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(71) Applicant (for all designated States except US): **SANDOZ AG** [CH/CH]; Lichstrasse 35, CH-4056 Basel (CH).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **SCHWARZ, Franz, Xaver** [AT/AT]; Brixentalerstrasse 66a, A-6300 Wörgl (AT).

(74) Agent: **LEHMEIER, Thomas**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

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(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract: The present invention relates to a novel solid dosage form comprising a β -lactam antibiotic and a β -lactamase inhibitor wherein the β -lactamase inhibitor is present in the film coating. The novel dosage form may be in a form of a coated tablet or multi-unit dosage form comprising coated particles.



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Pharmaceutical composition

The present invention belongs to the field of pharmaceutical industry and relates to novel medicaments for treatment of bacterial infections comprising a β -lactam antibiotic and a beta-lactamase inhibitor.

Combinations of β -lactam antibiotic and a β -lactamase inhibitor include for example the combination of amoxycillin trihydrate and potassium clavulanate which is widely used for treating bacterial infections. Preferred dosage forms are conventional immediate release tablets and powder mixtures for reconstitution into paediatric aqueous suspensions like flavoured syrup. Potassium clavulanate is extremely moisture sensitive to hydrolysis and requires manufacturing in very dry conditions. Therefore dosage forms are generally manufactured simply by mixing dry ingredients together or by dry compacting and compressing the material into tablets. The tablets are generally coated with a polymer film coating, which may be applied from aqueous or organic solvent medium.

The presence of β -lactamase inhibitor protects β -lactam antibiotic from degradation by β -lactamase enzymes. Therefore the β -lactamase inhibitor should preferably be available at the desired site of action before the antibiotic to ensure immediate protection of the antibiotic.

Amoxicillin trihydrate and potassium clavulanate differ substantially with respect to their solubility in water. Potassium clavulanate has significantly better solubility compared to most beta lactam antibiotics. Potassium clavulanate is very water soluble and amoxycillin trihydrate is relatively insoluble. For this reason dosage forms such as suspensions, sachet granulates, dispersible tablets, which are dissolved in water shortly before administration by being stirred in water, are preferable to conventional tablets wherefrom both active substances are released simultaneously.

What is therefore needed is an improved solid dosage form containing a β -lactam antibiotic such as amoxicillin and a β -lactamase inhibitor such as clavulanic acid, wherefrom the β -lactam inhibitor is released before the β -lactamase antibiotic.

One of the possible solutions is described in US 6756057. This patent discloses modified release amoxycillin / clavulanate tablets comprising immediate release phase comprising all clavulanate and a part of amoxycillin, and slow release phase comprising the second part of amoxycillin which is released slowly from the formulation.

This problem could also be resolved by a tablet having a coating that contains the β -lactamase inhibitor and is dissolved in the stomach before the tablet core begins to break down.

But a coating using conventional methods would not be successful because of insolubility of clavulanic acid in organic solvents and the high degree of sensitivity to hydrolysis.

We have now surprisingly found a process which enables coating of tablet cores with a film coating comprising potassium clavulanate. Film coating of a cooled aqueous solution of potassium clavulanate which is applied to the tablet core and effectively dried under suitable processing conditions yields chemically stable film-coated tablets, which are characterized by very fast release of the β -lactamase inhibitor, which is released before the tablet core begins to break down.

The new process also enables to prepare tablets with slow release of the β -lactamase antibiotic without influencing the dissolution of the potassium clavulanate.

In addition, in the case of larger doses, a part of the potassium clavulanate can be incorporated in the core of the tablet, allowing a part of it to be dissolved very quickly and another part to be dissolved simultaneously with the antibiotic. This would allow clavulanic acid to protect the amoxycillin immediately as soon as it releases from the formulation and before it reaches the absorption side.

Description of the invention

In one aspect, the present invention provides a pharmaceutical solid dosage form comprising β -lactam antibiotic and having a film coating comprising β -lactamase inhibitor. The dosage form of the invention may be a tablet or multi-units dosage form. Multi-units dosage form may comprise small film coated tablets or coated pellets. β -lactamase inhibitor may be present in the coating of the tablets or in the coating of the pellets. Optionally a part of β -lactamase inhibitor may be also present in the tablet core. The dosage form of the invention may consist of one coated tablet, of 1 to 10 small coated tablets, or a desired quantity of coated pellets.

