoxycilline de 4 µg/ml durant au moins 4,4 h et une concentration plasmatique moyenne maximum (C_{max}) d'amoxycilline d'au moins 12 µg/ml.

42. Utilisation selon la revendication 40, dans laquelle l'administration fournit une concentration plasmatique moyenne d'amoxycilline de 4 µg/ml durant au moins 4,8 h et une concentration plasmatique moyenne maximum (C_{max})

d'amoxycilline d'au moins 16 µg/ml.

43. Utilisation selon la revendication 40, dans laquelle l'administration fournit une concentration plasmatique moyenne d'amoxycilline de 8 µg/ml durant au moins 4,4 h.

44. Utilisation selon l'une quelconque des revendications de 40 à 43, dans laquelle l'infection est provoquée par les organismes *S pneumoniae* comprenant *S pneumoniae* résistant aux antibiotiques et à la pénicilline, *H. influenzae* et/ou *M catarrhalis*.

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Figure 1

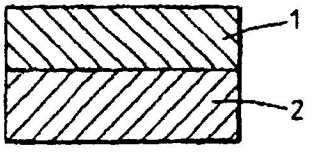


Fig. 1A

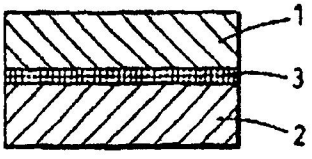


Fig. 1B

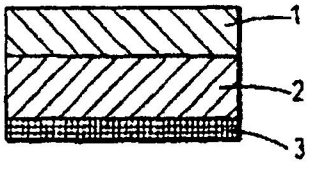


Fig. 1C

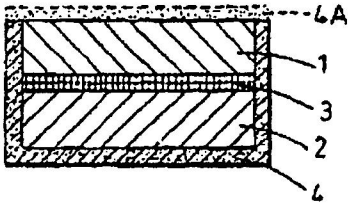


Fig. 1D

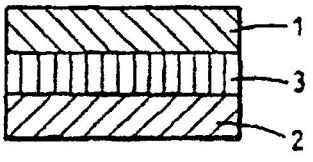
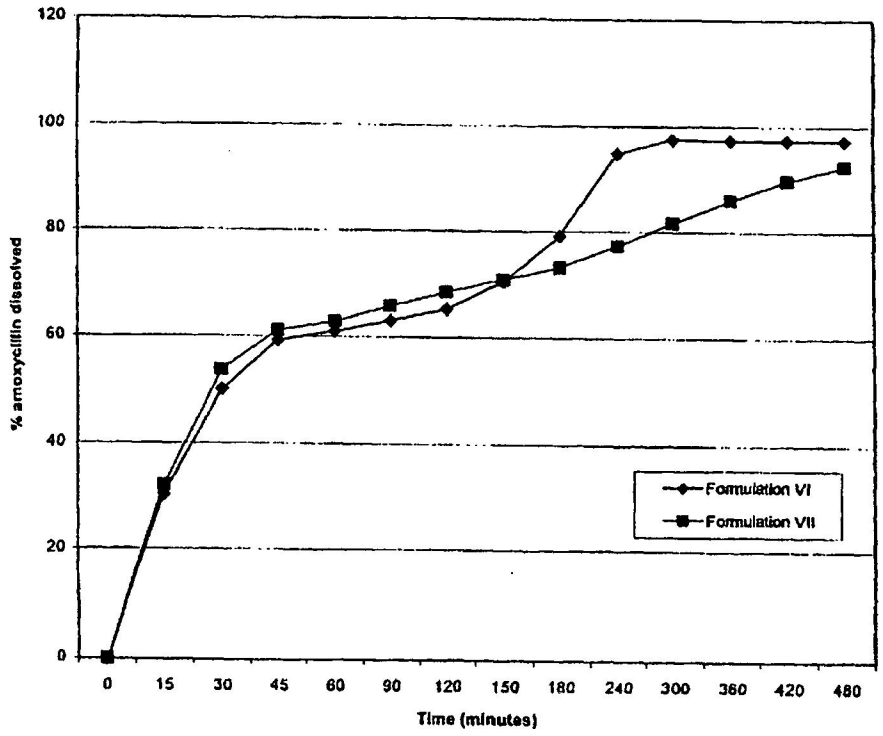


Fig. 1E

Figure 2 – Dissolution Profile for tablets of Examples 1 and 2



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Figure 3 – Mean Amoxycillin Plasma Profiles for Study A

