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(54) **Title:** PHARMACEUTICAL COMPOSITIONS USED IN TREATING BACTERIAL INFECTIONS

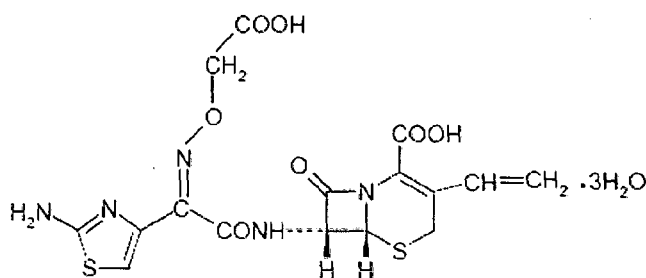
(57) **Abstract:** The present invention relates to formulations containing the combination of cefixime which is a third generation cephalosporin antibiotic and clavulanic acid which is a beta-lactamase inhibitor. Said formulations are characterized by their tablet form.



PHARMACEUTICAL COMPOSITIONS USED IN TREATING BACTERIAL INFECTIONS

The present invention relates to formulations containing the combination of cefixime which is a third generation cephalosporin antibiotic and clavulanic acid which is a beta-lactamase inhibitor. Said formulations are characterized by their tablet form.

Cefixime was first described in patent application no. EP0030630 (Formula-1). In said document, cefixime was first described as to be used in the treatment of infections caused by pathogenic microorganisms and that cefixime can be presented in solid forms such as tablet, granule, powder, and capsule or in liquid forms such as suspension, syrup, emulsion.

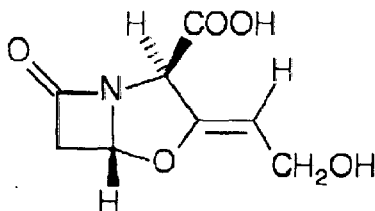


Formula - 1

In prior art, medicaments containing cefixime as an active ingredient can be found commercially in the form of a suspension and tablet.

A beta-lactam antibiotic can be used in combination with a beta-lactamase inhibitor in order to increase the efficacy of treatment. In the formulations of the present invention, cefixime is used in combination with clavulanic acid.

Clavulanic acid and its derivatives (such as potassium clavulanate salts) are known as beta-lactamase inhibitors which resists beta-lactamase enzyme activity through the suppression of beta-lactamase mediated resistance mechanism (Formula - 2).



Formula - 2

In the present state of prior art, in oral formulations, clavulanic acid is usually in the form of a pharmaceutically acceptable salt, particularly used in the form of potassium clavulanate.

However, potassium clavulanate is a material very difficult to formulate due to its hygroscopic property and the moisture sensitivity. Therefore during its production and use, it should be kept away from water and aqueous media otherwise it can be degraded.

The dry powder suspension forms which already exist can be stabilized maximum 5 days after reconstitution above 5 ° C. This extreme sensitivity to moisture of clavulanic acid leads to restrictions in the formulations.

When taken orally, the bioavailability and therapeutic efficacy of an active ingredient depends on the absorption in the gastrointestinal tract. The absorption of the drug is determined by its solubility properties. Cefixime is a member of the BCS class II drug having low solubility and high permeability. The bioavailability of cefixime tablets is between 40-50%. Cefixime suspensions provide about 25-50% greater bioavailability compared to the tablet form.

The inventors have previously conducted studies on formulations containing cefixime and clavulanic acid or a pharmaceutically acceptable salt thereof and effervescent dosage forms comprising said combination are disclosed in patent application numbered in TR 2010/00687. However, in terms of patient compliance and ease of use, effervescent dosage forms are not always preferred. Effervescent tablets are not preferred by the manufacturer since these dosage forms require the preparation of larger dosage forms, a complex production method and special packaging methods.

Therefore, dosage forms comprising the combination of cefixime and clavulanic acid or a pharmaceutically acceptable salt thereof as an active ingredient which provide ease of use to the patients and do not require expensive manufacturing methods are required. As a result of studies conducted, it has been surprisingly observed that formulations prepared in this invention containing cefixime and clavulanic acid or a pharmaceutically acceptable salt thereof do not require a complex production method, provide ease of use and have desired level of bioavailability because they are in tablet form.

Description of Invention

The present invention is directed to the formulation of pharmaceutical formulations cefixime and clavulanic acid or a pharmaceutically acceptable salt thereof in tablet form. Said tablet

formulations may be prepared in any of the oral tablet forms such as film coated tablets, modified-release, sustained-release tablets, prolonged-release tablets, controlled release tablets.

