Description

The present invention relates to pharmaceutical compositions for oral administration in the treatment of bacterial infections.

West German OLS No. 2843318 discloses pharmaceutical compositions suitable for oral administration which comprise 20 mg to 1500 of amoxycillin trihydrate, 20 mg to 500 mg of potassium clavulanate and a pharmaceutically acceptable carrier with the proviso that the weight ratio of amoxycillin trihydrate to potassium clavulanate is from 6:1 to 1:1.

DE—OS No. 2843318 further discloses a packaged pharmaceutical composition of enhanced storage stability which comprises a container closed to prevent ingress of moisture and which contains one or more unit-dose compositions as described above together with a desiccant. Suitable non-toxic desiccants are disclosed as being included in sachets or capsules within the packaging or enclosed in a receptacle or separate compartment, for example in the cap or on the floor of the container.

It has now been found that tablet formulations incorporating an edible desiccant within the tablet itself can be prepared. In addition to facilitating processing and handling of the formulation mix prior to compressing into tablets, the tablets are less susceptible to faults or imperfections in the packaging for the tablets, which may allow ingress of water vapour and hence degradation. Incorporation of the desiccant into the tablet obviates the need for special pack inserts containing desiccant as described in DE—OS 2843318.

Accordingly, the present invention provides a unit-dose pharmaceutical composition suitable for oral administration which composition comprises a pharmaceutically acceptable carrier, a desiccant, amoxycillin trihydrate equivalent to 20 mg to 1500 mg of amoxycillin and potassium clavulanate equivalent to 20 mg to 500 mg of clavulanic acid, with the proviso that the weight ratio of amoxycillin to clavulanic acid is in the range 12:1 to 1:1; characterised in that the composition is in tablet form, wherein the desiccant is edible and incorporated within the tablets.

The weights of amoxycillin trihydrate and potassium clavulanate are referred to herein in terms of the weights of the pure free acids (pfa) amoxycillin and clavulanic acid respectively.

Suitably the weight ratio of amoxycillin to clavulanic acid in the pharmaceutical composition of the present invention is from 8:1 to 2:1 for example 5:1, 4:1, 3:1 or 2:1. Preferred weight ratios of amoxycillin to clavulanic acid are 8:1, 4:1 and 2:1.

In general the oral dosage unit of this invention will contain from 125 mg to 1250 mg of amoxycillin, for example it may contain about 125, 250, 500 or 1000 mg of amoxycillin.

In general the dosage unit of this invention will contain from 20 to 300 mg of clavulanic acid for example it may contain about 25, 31.25, 50, 62.5, 100, 120, 125, 150, 200, 250 or 300 mg of clavulanic acid.

From the foregoing it will be realised that certain preferred compositions of this invention comprise from 80 mg to 600 mg of amoxycillin and from 20 mg to 300 mg of clavulanic acid with the proviso that the weight ratio of amoxycillin to clavulanic acid is either 2:1, 4:1 or 8:1.

Suitable amounts of clavulanic acid for use in those compositions include the aforementioned approximately 25, 31.25, 50, 62.5, 100, 120, 125, 150, 200, 250 or 300 mgs.

Certain preferred compositions of this invention will contain about 125—500 mg of amoxycillin and about 31.25—125 mg of clavulanic acid.

Suitable desiccants which may be used in the present invention include edible grades of silica gel or crystalline sodium, potassium or calcium aluminosilicate (commonly termed "Molecular Sieves").

A preferred edible grade of silica gel is Syloid AL/1 (Syloid AL/1 is manufactured by W R Grace Ltd, Northdale House, North Circular Road, London).

A preferred edible grade of Molecular Sieve is sodium aluminosilicate sold under the trade name Molecular Sieve Type 4A by Union Carbide Corporation.

Most suitably the desiccant will be present in an amount weight for weight less than that of the antibacterially active ingredients. The desiccant will represent 2.5 to 10% of the total weight of the formulated tablet, a particularly favoured amount is 5% w/w of the tablet.

In addition to the antibacterially active ingredients and the desiccant present in the tablets, such compositions may contain one or more conventional fillers such as microcrystalline cellulose, lubricants such as magnesium stearate, disintegrants such as sodium starch glycollate, crosslinked polyvinyl pyrrolidone or other similar known agents. In addition such compositions may contain flavouring agents, preservatives and colouring agents. The materials present in such compositions should have low free moisture contents and preferably be pre-dried. Tightly bound water, such as water of crystallisation normally has little adverse effect on stability.

Other typical agents which may be used in the carrier include microfine cellulose (as a filler), calcium carbonate or magnesium carbonate (usually light magnesium carbonate) (as fillers) and starch or crosslinked polyvinyl pyrrolidone (as a disintegrant).