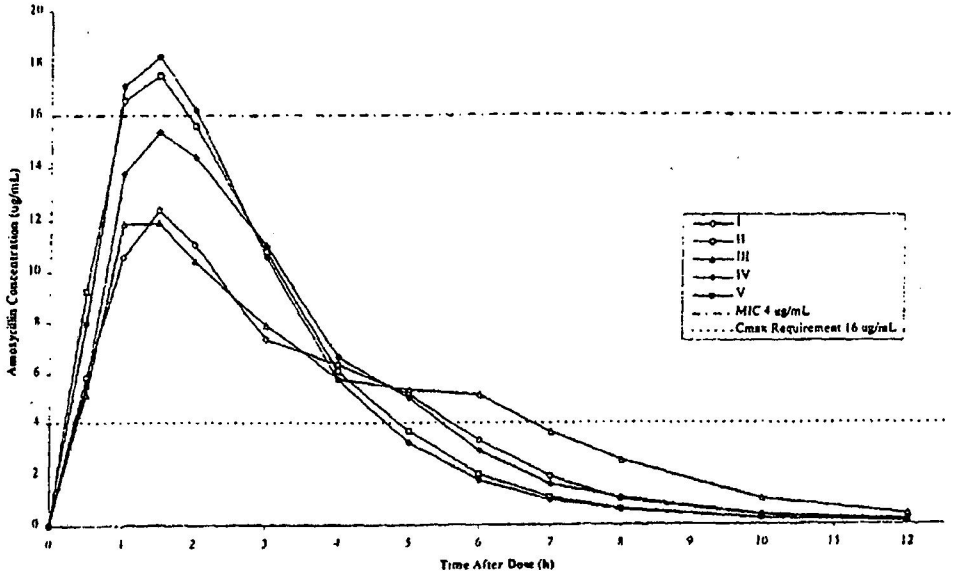
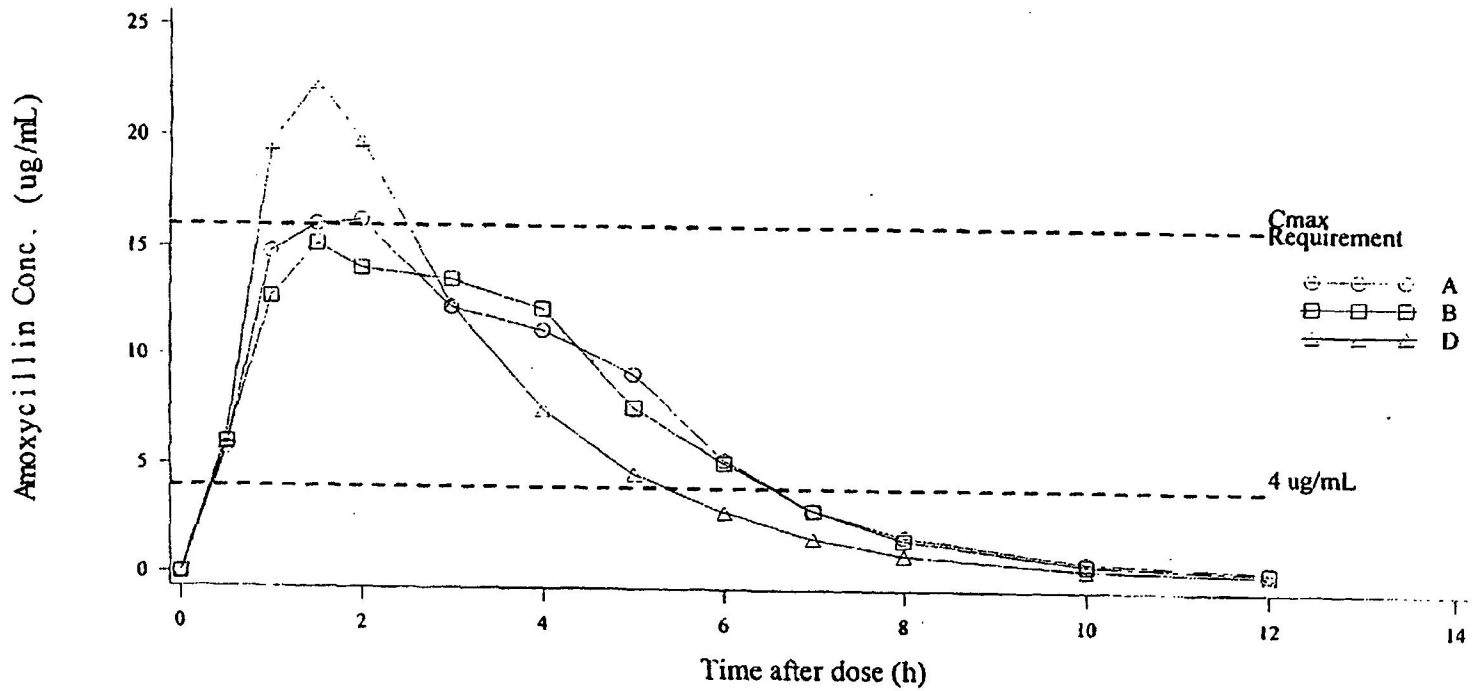


Figure 4 – Mean Amoxycillin Plasma Profiles for Study B



US006878386B1

(12) **United States Patent**
Conley et al.

