(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 December 2011 (08.12.2011)

PCT

(10) International Publication Number
WO 2011/152809 A2

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/545* (2006.01)
A61K 31/43 (2006.01)

(21) International Application Number:
PCT/TR2011/000149

(22) International Filing Date:
2 June 2011 (02.06.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2010/04462 3 June 2010 (03.06.2010) TR

(72) Inventor; and
(71) Applicant : **Mahmut BILGIC** [TR/TR]; Tozkoparan Mah. General AN Riza Gurcan Cad. Merter Is, Merkezi Bagimsiz Bolum No:2/13 Merter/lstanbul, 34173 Turkey (TR).

(74) Agent: **Meliha Merve KOSE**; Tozkoparan Mah. General Ali Riza Gurcan Cad. Merter Is, Merkezi Bagimsiz Bolum No:2/13 Merter/lstanbul, 34173 Turkey (TR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2011/152809 A2

(54) Title: EFFERVESCENT FORMULATIONS COMPRISING CEPHALOSPORIN AND CLAVULANIC ACID

(57) Abstract: The present invention relates to pharmaceutical formulations comprising cephalosporin antibiotic and clavulanic acid or any pharmaceutically acceptable derivative thereof and process for the preparation of said formulations.

EFFERVESCENT FORMULATIONS COMPRISING CEPHALOSPORIN AND CLAVULANIC ACID

The present invention relates to pharmaceutical formulations comprising a cephalosporin antibiotic and clavulanic acid or any pharmaceutically acceptable derivative thereof; processes for preparation of said formulations and their use in bacterial infections.

Like other beta-lactam antibiotics, cephalosporin induces bactericide effect. However, some types of bacteria such as Escherichia, Klebsiella, Proteus, Pseudomonas, Enterobacter and Staphylococcus produce beta-lactamase enzyme. Beta-lactamase enzyme breaks the beta-lactam ring in cephalosporins open and therefore, impedes them to induce bacterial effect. As a result, the patient cannot be treated by antibiotics administration.

In order to prevent bacterial infections and preclude the bacteria to inactivate the antibiotics, it has been alternatively developed that penicillins or cephalosporins are combined with beta lactamase enzyme inhibitors. Clavulanic acid which is a beta-lactamase inhibitor is a molecule with weak antibacterial activity that was disclosed in the patent numbered DE 2517316.

Oral solid dosage forms comprising cephalosporin antibiotics and clavulanic acid are not preferred to be administered especially by the patients having difficulty in swallowing. Suspension forms are also not preferable since they have the potential to cause high and/or uncontrolled dose intake and have difficulty for using and carrying.

Alternatively developed water soluble formulations like effervescent formulations comprising cephalosporin antibiotics and clavulanic acid are used to overcome said problems seen in the solid oral dosage forms and suspension forms.

However, it is known that cephalosporin antibiotics have low solubility in water, which results in non-homogenous and longtime dissolution of the formulations comprising cephalosporins. Moreover, clavulanic acid is sensitive to moisture and pH and accordingly it is not stable in aqueous medium.

Therefore, it is difficult to develop water soluble formulations comprising the combination of cephalosporin antibiotics and clavulanic acid due to low water solubility of cephalosporins and instability of clavulanic acid in aqueous media.

As is seen, there is need to develop new water soluble formulations comprising said combination that are stable and can be soluble in water entirely and quickly.

The inventors have surprisingly found that the present problems in the prior art can be solved by the effervescent formulations comprising cephalosporins and clavulanic acid or any pharmaceutically acceptable derivative thereof prepared according to the present invention.

Description of the Invention

The present invention relates to the effervescent formulations comprising a cephalosporin antibiotic and clavulanic acid or any pharmaceutically acceptable derivative thereof and their preparation methods. Surprisingly, it is seen that effervescent forms formulated with the formulation comprising 10-40% of a cephalosporin antibiotic, 5-25% clavulanic acid, 20-70% effervescent couple, 0.2-5% high molecular weight PEG and %1-20 other pharmaceutically acceptable excipients with respect to the total weight of unit dose, homogeneously and quickly dissolve in water and are stable.

The first aspect of the present invention is the effervescent formulations comprising a cephalosporin antibiotic and clavulanic acid or any pharmaceutically acceptable derivative thereof wherein said formulation comprises 10-40% of a cephalosporin antibiotic, 5-25% clavulanic acid, 20-70% effervescent couple, 0.2-5% high molecular weight PEG and %1-20 other pharmaceutically acceptable excipients with respect to the total weight of unit dose.