The tablets according to this invention may be film coated, if desired, with normal agents such as hydroxypropylmethyl cellulose, or with a coat that delays ingress of moisture. Suitable agents for such film coats include methacrylate polymers, methacrylic acid methacrylate copolymers, and natural resins such as shellec or copal resins or their conventional modifications.

Alternatively the coating may be an enteric coating, *ie* a coating that is insoluble in acidic gastric juice

but soluble in alkaline digestive juice; such a coating enables the medicament to pass through the stomach into the duodenum, from where it is absorbed. Suitable enteric coatings include cellulose acetate phthalate.

The compositions of the present invention are suitably packaged in protective packages such as, for example, screw-cap bottles, aluminium foil sachets and aluminium bister packs.

Also included within the scope of the present invention is a process for the preparation of a tablet composition as hereinbefore described which comprises bringing into association the components of said composition and thereafter compressing the blended mixture into a tablet.

It is preferable that the formulation of the composition is carried out in a dry atmosphere, eg one containing less than 30% relative humidity and preferably one containing less than 20% relative humidity.

In the following examples, which illustrate the invention, the compositions were formulated under a dry atmosphere.

Tablets of the following compositions were prepared:

Example 1

Ingredients	% w/w
Amoxycillin trihydrate as free acid	16.25
Potassium clavulanate as free acid	4.063
Syloid AL/1	5.00
Flavours	10.50
Crosslinked polyvinyl pyrrolidone	6.875
Magnesium stearate	0.625
Microcrystalline cellulose (Avicel PH102)	to 100.00

Example 2

Ingredients	% w/w
Amoxycillin trihydrate as free acid	15.294
Potassium clavulanate as free acid	7.65
Sodium alumino silicate	5.00
Flavours	10.00
Crosslinked polyvinyl pyrrolidone	6.47
Magnesium stearate	0.59
Microcrystalline cellulose (Avicel PH102)	to 100.00

Example 3

Ingredients	% w/w
Amoxycillin trihydrate as free acid	15.294
Potassium clavulanate as free acid	3.823
Sodium alumino silicate	5.00
Flavours	10.00
Crosslinked polyvinyl pyrrolidone	6.47
Magnesium stearate	0.59
Microcrystalline cellulose (Avicel PH102)	to 100.00

Example 4

Ingredients	% w/w
Amoxycillin trihydrate as free acid	16.25
Potassium clavulanate as free acid	8.125
Syloid AL/1	5.00
Flavours	10.00
Crosslinked polyvinyl pyrrolidone	6.875
Magnesium stearate	0.625
Microcrystalline cellulose (Avicel PH102)	to 100.00

Example 5

Ingredients	375 mg	% w/w	625 mg	% w/w
Potassium clavulanate≡pfa	125.00	16.34	125.00	11.90
Amoxycillin trihydrate≡pfa	250.00	32.68	500.00	47.62
Colloidal silica	7.65	1.00	10.50	1.00
Sodium starch glycollate	11.00	1.44	21.00	2.00
Silica gel (Syloid AL/1)	76.50	10.00	31.50	3.00
Magnesium stearate	4.85	0.63	7.27	0.69
Microcrystalline cellulose	765.00	to 100.0	1050.00	to 100.0
Film coat				
Titanium dioxide suspension solid residue	4.00		5.56	
Ethylcellulose	2.26		3.15	
Diethyl phthalate	2.67		3.70	
Hydroxypropylmethyl cellulose	9.07		12.59	
Silicone cream, non-volatile residue	—		0.05	
Film coated tablet weight	783.0		1075.0	

Example 6

Ingredients	375 mg	% w/w	281.25 mg	% w/w
Potassium clavulanate≡pfa	125.00	16.34	31.25	4.08
Amoxycillin trihydrate≡pfa	250.00	32.68	250.00	32.68
Colloidal silica	7.65	1.00	7.65	1.00
Sodium starch glycollate	11.00	1.44	11.00	1.44
Molecular sieve 4A	38.25	5.00	38.25	5.00
Magnesium stearate	4.85	0.63	4.85	0.63
Microcrystalline cellulose	765.00	to 100.00	765.00	to 100.00
Film coat	18 mg		18 mg	
Titanium dioxide suspension solid residue	4.00		4.00	
Ethylcellulose	2.26		2.26	
Diethyl phthalate	2.67		2.67	
Hydroxypropylmethylcellulose	9.07		9.07	
Silicone cream, non-volatile residue	—		—	
Film coated tablet weight	783.0		783.0	

Claims

1. A unit dose pharmaceutical composition suitable for oral administration which composition comprises a pharmaceutically acceptable carrier, a desiccant, amoxycillin trihydrate equivalent to 20 mg to 1500 mg of amoxycillin and potassium clavulanate equivalent to 20 mg to 500 mg of clavulanic acid, with the proviso that the weight ratio of amoxycillin to clavulanic acid is in the range 12:1 to 1:1; characterised in that the composition is in tablet form, wherein the desiccant is edible and incorporated within the tablets and represents between 2.5% and 10% of the total weight of the formulated tablet.