(10) **Patent No.: US 6,878,386 B1**
(45) **Date of Patent: Apr. 12, 2005**

(54) **METHOD OF TREATING A BACTERIAL INFECTION COMPRISING AMOXYCILLIN AND POTASSIUM CLAVULANATE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/544,019**

(22) Filed: **Apr. 6, 2000**

Related U.S. Application Data

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(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/20; A61K 9/46; A61K 9/14; A61K 9/00

(52) **U.S. Cl.** **424/468**; 424/464; 424/466; 424/489; 424/482; 424/441; 424/472; 424/470; 424/451; 424/400

(58) **Field of Search** 424/464, 466, 424/472, 489, 482, 451, 400, 468, 441

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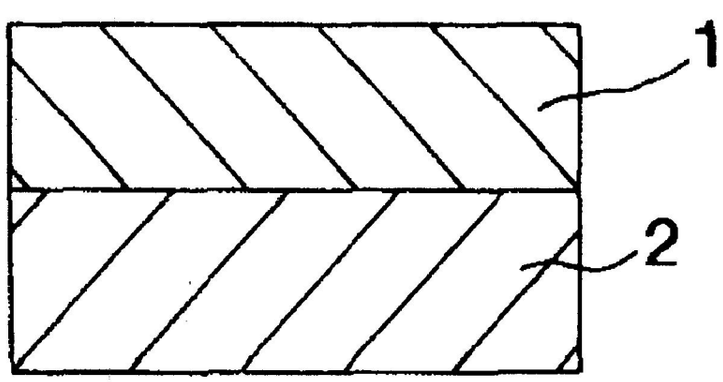
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(57) **ABSTRACT**

Bacterial infections may be treated using a high dosage regimen of amoxycillin and potassium clavulanate. Preferably, the dosage is provided by a bilayer tablet.

93 Claims, 7 Drawing Sheets



Results

Formulation	n	Cmax[1]	T > MIC[1,2]	AUC[1,3]
I	8	12.75 (4.96	4.5 (1.8)	47.83
II	8	18.56 (4.72	4.4 (1.0)	57.46
III	8	13.03 (2.34	5.73 (2.54)	54.93
IV	8	17.33 (4.66	4.8 (0.9)	56.71
V	40	20.21 (6.09	4.2 (0.9)	56.33

() standard deviation
[1]arithmetic mean value
[2]T > MIC is the time (h) above an amoxycillin concentration of 4 μg/ml
[3]Area under the curve (0 to 12 h, μg.h/mL)

The pharmacokinetic profile is shown in FIG. **4**.

Study B

The second study investigated two different modified release dosages of 2000/125 mg (formulations VI and VII) against an immediate release dosage of 2000/125 mg (formulation VIII), as follows:

(a) a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of two bilayer tablets according to Example 1 (formulation VI);

(b) a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of two bilayer tablets according to Example 2 (formulation VII);

(c) a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of a combination of three tablets each comprising 500 mg amoxycillin (Amoxyl, SmithKline Beecham) and one tablet comprising 500 mg amoxycillin and 125 mg potassium clavulanate (Augmentin, SmithKline Beecham) (formulation VI).

Results

Formulation	n	Cmax[1]	T > MIC[1,2]	T > MIC[1,3]	AUC[1,4]
VI	7	17.41 (1.93)	6.0 (1.3)	4.8 (1.2)	74.9
VII	8	17.46 (6.02)	5.9 (1.3)	4.0 (1.3)	71.5
VIII	12	23.75 (5.73)	4.9 (1.1)	3.5 (1.0)	69.2

() standard deviation
[1]arithmetic mean value
[2]T > MIC is the time (h) above an amoxycillin concentration of 4 μg/ml
[3]T > MIC is the time (h) above an amoxycillin concentration of 8 μg/ml
[4]Area under the curve (0 to 12 h, μg.h/mL).

Comparison of the AUC values for formulations VI and VII (bilayer tablets) against VIII (immediate release tablets) shows that the absorption of the amoxycillin component has not been compromised by formulating a part of it in a slow release layer. This means that there is no extra, unabsorbed amoxycillin which may otherwise cause problems further down in the GI tract, for instance due to a lack of absorption and destruction of symbiotic bacteria.

It was also found that for formulation VI, there was less inter-subject variability in the amoxycillin plasma concentrations than for formulation VII. These formulations were the same, except that formulation VI also comprised xanthan gum (2%) in the slow release layer.

The pharmacokinetic profile for amoxycillin plasma concentration is shown in FIG. **5** (in which A is formulation VI, B is formulation VII, D is formulation VIII).

