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(54) Title: EXTENDED-RELEASE CEFPODOXIME PROXETIL COMPOSITION

(57) Abstract: The present invention relates to a stable extended-release composition of cefpodoxime proxetil and a process for its preparation. The composition comprises cefpodoxime proxetil, a stabilizer, and a release-controlling agent, wherein the composition is characterized by having a pH of less than about 4. The composition is suitable for once-daily dosing for treating bacterial infections.



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EXTENDED-RELEASE CEFPODOXIME PROXETIL COMPOSITIONField of the Invention

The present invention relates to a stable extended-release composition of cefpodoxime proxetil and a process for its preparation. The composition comprises
5 cefpodoxime proxetil, a stabilizer, and a release-controlling agent, wherein the composition is characterized by having a pH of less than about 4. The composition is suitable for once-daily dosing for treating bacterial infections.

Background of the Invention

Cefpodoxime proxetil, a third generation cephalosporin antibiotic, is known to
10 have poor bioavailability because of its hydrophobic nature and poor aqueous solubility. Further, it has been reported that cefpodoxime exhibits gel formation and forms a gelatinous mass when it is in contact with aqueous media. These factors result in slow and erratic dissolution of the pharmaceutical compositions, which lead to poor bioavailability. Besides, cefpodoxime proxetil is susceptible to degradation in the presence of moisture,
15 heat, and alkaline pH.

Cefpodoxime proxetil has been widely used for treatment of infections caused by gram-positive and gram-negative bacteria. It is available in the form of a tablet or granules for oral suspension with a twice-daily dosage regimen.

The primary goal of an antibiotic dosage regimen is to maximize the time during
20 which the microorganism is exposed to the drug, since the bactericidal activity correlates more to duration above minimum inhibitory concentration (MIC) than to magnitude of dose. Consequently, it is expected that the concentration of cefpodoxime above the MIC for 40% to 60% duration of dosage interval should achieve optimal clinical results.

Extended-release compositions of cefpodoxime proxetil remain highly desirable as
25 they maintain therapeutic plasma concentrations of the antibiotic over a prolonged period of time, thereby contributing to better therapeutic action. Further, reducing the frequency of dosage administration leads to enhanced patient compliance.

The prior art discloses extended-release compositions of cefpodoxime proxetil with improved dissolution and bioavailability.

30 PCT Publication No. WO 2004/019901 discloses a sustained release pharmaceutical composition of a beta lactam antibiotic, such as cefpodoxime proxetil; a

mixture of polymers comprising a water soluble N-vinyl-2- pyrrolidone/vinyl acetate copolymer and polysaccharide(s); a release enhancer(s); and other pharmaceutically acceptable excipients.

PCT Publication No. WO 2008/010784 discloses a controlled release
5 nanoparticulate composition of a cephalosporin, such as cefpodoxime proxetil, comprising particles of a cephalosporin with an effective average particle size of less than 2000 nm and at least one surface stabilizer.

There remains a need in the art to formulate alternate extended-release compositions of cefpodoxime proxetil which are simple, easy to manufacture, and cost
10 effective.

The present invention provides extended-release compositions of cefpodoxime proxetil which maintain the plasma level over a prolonged period of time. The extended-release compositions are provided with a once-daily dosage regimen which is simple and convenient to use. Further, the extended-release compositions are provided with improved
15 dissolution and reduced gel formation of cefpodoxime proxetil, leading to enhanced bioavailability and stability.

Summary of the Invention

The present invention relates to a stable extended-release composition of cefpodoxime comprising cefpodoxime proxetil, a stabilizer, and a release-controlling
20 agent, wherein the composition is characterized by having a pH of less than about 4. It also relates to a process for its preparation. Further, the extended-release composition is suitable for once-daily dosing, which overcomes the problem of multiple administrations, thereby providing enhanced patient compliance.

Detailed Description of the Invention

25 A first aspect of the present invention provides a stable extended-release composition of cefpodoxime comprising cefpodoxime proxetil, a stabilizer, and a release-controlling agent, wherein the composition is characterized by having a pH of less than about 4.

In one embodiment of the above aspect, the pH of the composition is in a range of
30 about 2 to about 4. In a preferred embodiment of this aspect, the pH of the composition is in a range of about 3 to about 4.