Preferable dosage form of the present invention is a film coated tablet comprising β -lactam antibiotic in the tablet core and β -lactamase inhibitor present in the tablet coating.

Suitable β -lactam antibiotics include antibiotically active penicillins, cephalosporins, monobactams or carbapenems, including their pharmaceutically acceptable salts and solvates such as hydrates.

The composition of the tablet core may allow immediate or modified (slow, controlled, or more phases) release of β -lactam antibiotic. The tablet core as used herein relates to an uncoated tablet, comprising β -lactam antibiotic and optionally β -lactamase inhibitor and excipients.

The tablet core according to the present invention may include beside active ingredients pharmaceutically acceptable excipients, e.g. binders, fillers, disintegrants, releasing agents, lubricants which are standard in the preparation of tablets.

Diluents may be selected from a group consisting of calcium monocarbonate, calcium phosphate dibasic dihydrate, calcium phosphate tribasic, dextrans, dextrin, lactose, maltodextrin and sucrose. Glidants may be selected from the group consisting of glyceryl stearate, talc and glyceryl behenate. Lubricants may be selected from the group consisting of glyceryl behenate, glyceryl di/tripalmitostearate, hydrogenated vegetable oil, magnesium stearate, polyethylene glycol, potassium

benzoate, sodium benzoate, sodium stearyl fumarate, tribehenin, zinc stearate. Binders may be selected from corn starch pregelatinized, microcrystalline cellulose, starch pregelatinized, lactose monohydrate.

Disintegrants may be selected from the group consisting of maltose, sodium starch glycolate, maltodextrin, D-Mannitol, croscarmellose sodium, alginic acid, cellulose sodium starch glycolate and crospovidone.

The tablet core may additionally include releasing agents like alginates, xanthan gum, ethyl cellulose (EC), hydroxypropylmethyl cellulose (HPMC), methylcellulose, polyvinyl acetate phthalate, carboxymethyl hydroxyethyl cellulose, carboxymethylmethyl cellulose, methacrylic acid copolymer, ethyl acrylate/methyl methacrylate copolymer, ammonio methacrylate copolymer and mixtures thereof.

The tablet cores may be obtained by conventional manufacturing techniques, e.g. by mixing ingredients together and compressing into tablet cores or by dry compacting (slugging or roller compaction) a part of excipients, adding the remaining excipients and compressing the material into tablet cores. Wet granulation with suitable non aqueous solvents, or if the core is free of potassium clavulanate, also standard aqueous wet granulation can be used.

A film coating which is applied to the tablet core comprises β -lactamase inhibitor. Suitable β -lactamase inhibitors are β -lactamase inhibitors which, when combined with one or more β -lactam antibiotics may result in improved in vivo activity of β -lactam antibiotic. Such β -lactamase inhibitors include clavulanic acid in the form of a salt, such as potassium salt, tazobactam and sulbactam. Preferable β -lactamase inhibitor is potassium clavulanate.

The coating mixture according to the present invention may comprise film-forming polymers selected from the group comprising ethyl cellulose (EC), hydroxypropylmethyl cellulose (HPMC), methylcellulose, polyvinyl acetate phthalate, carboxymethyl hydroxyethyl cellulose, carboxymethylmethyl cellulose, methacrylic

acid copolymer, ethyl acrylate/methyl methacrylate copolymer, ammonio methacrylate copolymer and mixtures thereof, preferably a mixture of ethyl EC and HPMC. Ethylcellulose may be used as Aquacoat RCD.

The coating may further comprise other excipients such as plasticizers, glidants and pigments like titanium dioxide. Plasticizer may be selected from the group of triacetin, tributyl citrate, acetylated hydrogenated cotton seed glyceride, acetylated hydrogenated soybean oil glycerides, acetyl triethyl citrate, and triethyl citrate. Suitable glidant may be selected from glyceryl stearate, talc and glyceryl behenate.

The coating solution may be obtained e.g. by dissolving film-forming and other inactive ingredients in water, cooling the obtained solution to -5 to 15 °C and dissolving potassium clavulanate in the cooled solution.

The coating solution is sprayed onto the preheated tablet cores until the tablet cores are uniformly covered with the coating. Thickness of the coating depends on the dosage of β -lactamase inhibitor.

In another aspect the present invention provides a solid dosage form comprising amoxicillin and clavulanic acid. The dosage form may consist of one coated tablet, of 1 to 10 small coated tablets, or a desired quantity of coated pellets. Clavulanic acid is present in the coating of tablets or pellets and optionally in the tablet cores.