Formulations of the present invention may be preferably in the form of tablets, film-coated tablets or film-coated extended release tablet. Tablets having release properties may also
5 optionally be film coated.

In formulations of the present invention cefixime may be present in the form of cefixime and/or their pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and / or their
10 combinations.

In formulations according to the present invention, cefixime may be found preferably in the form of cefixime trihydrate.

In formulations of the present invention, the ratio of two active substances to each other is important in order to provide the desired therapeutic activity. During studies conducted, it has
15 been found that in pharmaceutical formulations prepared according to the present invention, in case the ratio of the first active ingredient cefixime to second active ingredient clavulanic acid or a pharmaceutically acceptable salt is 8:1 to 1:5, preferably 5:1 to 1:3, more preferably 3:1 to 1:2 by weight, the desired therapeutic activity is provided.

Accordingly, in one embodiment of formulations of the present invention, the ratio of
20 cefixime in the formulation to clavulanic acid in the formulation or a pharmaceutically acceptable salt thereof is 8:1 to 1:5, preferably 5:1 to 1:3, more preferably 3:1 to 1:2 by weight.

The second active ingredient, clavulanic acid and its derivative potassium clavulanate are extremely sensitive to moisture. Therefore, potassium clavulanate is used together with a
25 desiccant in pharmaceutical composition of the present invention preferably in a ratio of 1:1.

One or more of the followings may be used as desiccant: silica, colloidal silica, e.g. colloidal silica anhydrous, e.g. Aerosil[®] 200, magnesium trisilicate, pulverized cellulose, Cabosil[®], magnesium oxide, calcium silicate, Syloid[®], starch, microcrystalline cellulose and talc.

Potassium clavulanate is used together with Syloid[®] or microcrystalline cellulose in
30 pharmaceutical composition of the present invention preferably in a ratio of 1:1.

Tablet formulations of the present invention contain 50-1000 mg, preferably 50-800 mg and more preferably 50 to 500 mg of cefixime.

Tablet formulations of the present invention per unit dosage form 5-500 mg, preferably 20-400 mg and more preferably 50 to 250 mg of clavulanic acid.

- 5 Formulations of the present invention may comprise at least one pharmaceutically acceptable excipient in addition to cefixime and clavulanic acid used as active ingredients.

At least one excipient to be used in formulations of the present invention may be selected from a group comprising diluents, disintegrants, lubricants, binders, antiadherants, glidants, sweeteners, flavoring agents, speed-controlling agent, the film coating agent, solvent and/or
10 combinations thereof.

Binder to be used in formulation of the present invention can be selected from a group comprising carboxymethylcellulose sodium, ethyl cellulose, gelatin, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminum silicate, maltodextrin, methyl cellulose, polyvinyl pyrrolidone, starch.

- 15 Formulations of the present invention can be sensitive to the moisture since clavulanic acid or a pharmaceutically acceptable salt thereof is used as an active ingredient in addition to cefixime. Thus another problem encountered during the preparation of the formulation of the present invention is the sensitivity of the composition to moisture.

Moisture negatively affects several properties of the product such as stability and shelf-life. It
20 has been surprisingly found that formulations of the present invention is not affected from moisture when the ratio of clavulanic acid to diluent used is 5:1 to 1:5, preferably 3:1 to 1:3, more preferably 2:1 to 1:2 by weight.

Accordingly in another embodiment of formulations of the present invention, the ratio of clavulanic acid to diluent used is 5:1 to 1:5, preferably 3:1 to 1:3, more preferably 2:1 to 1:2
25 by weight.

At least one diluent is used in the formulations of the present invention. The diluent(s) can be selected from the group consisting of starch and derivatives, cellulose and derivatives, microcrystalline cellulose, lactose, sorbitol, silicon dioxide, dicalcium phosphate, or combinations thereof.

The amount of diluent used in said formulations is at a rate of 5-50%, preferably 10-40%, more preferably 15-35%.

The diluent used in the formulations of the present invention is preferably dicalcium phosphate, microcrystalline cellulose or combination thereof.

- 5 Disintegrant to be used in the formulations of the present invention can be selected from a group comprising carboxymethyl cellulose calcium, carboxymethylcellulose sodium, microcrystalline cellulose, silicon dioxide, croscarmellose sodium, crospovidone, hidrokspropilselüloz, methylcellulose, povidone, magnesium aluminum silicate, starch, and pregelatinized starch or combinations thereof.
- 10 Lubricant to be used in the formulations of the present invention is can be selected from a group comprising calcium stearate, magnesium stearate, sodium stearyl fumarate, polyethylene glycol, PEG 6000, polyvinyl alcohol, potassium benzoate, sodium benzoate.