A second aspect of the present invention provides a stable extended-release composition of cefpodoxime comprising cefpodoxime proxetil, a stabilizer, and a release-controlling agent, wherein the composition is characterized by having an *in-vitro* dissolution release profile as determined by USP type II apparatus at 100 r.p.m., in 900 mL of glycine buffer (pH 3) with 0.5% sodium lauryl sulfate at 37°C as follows:

- not more than 50% of cefpodoxime released at 1 hour,
- not more than 65% of cefpodoxime released at 4 hours,
- more than 75% of cefpodoxime released at 16 hours.

A third aspect of the present invention provides a stable extended-release composition of cefpodoxime comprising cefpodoxime proxetil, a stabilizer, and a release-controlling agent, wherein the cefpodoxime proxetil is present in an amount of not more than about 55% w/w based on the total weight of the composition.

In one embodiment of the above aspects, the stabilizer is a combination of an organic acid and a silicon dioxide.

In another embodiment of the above aspects, the organic acid and the silicon dioxide are present in a weight ratio of about 1:1 to 1:5.

In another embodiment of the above aspects, the silicon dioxide and cefpodoxime proxetil are present in a weight ratio of about 1:1 to about 1:10.

In another embodiment of the above aspects, the organic acid and cefpodoxime proxetil are present in a weight ratio of about 1:5 to about 1:20.

In another embodiment of the above aspects, the stable extended-release composition of cefpodoxime further comprises one or more pharmaceutically acceptable excipients.

In another embodiment of the above aspects, the stable extended-release composition of cefpodoxime is administered once daily for treating bacterial infections.

A fourth aspect of the present invention provides a process for the preparation of an extended-release composition of cefpodoxime comprising:

- (i) blending cefpodoxime proxetil, a silicon dioxide, an organic acid, and one or more pharmaceutically acceptable excipients;
- (ii) optionally granulating the blend of step (i);

(iii) mixing one or more release-controlling agents with the blend of step (i) or the granules of step (ii);

(iv) compressing the mixture of step (iii) to form a tablet; and

(v) optionally applying a coating comprising one or more film-forming polymers and coating additives onto the tablet of step (iv).

The term “extended-release,” as used herein, refers to cefpodoxime release over a longer period of time than is ordinarily experienced after administration of a corresponding immediate-release cefpodoxime proxetil formulation. In particular, the term “extended-release” as used herein refers to the release of cefpodoxime over a period of 6, 8, 12, 16, or 24 hours.

The term “about,” as used herein, refers to any value which lies within the range defined by a variation of up to $\pm 10\%$ of the value.

The term “cefpodoxime proxetil,” as used herein, refers to (RS)-1(isopropoxycarbonyloxy) ethyl (+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)-2-{(Z)methoxyimino}acetamido]-3-methoxymethyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylate. The cefpodoxime proxetil used in the extended-release composition of the present invention is present an amount of not more than about 55% w/w based on the total weight of the composition. Particularly, it is present in a range of about 25% to about 55% w/w based on the total weight of the composition.

The term “stabilizer,” as used herein, means a compound that prevents the degradation of cefpodoxime proxetil. The stabilizer as used herein is a combination of an organic acid and a silicon dioxide. The organic acid and silicon dioxide are present in a weight ratio of about 1:1 to 1:5.

The term “organic acid” as used herein, refers to a pharmaceutically acceptable organic compound which has acidic properties. The organic acid creates an acidic microenvironment around cefpodoxime proxetil particles. This acidic environment helps to prevent degradation and improve dissolution. Suitable examples of organic acids are selected from the group comprising fumaric acid, citric acid, tartaric acid, oxalic acid, malic acid, succinic acid, ascorbic acid, pyruvic acid, malonic acid, glutaric acid, adipic acid, gluconic acid, lactic acid, and mixtures thereof. The percentage of organic acid used in the extended-release composition of the present invention ranges from about 0.5% to

about 15% w/w, based on the total weight of the composition. Further, the organic acid and cefpodoxime proxetil are present in a weight ratio of about 1:5 to about 1:20.

The term "silicon dioxide," as used herein, refers to a chemical compound which is an oxide of silicon. Silicon dioxide prevents the gel formation of cefpodoxime proxetil as particles of silicon dioxide get evenly distributed between the particles of cefpodoxime proxetil, thereby reducing the electric charge and minimizing the attractive forces responsible for gelation. Additionally, silicon dioxide creates an acidic microenvironment around cefpodoxime proxetil particles, thereby preventing the degradation. The silicon oxide includes both hydrous and anhydrous forms of silicon dioxide. The silicon dioxide can be selected from various available forms such as colloidal silicon dioxide, fumed silica, precipitated silica, light anhydrous silicic acid, silicic anhydride, aluminum magnesium silicate, and mixtures thereof. The percentage of silicon dioxide used in the extended-release composition of the present invention ranges from about 1% to about 15% w/w, based on the total weight of the composition. Further, silicon dioxide and cefpodoxime proxetil are present in a weight ratio of about 1:1 to about 1:10.