Preferable dosage form is a tablet comprising amoxicillin in the core and clavulanic acid in the coating and optionally part of it in the core.

Amoxicillin may be in the form of amoxicillin trihydrate, anhydrous amoxicillin and alkali metal salts of amoxicillin such as sodium amoxicillin or a combination thereof. A combination of amoxicillin trihydrate and sodium amoxicillin may be used.

Preferably clavulanic acid is used in the form of potassium clavulanate.

Ratio of amoxicillin to clavulanate in the dosage form of the invention may vary between 2:1 and 30:1. Suitably the ratio may be between 4:1 to 16:1, preferably 4:1, 7:1, 8:1, 16:1.

The amount of amoxicillin per dose may be between 125 and 3000 mg, preferably between 250 and 2000 mg.

If a part of clavulanate is in the core the amount of the clavulanate inside the core may be between 1 to 95 % , preferably 10 to 50 %.

The tablets of the invention may be administered once, twice or three times daily.

In another aspect the present invention provides a process for the preparation of solid dosage forms of the invention, particularly a process for coating tablet or pellet cores with a coating comprising potassium clavulanate.

Preparation of tablet cores may comprise granulating amoxicillin with aqueous solution of binder (starch, povidone, cellulose derivates), sieving and drying the obtained granulate in a fluidized bed dryer, mixing the granulate with other excipients and pressing into tablet cores.

The process of coating tablet cores comprises the following steps:

- dissolving film-forming and other inactive ingredients in water
- cooling the obtained solution to -5 to 15 °C
- dissolving potassium clavulanate in the cooled solution
- applying the cooled solution to the preheated tablet cores.

The coating solution is sprayed onto the preheated (30 to 60°C) tablet cores until the tablet cores are uniformly covered with the coating. Weight of the coating depends on the dosage of clavulanate in the coating and may vary from 0.5 to 25 % of the core weight.

Preheated tablet cores may be coated in a coating pan which rotates at 6 to 12 rpm. For smaller tablets, or pellets, also a fluidbed coater (e.g. Glatt WSG Coater, Hüttlin Coater) may be used.

The inlet air may be in the range 50 – 100 °C, atomising air pressure 2 -8 bar.

In another aspect, the present invention provides a process for the preparation of tablet formulation comprising β -lactam antibiotic in the coating, said process comprises the following steps:

- preparation of tablet cores comprising β -lactam antibiotic and optionally β -lactamase inhibitor
- dissolving film-forming and other inactive ingredients in water and cooling the obtained solution to -5 to 15 °C
- dissolving β -lactamase inhibitor in the cooled solution.
- spraying the coating solution to the preheated tablet cores

The invention is further described by reference to the following examples. These examples are provided for illustration purposes and are not intended to be limiting.

EXAMPLES

Example 1: 1000/125 mg Tablet

	Ingredient	One tablet weight (g)	10.000 tablets weight (kg)
Core	amoxicillin trihydrate	1.0104	10.10 kg
	polyvinylpyrrolidone (Kollidon 25)	0.0350	0.35 kg
	silicon dioxide colloidal	0.0150	0.15 kg
	magnesium stearate, plant-based	0.0250	0.25 kg
	crosslinked polyvinylpyrrolidone (Polyplasdone XL-10)	0.1000	1.00 kg
	cellulose microcrystalline PH102	0.0646	0.65 kg
		1.2500	12.50 kg
Coating			
	titanium dioxide	0.0224	0.22 kg

	talc	0.0196	0.20 kg
	Aquacoat ECD 30* (dry substance)	0.0126	0.13 kg
	hydroxypropylmethylcellulose (Methocel E5)	0.0126	0.13 kg
	Triethylcitrate (Citroflex 2)	0.0028	0.03 kg
	potassium clavulanate	0.1488	1.49 kg
		1.3200	
	E-water (1)		4.00 kg
	E-water (2)		5.00 kg

Amoxicillin is granulated with an aqueous (1) solution of Kollidon 25, sieved, dried in a fluidized bed dryer, and equalized with another sieve.

The mixture is mixed with cellulose microcrystalline PH102, polyplasdone XL-10, silicon dioxide colloidal and magnesium stearate in a gravity mixer and pressed into tablets.

Hydroxypropylmethyl cellulose is dissolved in water (2), ethyl cellulose dispersion, ethyl citrate, talc and titanium dioxide are stirred in. The resulting film solution is cooled to 5°C. Then potassium clavulanate is dissolved in the solution.

