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(72) GROENENDAAL, Jan Willem, NL
(71) GIST-BROCADES B.V., NL

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(54) **GRANULES COMPRENANT DU CLAVULANATE ET UN OU PLUSIEURS EXCIPIENTS**

(54) **GRANULES COMPRISING CLAVULANATE AND ONE OR MORE EXCIPIENTS**

(57) L'invention concerne des granulés de clavulanate contenant des excipients inertes pour des formulations pharmaceutiques, ainsi qu'un procédé pour leur fabrication faisant intervenir un dispositif de tamisage utilisant de préférence un système à jet d'air.

(57) Granules of clavulanate containing inert excipients for pharmaceutical formulations have been provided for. Also a process to prepare the same by employing a sieving device preferably using an air jet system has been described.

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(71) Applicant *(for all designated States except US)*: GIST–BROCADES B.V. [NL/NL]; Wateringseweg 1, P.O. Box 1, NL–2600 MA Delft (NL).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: GROENENDAAL, Jan, Willem [NL/NL]; Koorenmarkt 4, NL–2611 EE Delft (NL).

(74) Agents: VISSER–LUIRINK, Gesina et al.; Gist–Brocades B.V., Patents and Trademarks Dept., Wateringseweg 1, P.O. Box 1, NL–2600 MA Delft (NL).

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(54) Title: GRANULES COMPRISING CLAVULANATE AND ONE OR MORE EXCIPIENTS

(57) Abstract

Granules of clavulanate containing inert excipients for pharmaceutical formulations have been provided for. Also a process to prepare the same by employing a sieving device preferably using an air jet system has been described.

GRANULES COMPRISING CLAVULANATE AND ONE OR MORE EXCIPIENTS

The present invention relates to granules of clavulanate containing excipients and a process to prepare the same.

Technological background and field of invention

It is generally known that crystalline β-lactam antibiotic powder itself is not suitable for the manufacturing of tablets and capsules containing oral grade β-lactam antibiotics because the crystalline material has no satisfactory flowability and density so that controlled dosage per tablet or capsule is not guaranteed. Therefore, normally a granulate is produced by mixing the crystalline product (1-150 μm) with other components as binders and fillers in a wet or dry granulation process. For preparing granules of potassium clavulanate, the situation is even more complex due to its hygroscopic nature and instability at already relative low humidities during the granulation process.

In German patent application DE 2251250, a process for relatively small tablets containing a high amount of antibiotic using a granulate prepared with a small amount (5-15%) of excipients (e.g. crystalline cellulose, binder, talc) has been described. European patent EP 281200 describes a pharmaceutical granulate comprising 35-45 wt% microcrystalline cellulose prepared by wet granulation, which granulate disintegrates quickly when immersed in water. Also, in PCT applications WO 9116893 and WO 9219227, for example, the antibiotic has been described to be mixed with excipients (e.g. an effervescent couple of excipients or intra-granular disintegrant, flavour, magnesium stearate) for granulation using slugging or a roller compactor for compacting. Thereafter, the granules have been sieved to the desired particle size and finer material is recycled to the compaction process. In PCT application WO 9528927, a pharmaceutical tablet formulation

having a structure comprising compacted granules of amoxicillin and clavulanate in a weight ratio of 6:1 to 8:1, excipients and having a coating of polymers has been described.

International patent application WO 9717960 also describes an oral composition containing clavulanate and amoxicillin in which a metal salt desiccant, for example sodium, calcium or magnesium chloride has been added in order to increase the stability of potassium clavulanate. European patent EP 0002574 describes the preparation of particles comprising an anhydrous salt of clavulanic acid dispersed in a semi-synthetic polymer binder of low water vapour permeability. In International patent application WO 9427557 a process has been claimed for the preparation of thermal infusion granules of clavulanate. These thermal infusion granules have been prepared by compacting blends of clavulanate, a hydrophobic waxy material, optionally excipients, milling, screening and, subsequently, subjecting the same to thermal infusion.