The term "stable," as used herein, means not more than 10% w/w of total related substances are formed on storage at a temperature of 40°C and a relative humidity of 75% or at a temperature of 25°C and a relative humidity of 60% for a period of at least three months to the extent necessary for the sale and use of the extended-release cefpodoxime composition.

In the present invention, the mixing of cefpodoxime proxetil with a silicon dioxide and an organic acid is done by conventional methods known in the art.

The term "release-controlling agent," as used herein, refers to an agent that helps to control the release of cefpodoxime proxetil. Suitable examples of release-controlling agents are selected from the group comprising cellulosic polymers such as hydroxypropylmethyl cellulose *e.g.*, Hypromellose K4M and Hypromellose K100 LVCR, methyl cellulose, hydroxypropyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, carboxy methylcellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, cellulose acetate butyrate, cellulose acetate, and cellulose acetate trimellitate; acrylic copolymers such as methacrylic acid copolymers, *e.g.*, Eudragit[®] RS, Eudragit[®] RL, and Eudragit[®] NE 30 D; polyvinyl alcohol; polyvinyl acetate; polyalkylene glycol

such as polyethylene glycol; triglycerides; waxes, *e.g.*, Compritol[®], Lubritab[®], and Gelucire[®]; lipids; fatty acids or their salts/derivatives; a mixture of polyvinyl acetate and polyvinyl pyrrolidone, *e.g.*, Kollidon[®] SR; and mixtures thereof. The release-controlling agent may control the release of cefpodoxime proxetil based on a matrix or a reservoir system. The percentage of release-controlling agent used in the extended-release composition of the present invention ranges from about 5% to about 30% w/w, based on the total weight of the composition.

The term "composition," as used herein, includes tablets, granules, powders, capsules, pellets, and spheroids, in particular tablets.

The term "pharmaceutically acceptable excipients," as used herein, refers to excipients that are routinely used in pharmaceutical compositions. The pharmaceutically acceptable excipients may comprise fillers, binders, glidants, disintegrants, lubricants, wetting agents, and combinations thereof.

Suitable fillers are selected from the group comprising microcrystalline cellulose, mannitol, sorbitol, lactose, dibasic calcium phosphate, sodium phosphate, kaolin, calcium carbonate, sodium carbonate, calcium sulfate, starch, magnesium oxide, cellulose acetate, dextrates, dextrin, erythritol, maltodextrin, maltose, sodium chloride, and mixtures thereof.

Suitable binders are selected from the group comprising polyvinyl pyrrolidone; celluloses, *e.g.*, methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, ethyl cellulose, and sodium carboxy methyl cellulose; polymethacrylates; carboxyvinyl polymers; gums, *e.g.*, acacia, alginic acid, sodium alginate, tragacanth, and guar gum; sugars, *e.g.*, lactose, liquid glucose, sucrose, and dextrin; polydextroses; starch or its derivatives; kaolin; povidone; copovidone; polyethylene oxide; polyvinyl alcohol; poly-N-vinyl amide; polyethylene glycol; gelatin; polypropylene glycol; glyceryl behenate; oils, *e.g.*, hydrogenated vegetable oil, castor oil, and sunflower oil; zein; paraffin; higher aliphatic alcohols; higher aliphatic acids; fatty acid esters; fatty acid glycerides; agar; chitosan; maltodextrin; magnesium aluminum silicate; inulin; waxes; and mixtures thereof.

Suitable glidants/lubricants are selected from the group comprising sodium stearyl fumarate, calcium stearyl fumarate, magnesium stearate, aluminum stearate, calcium stearate, zinc stearate, silica, calcium silicate, magnesium silicate, aluminum silicate, colloidal silicon dioxide, polyethylene glycol, poloxamer, cornstarch, talc, polyvinyl

alcohol, glyceryl behenate, glyceryl monostearate, glyceryl palmitostearate, potassium benzoate, sodium benzoate, mineral oil, palmitic acid, myristic acid, stearic acid, hydrogenated vegetable oil, sodium lauryl sulfate, and mixtures thereof.