This way it was observed that the clavulanic acid or any pharmaceutically acceptable derivative thereof remains stable due to the fact that the composition is kept in solid form. Furthermore the composition is dissolved in water completely and homogeneously prior to administration owing to the use of active agents, the effervescent couple, high molecular weight PEG and other excipients in the amounts given above.

The term "total weight of unit dose" comprises the weight of a cephalosporin antibiotic, clavulanic acid, high molecular weight PEG, effervescent couple and the other pharmaceutically acceptable excipients.

The effervescent formulation of the present invention can be in granule, powder or tablet form. Preferably, it is in tablet form.

When the effervescent formulations comprising cephalosporin antibiotic and clavulanic acid are formulated in effervescent tablet form, it is observed that the final tablet forms can

dissolve in water in less than 5 minutes which is a short time for a drug to dissolve before administration.

Accordingly, another aspect of the present invention is the effervescent tablet forms comprising a cephalosporin antibiotic and clavulanic acid which dissolve in water less than 5 minutes.

The said cephalosporin antibiotic used in the effervescent formulation of the present invention can be selected from a group comprising cefazolin, cefacetrile, cephadroxyl, cephalexin, cephaloglycin, cefalonium, cephaloridine, cephalothin, cephaprin, cefatrizine, cefazedone, cefazaflur, cefradine, cefroxadine, ceftezole, cefaclor, cefamandole, cefminox, cefocinid, ceforanide, cefotiam, cefprozil, cefbuperazone, cefuroxime, cefuzonam, cephamycin (cefoxitin, cefotetan, cefmetazole), carbacephem (loracarbef), cefixime, ceftazidime, ceftriaxone, cefcapene, cefdaloxime, cefdinir, cefditoren, cefetamet, cefmenoxime, cefodizime, cefoperazone, cefotaxime, cefpimizole, cefpiramide, cefpodoxime, cefsulodin, cefteram, ceftibuten, ceftiolene, ceftizoxime, oxacephem (flomoxef, latamoxef), cefepime, cefozopran, cefpirome, cefquinome, ceftobiprole, ceftiofur, cefquinome, cefovecin or any pharmaceutically acceptable derivative thereof.

The cephalosporin antibiotic that is used in the effervescent formulation of the present invention is preferably selected from the group comprising cefaclor, cefprozil, cefuroxime, cefdinir, cefditoren, cefetamet, ceftibuten or a pharmaceutically acceptable derivative thereof.

The cephalosporin antibiotic that is used in the effervescent formulation of the present invention is more preferably selected from the group comprising cefaclor, cefprozil, cefuroxime and cefetamet or any pharmaceutically acceptable derivative thereof.

The cephalosporin antibiotic that is used in the effervescent formulation of the present invention can be in the form of its pharmaceutically acceptable hydrates, solvates, esters, enantiomers, polymorphs, crystal forms, amorphous forms, salt forms or free base form and/or a combination thereof.

The formulation of the present invention comprises a cephalosporin antibiotic in the range of 100-1400 mg, preferably in the range of 300-800 mg or a pharmaceutically acceptable derivative thereof in an equal amount.

The formulation of the present invention comprises a cephalosporin antibiotic preferably in the range of 15-35%, more preferably 20-30% by weight with respect to the total weight of unit dose.

Clavulanic acid that the effervescent formulation of the present invention comprises can be in the form of its pharmaceutically acceptable hydrates, solvates, esters, enantiomers, polymorphs, crystal forms, amorphous forms, salt forms or free base form and/or a combination thereof.

Clavulanic acid that the pharmaceutical formulation of the present invention comprises can be in salt form, preferably in sodium, potassium, calcium, magnesium, aluminum, ammonium and modified ammonium salt form.

Clavulanic acid comprised in the pharmaceutical formulation of the present invention is preferably potassium clavulanate.

The formulation of the present invention comprises clavulanic acid in the range of 50-400 mg, preferably in the range of 50-300 mg, preferably in the range of 70-125 mg or a pharmaceutically acceptable derivative thereof in an amount equivalent to that.

The formulation of the present invention comprises clavulanic acid or a pharmaceutically acceptable derivative thereof in the range of 8-22%, more preferably 10-20% by weight with respect to the total weight of unit dose.

High molecular weight PEG that is used in the effervescent formulation of the present invention can be PEG 6000 or PEG 4000 or a combination thereof.

The formulation of the present invention comprises high molecular weight PEG preferably in the range of 0.3-3%, more preferably 0.5-2% by weight with respect to the total weight of unit dose.

The effervescent couple comprises an effervescent acid and an effervescent base.

The pharmaceutically acceptable effervescent acid of the present invention can be selected from a group comprising acetic acid, citric acid, lactic acid, malic acid, phosphoric acid, propionic acid, tartaric acid or combinations thereof.