Difficulties one may encounter by using wet granulation are in the first place decomposition of potassium clavulanate because of use of water and/or organic solvents combined with elevated temperature during granulation. Besides that the use of organic solvents is restricted by governmental rules concerning environmental protection. Furthermore, the wet granulation process is labour intensive, expensive and time consuming because of the large number of processing steps like mixing, granulating, wet sieving, drying etc. and a lot of energy is needed to dry the wet granules. Besides this, the granules produced by wet granulation are rather porous and high bulk volumes are not or difficult to reach, whereby it is often not possible to achieve high dosages in gelatin capsules. Finally the binder dissolved in a binder solution or dry mixed with the compound to be granulated usually gives problems with a homogeneous distribution because of its sticking nature. This results in an inhomogeneous composition which can cause differences in dissolution and/or tablet hardness between dosage forms of various batches and therefore differences in bioavailability. Difficulties one may encounter by using dry

granulation together with amoxicillin trihydrate are decomposition of potassium clavulanate because of a too high water activity during roller compaction or slugging developed by amoxicillin trihydrate.

It has been found that directly after roller compaction the water activity of compacted amoxicillin trihydrate was increased from 0.15 to 0.25 for the powder to 0.35 to 0.45 for the compacts. Furthermore it has been found with Dynamic Vapour Sorption Analyses that potassium clavulanate starts to decompose at relative humidities of 20% and higher at ambient temperatures because of volatile decomposition products formed.

Difficulties one may encounter by storing and transporting mixtures of granulated amoxicillin trihydrate and potassium clavulanate are decomposition of potassium clavulanate because of a too high water activity in the mixture developed by the granulated amoxicillin trihydrate. Furthermore, during transportation and processing of mixtures of granulated amoxicillin trihydrate and potassium clavulanate powder, segregation will take place because of the difference in particle size resulting in inhomogeneous mixtures.

It has been found that during a long period after dry or wet granulation of amoxicillin trihydrate this material still shows water activity of 0.2 to 0.5 that is too high for stable storage conditions of potassium clavulanate. It also has been found that this too high value of water activity was developed by only 0.2 to 0.5 w/w% of free, not crystal bound, water that was detected by Differential Thermal Analyses. Also the active ingredient may dissolve partially in the granulation solution, which after drying will cause a decreased disintegration and dissolution of these granules that are therefore less suitable for tablets, especially disperse tablets.

Surprisingly it is found that granules comprising potassium clavulanate and an inert excipient are relatively stable. Such granules have nowhere been described or suggested in the prior art.

Summary of the invention

The present invention provides granules of clavulanate containing inert excipients which are preferably substantially free of solvents with the provisio that the clavulanate has not been dispersed in a polymeric binder of low water vapour permeability. The clavulanate granules are preferably potassium clavulanate and the inert excipient is a cellulose, preferably microcrystalline cellulose, more preferably with a water activity of less than 0.2 at 25°C, most preferably Avicel® PH112. The ratio of potassium clavulanate related to microcrystalline cellulose such as Avicel® PH112 is 1: 5 - 0.2 wt%, preferably 1: 2-0.5 wt% and more preferably about 1:1 wt%. These granules are of a particle size between 50 μm and 1500 μm, preferably between 125 μm and 1000 μm.

Furthermore, a process to prepare said granules has been provided for. The process comprises of feeding, for example, potassium clavulanate powder and inert excipients to a roller compactor to produce compacts, followed by milling said compacts to give granules. These granules are, then, sieved with a sieving device to separate the granules from fine particles, preferably fine particles of <150 μm, more preferably fine particles of <125 μm. The sieving device comprises a tumbler or vibratory sieving machine, preferably a tumbler sieving machine equipped with an air jet system. The fine particles are optionally recirculated to the roller compactor.

The present invention also provides a pharmaceutical composition prepared from blending granules of potassium clavulanate of the invention together with crystals or granules of amoxicillin trihydrate optionally containing excipients and specific excipients specifically used for the preparation of compositions of oral dosage forms like tablets with or without coating, disperse tablets, chewable tablets and oral dry suspension.

