The present invention relates to pharmaceutical compositions comprising cefpodoxime proxetil and clavulanic acid and/or its derivatives as the active agents.
FORMULATION COMPRISING CEFPODOXIME PROXETIL AND CLAVULANIC ACID

The present invention relates to pharmaceutical compositions comprising cefpodoxime proxetil and clavulanic acid and/or derivatives thereof as the active agents.

Background of the Invention

Cefpodoxime proxetil (Formula 1), chemical name of which is pivaloyloxymethyl 7-[2-(2-amino-thiazole-4-yl]-2-(syn)-methoxyimino-acetamido]-3-methoxymethyl-3-cefem-4-carboxylate, was first disclosed in the patent numbered EP00491 18.

Formula 1

Clavulanic acid, on the other hand, is a beta-lactamase inhibitor illustrated in Formula 2.

Formula 2

Clavulanic acid and derivatives thereof (for instance its salts such as potassium clavulanate) are known as the beta-lactamase inhibitors which withstand the beta-lactamase-originated resistance mechanism by suppressing the activity of beta-lactamase enzymes.

The patent numbered EP0593573 comprises a formulation relating to suspension forms of beta-lactam antibiotics and beta lactamase inhibitors.
However, suspension forms are not preferred much as they have the potential of high and/or uncontrolled dose intake; there appear problems in their physical and chemical stability; they have high manufacture costs and they cause problems in use and carrying.

To this end, the inventors have aimed to develop stable oral pharmaceutical formulations which comprise cefpodoxime proxetil and clavulanic acid derivatives thereof together and eliminate the low solubility problem of cefpodoxime proxetil.

**Description of the Invention:**

The present invention relates to stable pharmaceutical compositions with good solubility characteristics in which cefpodoxime proxetil and clavulanic acid are formulated together. It has surprisingly been seen that when the pharmaceutical composition comprising cefpodoxime proxetil and clavulanic acid wherein

- a combination of croscarmellose sodium and microcrystalline cellulose is used as the disintegrant and
- each one of the cellulose-based disintegrants is present in an amount more than 7% by weight with respect to the weight of the unit dose

is developed, dissolution of the cefpodoxime proxetil increases and dissolution time of the composition decreases.

According to this, the first aspect of the present invention is the pharmaceutical compositions comprising cefpodoxime proxetil and clavulanic acid as the active agents wherein a combination of croscarmellose and microcrystalline cellulose is used as the disintegrant and each one of the cellulose-based disintegrants is present in an amount more than 7% with respect to the unit dose.

Cefpodoxime proxetil that can be used in the pharmaceutical composition of the present invention can be in the form of its solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystalline and amorphous forms or in free base form and/or a combination thereof.

Clavulanic acid that can be used in the pharmaceutical composition of the present invention can be in the form of its solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystalline and amorphous forms or free base form and/or a combination thereof. Preferably, potassium clavulanate is used in the present invention.
Croscarmellose sodium used in the pharmaceutical composition according to the present invention is present in an amount more than 7%, preferably in the range of 8-15%, more preferably in the range of 9-12% with respect to unit dose amount. Although the use of croscarmellose sodium in this specified amount is more than the amount disclosed in the prior art, the inventors have found that the dissolution rate of the composition increases in contrast to expectations.

Another aspect of the present invention is the pharmaceutical compositions comprising cefpodoxime proxetil and clavulanic acid or its derivatives wherein croscarmellose sodium is preferably used in an amount in the range of 8-15%, more preferably in an amount in the range of 9-12% by weight with respect to the weight of the unit dose.

Microcrystalline cellulose used in the pharmaceutical composition according to the present invention is present in an amount more than 7%, preferably in the range of 8-15%, more preferably in the range of 9-13% with respect to unit dose amount. The inventors have found that the dissolution time reduces by 60% in the case that microcrystalline cellulose is used in said amount.

Another aspect of the present invention is the pharmaceutical compositions comprising cefpodoxime proxetil and clavulanic acid or its derivatives wherein microcrystalline cellulose is preferably used in an amount in the range of 8-15%, more preferably in an amount in the range of 9-13% by weight with respect to the weight of the unit dose.