Suitable disintegrants are selected from the group comprising cross-linked
5 polyvinyl pyrrolidone (crospovidone); starches, *e.g.*, starch, pregelatinized starch, hydroxypropyl starch, sodium carboxymethyl starch, and sodium starch glycolate; cellulose or its derivatives, *e.g.*, low-substituted hydroxypropyl cellulose, cross-linked sodium carboxymethyl cellulose, carboxymethyl calcium cellulose, and microcrystalline cellulose; gums, *e.g.*, guar gum, sodium alginate, calcium alginate, and alginic acid; ion-
10 exchange resins, *e.g.*, polacrillin potassium; clays, *e.g.*, bentonite and veegum; povidone; cross-linked polyvinyl pyrrolidone; formalin-casein; chitosan; magnesium aluminum silicate; colloidal silicon dioxide; and mixtures thereof.

Suitable wetting agents are selected from the group comprising surfactants such as nonionic, cationic, anionic, and zwitterionic surfactants. Suitable anionic surfactants
15 include those containing carboxylate, sulfonate, and sulfate ions such as sodium lauryl sulfate, sodium laurate, dialkyl sodium sulfosuccinates, particularly bis-(2-ethylhexyl) sodium sulfosuccinate, sodium stearate, potassium stearate, and sodium oleate. Suitable cationic surfactants include those containing long chain cations, such as benzalkonium chloride and bis-2-hydroxyethyl oleyl amine. Suitable non-ionic surfactants include
20 polyoxyethylene sorbitan fatty acid esters; fatty alcohols such as lauryl, cetyl, and stearyl alcohols; glyceryl esters such as the naturally occurring mono-, di-, and tri-glycerides; fatty acid esters of fatty alcohols and other alcohols such as propylene glycol, polyethylene glycol, sorbitan, sucrose, and cholesterol.

The extended-release compositions of the present invention can be prepared by any
25 method known in the art, such as blending, dry granulation, wet granulation, direct compression, melt granulation, or extrusion-spheronization.

The extended-release compositions of the present invention may further comprise an immediate-release portion of cefpodoxime proxetil.

The tablets of the present invention may be coated with one or more non-functional
30 coating layers. The non-functional coating layer comprises one or more film-forming polymers and coating additives.

Suitable film-forming polymers are selected from the group comprising cellulose or its derivatives, *e.g.*, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, ethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, cellulose acetate, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate; waxes, *e.g.*, polyethylene glycol; methacrylic acid polymers, *e.g.*, Eudragit[®]; and polyvinyl pyrrolidone. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry[®], may also be used.

Pharmaceutically acceptable coating additives may be selected from the group consisting of film-forming polymers, binders, diluents, plasticizers, opacifiers, coloring agents, lubricants, and pore-formers.

Suitable plasticizers are selected from the group comprising triethyl citrate, dibutyl sebacate, acetylated triacetin, tributyl citrate, glycerol tributyrate, acetyl tributyl citrate, diacetylated monoglyceride, rapeseed oil, olive oil, sesame oil, glycerin, sorbitol, diethyl oxalate, diethyl phthalate, diethyl malate, diethyl fumarate, dibutyl succinate, diethyl malonate, dioctyl phthalate, and combinations thereof.

Suitable opacifiers are selected from the group comprising titanium dioxide, manganese dioxide, iron oxide, silicon dioxide, and combinations thereof.

Suitable pore-formers are selected from the group comprising polyethylene glycols, *e.g.*, polyethylene glycol 6000 and polyethylene glycol 400; celluloses, *e.g.*, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and methyl cellulose; polysaccharides, *e.g.*, alginates, xanthan gum, chitosan, carrageenan, and dextran; polyalkylene oxides, *e.g.*, polyethylene oxide; vinyl acetate copolymers; methacrylic acid copolymers; maleic anhydride/methyl vinyl ether copolymers; carboxyvinyl polymers; and combinations thereof.

Coating may be performed by applying the coating composition as a solution/suspension/blend using any conventional coating technique known in the art, such as spray coating in a conventional coating pan or fluidized bed processor, dip coating, or compression coating.

Examples of solvents used for preparing the solution/dispersion of coating substances and for granulation include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, purified water, and the like.

The extended-release composition of the present invention maintains the drug concentration in the blood above MIC for more than 40% of dosing interval so as to achieve the desired clinical effect.