The pharmaceutically acceptable effervescent base of the present invention can be selected from a group comprising potassium carbonate, potassium bicarbonate, potassium citrate,

potassium hydroxide, sodium carbonate, sodium hydrogen carbonate, sodium hydrogen citrate or combinations thereof.

The effervescent formulation of the present invention comprises other pharmaceutically acceptable excipients in addition to the active agent cephalosporin antibiotic, clavulanic acid, effervescent couple and high molecular weight PEG.

The effervescent formulation of the present invention comprise one or more of the other pharmaceutically excipients selected from the group comprising binders, glidants, diluents, disintegrants, flavoring agents, sweeteners, coloring agents, anti-foam agent, stabilizing agents.

The binder that is used in the formulation according to the present invention can be selected from a group comprising starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatin; cellulose derivatives such as microcrystalline cellulose, HPC, HEC, HPMC, carboxymethyl cellulose, methyl cellulose, ethyl cellulose; polyvinylpyrrolidone (povidone), polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as sorbitol, xylitol, mannitol, and water or a combination thereof.

The flavoring agent that is used in the formulation according to the present invention can be selected from a group comprising natural aroma oils, menthol, menthane, anethole, methyl salicylate, eucalyptol, cinnamon, 1-methyl acetate, sage, eugenol, oxanone, alpha irisone, marjoram, lemon, orange, blackberry, propenyl guaetol acetyl, cinnamon, vanilla, thymol, linalol, cinnamaldehyde glycerol acetal or a combination thereof.

The sweetener that is used in the formulation according to the present invention can be selected from a group comprising sucralose, sucrose, fructose, glucose, galactose, xylose, dextrose, laevulose, lactose, maltose, maltodextrin, mannitol, maltitol, maltol, sorbitol, xylitol, erythritol, lactitol, isomalt, corn syrup, saccharine, saccharine salts, acesulfame potassium, aspartame, D and cyclamates or a combination thereof.

The coloring agent that is used in the formulation according to the present invention can be selected from a group comprising carotenoids and chlorophyl or a combination thereof.

The glidant that can be used in the formulation according to the present invention can be selected from a group comprising sodium benzoate, sodium chloride, sodium acetate, sodium fumarate, carbowax 4000, L-leucine, PEG or a combination thereof.

The diluents that can be used in the formulation according to the present invention can be selected from a group comprising lactose, maltose, dextrin, maltodextrin, mannitol, sorbitol, starch or a combination thereof.

The disintegrant that can be used in the formulation according to the present invention can be selected from a group comprising starches such as potato starch, corn starch, wheat starch, pregelatinized starch, sodium starch glycolate; cellulose derivatives such as croscarmellose sodium or microcrystalline cellulose; polyvinylpyrrolidone; crospovidone; alginic acid and its salts; clays such as xanthan gum or veegum; ion exchange resins or a combination thereof.

The antifoam agent that can be used in the formulation according to the present invention can be selected from a group comprising simethicone emulsion and dimethyl siloxane, silicon oil or a combination thereof.

The stabilizing agent and/or agents that can be used in the formulation according to the present invention can be selected from a group comprising antioxidants, chelating agents, alkalinizing agents and photoprotective agents.

In another aspect, the present invention relates to the process for the preparation of the effervescent formulations comprising a cephalosporin antibiotic and clavulanic acid includes the following steps of granulating effervescent couple and at least one excipient; adding cephalosporin antibiotic, clavulanic acid and the other excipients to the obtained granules and optionally compressing the final mixture into tablets.

In another aspect, the present invention relates to use of said effervescent formulation in upper respiratory tract infections such as pharyngitis, tonsillitis, otitis media, sinusitis; lower respiratory tract infections such as chronic bronchitis and pneumonia; skin and soft tissue infections, urinary system infections and gonorrhea.

The effervescent formulations pertaining to the present invention can be prepared as described below, but not limited to these examples.

Example 1 The formulation of the effervescent tablet and its preparation

Component	Amount (% weight)
Cefaclor	27
Potassium clavulanate	15
Effervescent couple	48.5
PEG 6000	1.5
Other excipient	8

The effervescent formulation comprising cefaclor and potassium clavulanate is prepared by granulating effervescent couple and at least one excipient; adding cefaclor, potassium clavulanate and the other excipients to the obtained granules and finally compressing the final mixture into tablets.