According to these, it has been found that the use of each cellulose-based disintegrand in an amount more than 7% with respect to the unit dose has an important effect on both the increase of dissolution of cefpodoxime proxetil and decrease in dissolution time of the composition comprising cefpodoxime proxetil and clavulanic acid.

The inventors have observed that an optimum particle size of the cellulose-based disintegrand used in the composition of the present invention has a considerable effect on the disintegration and dissolution of the composition. They have found that when the particle size of microcrystalline cellulose used in the present invention is less than 100 μm, preferably in the range of 30-90 μm and more preferably in the range of 40-60 μm, the dissolution of the composition increases and also dissolution time decreases.

According to this, another aspect of the present invention is pharmaceutical compositions comprising cefpodoxime proxetil and clavulanic acid or its derivatives wherein
microcrystalline cellulose with a particle size less than 100 µη, preferably in the range of 30-90 µη and more preferably in the range of 40-60 µη is used in the disintegrant combination.

In addition to cefpodoxime proxetil, clavulanic acid, microcrystalline cellulose, croscarmellose, the formulation of the present invention can comprise various excipients such as, but not limited to, glidants, lubricants, diluents, surfactants and optionally coating agents.

The glidant that can be used in the pharmaceutical composition of the present invention can be selected from, but not limited to, a group comprising magnesium silicate, silicon dioxide, starch, talc, tribasic calcium phosphate or combinations thereof.

The lubricant that can be used in the pharmaceutical composition of the present invention can be selected from, but not limited to, a group comprising calcium stearate, magnesium stearate, polyoxyethylene glycol, PEG 6000, polyvinyl alcohol, potassium benzoate, talc, sodium benzoate or combinations thereof. Preferably, magnesium stearate is used as the lubricant in the pharmaceutical composition of the present invention.

The diluent that can be used in the pharmaceutical composition of the present invention can be selected from, but not limited to, a group comprising calcium carbonate, calcium sulfate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, lactose, magnesium carbonate, magnesium oxide, maltodextrin, maltose, mannitol, sodium chloride, sorbitol, starch, xylitol or combinations thereof.

The surfactant that can be used in the pharmaceutical composition of the present invention can be selected from, but not limited to, a group comprising docusate sodium, sorbitan esters, cetrimide and sodium lauryl sulfate. In the present invention, sodium lauryl sulfate is preferably used as the surfactant.

The pharmaceutical composition of the present invention can comprise 20-800 mg cefpodoxime proxetil or its pharmaceutically acceptable salts, hydrates, solvates or combinations thereof in an equal amount.

The pharmaceutical composition of the present invention can comprise 50-500 mg clavulanic acid or its pharmaceutically acceptable salts, hydrates, solvates or combinations thereof in an equal amount.
Clavulanic acid and its derivatives (e.g. potassium clavulanate) are extremely susceptible to moisture. To this respect, potassium clavulanate in the pharmaceutical composition is preferably used with a humectant in the ratio of 1:1.

One or more of the substances comprising silica; colloidal silica, for instance colloidal silica anhydrous, for example Aerosil® 200, magnesium trisilicate, cellulose powder, Cabosil®, magnesium oxide, calcium silicate, Syloid®, starch, microcrystalline cellulose, talc can be used as the humectant.

In the pharmaceutical composition of the present invention, potassium clavulanate is used with microcrystalline cellulose preferably in the ratio of 1:1.

The pharmaceutical composition of the present invention can comprise 5-60% cefpodoxime proxetil in proportion to total weight of unit dose or pharmaceutically acceptable solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystalline and amorphous forms thereof.

The pharmaceutical composition of the present invention can comprise 5-50% clavulanic acid in proportion to total weight of unit dose or pharmaceutically acceptable salts, hydrates, solvates or combinations thereof in an equal amount.

The pharmaceutical composition of the present invention can comprise 5-60% cefpodoxime proxetil; 5-50% potassium clavulanate; 0,5-5% glidant; 0,1-5% lubricant; 0,1-25% disintegrant and/or disintegrants; 1-30% diluent; 0,1-5% surfactant and optionally coating agent of 1-5% of the core weight.