- The invention may be further illustrated by the following examples, which are for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Example 1

Ingredients	Quantity (mg/tablet)
Intragranular	
Cefpodoxime proxetil	521.79
Microcrystalline cellulose	78.21
Fumaric acid	40.00
Colloidal silicon dioxide	84.00
Sodium lauryl sulfate	30.00
Sodium stearyl fumarate	6.00
Extragranular	
Crospovidone	150.00
Hypromellose K4M	140.00
Hypromellose K100 LVCR	40.00
Polyvinyl pyrrolidone	10.00
Mannitol	94.00
Sodium stearyl fumarate	6.00
Tablet Weight	1200.00
Coating	
Opadry®	48.00
Purified water	q.s.
Coated tablet weight	1248.00
pH	3.21

10 Procedure:

1. Cefpodoxime proxetil, microcrystalline cellulose, fumaric acid, colloidal silicon dioxide, sodium lauryl sulfate, and sodium stearyl fumarate were sifted and blended.
2. The blend of step 1 was compacted and milled to form granules.

3. Crospovidone, hydroxypropylmethyl cellulose (Hypromellose K4M CR and Hypromellose K100 LVCR), polyvinyl pyrrolidone, and mannitol were sifted and mixed.
4. The mixture of step 3 was blended with the granules of step 2.
5. Sodium stearyl fumarate was sifted and blended with the mixture of step 4.
6. The mixture of step 5 was compressed into a tablet.
7. Opadry® was dispersed in purified water and stirred to form a dispersion.
8. The tablet of step 6 was coated with the dispersion of step 7.

pH Determination

- 10 The pH of the extended-release tablet of cefpodoxime proxetil prepared as per Example 1 was determined by crushing the extended-release tablet using a mortar and pestle. The crushed powder was transferred to a flask containing 100 mL of purified water. The flask was shaken for 5 minutes and the pH of the medium was measured. The pH of the composition prepared as per Example 1 was found to be 3.21.

In-Vitro Release Studies

The *in-vitro* dissolution profile of the extended-release tablet of cefpodoxime proxetil prepared as per Example 1 was determined using a USP type II apparatus at 100 r.p.m., in 900 mL of glycine buffer (pH 3) + 0.5% sodium lauryl sulfate using 10 mesh sinkers at 37°C. The results of the release studies are represented in Table 1.

20 **Table 1: Percentage (%) of the *In-Vitro* Cefpodoxime Release in USP Type II Apparatus (Media: Glycine buffer (pH 3) + 0.5% sodium lauryl sulfate, 900 mL, at 100 r.p.m.)**

Time (hours)	Percentage (%) of Cefpodoxime Release
1	36
4	56
10	79
16	93

Stability

- 25 The extended-release tablets of cefpodoxime proxetil prepared as per Example 1 were stored at a temperature of 40°C and a relative humidity (RH) of 75% for a period of three and six months, and analyzed for cefpodoxime content by an HPLC method. The results of the analysis are represented in Table 2.

Table 2: Stability Data for the Cefpodoxime Proxetil Extended Release Tablets

Conditions (40°C/75% RH)	Assay (%)	Related substances (% w/w)
Initial	100.9	4.2
3 Months	95.0	5.5
6 Months	97.7	6.4

Example 2

Ingredients	Quantity (mg/tablet)
Intragranular	
Cefpodoxime proxetil	521.79
Microcrystalline cellulose	78.21
Fumaric acid	40.00
Colloidal silicon dioxide	84.00
Sodium lauryl sulfate	30.00
Sodium stearyl fumarate	6.00
Extragranular	
Crospovidone	150.00
Hydroxypropylmethyl cellulose	180.00
Polyvinyl pyrrolidone	10.00
Mannitol	94.00
Sodium stearyl fumarate	6.00
Core Tablet weight	1200.00
Opadry®	48.00
Purified water	q.s.
Tablet weight	1248.00

5 Procedure:

1. Cefpodoxime proxetil, microcrystalline cellulose, fumaric acid, colloidal silicon dioxide, sodium lauryl sulfate, and sodium stearyl fumarate were sifted and blended.
2. The blend of step 1 was compacted and milled to form granules.
- 10 3. Crospovidone, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, and mannitol were sifted and mixed.
4. The mixture of step 3 was blended with granules of step 2.
5. Sodium stearyl fumarate was sifted and blended with the mixture of step 4.
6. The mixture of step 5 was compressed into a tablet.
- 15 7. Opadry® was dispersed in purified water and stirred to form a dispersion.
8. The tablet of step 6 was coated with the dispersion of step 7.