The film solution is sprayed onto the preheated tablets in an Accela Cota. The film-coated tablets are dried with very dry air (<5% moisture) after the coating process.

Dissolution test :

Dissolution USP <711> apparatus 2 75 rpm water

Example 1	0 min	2 min	6 min	10 min	15 min	30 min
Amoxicillin	0,0	29,3	59,6	91,9	100,0	100,0
Clavulanic acid	0,0	79,6	99,2	100,1	100,2	100,0

Example 2: 1000/62.5 mg Tablet

	Ingredient	One tablet weight (g)	10.000 tablets weight (kg)
Core	amoxicillin DC	1.0104	10.10 kg
	silicon dioxide colloidal	0.0150	0.15 kg
	magnesium stearate, plant-based	0.0250	0.25 kg
	cellulose microcrystalline PH102	0.0646	0.65 kg
	potassium clavulanate	0.0744	0.74 kg
		1.2500	12.50 kg
Coating	titanium dioxide	0.0224	0.22 kg
	talc	0.0196	0.20 kg
	Aquacoat ECD 30		
	(dry substance)	0.0126	0.13 kg
	Methocel E5	0.0126	0.13 kg
	Citroflex 2	0.0028	0.03 kg
	potassium clavulanate	0.0744	0.74 kg
		1.3200	
	E-water (1)		4.00 kg
	E-water (2)		4.00 kg
	E-water (3)		5.00 kg

Amoxicillin DC, potassium clavulanate, silicon dioxide colloidal, cellulose microcrystalline PH102 and magnesium stearate are mixed in gravity mixer and pressed into tablets.

Potassium clavulanate is dissolved in water (2) at a temperature of 5°C.

Hydroxypropylmethyl cellulose is dissolved in water (3), ethyl cellulose dispersion, ethyl citrate, talc and titanium dioxide are stirred in.

The potassium clavulanate solution and then the film solution are sprayed onto the preheated tablets in an Accela Cota. The resulting film-coated tablets are dried with very dry air (<5% moisture) after the coating process.

Dissolution test results

Dissolution USP <711> apparatus 2 75 rpm water

Example 2	0 min	2 min	6 min	10 min	15 min	30 min
Amoxicillin	0,0	25,1	55	77,8	91,3	97,5
Clavulanic acid	0,0	39,0	54,3	68,6	88,6	100,9

Example 3: 1000/62.5 Tablet

	Ingredient	One tablet weight (g)	10.000 tablets weight (kg)
Core	amoxicillin DC	1.0104	10.10 kg
	silicon dioxide colloidal	0.0150	0.15 kg
	magnesium stearate, plant-based	0.0250	0.25 kg
	cellulose microcrystalline PH102	0.0646	0.65 kg
	potassium clavulanate	0.0744	0.74 kg
		1.2500	12.50 kg
Coating	titanium dioxide	0.0224	0.22 kg
	talc	0.0196	0.20 kg

	Aquacoat ECD 30		
	(dry substance)	0.0126	0.13 kg
	Methocel E5	0.0126	0.13 kg
	Citroflex 2	0.0028	0.03 kg
	potassium clavulanate	0.0744	0.74 kg
		1.3200	
	E-water (1)		5.00 kg

Amoxicillin DC, potassium clavulanate, silicon dioxide colloidal, cellulose microcrystalline PH102 and magnesium stearate are mixed in gravity mixer and pressed into tablets.

Hydroxypropylmethyl cellulose is dissolved in water (2), ethyl cellulose dispersion, ethyl citrate, talc and titanium dioxide are stirred in. The resulting film solution is cooled to 5°C. Then potassium clavulanate is dissolved in the solution.

The film solution is sprayed onto the preheated tablets in an Accela Cota. The resulting film-coated tablets are dried with very dry air (<5% moisture) after the coating process.