The pharmacokinetic profile for the clavulanate component was substantially the same for the bilayer tablets and the immediate release tablets, showing that the bioavailability thereof was not compromised by incorporation into the immediate release layer of a bilayer tablet.

The present invention also extends to formulations which are bioequivalent to the tablets of formulations VI and VII, in terms of both rate and extent of absorption, for instance as defined by the US Food and Drug Administration and discussed in the so-called "Orange Book" (Approved Drug Products with Therapeutic Equivalence Evaluations, US Dept of Health and Human Services, 19th edn, 1999).

Reference Data

The existing Augmentin 875/125 mg tablet has a C_{max} value of 11.6±2.8 μg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802). The time above MIC was about 40% of the 12 hour dosing interval for an MIC of 2 μg/ml and about 30% for an MIC of 4 μg/ml (SmithKline Beecham data).

What is claimed is:

1. A method for treating a bacterial infection in a human in need thereof, which method comprises administering to said human, at a dosage regimen interval of about 12 hours, a dosage of about 2000 mg of amoxicillin and about 125 mg potassium clavulanate, in which the dosage is delivered from a modified release formulation, adapted to provide a mean maximum plasma concentration (C_{max}) of amoxicillin of at least 12 μg/ml, an Area under the Curve (AUC) value of amoxicillin which is at least 80% of that of the same amount if taken as an immediate release formulation over the same dosage regimen interval, and a mean plasma concentration of amoxicillin of at least 4 μg/ml for at least 4.2 hours, and further adapted to provide for immediate release of the potassium clavulanate.

2. The method according to claim **1** wherein the formulation provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 hours and a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 12 μg/mL.

3. The method according to claim **2** wherein the formulation provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.8 hours and a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 16 μg/mL.

4. The method according to claim **1** wherein the formulation provides a mean plasma concentration of amoxycillin of 8 μg/mL for at least 4.4 hours.

5. The method according to claim **1** in which the bacterial infection is caused by at least one of the organisms *S. pneumoniae, H. influenzae,* and *M. catarrhalis.*

6. The method according to claim **1** wherein the formulation provides a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 16 μg/mL.

7. The method according to claim **1** wherein the formulation provides a mean plasma concentration of amoxycillin of 8 μg/mL for at least 4.8 hours.

8. The method according to claim **1** wherein the formulation provides a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 16 μg/mL.

9. A method of treating a bacterial infection in a human in need thereof, which method comprises administering to said human, at a dosage regimen interval of about 12 hours, a dosage of about 2000 mg of amoxicillin and about 125 mg potassium clavulanate, wherein the dosage is delivered from a modified release formulation which has an in vitro dissolution profile wherein about 45% to about 65% of the amoxycillin content is dissolved within 30 min, measured in <711> dissolution test, Apparatus 2, USP 23, 1995, at 37.0±0.5° C., using deionised water (900 mL) and a paddle speed of 75 rpm.

10. The method according to claim **9** wherein about 50% to about 75% of the amoxycillin content is dissolved within 60 minutes.

11. The method according to claim **9** wherein about 55% to about 85% of the amoxycillin content is dissolved within 120 minutes.

12. The method according to claim 9 wherein about 70% to about 95% of the amoxycillin content is dissolved within 180 minutes.

13. The method according to claim 9 wherein about 70% to about 100% of the amoxycillin content is dissolved within 240 minutes.

14. The method according to claim 13 wherein about 75% to about 100% of the amoxycillin content is dissolved within 240 minutes.

15. The method according to claim 9 wherein the formulation is adapted to provide a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.2 hours.

16. The method according to claim 9 wherein the formulation is adapted to provide a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 hours.

17. The method according to claim 9 wherein the formulation is adapted to provide a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.8 hours.

18. The method according to claim 9 wherein the formulation is adapted to provide a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 12 μg/mL.

19. The method according to claim 9 wherein the formulation is adapted to provide a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 16 μg/mL.

20. The method according to claim 9 wherein the formulation is adapted to provide over the dosage regimen a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 12 μg/mL, and a mean plasma concentration of amoxicillin of at least 4 μg/ml for at least 4.2 hours.

21. The method according to claim 20 wherein the formulation is adapted to provide an Area under the Curve (AUC) value of amoxicillin which is at least 80% of that of the same amount if taken as an immediate release formulation over the same dosage regimen interval.