Cefixime - clavulanic acid formulations of the present invention may contain cefixime, potassium clavulanate, diluent, disintegrant and film-coating agent, respectively, at a rate of

15 20-60 %, 51-50 %, 5-50 %, 5-25 %, 0,1-5 % and 0,1-10 %.

Formulations of the present invention are preferably prepared in film-coated tablet form. Film coating agent to be used in said film-coating can be selected from a group comprising sugar-based coating agents, coating agents, water-soluble coating agents, enteric coating agents, and delayed- release coating agents or combinations thereof.

- 20 As sugar-based coatings, sucrose alone or with talc, calcium carbonate, calcium phosphate , calcium sulfate, gelatin, gum arabic, carnauba gum, polyvinylpyrrolidone and pullulan can be used with or combination thereof can be used.

Water-soluble coating agents can be selected from a group comprising hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, metal hydroxyethyl

25 cellulose and sodium carboxymethyl cellulose, cellulose derivatives, polyvinyl acetate, diethyl amino acetate, aminoalkyl methacrylate copolymer and/or combinations thereof.

Enteric coating agents can be selected from a group comprising hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose, cellulose derivatives such as cellulose acetate phthalate, methacrylic acid

copolymer L, methacrylic acid copolymer LD and acrylic acid derivatives such as methacrylic acid copolymer S.

Other film-coating agents used for the film-coating of tablet obtained in formulations of the present invention may be selected from a group comprising titanium dioxide, polyvinyl
5 alcohol, polyethylene glycol, talc, lecithin or combinations thereof. For example, film-coating agent marketed under the trademark of Opadry Yellow® can be used.

In formulations of the present invention, second active agent is preferably in the form of potassium clavulanate salt.

The method used to prepare formulations of the present invention can be to formulate
10 cefixime and potassium clavulanate together or separately and to compress as single and/or double layered tablets.

Said formulation process may comprise one or more known methods such as dry and/or wet granulation, dry blending, mixing, and compacting.

In case of wet granulation is used in formulations of the present invention at least one
15 pharmaceutically acceptable solvent is used. Solvents to be used in said formulations are water and/or ethyl alcohol.

In another embodiment of the present invention, formulations of the present invention can be prepared by mixing a mixture resulting from the formulation of cefixime alone with a mixture resulting from the formulation of cefixime together with potassium clavulanate and
20 transferring these mixtures together to tablet compression to obtain single-layered tablet or separately to obtain a double-layered tablet.

The formulations of the present invention are used in the treatment of varying severity of acute and chronic bacterial infection caused by susceptible bacteria.

The following examples are given with the purpose to illustrate the invention. These
25 examples, although not limiting the scope of the present invention, are viewed in conjunction with the specification described in detail above.

Example – 1: Film Coated Tablet Formulations Comprising Cefixime and Clavulanic Acid Combination

Component Name	% Amount in Unit Dose
Cefixime trihydrate	38
Potassium Clavulanate: desiccant	30
Diluent 1	15
Diluent 2	13
Disintegrant	1
Lubricant	1,5
Film Coating Agent	1,5
TOTAL	100

For preparation of the formulation given above cefixime trihydrate, potassium clavulanate, diluents and dispersing are mixed. Lubricant is added to the mixture and the whole mixture is stirred again. The resulting final mixture is sent to tablet compression. The resulting tablets are coated with the film coating solution containing film coating agent.

Example – 2: Double Layered Tablet Comprising Cefixime and Clavulanic Acid Combination

Component Name	% Amount in Unit Dose
Cefixime trihydrate	35
Potassium Clavulanate: desiccant	20
Diluent 1	13
Diluent 2	21
Disintegrant	7
Lubricant	3
Film Coating Agent	1
TOTAL	100

In the formulation given above cefixime trihydrate and diluent 1 are granulated by compaction. On the other hand, potassium clavulanate and diluent 2 are mixed. Resulting mixture and the granules obtained previously are transferred to tablet compression separately and compressed in the form of double-layered tablet. Tablets are coated with a film-coating solution containing film-coating agent.