Detailed description of the invention

The granulation method, wherein clavulanate with inert excipients are used, consists of dry granulation by using compaction forces to build up agglomerates. This may be performed by slugging or roller compacting. The compacts are milled and, then, sieved with a sieving device. The separation of fine particles from coarse granules may be carried out by a dry air sieving procedure.

In dry air sieving, the milled compacts are placed on the sieve and air is blown through the bed of milled compacts to separate the granules from the fine particles. The sieving device comprises preferably an air jet system using air with a relative humidity of $<30\%$, preferably $<20\%$ and a temperature between 15 and 25°C. Furthermore, the sieving device can be coupled directly to the roller compactor or stands separately from the same.

The application of this granulation method results in granules with a satisfactory particle size distribution, viz. between 50 μm and 1500 μm, preferably between 125 μm and 1000 μm. Moreover, these granules are preferably substantially free of organic solvents and/or water, because during the process of compaction use of these solvents is usually avoided. The only traces of solvent(s) which may be present in the said granules are already present in the starting compound. Furthermore, the present technique eliminates problems in granulation processes due to heat and moisture because potassium clavulanate should be processed in an environment with a relative humidity of 20% or lower at a temperature between 20 and 25°C because higher humidities start decomposition processes with small amounts of water as reaction products which on their turn continue the decomposition reaction. Since potassium clavulanate is dry granulated together with an inert excipient, preferably Avicel® PH112 this has strongly reduced the run-away hazard in comparison with that of the unblended potassium clavulanate. The unblended potassium clavulanate is classified as highly flammable, both

according to the European notification directories and the UN transport recommendations. The blend potassium clavulanate in the concentration with Avicel® PH112 1:1 weight ratio is not flammable. The inert excipients with sufficient binding properties also increase the flowability of the blend with potassium clavulanate to improve the flow through the compacting equipment. Moreover, the dry granulation of potassium clavulanate according to the present invention results in granules with a sufficient high density. This is an advantage because potassium clavulanate is always used in admixture with amoxicillin in relatively high dosages resulting in large tablets. A too low density of the granules would further enlarge the large, difficult swallowable tablets. The clavulanate granules also allow for disintegration of dosage forms into primary drug particles followed by a high dissolution rate because no wet binders are used. This is especially important when dispersable tablets are produced which should have a disintegrating time less than a few minutes.

Thus, the resulting potassium clavulanate granules showing excellent flow properties and almost no dust can be mixed with amoxicillin, preferably amoxicillin granules as mentioned in European patent application No. PCT/EP 98/05902 filed on 27-08-1998, which granules possess the same particle size forming a mixture of both granules not susceptible to segregation.

For the preparation of clavulanate granules, a certain amount of clavulanate powder, for instance potassium clavulanate and the excipients, for instance Avicel® PH112 with a water activity of less than 0.2 measured at a temperature of 25°C, is fed to a roller compactor. The compact materials are milled and, thereafter, sieved by using an air jet system. The sieving device is coupled directly to the roller compactor in order to avoid extra steps or stands separately. The fine particles, preferably the material < 125 μm, are recycled to the roller compacting process.

The granules of clavulanate, preferably of potassium clavulanate in combination with granules of amoxicillin, preferably of amoxicillin trihydrate as described in European patent application No. PCT/EP 98/05902 indicated above can be used for all formulations to produce chew, swallow, disperse,

effervescent or normal tablets of all sizes, forms and weights, also to fill hard gelatin capsules and to formulate dry syrups and for administering drugs with the help of a dose sipping device. To produce tablets, only excipients have to be mixed with the granules and tablets can be pressed.

To fill hard gelatin capsules no excipients are necessary, the granules can directly be filled into capsules or when fast running capsules filling machines are used, some lubricant like magnesium stearate can be mixed with the granules to facilitate the filling process.