22. The method according to claim 9 wherein the bacterial infection is caused by at least one of the organisms *S. pneumoniae, H. infuenzae,* and *M. catarrhalis.*

23. The method according to claim 22 wherein the *S. pneumoniae* organism is drug resistant and penicillin resistant.

24. The method according to claim 9 which has a dosage regimen administered over a period of 7 to 14 days.

25. A method of treating a bacterial infection in a human in need thereof, which method comprises administering to said human a dosage of about 2000 mg of amoxicillin and about 125 mg potassium clavulanate, wherein the dosage is delivered from a modified release formulation which has an in vitro dissolution profile wherein about 45% to about 65% of the amoxycillin content is dissolved within 30 minutes; about 50% to about 75% of the amoxycillin content is dissolved within 60 minutes; about 55% to about 85% of the amoxycillin content is dissolved within 120 minutes; about 70% to about 95% of the amoxycillin content is dissolved within 180 minutes; and about 70% to about 100% of the amoxycillin content is dissolved within 240 minutes, measured in the <711> dissolution test, Apparatus 2, USP 23, 1995, at 37.0±0.5° C., using deionised water (900 mL) and a paddle speed of 75 rpm.

26. The method according to claim 25 wherein the bacterial infection caused by at least one of the organisms *S. pneumoniae, H. influenzae,* and *M. catarrhalis.*

27. The method according to claim 26 wherein the *S. pneumoniae* organism is drug resistant and penicillin resistant.

28. A method for treating a bacterial infection in a human in need thereof, which method comprises administering to said human, at a dosage regimen interval of about 12 hours, a dosage of about 2000 mg of amoxicillin and about 125 mg potassium clavulanate, wherein the dosage is delivered from a modified release formulation, adapted to provide a mean maximum plasma concentration (Cmax) of amoxicillin of at least 16 μg/ml, an Area under the Curve (AUC) value of amoxicillin which is at least 80% of that of the same amount if taken as an immediate release formulation over the same dosage regimen interval, and a mean plasma concentration of amoxicillin of at least 4 μg/ml for at least 4.2 hours, and further adapted to provide for immediate release of the potassium clavulanate.

29. The method according to claim 28 wherein the formulation provides an AUC of at least 90%.

30. The method according to claim 28 wherein the formulation provides an AUC of at least 100%.

31. The method according to claim 28 wherein the formulation provides an AUC of at least 110%.

32. The method according to claim 28 wherein the formulation provides an AUC of at least 120%.

33. The method according to claim 28 wherein the formulation provides a mean plasma concentration of amoxicillin of at least 4 micrograms/ml for at least 4.4 hours.

34. The method according to claim 28 wherein the formulation provides a mean plasma concentration of amoxicillin of at least 4 micrograms/ml for at least 4.8 hours.

35. The method according to claim 28 wherein the formulation provides a mean plasma concentration of amoxicillin of at least 4 micrograms/ml for about 6 hours.

36. The method according to claim 28 wherein the formulation provides a mean plasma concentration of amoxicillin of at least 8 micrograms/ml for at least 4.4 hours.

37. The method according to claim 28 wherein the formulation provides a mean plasma concentration of amoxicillin of at least 8 micrograms/ml for at least 4.8 hours.

38. The method according to claim 28 wherein the bacterial infection is caused by at least one of the organisms *S. pneumoniae, H. influenzae,* and *M. catarrhalis.*

39. The method according to claim 38 wherein the *S. pneumoniae* organism is drug resistant and penicillin resistant.

40. A method for treating a bacterial infection in a human in need thereof, which method comprises administering to said human, at a dosage regimen interval of about 12 hours, a dosage of about 2000 mg of amoxicillin and about 125 mg potassium clavulanate, wherein the dosage is delivered from a biphasic modified release formulation, adapted to provide a mean maximum plasma concentration (Cmax) of amoxicillin of at least 12 μg/ml, an Area under the Curve (AUC) value of amoxicillin which is at least 80% of that of the same amount if taken as an immediate release formulation over the same dosage regimen interval, and a mean plasma concentration of amoxicillin of at least 4 μg/ml for at least 4.2 hours, and further adapted to provide for immediate release of the potassium clavulanate.

41. The method according to claim 40 wherein the bacterial infection is caused by at least one of the organisms *S. pneumoniae, H. infuenzae,* and *M. catarrhalis.*

42. The method according to claim 41 wherein the *S. pneumoniae* organism is drug resistant and penicillin resistant.

43. The method according to claim 40 wherein the formulation provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 hours.

44. The method according to claim 40 wherein the formulation provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.8 hours.

45. The method according to claim 40 wherein the formulation provides a mean plasma concentration of amoxicillin of at least 4 micrograms/ml for about 6 hours.

46. The method according to claim **40** wherein the formulation provides a mean plasma concentration of amoxicillin of at least 8 micrograms/ml for at least 4.4 hours.

47. The method according to claim **40** wherein the formulation provides a mean plasma concentration of amoxicillin of at least 8 micrograms/ml for at least 4.8 hours.

48. The method according to claim **40** wherein the formulation provides a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 16 μg/mL.