Dissolution test results:

Dissolution USP <711> apparatus 2 75 rpm water

Example 3	0 min	2 min	6 min	10 min	15 min	30 min
Amoxicillin	0,0	25,1	55	77,8	91,3	97,5
Clavulanic acid	0,0	40,3	50,7	69,0	86,3	97,6

Example 4: 1000 g + 62.5 mg Tablet

	Ingredient	One tablet weight (g)	10.000 tablets weight (kg)
Core	amoxicillin trihydrate	1.036	10.36 kg
	Na-amoxicillin	0.104	1.04 kg
	Magnesium Stearate. plant base	0.011	0.11 kg
	Microcrystalline cellulose 101	0.058	0.58 kg
	Xanthan Gum	0.024	0.24 kg
Coating	Potassium clavulanate	0.074	0.74 kg
	Triethylcitrat	0.030	0.30 kg
	Aquacoat ECD 30	0.250	0.25 kg
	Talk	0.050	0.50 kg
	Methocel E 15	0.004	0.04 kg
	Methocel E 5	0.012	0.12 kg
	Titandioxid	0.015	0.15 kg
	Polyethylene glycol (PEG 8000)	0.002	0.02 kg
	Polyglykol 3350 P	0.002	0.02 kg
	E - water		5.00 kg

Amoxicillin, sodium amoxicillin, cellulose, xanthan gum microcrystalline PH102 are compacted together, and screened. The granules are mixed with magnesium stearate in a gravity mixer and pressed into tablets.

Hydroxypropylmethyl cellulose is dissolved in water (2), ethyl cellulose dispersion, ethyl citrate, talc polyglycol and titanium dioxide are stirred in. The resulting film solution is cooled to 5°C. Then potassium clavulanate is dissolved in the solution.

The film solution is sprayed onto the preheated tablets in an Accela Cota. The resulting film-coated tablets are dried with very dry air (<5% moisture) after the coating process.

1000 g + 62.5 mg Tablet Dissolution water 75 rpm/USP

Dissolution test results

Dissolution USP <711> apparatus 2 75 rpm water

Example 4	0 min	15 min	30 min	45 min	60 min	90 min	120 min	150 min	180 min	240 min	300 min	360 min
Amoxicillin	0	2,6	8,5	16,7	25,2	43,2	58,3	72,7	85	92,6	93,5	93,3
Clavulanic acid	0	91,4	93,7	97,2	99,1							

CLAIMS

1. A pharmaceutical solid dosage form comprising a β -lactam antibiotic and having a film coating comprising a β -lactamase inhibitor.
2. The dosage form according to claim 1, which is a tablet or a multi-units dosage form.
3. The dosage form according to claim 1, wherein the coating is applied to a tablet or a pellet core.
4. The dosage form according to claim 1 wherein the β -lactam antibiotic is amoxycillin.
5. The dosage form according to claim 1 wherein the β -lactamase inhibitor is clavulanic acid .
6. The dosage form according to claims 1 and 4 wherein amoxycillin is in a form of amoxycillin trihydrate
7. The dosage form according to claim 1 and 5 wherein clavulanic acid is in a form of potassium clavulanate.
8. The dosage form according to any of the proceedings claims wherein the ratio between amoxycillin trihydrate and potassium clavulanate is from 1:1 to 20:1.
9. The dosage form according to any of the previous claims, wherein the tablet core further comprises diluents, binders, disintegrants, releasing agents, glidants and lubricants.
10. The dosage form according to claim 1, wherein the coating further comprises polymers, plasticizers, pigments and glidants.
11. A process for the coating of a tablet or pellet core comprising an effective amount of β -lactam antibiotic and optionally β -lactamase inhibitor, said process comprising:
 - dissolving film-forming and other inactive ingredients in water
 - cooling the obtained solution to -5 to 15 °C
 - dissolving β -lactamase inhibitor in the cooled solution

- applying the cooled solution to the preheated tablet or pellet cores.
12. The process according to claim 11, wherein the coating solution is prepared by dissolving the film forming and other inactive ingredients in water, cooling the obtained film solution to -5 to 15°C and dissolving β -lactamase inhibitor in the cold solution.
13. The process according to claim 11, wherein β -lactam antibiotic is amoxicillin and β -lactamase inhibitor is clavulanic acid.
14. The process according to claim 11, wherein the coating comprises potassium clavulanate.
15. A process for the preparation of dosage form according to claim 1, wherein the process comprising the following steps:
- preparation of tablet or pellet cores comprising β -lactam antibiotic and optionally β -lactamase inhibitor.
 - dissolving film-forming and other inactive ingredients in water and cooling the obtained solution to -5 to 15 °C.
 - dissolving β -lactamase inhibitor in the cooled solution.
 - spraying the coating solution to the preheated tablet or pellet cores.
16. A process according to claim 15, wherein the β -lactam antibiotic is amoxicillin and β -lactamase inhibitor is clavulanic acid.