2. A composition as claimed in claim 1, wherein the weight ratio of amoxycillin to clavulanic acid if from 8:1 to 2:1.

3. A composition as claimed in claim 1, wherein the weight ratio of amoxycillin to clavulanic acid is 8:1, 4:1 or 2:1.

4. A composition as claimed in any one of claims 1 to 3, wherein the composition contains 125—500 mg of amoxycillin.

5. A composition as claimed in any one of claims 1 to 3, wherein the composition contains 31.25—125 mg of clavulanic acid.

6. A composition as claimed in any one of claims 1 to 5, wherein the desiccant is an edible grade of silica gel or crystalline sodium, potassium or calcium aluminosilicate.

7. A composition as claimed in any one of claims 1 to 6 packaged in a protective package.

8. A process for the preparation of a composition as claimed in any one of claims 1 to 6, which comprises bringing into association the components of said composition and thereafter compressing the blended mixture into a tablet.

Patentansprüche

1. Eine für die orale Verabreichung geeignete pharmazeutische Zusammensetzung in Einzeldosisform, welche Zusammensetzung einen pharmazeutisch verträglichen Träger, ein Trockenmittel, Amoxycillintrihydrat in einer Menge äquivalent zu 20 mg bis 1500 mg Amoxycillin und Kaliumclavulanat in einer Menge äquivalent zu 20 mg bis 500 mg Clavulansäure enthält, mit der Maßgabe, daß das Gewichtsverhältnis von Amoxycillin zu Clavulansäure im Bereich von 12:1 bis 1:1 liegt, dadurch gekennzeichnet, daß die Zusammensetzung in Tablettenform vorliegt, wobei das Trockenmittel eßbar und Bestandteil der Tabletten ist und zwischen 2,5 und 10% des Gesamtgewichts der so gebildeten Tablette ausmacht.

Example 6

Ingredients	375 mg	% w/w	281.25 mg	% w/w
Potassium clavulanate≡pfa	125.00	16.34	31.25	4.08
Amoxycillin trihydrate≡pfa	250.00	32.68	250.00	32.68
Colloidal silica	7.65	1.00	7.65	1.00
Sodium starch glycollate	11.00	1.44	11.00	1.44
Molecular sieve 4A	38.25	5.00	38.25	5.00
Magnesium stearate	4.85	0.63	4.85	0.63
Microcrystalline cellulose	765.00	to 100.00	765.00	to 100.00
Film coat	18 mg		18 mg	
Titanium dioxide suspension solid residue	4.00		4.00	
Ethylcellulose	2.26		2.26	
Diethyl phthalate	2.67		2.67	
Hydroxypropylmethylcellulose	9.07		9.07	
Silicone cream, non-volatile residue	—		—	
Film coated tablet weight	783.0		783.0	

Claims

1. A unit dose pharmaceutical composition suitable for oral administration which composition comprises a pharmaceutically acceptable carrier, a desiccant, amoxycillin trihydrate equivalent to 20 mg to 1500 mg of amoxycillin and potassium clavulanate equivalent to 20 mg to 500 mg of clavulanic acid, with the proviso that the weight ratio of amoxycillin to clavulanic acid is in the range 12:1 to 1:1; characterised in that the composition is in tablet form, wherein the desiccant is edible and incorporated within the tablets and represents between 2.5% and 10% of the total weight of the formulated tablet.

2. A composition as claimed in claim 1, wherein the weight ratio of amoxycillin to clavulanic acid if from 8:1 to 2:1.

3. A composition as claimed in claim 1, wherein the weight ratio of amoxycillin to clavulanic acid is 8:1, 4:1 or 2:1.

4. A composition as claimed in any one of claims 1 to 3, wherein the composition contains 125—500 mg of amoxycillin.

5. A composition as claimed in any one of claims 1 to 3, wherein the composition contains 31.25—125 mg of clavulanic acid.

6. A composition as claimed in any one of claims 1 to 5, wherein the desiccant is an edible grade of silica gel or crystalline sodium, potassium or calcium aluminosilicate.