49. The method according to claim **40** wherein the formulation provides an AUC of at least 90%.

50. The method according to claim **40** wherein the formulation provides an AUC of at least 100%.

51. The method according to claim **40** wherein the formulation provides an AUC of at least 110%.

52. The method according to claim **40** wherein the formulation provides an AUC of at least 120%.

53. The method according to claim **41** wherein the bacterial infection is a respiratory tract infection.

54. The method according to claim **53** wherein the respiratory tract infection is community acquired pneumoniae (CAP), acute exacerbation of chronic bronchitis (AECB) or acute bacterial sinusitis (ABS).

55. The method according to claim **40** wherein the dosage regimen is administered over 7 to 14 days.

56. The method according to claim **40** wherein the dosage is provided by two tablets each comprising about 1000/62.5 mg amoxycillin/potassium clavulanate, or four tablets of 500/32.25 mg amoxycillin/potassium clavulanate.

57. The method according to claim **40** wherein all of the potassium clavulanate and a first part of amoxycillin are formulated with at least one pharmaceutically acceptable excipient which allows for immediate release of the potassium clavulanate and the first part of amoxycillin, to form an immediate release phase, and wherein a second part of amoxycillin is formulated with at least one pharmaceutically acceptable excipient to allow for slow release of the second part of amoxycillin, to form a slow release phase.

58. A method for treating a bacterial infection in a human in need thereof which method comprises administering to said human, at a dosage regimen interval of about 12 hours, a dosage of about 2000 mg of amoxicillin and about 125 mg potassium clavulanate, wherein the dosage is delivered from a biphasic modified release formulation, adapted to provide a mean maximum plasma concentration (Cmax) of amoxicillin of about 17.4 μg/ml, an Area under the Curve (AUC) value of amoxicillin which is at least 74.9% of that of the same amount if taken as an immediate release formulation over the same dosage regimen interval, and a mean plasma concentration of amoxicillin of at least 4 μg/ml for about 6 hours, and further adapted to provide for immediate release of the potassium clavulanate.

59. The method according to claim **58** wherein the formulation provides an AUC of at least 80% of the value displayed by the biphasic formulation.

60. The method according to claim **58** wherein the formulation provides an AUC of at least 90% of the value displayed by the biphasic formulation.

61. The method according to claim **58** wherein the formulation provides an AUC of at least 100% of the value displayed by the biphasic formulation.

62. The method according to claim **58** wherein the formulation provides an AUC of at least 110% of the value displayed by the biphasic formulation.

63. The method according to claim **58** wherein the formulation provides an AUC of at least 120% of the value displayed by the biphasic formulation.

64. The method according to claim **58** wherein the biphasic modified release formulation comprises an immediate release of amoxicillin and a modified release of amoxicillin.

65. The method according to claim **58** wherein the bacterial infection caused by at least one of the organisms *S. pneumoniae, H. influenzae*, and *M. catarrhalis*.

66. The method according to claim **65** wherein the *S. pneumoniae* organism is drug resistant and penicillin resistant.

67. The method according to claim **58** wherein the formulation provides a pharmacokinetic plasma profile for amoxycillin substantially as shown in FIG. **5**, formulation A.

68. The method according to claim **58** comprising two tablets of about 1000 mg±5% amoxycillin and about 62.5 mg±5% potassium clavulanate, wherein the immediate release phase comprises about 563 mg±5% amoxycillin and about 62.5 mg±5% of potassium clavulanate, and the slow release phase comprises about 438 mg±5% of amoxycillin.

69. The method according to claim **64** wherein the amoxycillin in the modified release phase is sodium amoxycillin.

70. The method according to claim **69** wherein the sodium amoxycillin is crystallized sodium amoxycillin.

71. The method according to claim **64** wherein the amoxycillin in the immediate release phase is amoxycillin trihydrate.

72. The method according to claim **65** wherein the bacterial infection is a respiratory tract infection.

73. The method according to claim **72** wherein the respiratory tract infection is community acquired pneumoniae (CAP), acute exacerbation of chronic bronchitis (AECB) or acute bacterial sinusitis (ABS).

74. The method according to claim **58** wherein the dosage regimen is administered over 7 to 14 days.

75. The method according to claim **1** wherein the dosage is provided by two tablets each comprising about 1000/62.5 mg amoxycillin/potassium clavulanate, or four tablets of 500/32.25 mg amoxycillin/potassium clavulanate.

76. The method according to claim **1** wherein all of the potassium clavulanate and a first part of amoxycillin are formulated with at least one pharmaceutically acceptable excipient which allows for immediate release of the potassium clavulanate and the first part of amoxycillin, to form an immediate release phase, and wherein a second part of amoxycillin is formulated with at least one pharmaceutically acceptable excipient to allow for slow release of the second part of amoxycillin, to form a slow release phase.