In another aspect, the pharmaceutical composition comprising cefpodoxime proxetil and clavulanic acid prepared according to the present invention can be in conventional tablet, film coated tablet, sachet or capsule form.

In another aspect, the present invention relates to processes for preparation of pharmaceutical compositions comprising pharmaceutically acceptable excipients in addition to cefpodoxime proxetil and clavulanic acid or its derivatives as the active agents.

According to this, the process of the present invention comprises the steps of granulating the active agent cefpodoxime proxetil and clavulanic acid or its derivatives by conventional wet and/or dry granulation methods; or powdering cefpodoxime proxetil, clavulanic acid derivatives and other excipients after mixing them by dry blending method and
- compressing the pharmaceutical composition of the present invention in tablet form and optionally coating the tablets with a coating agent in the case that the product is developed in tablet form and/or,
- filling the pharmaceutical composition of the present invention in capsules in the case that the product is developed in tablet form and/or,
- filling the pharmaceutical composition of the present invention in packs in the case that the product is developed in sachet form.

Another aspect of the present invention is that the formulation prepared according to said invention is used in the treatment of diseases related with infections caused by gram negative and gram positive bacteria.

According to another aspect of the present invention, the pharmaceutical composition prepared according to the present invention is used in the production of a medicament so as to be used in upper respiratory infections such as ear, nose, throat, otitis media, sinusitis, tonsillitis, pharyngitis; lower respiratory tract infections such as pyelonephritis, cystitis and urethritis; skin or soft tissue infections such as froncle, pyoderma, impetigo; in the treatment and prophylaxis of gonorrhea and lyme diseases.

The pharmaceutical composition of the present invention can be prepared as described below, but not limited to the examples given.
EXAMPLE 1: Formulation and process for preparation of film tablet comprising cefpodoxime proxetil and potassium clavulanate

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<td><strong>CORE</strong></td>
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<tr>
<td>Cefpodoxime proxetil</td>
<td>32%</td>
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<td>Potassium clavulanate: Avicel</td>
<td>36%</td>
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<td>Croscarmellose sodium</td>
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<td>Microcrystalline cellulose</td>
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<tr>
<td>Diluent</td>
<td>9%</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1%</td>
</tr>
<tr>
<td>Lubricant</td>
<td>1%</td>
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<tr>
<td>Glidant</td>
<td>1%</td>
</tr>
<tr>
<td><strong>COATING</strong></td>
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</tr>
<tr>
<td>Coating agent</td>
<td>2.5%</td>
</tr>
<tr>
<td>Total tablet weight</td>
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According to this, a process for preparation of pharmaceutical compositions is composed of the steps of mixing and compressing cefpodoxime proxetil, the disintegrant and the diluent and then sieving them; adding the surfactant, potassium clavulanate: avicel, disintegrant, glidant and lubricant into the granules obtained and mixing them; and then compressing tablets of the mixture obtained and coating the tablets with coating material.
CLAIMS

1. A pharmaceutical composition composed of a combination of cefpodoxime proxetil and clavulanic acid or its derivatives, wherein:
   - said composition comprises a combination of croscarmellose sodium and microcrystalline cellulose mixture as the disintegrant
   - each one of the cellulose-based disintegrants is present in an amount more than 7% by weight with respect to the weight of the unit dose.
2. The pharmaceutical composition according to claim 1, wherein cefpodoxime proxetil comprised in said composition is in the form of its solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystalline and amorphous forms or in free form and/or combinations thereof.
3. The pharmaceutical composition according to claim 1, wherein clavulanic acid comprised in said composition is in the form of its solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystalline and amorphous forms or in free form and/or combinations thereof.
4. The pharmaceutical composition according to claim 3, wherein potassium clavulanate is used in said composition.
5. The pharmaceutical composition according to claim 1, wherein said composition comprises 8-15% croscarmellose sodium.
6. The pharmaceutical composition according to claim 5, wherein said composition comprises 9-12% croscarmellose sodium.
7. The pharmaceutical composition according to claim 1, wherein the particle size of microcrystalline cellulose used is less than 100 μm.
8. The pharmaceutical composition according to claim 7, wherein the particle size of microcrystalline cellulose used is in the range of 30-90 μm.
9. The pharmaceutical composition according to claim 8, wherein the particle size of microcrystalline cellulose used is in the range of 40-60 μm.
10. The pharmaceutical composition according to claim 1, wherein said composition comprises 8-15% microcrystalline cellulose.
11. The pharmaceutical composition according to claim 10, wherein said composition comprises 9-13% microcrystalline cellulose.
12. The pharmaceutical composition according to claim 1, wherein said composition comprises one or more excipients such as glidant, lubricant, surfactant and optionally
coating agents in addition to cefpodoxime proxetil, potassium clavulanate, microcrystalline cellulose and croscarmellose sodium.