Examples 3-6

Example	3	4	5	6
Ingredients	Quantity (mg/tablet)			
Intragranular				
Cefpodoxime proxetil	521.79	521.79	521.79	521.79
Microcrystalline cellulose	78.21	78.21	78.21	78.21
Fumaric acid	62.00	62.00	62.00	62.00
Colloidal silicon dioxide	63.00	63.00	63.00	63.00
Sodium lauryl sulfate	29.00	29.00	29.00	29.00
Sodium stearyl fumarate	6.00	6.00	6.00	6.00
Extragranular				
Crospovidone	150.00	150.00	150.00	150.00
Hypromellose K4M	80.00	80.00	100.00	150.00
Hypromellose K100 LVCR	120.00	100.00	50.00	34.47
Polyvinyl pyrrolidone	40.00	40.00	70.00	50.00
Mannitol	44.47	64.47	64.47	50.00
Sodium stearyl fumarate	6.00	6.00	6.00	6.00
Core tablet weight	1200.47	1200.47	1200.47	1200.47

Procedure:

1. Cefpodoxime proxetil, microcrystalline cellulose, fumaric acid, colloidal silicon dioxide, sodium lauryl sulfate, and sodium stearyl fumarate were sifted and blended.
2. The blend of step 1 was compacted and milled to form granules.
3. Crospovidone, hydroxypropylmethyl cellulose (Hypromellose K4M CR and Hypromellose K100 LVCR), polyvinyl pyrrolidone, and mannitol were sifted and mixed.
4. The mixture of step 3 was mixed with the granules of step 2.
5. Sodium stearyl fumarate was sifted and blended with the mixture of step 4.
6. The mixture of step 5 was compressed into a tablet.

Examples 7-8

Example	7	8
Ingredients	Quantity (mg/tablet)	
Intragranular		
Cefpodoxime proxetil	521.79	521.79
Microcrystalline cellulose	78.21	78.21
Tartaric acid	40.00	40.00
Colloidal silicon dioxide	84.00	-
Aluminum magnesium silicate	-	84.00
Sodium lauryl sulfate	30.00	30.00
Sodium stearyl fumarate	6.00	6.00
Extragranular		
Crospovidone	150.00	150.00
Hypromellose K4M	150.00	150.00
Hypromellose K100 LVCR	60.00	60.00
Polyvinyl pyrrolidone	10.00	10.00
Mannitol	64.00	64.00
Sodium stearyl fumarate	6.00	6.00
Total Weight	1200.00	1200.00
pH	3.03	3.63

Procedure:

1. Cefpodoxime proxetil, microcrystalline cellulose, tartaric acid, colloidal silicon dioxide/aluminum magnesium silicate, sodium lauryl sulfate, and sodium stearyl fumarate were sifted and blended.
2. The blend of step 1 was compacted and milled to form granules.
3. Crospovidone, hydroxypropylmethyl cellulose (Hypromellose K4M CR and Hypromellose K100LVCR), polyvinyl pyrrolidone, and mannitol were sifted and mixed.
4. The mixture of step 3 was blended with the granules of step 2.
5. Sodium stearyl fumarate was sifted and blended with the mixture of step 4.
6. The mixture of step 5 was compressed into a tablet.

Examples 9-13

Example	9	10	11	12	13
Ingredients	Quantity (mg/tablet)				
Cefpodoxime proxetil	521.79	260.89	260.89	260.89	260.89
Microcrystalline cellulose	78.21	39.11	39.11	39.11	39.11
Fumaric acid	40.00	20.00	20.00	20.00	20.00
Colloidal silicon dioxide	84.00	42.00	42.00	42.00	42.00
Sodium lauryl sulfate	30.00	15.00	15.00	15.00	15.00
Sodium stearyl fumarate	6.00	3.00	3.00	3.00	3.00
Extragranular					
Crospovidone	150.00	190.18	200.10	210.10	210.10
Hypromellose K4M	140.00	99.90	99.90	89.90	89.90
Hypromellose K100 LVCR	40.00	79.92	70.00	70.00	60.00
Polyvinyl pyrrolidone	10.00	10.00	10.00	10.00	10.00
Mannitol	94.00	134.00	134.00	134.00	144.00
Sodium stearyl fumarate	6.00	6.00	6.00	6.00	6.00
Tablet Weight	1200.00	900.00	900.00	900.00	900.00
Coating					
Opadry®	48.00	27.00	27.00	27.00	27.00
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Coated tablet weight	1248.00	927.00	927.00	927.00	927.00