To formulate dry oral syrups, flavours, bulking agents such as sugars and preservatives are often used. These excipients are mixed with the granules and bottles for multi dosage use or sachets for single dosage use. Optionally a premix of excipients is prepared and filled into bottles or sachets after which the granules are added separately.

For dose sipping devices, for example, the granules can be placed over a support in a tube having a liquid inlet end and a liquid outlet end; excipients can also be placed over the support, together with the drug granules. Oral administration of therapeutical agents with the help of a dose sipping device has been described in European patent application EP 383503.

The invention will now be described with reference to the following Examples, which are provided purely for illustrative purposes.

Example 1

Preparation of a granulate using slugging and conventional vibration sieving on a small scale

During the preparation procedures the temperature was between 20 and 25°C and the relative humidity <20%. Potassium clavulanate powder (100 g) was mixed with microcrystalline cellulose (Avicel® PH112)(100 g) using a Turbula® T2C mixer during 10 minutes. Magnesium stearate (1 g) was added and mixed during 2 minutes. The powder mixture was fed to a Korsch

EK-0 excenter tablet press equipped with a die and an upper and lower flat punch with a diameter of 16 mm.

Slugs were pressed with a thickness of about 3 mm, and a hardness of about 25 N measured with an Erweka® TBH28 hardness tester. The slugs were crushed using an Erweka T32 tablet crusher followed by a milling process using a Peppink® N100 hammer mill equipped with a 3 mm sieve.

The milled material (30 g) was treated as presented below:

The coarse particles and the fines were separated from the milled material using a Retsch Vibro vibrating-sieve working with a vibration amplitude of 2 mm, during 10 minutes, and using a 1000 μm and a 125 μm sieve.

The amount of fines < 125 μm was 19 % w/w.

The amount of coarse particles > 1000 μm was 8 % w/w.

The yield of granules between 125 and 1000 μm was 73 % w/w.

The flowability was determined using flow funnels with the following size of apertures: 18 - 12 - 8 - 5 and 2.5 mm.

The granules flowed freely through a funnel with an aperture of 12 mm but not through 8 mm, which indicates just sufficient flowability.

Example 2

Preparation of a granulate using slugging and air sieving on a small scale

The milled material (30 g) of example 1 was treated as presented below:

The coarse particles and the fines were separated from the milled material using an Alpine® 200LS-N air-sieve working with an under pressure of 2000 Pa during 3 minutes, and using a 1000 and a 125 μm sieve. The used air had a relative humidity of <20% and a temperature of 25°C.

The amount of fines < 125 μm was 42 % w/w.

The amount of coarse particles > 1000 μm was 7 % w/w.

The yield of granules between 125 and 1000 μm was 51 % w/w.

The flowability was determined using flow funnels with the following size of apertures: 18 - 12 - 8 - 5 and 2.5 mm.

The granules flowed freely through a funnel with an aperture of 5 mm but not through 2.5 mm, which indicates good flowability.

It is obvious that the air-sieve method separates the fines much more efficient from the coarse particles than the conventional vibrating sieve resulting in a much better flowability of the granules and lower dust content.

Example 3

Preparation of a granulate using roller compaction and air sieving on larger scale

During the preparation procedures the temperature was between 20 and 25°C and the relative humidity< 20%. Potassium clavulanate powder was mixed with microcrystalline cellulose (Avicel® PH112), with a water activity of less than 0.2 at 25°C. The mixture was fed to a roller compactor. The produced compacts were milled and sieved with an air jet system using a sieve with apertures of 150 μm. The particles < 150 μm were recycled to the roller compactor.

The amount of fines < 150 μm was 32 % w/w.

The amount of coarse particles > 1000 μm was 5 % w/w.

The yield of granules between 150 and 1000 μm was 63 % w/w.

The flowability was determined using flow funnels with the following size of apertures: 18 - 12 - 8 - 5 and 2.5 mm.

The granules flowed freely through a funnel with an aperture of 5 mm but not through 2.5 mm, which indicates good flowability.