13. The pharmaceutical composition according to claim 12, wherein the diluent is selected from a group comprising calcium carbonate, calcium sulfate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, lactose, magnesium carbonate, magnesium oxide, maltodextrin, maltose, mannitol, sodium chloride, sorbitol, starch, xylitol or combinations thereof.

14. The pharmaceutical composition according to claim 12, wherein the glidant is selected from a group comprising magnesium silicate, silicon dioxide, starch, talc, tribasic calcium phosphate or combinations thereof.

15. The pharmaceutical composition according to claim 12, wherein the lubricant is selected from a group comprising calcium stearate, magnesium stearate, polyoxyethylene glycol, PEG 6000, polyvinyl alcohol, potassium benzoate, talc, sodium benzoate or combinations thereof.

16. The pharmaceutical composition according to claim 15, wherein magnesium stearate is used as the lubricant in said formulation.

17. The pharmaceutical composition according to claim 12, wherein the surfactant is selected from a group comprising docusate sodium, sorbitan esters, cetrimide and sodium lauryl sulfate.

18. The pharmaceutical composition according to claim 1, wherein said composition comprises 20-800 mg cefpodoxime proxetil or its pharmaceutically acceptable salts, hydrates, solvates or combinations thereof in an equal amount.

19. The pharmaceutical composition according to claim 1, wherein said composition comprises 50-500 mg clavulanic acid or its pharmaceutically acceptable salts, hydrates, solvates or combinations thereof in an equal amount.

20. The pharmaceutical composition according to claim 1, wherein clavulanic acid or its derivative is used with a humectant in the ratio of 1:1.

21. The pharmaceutical composition according to claim 20, wherein the humectant to be used together with clavulanic acid is selected from a group comprising silica, colloidal silicon dioxide, magnesium trisilicate, cellulose powder, magnesium oxide, calcium silicate, starch, talc or microcrystalline cellulose.

22. The pharmaceutical composition according to claim 21, wherein the humectant to be used together with clavulanic acid is microcrystalline cellulose.
23. The pharmaceutical composition according to claim 1, wherein said composition comprises 5-60% cefpodoxime proxetil or pharmaceutically acceptable solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystalline and amorphous forms thereof in an equal amount.

24. The pharmaceutical composition according to claim 1, wherein said composition comprises 5-50% clavulanic acid or pharmaceutically acceptable solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystalline and amorphous forms thereof in an equal amount.

25. The pharmaceutical composition according to claim 1, wherein said composition comprises 5-60% cefpodoxime proxetil; 5-50% potassium clavulanate; 0.5-5% glidant; 0.1-5% lubricant; 0.1-25% disintegrant and/or disintegrants; 1-30% diluent; 0.1-5% surfactant in proportion to total weight of unit dose amount and optionally coating agent of 1-5% of the core weight.

26. The pharmaceutical composition according to claim 1, wherein said composition is used in conventional tablet, film coated tablet, sachet or capsule.

27. A process for preparation of the pharmaceutical composition claimed in claim 1, wherein said process composes the steps of granulating the active agents cefpodoxime proxetil and clavulanic acid or its derivatives by conventional wet and/or dry granulation methods; or powdering cefpodoxime proxetil, clavulanic acid and other excipients after mixing them by dry blending method.
### A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/16  A61K9/20

**ADD.**

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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)

EPO-Internal, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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*Further documents are listed in the continuation of Box C.*

**X** See patent family annex.

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**Date of the actual completion of the international search**

3 November 2011

**Date of mailing of the international search report**

14/11/2011

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Giese, Hans-Hermann

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