Procedure:

1. Cefpodoxime proxetil, microcrystalline cellulose, fumaric acid, colloidal silicon dioxide, sodium lauryl sulfate, and sodium stearyl fumarate were sifted and blended.
2. The blend of step 1 was compacted and milled to form granules.
3. Crospovidone, hydroxypropylmethyl cellulose (Hypromellose K4M CR and Hypromellose K100LVCR), polyvinyl pyrrolidone, and mannitol were sifted and mixed.
4. The mixture of step 3 was blended with the granules of step 2.
5. Sodium stearyl fumarate was sifted and blended with the mixture of step 4.
6. The mixture of step 5 was compressed into a tablet.

7. Opadry[®] was dispersed in purified water and stirred to form a dispersion.

8. The tablet of step 6 was coated with the dispersion of step 7.

In-Vitro Release Studies

5 The *in-vitro* dissolution profiles of the extended-release tablets of cefpodoxime proxetil prepared as per Examples 9-13 were determined using a USP type II apparatus at 100 r.p.m., in 900 mL of glycine buffer (pH 3) + 0.5% sodium lauryl sulfate using 10 mesh sinkers at 37°C. The results of the release studies are represented in Table 3.

Table 3: Percentage (%) of the In-Vitro Cefpodoxime Release in USP Type II Apparatus (Media: Glycine buffer (pH 3) + 0.5% sodium lauryl sulfate, 900 mL, and
10 **100 r.p.m.)**

Example	9	10	11	12	13
Time (hours)	Percentage (%) of Cefpodoxime Release				
1	33	23	25	30	33
2	44	35	34	42	44
4	58	51	50	58	60
6	-	64	62	70	73
8	79	76	73	82	84
12	93	91	89	94	94
16	98	96	94	98	97

We claim:

- 1 1. A stable extended-release composition of cefpodoxime comprising cefpodoxime
2 proxetil, a stabilizer, and a release-controlling agent, wherein the composition is
3 characterized by having a pH of less than about 4.
- 1 2. A stable extended-release composition of cefpodoxime comprising cefpodoxime
2 proxetil, a stabilizer, and a release-controlling agent, wherein the composition is
3 characterized by having an *in-vitro* dissolution release profile as determined by USP type
4 II apparatus at 100 r.p.m., in 900 mL of glycine buffer (pH 3) with 0.5% sodium lauryl
5 sulfate at 37°C as follows:
 - 6 - not more than 50% of cefpodoxime released at 1 hour,
 - 7 - not more than 65% of cefpodoxime released at 4 hours,
 - 8 - more than 75% of cefpodoxime released at 16 hours.
- 1 3. A stable extended-release composition of cefpodoxime comprising cefpodoxime
2 proxetil, a stabilizer, and a release-controlling agent, wherein the cefpodoxime proxetil is
3 present in an amount of not more than about 55% w/w based on the total weight of the
4 composition.
- 1 4. The stable extended-release composition of claim 1, wherein the pH of the
2 composition is in a range of about 2 to about 4.
- 1 5. The stable extended-release composition of any one of claims 1, 2, or 3, wherein
2 the stabilizer is a combination of an organic acid and a silicon dioxide.
- 1 6. The stable extended-release composition claim 5, wherein the organic acid and
2 silicon dioxide are present in a weight ratio of about 1:1 to about 1:5.
- 1 7. The stable extended-release composition of claim 5, wherein the organic acid is
2 selected from the group comprising fumaric acid, citric acid, tartaric acid, oxalic acid,
3 malic acid, succinic acid, ascorbic acid, pyruvic acid, malonic acid, glutaric acid, adipic
4 acid, gluconic acid, lactic acid, and mixtures thereof.
- 1 8. The stable extended-release composition of claim 5, wherein the silicon dioxide is
2 selected from the group comprising colloidal silicon dioxide, fumed silica, precipitated
3 silica, light anhydrous silicic acid, silicic anhydride, aluminum magnesium silicate, and
4 mixtures thereof.