Example 2 The formulation of the effervescent granule/ powder and its preparation

Component	Amount (% weight)
Cefprozil	23.5
Potassium clavulanate	16
Effervescent couple	51
PEG 6000	1
Other excipient	8.5

The effervescent formulation comprising cefprozil and potassium clavulanate is prepared by granulating effervescent couple and at least one excipient; adding cefprozil, potassium clavulanate and the other excipients to the obtained granules and finally filling the final mixture into sachets.

Example 3 The formulation of the effervescent tablet and its preparation

Component	Amount (% weight)
Cefdinir	22
Potassium clavulanate	16
Effervescent couple	57
PEG 6000	1.5
Other excipient	3.5

The effervescent formulation comprising cefdinir and potassium clavulanate is prepared by granulating effervescent couple and at least one excipient; adding cefdinir, potassium clavulanate and the other excipients to the obtained granules and finally compressing the final mixture into tablets.

Example 4 The formulation of the effervescent granule/ powder and its preparation

Component	Amount (% weight)
Cefuroxime axetil	26
Potassium clavulanate	12
Effervescent couple	53
PEG 6000	1
Other excipient	8

The effervescent formulation comprising cefuroxime axetil and potassium clavulanate is prepared by granulating effervescent couple and at least one excipient; adding cefuroxime axetil, potassium clavulanate and the other excipients to the obtained granules and finally filling the final mixture into sachets.

Example 5 The formulation of the effervescent tablet and its preparation

Component	Amount (% weight)
Ceftibuten	27.5
Potassium clavulanate	12.5
Effervescent couple	55
PEG 6000	1.3
Other excipient	3.7

The effervescent formulation comprising ceftibuten and potassium clavulanate is prepared by granulating effervescent couple and at least one excipient; adding ceftibuten, potassium clavulanate and the other excipients to the obtained granules and finally compressing the final mixture into tablets.

Example 6 The formulation of the effervescent tablet and its preparation

Component	Amount (% weight)
Cefditoren	28
Potassium clavulanate	11.8
Effervescent couple	54
PEG 6000	1.2
Other excipient	5

The effervescent formulation comprising cefditoren and potassium clavulanate is prepared by granulating effervescent couple and at least one excipient; adding cefditoren, potassium clavulanate and the other excipients to the obtained granules and finally compressing the final mixture into tablets.

Example 7 The formulation of the effervescent granule/ powder and its preparation

Component	Amount (% weight)
Cefetamet	25
Potassium clavulanate	13
Effervescent couple	53
PEG 6000	1.75
Other excipient	7.25

The effervescent formulation comprising cefetamet and potassium clavulanate is prepared by granulating effervescent couple and at least one excipient; adding cefetamet, potassium clavulanate and the other excipients to the obtained granules and finally filling the final mixture into sachets.

CLAIMS

1. An effervescent formulation comprising the combination of a cephalosporin antibiotic and clavulanic acid or pharmaceutically acceptable derivatives thereof characterized in that said formulation comprises;
   - 10-40% of a cephalosporin antibiotic,
   - 5-25% clavulanic acid,
   - 20-70% effervescent couple,
   - 0.2-5% high molecular weight PEG and
   - 1-20% other pharmaceutically acceptable excipients with respect to the total weight of unit dose.
2. The effervescent formulation according to claim 1 wherein cephalosporin antibiotic used in said formulation is selected from a group comprising cefazolin, cefacetrile, cephadroxyl, cephalexin, cephaloglycin, cefalonium, cephaloridine, cephalothin, cephaprin, cefatrizine, cefazedone, cefazaflur, cefradine, cefroxadine, ceftezole, cefaclor, cefamandole, cefminox, cefocinid, ceforanide, cefotiam, cefprozil, cefbuperazone, cefuroxime, cefuzonam, cephamycin (cefoxitin, cefotetan, cefmetazole), carbacephem (loracarbef), cefixime, ceftazidime, ceftriaxone, cefcapene, cefdaloxime, cefdinir, cefditoren, cefetamet, cefmenoxime, cefodizime, cefoperazone, cefotaxime, cefpimizole, cefpiramide, cefpodoxime, cefsulodin, cefteram, ceftibuten, ceftiolene, ceftizoxime, oxacephem (flomoxef, latamoxef), cefepime, cefozopran, cefpirome, cefquinome, ceftobiprole, ceftiofur, cefquinome, cefovecin or a pharmaceutically acceptable derivative thereof.
3. The effervescent formulation according to claim 2 wherein the cephalosporin antibiotic used in said formulation is selected from the group comprising cefaclor, cefprozil, cefuroxime, cefdinir, cefditoren, cefetamet, ceftibuten or any pharmaceutically acceptable derivative thereof.
4. The effervescent formulation according to claim 3 wherein the cephalosporin antibiotic used in said formulation is selected from the group comprising cefaclor, cefprozil, cefuroxime and cefetamet or any pharmaceutically acceptable derivative thereof.
5. The effervescent formulation according to claim 2 wherein the cephalosporin antibiotic used in said formulation is in the form of its pharmaceutically acceptable

hydrates, solvates, esters, enantiomers, polymorphs, crystalline forms, amorphous forms, salt forms or free base form and/or a combination thereof.