Example 4

Preparation of disperse tablets of granules of potassium clavulanate and granules of amoxicillin trihydrate

During the preparation procedures the temperature was between 20 and 25°C and the relative humidity <20%. Potassium clavulanate granules (1.52 kg), with a potency of 41.1% clavulanic acid, prepared according to example 3, amoxicillin trihydrate granules (2.925 kg), with a potency of 85.5% amoxicillin, 0.095 kg sodium starch glycolate (Explotab®), 0.047 kg magnesium stearate and 0.162 kg microcrystalline cellulose (Avicel® PH 112) were mixed.

About 5000 round, flat tablets were pressed using a Korsch EKO excenter tablet press with the following characteristics: weight 950 mg, diameter 18 mm, thickness 6 mm, hardness between 110 and 150 N, disintegration in water of 20°C in less than 60 seconds, dissolution of the labelled amount of amoxicillin within 30 minutes by using the method as described in the U.S. Pharmacopoeia XXIII 1994, The United States Pharmacopeial Convention Inc. Rochville MD, USA.

The amoxycillin trihydrate granules were prepared as follows:

Amoxicillin trihydrate powder was fed to a Fitzpatrick roller compacter type Chilsonator 4L X 10D. The used rolls had a diameter of 25.4 cm and a roll wide of 10.2 cm, the roll surface was sinus waved grooved, the roll gap was 3.1 mm. The roll speed was 11 rpm, the horizontal feeder speed was 17 rpm, the vertical feeder speed 450 rpm and the applied roll pressure 1100 psi.

The compacts were milled using a Minox sieve type MTS 1200 equipped with an air jet system. The sieve applied had a diameter of 120 cm and apertures of 150 μm. The air was escaping upwards from a rotating perforated blade fixed horizontal under the sieve. By this action the fine

particles were blown off from the coarse particles and sucked downwards through the sieve to the receiver by the action of an under pressure.

The fines <150 µm were recycled from the receiver to the roller compacting process, the material >150 µm, collected from the 150 µm sieve, was the final product.

CLAIMS

1. Granules comprising clavulanate and one or more excipients, with the proviso that the clavulanate has not been dispersed in a polymeric binder of low water vapour permeability.

2. Granules according to claim 1 wherein the clavulanate is potassium clavulanate.

3. Granules according to anyone of the claims 1 or 2 wherein one or more of the excipients is an inert excipient.

4. Granules according to anyone of the claims 1-3 wherein one or more of the excipients is a cellulose.

5. Granules according to claim 4 wherein the cellulose is a microcrystalline cellulose.

6. Granules according to anyone of the claims 1-5 wherein the ratio of potassium clavulanate to the inert excipients is 1: 0.2 - 5 wt%.

7. Granules according to any one of the claims 1-6 essentially free of solvents.

8. Granules according to anyone of the claims 1-7 with a particle size between 50 and 1500 μm, preferably between 125 and 1000 μm.

9. A process for the preparation of granules defined in anyone of the claims 1-8, comprising:

- feeding a mixture consisting of the powder clavulanate and the excipients to a roller compactor producing compacts,

- milling the compacts to produce granules,
- sieving the granules with a sieving device optionally coupled to the roller compactor to separate the granulates from fine particles of <150 μm, preferably <125 μm,
- optionally recirculating said fine particles to the roller compactor.

10. A process according to claim 9 wherein the sieving device comprises an air jet system.

11. A process according to claim 10, wherein the sieving device stands separately from the roller compactor.

12. Pharmaceutical composition comprising granules of clavulanate as defined in anyone of the claims 1-8 and amoxicillin suitable for oral administration.

13. Pharmaceutical composition according to claim 12 comprising granules of potassium clavulanate and granules of amoxicillin trihydrate.

14. Oral dosage forms as tablets, capsules, syrups, sachets, dry instant or ready to use, multiple or single dose produced from granules as defined in anyone of the claims 11-13.

15. Oral delivery form produced from granules as defined in anyone of the claims 11-13 for using as a dose sipping device.

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