- 1 9. The stable extended-release composition of claim 5, wherein the organic acid and
2 cefpodoxime proxetil are present in a weight ratio of about 1:5 to about 1:20.
- 1 10. The stable extended-release composition of claim 5, wherein the silicon dioxide
2 and cefpodoxime proxetil are present in a weight ratio of about 1:1 to about 1:10.
- 1 11. The stable extended-release composition of any one of claims 1, 2, or 3, wherein
2 the release-controlling agent is selected from the group comprising cellulosic polymers
3 such as hydroxypropylmethyl cellulose, methyl cellulose, hydroxypropyl cellulose, ethyl
4 cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, carboxy methylcellulose,
5 cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate,
6 hydroxypropylmethyl cellulose acetate succinate, cellulose acetate butyrate, cellulose
7 acetate, and cellulose acetate trimellitate; acrylic copolymers such as methacrylic acid
8 copolymers; polyvinyl alcohol; polyvinyl acetate; polyalkylene glycol such as
9 polyethylene glycol; triglycerides; waxes; lipids; fatty acids or their salts/derivatives; a
10 mixture of polyvinyl acetate and polyvinyl pyrrolidone; and mixtures thereof.
- 1 12. The stable extended-release composition of the any of the preceding claims,
2 wherein the composition further comprises one or more pharmaceutically acceptable
3 excipients selected from the group comprising fillers, binders, glidants, disintegrants,
4 lubricants, wetting agents, and combinations thereof.
- 1 13. The stable extended-release composition of any of the preceding claims, wherein
2 the composition is in the form of a tablet, granule, powder, capsule, pellet, or a spheroid.
- 1 14. The stable extended-release composition of claim 13, wherein the composition is a
2 tablet.
- 1 15. The stable extended-release composition of claim 14, wherein the tablet is further
2 coated with a non-functional coating comprising a film-forming polymer and coating
3 additives.
- 1 16. The stable extended-release composition of any one of claims 1, 2, or 3, wherein
2 the composition is administered once daily for treating bacterial infections.
- 1 17. A process for the preparation of the extended-release composition of any one of
2 claims 1, 2, or 3, wherein the process comprises:
- 3 (i) blending cefpodoxime proxetil, a silicon dioxide, an organic acid, and one or
4 more pharmaceutically acceptable excipients;

- 5 (ii) optionally granulating the blend of step (i);
- 6 (iii) mixing one or more release-controlling agents with the blend of step (i) or the
- 7 granules of step (ii);
- 8 (iv) compressing the mixture of step (iii) to form a tablet; and
- 9 (v) optionally applying a coating comprising one or more film-forming polymers
- 10 and coating additives onto the tablet of step (iv).

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 15/59254

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 31/04; A61K 31/546; 9/20; C07D 501/00 (2016.01)

CPC - C07D 501/00; A61K 31/546; A61K 9/20

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(8): A61P 31/04; A61K 31/546; 9/20; C07D 501/00 (2016.01)

CPC: C07D 501/00; A61K 31/546; A61K 9/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/207; 540/222; 540/228; 424/464 (keyword limited; see search terms below)

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

PatBase, Google Patents, Google Scholar

Search terms used: cefpodoxime proxetil, organic/fumaric/citric/tartaric/oxalic/malic/succinic/ascorbic/pyruvic/malonic/ glutaric/adipic, acid, silicon dioxide/silica/silicic/silicate, cellulose/hypromellose

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/060786 A2 (BILGIC, MAHMUT) 10 May 2012 (10.05.2012); pg 2 ln 20-21; pg 3 ln 8-9; pg 4 ln 26-31; pg 5 ln 7, 20; pg 6 ln 1-5, ln 26-30; pg 7 ln 19-20; pg 7 ln 27-pg 8 ln 2; pg 8 ln 3-6, ln 9-11, ln 15	1-11, 16-17
Y	WO 2004/019901 A2 (ORCHID CHEMICALS & PHARMACEUTICALS LTD.) 11 March 2004 (11.03.2004); pg 1 ln 11-13; pg 13 ln 15-18, 22-24, 26; pg 16 ln 17-19; pg 18 ln 19-20, 22-23; pg 21 ln 18; pg 22 ln 11, 13;	1-11, 16-17
A	WO 2012/068076 A2 (DR. REDDY'S LABORATORIES LTD) 24 May 2012 (24.05.2012); entire document	1-11, 16-17
A	US 7,976,871 B2 (VAYA et al.) 12 July 2011 (12.07.2011); entire document	1-11, 16-17
A	US 2009/0269400 A1 (DEVANE et al.) 29 October 2009 (29.10.2009); entire document	1-11, 16-17

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 February 2016 (18.02.2016)

Date of mailing of the international search report

17 MAR 2016

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 15/59254

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 12-15
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.