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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING AMOXYCILLIN AND CLAVULANATE AND A DESICCANT

(57) Abstract

A solid pharmaceutical composition for oral administration, comprising amoxycillin trihydrate, potassium clavulanate and a desiccant, wherein the desiccant comprises a desiccating metal salt which is pharmaceutically acceptable by oral administration.

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PHARMACEUTICAL COMPOSITION COMPRISING AMOXICILLIN AND CLAVULANATE AND A DESICCANT

The present invention relates to pharmaceutical compositions for oral administration in the treatment of bacterial infections. In particular the invention relates to compositions comprising the antibiotic amoxycillin in the form of its trihydrate and the beta-lactamase inhibitor clavulanic acid in the form of potassium clavulanate. Potassium clavulanate is extremely moisture sensitive, and compositions which include it normally need to be desiccated.

GB 2005384 discloses pharmaceutical compositions suitable for oral administration which use colloidal silica in the form of Syloid ™ as a desiccant.

EP 0049061 discloses pharmaceutical compositions for oral administration which comprise amoxycillin trihydrate and potassium clavulanate, and further types of desiccant which are edible.

PCT/EP 95/02127 discloses compositions suitable for injection or infusion which comprise potassium clavulanate and sodium amoxycillin, and which *use inter alia* desiccating metal salts as desiccants.

It has now been found that compositions for oral administration incorporating another type of desiccant within the tablet itself can be prepared, and which give an improved desiccating effect in preserving the amoxycillin and clavulanate content.

Accordingly, the present invention provides a solid pharmaceutical composition suitable for oral administration, which composition comprises amoxycillin trihydrate, potassium clavulanate and a desiccant, wherein the desiccant comprises a desiccating metal salt which is pharmaceutically acceptable by oral administration.

The solid composition of the invention may for example be a tablet formulation in which one or more such tablets provide a unit dose of the active ingredients amoxycillin trihydrate and potassium clavulanate. The solid composition of the invention may alternatively for example be a granulate formulation, either provided in a unit dose quantity such as in a sachet, or provided in a bulk of several unit dose quantities for subdivision into unit doses, or for subsequent compaction to form a tablet.

The weights of amoxycillin trihydrate and potassium clavulanate are referred to herein in terms of the weights of the corresponding pure parent 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 30 :1 to 2:1 for example from 15:1 to 2:1, for example 8:1, 7:1, 6:1 or 4:1 ± 10%.

In general the oral unit dose quantity of a composition of this invention will contain from 125 mg to 1250 mg of amoxycillin, for example it may contain about 125, 250, 500, 875 or 1000 mg of amoxycillin.

In general the oral unit dose quantity of a composition 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.

In general the amounts of amoxycillin trihydrate and potassium clavulanate in the compositions of this invention may be similar to those in known solid compositions intended for oral administration.

Suitable desiccating metal salts which may be used in the present invention are pharmaceutically acceptable when administered orally. Examples of such salts include Group I and Group II metal halides, particularly chlorides, or mixtures thereof, such as desiccating forms of sodium chloride, calcium chloride and magnesium chloride.

A suitable desiccating form of sodium chloride is an amorphous form for example obtainable by spray-drying and containing a low moisture content. A suitable desiccating form of calcium chloride is an at least partly dehydrated form, e.g. containing 5% or less of water, for example obtainable by heat treatment of calcium chloride having a higher water content than this, under vacuum. A suitable desiccating form of magnesium chloride is an at least partly dehydrated form, for example obtainable by heat treatment of magnesium chloride hexahydrate under vacuum until it has a water content less than 40 wt. %.

Other metal salts which may be suitable include disodium phosphate in an at least partly anhydrous form e.g. containing around 0.1% water. Such salts may be used singly or in mixtures, for example a mixture of sodium chloride and magnesium chloride.

The quantity of a desiccating metal salt needed to provide adequate desiccation of the pharmaceutical composition of the invention will depend upon the quantity of the amoxycillin trihydrate and potassium clavulanate in the composition but can easily

be determined by experimentation, for example by determination of the stabilisation of the amoxycillin trihydrate and potassium clavulanate content.