6. The effervescent formulation according to claim 5 wherein said formulation comprises the cephalosporin antibiotic in an amount in the range of 100-1400 mg by weight.
7. The effervescent formulation according to claim 6 wherein said formulation comprises the cephalosporin antibiotic in an amount in the range of 300-800 mg by weight.
8. The effervescent formulation according to claim 1 wherein clavulanic acid used in said formulation is in the form of its pharmaceutically acceptable hydrates, solvates, esters, enantiomers, polymorphs, crystalline forms, amorphous forms, salt forms or free base form and/or a combination thereof.
9. The effervescent formulation according to claim 8 wherein clavulanic acid used in said formulation is in salt form.
10. The effervescent formulation according to claim 9 wherein clavulanic acid used in said process is in sodium, potassium, calcium, magnesium, aluminum, ammonium or modified ammonium salt form.
11. The effervescent formulation according to claim 10 wherein clavulanic acid used in said formulation is potassium clavulanate.
12. The effervescent formulation according to claim 8 wherein clavulanic acid is used in an amount in the range of 50-400 mg.
13. The effervescent formulation according to claim 1 wherein high molecular weight PEG used in said formulation is selected from PEG 4000, PEG 6000 or a combination thereof.
14. The effervescent formulation according to claim 1 wherein said formulation is formulated in granule, powder or tablet form.
15. The effervescent formulation according to claim 14 wherein said formulation is formulated in tablet form.
16. The effervescent formulation according to claim 1 wherein the effervescent couple comprises an effervescent acid and an effervescent base.
17. The effervescent formulation according to claim 16 wherein the effervescent acid is selected from comprising acetic acid, citric acid, lactic acid, malic acid, phosphoric acid, propionic acid, tartaric acid or combinations thereof.
18. The effervescent formulation according to claim 16 wherein the effervescent base is selected from a group comprising potassium carbonate, potassium bicarbonate,

potassium citrate, potassium hydroxide, sodium carbonate, sodium hydrogen carbonate, sodium hydrogen citrate or combinations thereof.

19. The effervescent formulation according to claim 1 wherein said formulation comprises other pharmaceutically acceptable excipients in addition to the active agent cephalosporin antibiotic, clavulanic acid, effervescent couple and high molecular weight PEG.
20. The effervescent formulation according to claim 19 wherein said formulation comprises other pharmaceutically acceptable excipients selected from the group comprising binders, glidants, diluents, disintegrants, flavoring agents, sweeteners, coloring agents, anti-foam agent, stabilizing agents.
21. The effervescent formulation according to claim 20 wherein the binder used in said formulation is selected from a group comprising starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatin; cellulose derivatives such as microcrystalline cellulose, HPC, HEC, HPMC, carboxymethyl cellulose, methyl cellulose, ethyl cellulose; polyvinylpyrrolidone (povidone), polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as sorbitol, xylitol, mannitol, and water or a combination thereof.
22. The effervescent formulation according to claim 20 wherein the flavoring agent used in said formulation is selected from a group comprising natural aroma oils, menthol, menthane, anethole, methyl salicylate, eucalyptol, cinnamon, 1-methyl acetate, sage, eugenol, oxanone, alpha irisone, marjoram, lemon, orange, blackberry, propenyl guaetol acetyl, cinnamon, vanilla, thymol, linalol, cinnamaldehyde glycerol acetal or a combination thereof.
23. The effervescent formulation according to claim 20 wherein the sweetener used in said formulation is selected from a group comprising sucralose, sucrose, fructose, glucose, galactose, xylose, dextrose, laevulose, lactose, maltose, maltodextrin, mannitol, maltitol, maltol, sorbitol, xylitol, erythritol, lactitol, isomalt, corn syrup, saccharine, saccharine salts, acesulfame potassium, aspartame, D and cyclamates or a combination thereof.
24. The effervescent formulation according to claim 20 wherein the coloring agent used in said formulation is selected from a group comprising carotenoids and chlorophyl or a combination thereof.

25. A process for preparation of the effervescent formulation as claimed in claim 1 wherein said process comprises the steps of granulating effervescent couple and at least one excipient; adding cephalosporin antibiotic, clavulanic acid and the other excipients to the obtained granules.