7. A composition as claimed in any one of claims 1 to 6 packaged in a protective package.

8. A process for the preparation of a composition as claimed in any one of claims 1 to 6, which comprises bringing into association the components of said composition and thereafter compressing the blended mixture into a tablet.

Patentansprüche

1. Eine für die orale Verabreichung geeignete pharmazeutische Zusammensetzung in Einzeldosisform, welche Zusammensetzung einen pharmazeutisch verträglichen Träger, ein Trockenmittel, Amoxycillintrihydrat in einer Menge äquivalent zu 20 mg bis 1500 mg Amoxycillin und Kaliumclavulanat in einer Menge äquivalent zu 20 mg bis 500 mg Clavulansäure enthält, mit der Maßgabe, daß das Gewichtsverhältnis von Amoxycillin zu Clavulansäure im Bereich von 12:1 bis 1:1 liegt, dadurch gekennzeichnet, daß die Zusammensetzung in Tablettenform vorliegt, wobei das Trockenmittel eßbar und Bestandteil der Tabletten ist und zwischen 2,5 und 10% des Gesamtgewichts der so gebildeten Tablette ausmacht.

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2. Eine Zusammensetzung wie in Anspruch 1 beansprucht, in welcher das Gewichtsverhältnis von Amoxycillin zu Clavulansäure im Bereich zwischen 8:1 bis 2:1 liegt.

3. Eine Zusammensetzung wie in Anspruch 1 beansprucht, in welcher das Gewichtsverhältnis von Amoxycillin zu Clavulansäure 8:1, 4:1 oder 2:1 beträgt.

4. Eine Zusammensetzung wie in irgendeinem der Ansprüche 1 bis 3 beansprucht, wobei die Zusammensetzung 125 bis 500 mg Amoxycillin enthält.

5. Eine Zusammensetzung wie in irgendeinem der Ansprüche 1 bis 3 beansprucht, wobei die Zusammensetzung 31,25 bis 125 mg Clavulansäure enthält.

6. Eine Zusammensetzung wie in irgendeinem der Ansprüche 1 bis 5 beansprucht, in welcher das Trockenmittel eine eßbare Gütestufe von Silikagel, oder kristallinem Natrium-, Kalium- oder Calciumaluminiumsilikat ist.

7. Eine Zusammensetzung wie in irgendeinem der Ansprüche 1 bis 6 beansprucht, welche in einer Schutzverpackung abgepackt ist.

8. Ein Verfahren zur Herstellung einer Zusammensetzung wie in irgendeinem der Ansprüche 1 bis 6 beansprucht, welches das Miteinander-Vereinigen der Komponenten der genannten Zusammensetzung und anschließend das Verpressen der erhaltenen Mischung zu Tablettenform umfaßt.

Revendications

1. Composition pharmaceutique en dose unitaire convenable pour l'administration orale, comprenant un support acceptable du point de vue pharmaceutique, un dessicateur, de l'amoxycilline trihydratée en une quantité équivalente à 20 à 1500 mg d'amoxycilline et du clavulanate de potassium en une quantité équivalente à 20 à 500 mg d'acide clavulanique, à la condition que le rapport pondéral d'amoxycilline à l'acide clavulanique soit dans la gamme de 12:1 à 1:1, caractérisée en ce que la composition est sous forme de comprimé, que le dessicateur est comestible et incorporé dans les comprimés et qu'il représente entre 2,5 et 10% du poids total du comprimé formulé.

2. Composition suivant la revendication 1, caractérisée en ce que le rapport molaire d'amoxycilline à l'acide clavulanique est de 8:1 à 2:1.

3. Composition suivant la revendication 1, caractérisée en ce que le rapport molaire d'amoxycilline à l'acide clavulanique est de 8:1, 4:1 ou 2:1.

4. Composition suivant l'une quelconque des revendications 1 à 3, caractérisée en ce qu'elle comprend 125 à 500 mg d'amoxycilline.

5. Composition suivant l'une quelconque des revendications 1 à 3, caractérisée en ce qu'elle comprend 31,25 à 125 mg d'acide clavulanique.

6. Composition suivant l'une quelconque des revendications 1 à 5, caractérisée en ce que l'agent de dessication est une qualité comestible de gel de silice ou d'aluminosilicate cristallin de sodium, de potassium ou de calcium.

7. Composition suivant l'une quelconque des revendications 1 à 6, caractérisée en ce qu'elle est conditionnée dans un emballage protecteur.

8. Procédé de préparation d'une composition suivant l'une quelconque des revendications 1 à 6, caractérisé en ce qu'on associe les composants de cette composition puis que l'on presse le mélange résultant en un comprimé.