Most suitably the desiccant will be present in an amount, weight for weight less than that of the amoxycillin trihydrate and potassium clavulanate content. The desiccant may for example represent 0.5 to 20% of the total weight of the composition, e.g. of a formulated tablet, optimally around 2 to 8% w/w, a particularly favoured amount being around 3±1% w/w of the solid form.

In addition to the antibacterially active ingredients and the desiccant present in the solid form, such compositions may contain one or more conventional excipients as appropriate to the solid form, for example fillers such as micro-crystalline cellulose, lubricants such as magnesium stearate, disintegrants such as sodium starch glycollate, crosslinked polyvinyl pyrrolidone or other similar known agents, granulating aids etc. 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 solid form include microfine cellulose (as a tablet filler), calcium carbonate or magnesium carbonate (usually light magnesium carbonate) (as tablet fillers) and starch or crosslinked polyvinyl pyrrolidone (as tablet disintegrant). Granular formulation may contain any of the conventional excipients such as diluents, fillers, bulking agents etc. used in granulate pharmaceutical formulations, in conventional quantities.

Suitably the desiccating metal salt may be incorporated within the solid form. With tablet solid forms the desiccating metal salt may suitably be included within the compacted tablet. With granulate formulations the desiccating metal salt may be included within the granulates, or additionally or alternatively the desiccating metal salt may be included externally to the granulates together with the granulates in a suitable moisture-tight contaner such as a sachet.

Tablet solid forms according to this invention may be film coated, if desired, with known film coating 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 shellac or copal resins or their conventional modifications.

Alternatively the tablet coating may be an enteric coating, i.e. 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 blister 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. The process by which a tablet solid form is made may be one in which the powdered ingredients are directly compressed in a die, or alternatively the ingredients may be pre-granulated then tabletted. Suitably the granulation process is a dry granulation process such as slugging or roller compaction then milling.

Also included within the scope of the present invention is a process for the preparation of a granulate composition as hereinbefore described which comprises bringing into association the components of said composition and thereafter forming the blended mixture into granules. Again suitably the granulation process is a dry granulation process such as slugging or roller compaction then milling.

It is preferable that the composition of the composition is carried out in a dry atmosphere, e.g. one containing less than 30% relative humidity and preferably one containing less than 20% relative humidity. Such dryness is desirable for the preservation of the highly moisture sensitive potassium clavulanate.

The present invention also provides such a composition for use as an active therapeutic substance in the treatment of bacterial infections.

The present invention also provides the use of such a composition in the preparation of a medicament for oral administration in the treatment of bacterial infections.

The present invention also provides a method for protecting a co-composition of amoxycillin trihydrate and potassium clavulanate in a solid composition for oral

administration from degradation by moisture, by means of the use of a desiccating metal salt which is pharmaceutically acceptable by oral administration.

The present invention also provides a method of treatment of a human patient which includes the step of the oral administration to a patient in need of such treatment of a composition as described above.

The following examples, which illustrate the invention and compare a composition of the invention with comparison compositions. In order to verify the effect of internal metal salt desiccants, three different batches (A), (B) and MG1 of amoxycillin potassium clavulanate tablets were prepared in a low humidity area. MG1 is a composition of this invention using dehydrating magnesium chloride, (A) includes no desiccant, and (B) includes syloid as desiccant.

The composition of these three batches is as follows per tablet:

	Batch (A)	**Batch (B)**	**Batch MG1**
Amoxycillin trihydrate (mg)	1004.5	1004.5	1004.5
Potassium clavulanate (mg)	148.9	148.9	148.9
Aerosil 200 (mg)	10.0	10.0	10.0
Magnesium stearate (mg)	14.5	14.5	14.5
Sodium starch glycolate (mg)	29.0	29.0	29.0
Microcrystalline cellulose (mg)	243.1	243.1	243.1
Syloid AL-1 (mg)	------	50.0	------
Magnesium chloride (*) (mg)	------	------	50.0

Note: (*) $MgCl_2.6H_2O$ was previously desiccated for 6 h at 120°C under vacuum; final water content (KF method) : 34.68%

The tablets were made by preparing a standard production final mixture for amoxycillin:potassium clavulanate tablets, without Syloid™ or magnesium chloride. This mixture was divided into three parts:

- the first part was directly tabletted, obtaining batch (A).