77. The method according to claim **76** wherein the amoxycillin in the immediate release phase is amoxycillin trihydrate or a sodium amoxycillin or a combination thereof.

78. The method according to claim **76** wherein the amoxycillin in the slow release phase is sodium amoxycillin.

79. The method according to claim **78** wherein the sodium amoxycillin is crystallized sodium amoxycillin.

80. The method according to claim **1** comprising two tablets of about 1000 mg±5% amoxycillin and about 62.5 mg±5% potassium clavulanate, wherein the immediate release phase comprises about 563 mg±5% amoxycillin and about 62.5 mg±5% of potassium clavulanate, and the slow release phase comprises about 438 mg±5% of amoxycillin.

81. The method according to claim **5** wherein the *S. pneumoniae* organism is drug resistant and penicillin resistant.

82. The method according to claim **1** wherein the dosage regimen is administered over 7 to 14 days.

83. The method according to claim **5** wherein the bacterial infection is a respiratory tract infection.

84. The method according to claim **83** wherein the respiratory tract infection is community acquired pneumoniae (CAP), acute exacerbation of chronic bronchitis (AECB) or acute bacterial sinusitis (ABS).

85. The method according to claim **22** wherein the bacterial infection is a respiratory tract infection.

86. The method according to claim **85** wherein the respiratory tract infection is community acquired pneumoniae (CAP), acute exacerbation of chronic bronchitis (AECB) or acute bacterial sinusitis (ABS).

87. The method according to claim **22** wherein the dosage regimen is administered over 7 to 14 days.

88. The method according to claim **26** wherein the bacterial infection is a respiratory tract infection.

89. The method according to claim **88** wherein the respiratory tract infection is community acquired pneumoniae (CAP), acute exacerbation of chronic bronchitis (AECB) or acute bacterial sinusitis (ABS).

90. The method according to claim **26** wherein the dosage regimen is administered over 7 to 14 days.

91. The method according to claim **38** wherein the bacterial infection is a respiratory tract infection.

92. The method according to claim **91** wherein the respiratory tract infection is community acquired pneumoniae (CAP), acute exacerbation of chronic bronchitis (AECB) or acute bacterial sinusitis (ABS).

93. The method according to claim **38** wherein the dosage regimen is administered over 7to 4days.

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339

346 2005-12-07 375

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

RESPUESTA AL RECURSO DE REPOSICIÓN

2020
Bogotá, D.C., Diciembre 7 de 2005

Doctor
GERMAN CASTILLO GARU

REFERENCIA:	Radicación No.	00 026 419
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	
	Folios	00

TÍTULO "Tabletas de liberación modificada que incluyen Amoxicilina y Clavulanato de Potasio"

En atención al Recurso de Reposición interpuesto, se hacen las siguientes aclaraciones:

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 279 - 282 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 21 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.

Las reivindicaciones 22 -23 se refieren al uso de amoxicilina y clavulanato de potasio en la manufactura de un medicamento.

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. Usos

El artículo 21 de la Decisión 486 de la Comisión de la Comunidad Andina que establece: *"Los productos o procedimientos ya patentados, comprendidos en el estado de la tècnica, de conformidad con el artìculo 16 de la presente Decisiòn, no seràn objeto de nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial".*

Las reivindicaciones 22 -23 se refieren al uso de amoxicilina y clavulanato de potasio en la manufactura de un medicamento.

Se aclara que el uso de amoxicilina y clavulanato de potasio en la manufactura de un medicamento reivindicado no puede ser objeto de nueva patente, porque estos se conocían originalmente en D2 (ver folio 264, reivindicación 32); donde se mencionaba el uso de una formulación de las reivindicaciones 1 -29 (es decir de amoxicilina y clavulanato de potasio) en la manufactura de un medicamento.

4. Respuesta a los Argumentos del Solicitante

En atención a los argumentos del solicitante se hacen las siguientes aclaraciones:

1. Dice el solicitante que desiste de las reivindicaciones 22 y 23.

Se aclara al solicitante que se acepta el desistimiento.

2. Dice el solicitante que D1 no afecta la patentabilidad de esta solicitud porque es diferente la liberación lenta de la liberación retardada.