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CLAIMS

1. A pharmaceutical tablet formulation comprising cefixime and clavulanic acid or a pharmaceutically acceptable salt thereof wherein the ratio of cefixime in the formulation to clavulanic acid in the formulation or a pharmaceutically acceptable salt thereof is 8:1 to 1:5 by weight.
2. A pharmaceutical tablet formulation according to claim 1, wherein the ratio of cefixime in the formulation to clavulanic acid in the formulation or a pharmaceutically acceptable salt thereof is 5:1 to 1:3 by weight.
3. A pharmaceutical tablet formulation according to claim 2, wherein the ratio of cefixime in the formulation to clavulanic acid in the formulation or a pharmaceutically acceptable salt thereof is 3:1 to 1:2 by weight.
4. A pharmaceutical tablet formulation according to claims 1-3, wherein cefixime is in the form of cefixime and/or their pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and / or their combinations.
5. A pharmaceutical tablet formulation according to claim 4 wherein cefixime is in trihydrate form.
6. A pharmaceutical tablet formulation according to any of the preceding claims, wherein at least one pharmaceutically acceptable excipient in addition to cefixime and clavulanic acid is used and said excipient is selected from a group comprising diluents, disintegrants, lubricants, binders, antiadherants, glidants, sweeteners, flavoring agents, speed-controlling agent, the film coating agent, solvent and/or combinations thereof.
7. A pharmaceutical tablet formulation according to any of the preceding claims wherein the ratio of clavulanic acid to diluent used is 5:1 to 1:5 by weight.
8. A pharmaceutical tablet formulation according to claim 7, wherein the ratio of clavulanic acid to diluent used is 3:1 to 1:3 by weight.
9. A pharmaceutical tablet formulation according to claim 8, wherein the ratio of clavulanic acid to diluent used is 2:1 to 1:2 by weight.
10. A pharmaceutical tablet formulation according to claims 6-9 wherein the diluent is selected from a group comprising starch and derivatives, cellulose and derivatives, microcrystalline cellulose, lactose, sorbitol, silicon dioxide, dicalcium phosphate, or combinations thereof.

11. A pharmaceutical tablet formulation according to claim 10, wherein the amount of diluent used in said formulations is at a rate of 5-50%.
12. A pharmaceutical tablet formulation according to claim 11, wherein the amount of diluent used in said formulations is at a rate of % 10-40.
- 5 13. A pharmaceutical tablet formulation according to claim 12 wherein the amount of diluent used in said formulations is at a rate of % 15-35.
14. A pharmaceutical tablet formulation according to any of the preceding claims, wherein said formulations contain cefixime, potassium clavulanate, diluent, disintegrant and film-coating agent, respectively, at a rate of 20-60 %, 51-50 %, 5-50 %, 5-25 %, 0,1-5
10 % and 0,1-10 %.
15. A pharmaceutical formulation according to any of the preceding claims, wherein clavulanic acid or a pharmaceutically acceptable salt thereof used in said formulations is potassium clavulanate.
16. A process to prepare formulations according to any of the preceding claims, wherein
15 cefixime and potassium clavulanate are formulated together and/or separately and compressed as single and/or double layered tablets.
17. A process according to claim 16, wherein formulation process may comprise one or more known methods such as dry and/or wet granulation, dry blending, mixing and compacting.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2014/000041

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/424 A61K31/545
ADD.

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)
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 practicable, search terms used)

EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SANDIP KUMER MANGAL BHAI PATEL ET AL: "Formulation, development and evaluation of film coated tablet containing Cefixime and Potassium clavulanate", JOURNAL OF PHARMACY RESEARCH, ASSOCIATION OF PHARMACEUTICAL INNOVATORS, INDIA, vol. 4, no. 6, 11 June 2011 (2011-06-11), pages 1861-1863, XP002698642, ISSN: 0974-6943 abstract table 1	1-17
X	----- WO 2011/142730 A1 (BILGIC MAHMUT [TR]) 17 November 2011 (2011-11-17) page 5, paragraph 3-6 example 1 claim 1 ----- -/--	1-17

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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"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

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"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/093822 A1 (BILGIC MAHMUT [TR]) 4 August 2011 (2011-08-04) example 1 claim 1	1-17
X	----- WO 2012/131690 A1 (AGGARWAL KUMAR VIJAY [IN]; GOEL SANJEEV [IN]; MISHRA UMAKANT [IN]) 4 October 2012 (2012-10-04) claim 1 -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/TR2014/000041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011142730 A1	17-11-2011	EP 2568957 A1 WO 2011142730 A1	20-03-2013 17-11-2011
WO 2011093822 A1	04-08-2011	EP 2528586 A1 TR 201000687 A1 WO 2011093822 A1 WO 2011093829 A1	05-12-2012 22-08-2011 04-08-2011 04-08-2011
WO 2012131690 A1	04-10-2012	NONE	