- the second part was mixed with Syloid AL-1™ and then tabletted obtaining batch (B).

- the third part was mixed with the dried magnesium chloride and then tabletted obtaining batch MG1.

A standard powder compression process was used to form the tablets.

The tablets so obtained, without any film coat and without any further treatment, were packed in glass bottles and the glass bottles were stored at 50°C for 15 and 30 days.

The analytical results, carried out on the tablets showed the following, expressed as percentages of the initial values:

	Batch (A)	**Batch (B)**	**Batch MG 1**
15 days at 50°C			
Amoxycillin	99.1%	98.5%	98.1%
Clavulanate	93.7%	94.3%	97.2%
30 days at 50°C			
Amoxycillin	98.8%	99.4%	99.4%
Clavulanate	89.8%	92.7%	97.7%

These results indicate a significant reduction in decomposition of the amoxycillin and clavulanate content of these tablets, by the use of magnesium chloride desiccant, relative to the use of no desiccant, or conventional silicon dioxide.

Such tablets could be milled by known processes to form a granulate composition of this invention.

Claims:

1. A solid pharmaceutical composition suitable for oral administration, which comprises amoxycillin trihydrate, potassium clavulanate and a desiccant, wherein the desiccant is incorporated within the solid form and comprises a desiccating metal salt which is pharmaceutically acceptable by oral administration.

2. A composition according to claim 1 being a tablet formulation or a granulate formulation.

3. A composition according to claim 1 or 2 wherein the desiccating metal salt is selected from Group I and Group II metal halides.

4. A composition according to claim 3 wherein the desiccating metal salt is selected from desiccating forms of sodium chloride, calcium chloride and magnesium chloride and mixtures thereof.

5. A composition according to claim 4 wherein the desiccating metal salt is sodium chloride in an amorphous form.

6. A composition according to claim 4 wherein the desiccating metal salt is calcium chloride is an at least partly dehydrated form.

7. A composition according to claim 6 wherein the desiccating metal salt is calcium chloride containing 5% or less of water.

8. A composition according to claim 4 wherein the desiccating metal salt is magnesium chloride is an at least partly dehydrated form.

9. A composition according to claim 8 wherein the desiccating metal salt is magnesium chloride having a water content less than 40 wt. %.

10. A composition according to claim 1 or 2 wherein the desiccating metal salt is disodium phosphate in an at least partly anhydrous form.

11. A composition according to any one of the preceding claims wherein the desiccating metal salt represents 0.5 to 20% of the total weight of the composition.

12. A composition according to any one of the preceding claims wherein the desiccating metal salt represents around 2 to 8 % of the total weight of the composition.

13. A composition according to any one of the preceding claims wherein the desiccating metal salt is incorporated within the solid form.

14. A composition according to any one of claims 1 to 12 being a granulate formulation wherein the desiccating metal salt is included within the granules, or additionally or alternatively the desiccating metal salt is included externally to the granules together with the granules in a suitable moisture-tight contaner.

15. A process for the preparation of a tablet composition as hereinbefore claimed which comprises bringing into association the components of said composition and thereafter compressing the blended mixture into a tablet.

16. A process for the preparation of a granulate composition as hereinbefore claimed which comprises bringing into association the components of said composition and thereafter forming the blended mixture into granules.

17. The use of such a composition as claimed in any one of claims 1 to 14 in the preparation of a medicament for oral administration in the treatment of bacterial infections.

18. A method for protecting a co-composition of amoxycillin trihydrate and potassium clavulanate in a solid composition for oral administration from degradation by moisture, by means of the use of a desiccating metal salt which is pharmaceutically acceptable by oral administration.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/42 A61K31/43 A61K9/20 //(A61K31/43,A61K31:42)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	EP,A,0 049 061 (BEECHAM GROUP PLC) 7 April 1982 cited in the application see page 3, line 13-28; claim 1 ---	1-18
Y	GB,A,2 005 538 (BEECHAM GROUP LTD) 25 April 1979 cited in the application see page 2, line 5-7; claim 1 ---	1-18

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[X] Further documents are listed in the continuation of box C.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

formation on patent family members

Inter ·onal Application No
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