Se aclara al solicitante que la liberación **retardada** es lo mismo que liberación **lenta** ó **entérica**, es decir que se libera en el intestino; por esta razón, en D2 (ver folio 251, renglón 22) se aclara que la liberación **lenta** se obtiene con polímeros **retardantes**, como p. ej. Eudragit. Y la liberación **prolongada** tiene por objeto extender la liberación de la droga durante un período y se llama también liberación **sostenida ó controlada**. La liberación lenta, es entonces, otro nombre para la liberación retardada, diferente de la liberación prolongada. Luego de aclarar a lo que se refieren estos términos, se observa que la composición reivindicada contiene el mismo tipo de componentes que D1, es decir: amoxicilina, clavulanato de potasio y polímeros de liberación retardada (metilcelulosa (MC), carboxi metilcelulosa (CMC), hidroxi propil metilcelulosa (HPMC), alcohol pilivinílico (PVA), polioxietilenglicol (POEG), polivinilpirrolidona (PVP) ó goma xantan). Y tienen el mismo tipo de estructura: de liberación inmediata y de liberación modificada (es decir de liberación prolongada, sostenida ó controlada y de liberación retardada ó entérica). Así que el efecto obtenido será el mismo para ambos casos, razón por la cual se considera que no hay novedad ni nivel inventivo.

3. Dice el solicitante que D2 enseña una formulación donde el clavulanato es de liberación lenta y de liberación inmediata y tiene capa de barrera y esta solicitud menciona una formulación donde todo el clavulanato y parte de la amoxicilina están en la capa de liberación inmediata, la otra parte de la amoxicilina está en la capa de liberación lenta y que no tiene capa de barrera.

Se aclara al solicitante que D2 enseña (ver folios 259 a 264, en especial 261) tabletas que contienen amoxicilina y/o clavulanato en la capa de liberación inmediata; amoxicilina y/o clavulanato y polímeros retardantes en la capa de liberación lenta y tienen capa de barrera. También enseña tabletas que contienen amoxicilina y/o clavulanato en la capa de liberación inmediata, amoxicilina y/o clavulanato y polímeros retardantes en la capa de liberación lenta y no tienen capa de barrera. De manera que D2 afecta la novedad de esta solicitud.

4. Dice el solicitante en el folio 303 que D3 enseña una tableta bicapa de amoxicilina. Reitera que D2 enseña una formulación que tiene capa de barrera y esta solicitud no tiene tal capa de barrera.

Se reitera al solicitante que D2 enseña tabletas que tienen una capa de liberación inmediata, otra capa de liberación lenta (que contiene polímeros retardantes) y tienen capa de barrera; también enseña tabletas que contienen una capa de liberación inmediata, otra capa de liberación lenta (que contiene polímeros retardantes) y no tienen capa de barrera. De manera que D2 afecta la novedad de esta solicitud. Y D3 enseña tabletas que tienen una capa de liberación inmediata, otra capa de liberación lenta (que contiene polímeros retardantes) y tienen capa de barrera.

5. Dice el solicitante en el folio 304 que en Europa se concedió una patente correspondiente a esta solicitud, bajo el número EP 1 044 680, Estados Unidos concedió dos patentes (US 6 746 692 y 6878 386) y Reino Unido también..

Se aclara al solicitante que los conceptos son independientes. Y, como ya se aclaró, en esta oficina se encontraron los documentos D1, D2 y D3 que afectan la novedad y el nivel inventivo. Como se observa, los capítulos reivindicatorios son diferentes porque EP 1 044 680 tiene 44 reivindicaciones y la solicitud presentada en este país tiene 23. Además la legislación es diferente aquí y en USA porque en este país solo se concede una patente para un mismo invento, mientras que pareciera que en USA se pueden conceder dos. Se observa (ver folios 336 – 345) que tales patentes tienen fechas tan disímiles como son Nov 14, 2002 y Abr 12, 2005. La primera patente trata sobre método de tratamiento, que en Colombia no es patentable y sobre Tabletas de liberación inmediata y sobre tabletas que tienen una capa de liberación inmediata y otra capa de liberación lenta. Y la segunda patente trata sobre método de tratamiento, que en Colombia no es patentable. Así que no hay un punto sobre el que se pueda hacer comparación.

5. CONCLUSIÓN

Teniendo en cuenta lo anterior, se recomienda negar el privilegio solicitado para las reivindicaciones1 - 23, folios 279 - 282.

Bogotá, D. C., Diciembre 7 de 2005

CONCEPTO TÉCNICO 1989	JEFE DIVISIÓN NUEVAS CREACIONES	EXAMINADOR TÉCNICO 202007

343

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: **0-26419** EDICTO No. **5810**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución** No. **7003** de **27-MAR-2006**. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Confirmar la decisión contenida en la Resolución 24080 de 23 de septiembre de 2005 por medio de la cual se negó una patente de invención.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Germán Castillo Grau, en su calidad de apoderado de BEECHAM PHARMACEUTICALS (PTE) LIMITED, o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella no procede recurso alguno por encontrarse agotada la vía gubernativa.

NOTIFIQUESE Y CUMPLASE
Dada en Bogotá, D. C., a los 27 MAR. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E),

GIANCARLO MARCENARO JIMENEZ

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) díez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **12-ABR-2006** Este edicto se desfija hoy **27-ABR-2006** a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. **5810**