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(54) Title: TABLET FORMULATIONS COMPRISING CEFUROXIME

(57) Abstract: The present invention relates to pharmaceutical tablet formulations comprising cefuroxime to be used for upper respiratory tract infections such as otorhinolaryngological infections, otitis media, sinusitis, tonsillitis, pharyngitis; lower respiratory tract infections such as cystitis and urethritis; skin and soft tissue infections such as furuncle, pyoderma, impetigo; in the treatment of gonorrhea and lyme diseases caused by gram positive and gram negative bacteria.

TABLET FORMULATIONS COMPRISING CEFUROXIME

The present invention relates to pharmaceutical tablet formulations comprising cefuroxime to be used in the treatment of upper respiratory tract infections such as otorhinolaryngological infections, otitis media, sinusitis, tonsillitis, pharyngitis; lower respiratory tract infections such as cystitis and urethritis; and skin and soft tissue infections such as furuncle, pyoderma, impetigo; gonorrhea and lyme diseases caused by gram positive and gram negative bacteria.

Cefuroxime was first disclosed with the patent application numbered US3974153. In said document, cefuroxime was indicated to be effective in use for upper respiratory tract infections such as otorhinolaryngological infections, otitis media, sinusitis, tonsillitis, pharyngitis; lower respiratory tract infections such as cystitis and urethritis; and skin and soft tissue infections such as furuncle, pyoderma, impetigo; in the treatment of gonorrhea and lyme diseases caused by gram positive and gram negative bacteria.

Cefuroxime physically appears in the forms of suspension and 100-5000 mg tablets on the market.

In the sense of pharmaceutical technology, physical properties of dosage form for every type of tablet dosage form are directly related to durability in storage conditions; dissolution and bioavailability of the dosage form obtained.

Tablet hardness is an important physical parameter in pharmaceutical tablet formulations and is related to resistance of tablets to storage, transport, coating and erosion-breakage before usage. Tablets with low hardness are more exposed to erosion, friability or breakage and this case leads;

I. To loss of active agent and thus decrease of the amount of dose taken;
II. To erosion of tablet surface during coating process and to dosage forms which have uneven surfaces and variable amounts of active agent in the final product while producing coated tablet forms.

On the other hand, there is a close connection between tablet hardness and dispersibility and solubility of a tablet. Tablets that are too hard do not disperse or dissolve adequately; in this case, bioavailability of said dosage forms will decrease and therefore the time for desired biological response to occur will extend. The same case is also true for all types of tablets

such as effervescent, film-coated, soluble, extended-release, modified-release, delayed-release tablets etc.

Attaining appropriate tablet hardness is influenced by many parameters such as the types of active agents and excipients used, particle sizes thereof, flowability of the powder or granules prepared for tablet compressing and tablet compression force.

When all of these parameters are considered, hardness value of tablets are aimed to be so low as to quickly disintegrate in the stomach but so high as to preserve tablet uniformity during packaging, carrying and storing phases from the time of production until used by patient.

As a result of the development studies conducted on pharmaceutical tablet formulations, the inventors have found that the most perfect mechanical tablet resistance, the most appropriate dissolution rate and accordingly the highest bioavailability are attained with the tablet formulations that have a tablet hardness value between 3 kP and 50 kP.

According to this, another characteristic of the tablet formulations of the present invention is that said tablet formulations comprise cefuroxime as active agent and at least one pharmaceutically acceptable excipient, and the value of tablet hardness is between 3 kP and 50 kP.

Another characteristic of the tablet formulations of the present invention is that said tablet formulations comprise cefuroxime as active agent and at least one pharmaceutically acceptable excipient, and the value of tablet hardness is between 4 kP and 40 kP.

Another characteristic of the tablet formulations of the present invention is that said tablet formulations comprise cefuroxime as active agent and at least one pharmaceutically acceptable excipient, and the value of tablet hardness is between 5 kP and 30 kP.

The word "tablet" used throughout the text refers to tablet types such as tablet, effervescent tablet, film-coated tablet, enteric-coated tablet, orodispersible tablet, water-soluble tablet, extended-release tablet, modified-release tablet, delayed-release tablet.

Cefuroxime comprised in the pharmaceutical formulations of the present invention can be in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations thereof in terms of chemical structure; and in crystalline, amorphous forms or combinations thereof in terms of polymorphic structure. The active agent cefuroxime is preferably in the form of cefuroxime axetil.

The pharmaceutical formulations of the present invention comprise at least one pharmaceutically acceptable excipient selected from the group comprising disintegrant, diluent, lubricant, glidant, binder, effervescent couple composed of at least one effervescent acid and at least one effervescent base, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent.

The diluent that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol or combinations thereof.

The lubricant that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising calcium stearate, magnesium stearate, polythylene glycol, sodium benzoate, potassium benzoate, sodium lauryl sulphate, talc, stearic acid, zinc stearate or combinations thereof.

The glidant that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising tribasic calcium phosphate, colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, talc or combinations thereof.

The binder that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising carboxymethyl cellulose sodium, ethyl cellulose, gelatin, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminum silicate, maltodextrin, methyl cellulose, povidone, starch or combinations thereof.

The effervescent acids that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising organic acids such as malic acid, citric acid, tartaric acid, fumaric acid; and said effervescent bases can selected from a group comprising agents such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or combinations thereof.

The pH regulating agent that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising citrate, phosphate, carbonate, tartrate, fumarate, acetate and amino acid salts or combinations thereof.

The surfactant that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising sodium lauryl sulphate, polysorbate, polyoxyethylene, polyoxypropylene glycol or combinations thereof.

The sweetener and/or the taste regulating agent that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising acesulfame, aspartame, dextrose, fructose, maltitol, maltose, mannitol, saccharine, saccharine sodium, sodium cyclamate, sorbitol, sucralose, sucrose, xylitol, sodium chloride or combinations thereof.

The flavoring agent that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising flavors such as menthol, lemon, orange, vanilla, strawberry, raspberry, caramel, and the like or combinations thereof.

The solvents that can be used in the pharmaceutical formulations of the invention can be selected from a group comprising ethyl alcohol, methyl alcohol, propyl alcohol, benzene, toluene, acetone, deionized water or combinations thereof.

The pharmaceutical formulations of the invention comprising cefuroxime as active agent comprise cefuroxime in the range of 0.1-99.9%, preferably in the range of 1-99%, more preferably in the range of 5-95% by weight.

The pharmaceutical formulations of the invention comprising cefuroxime as active agent can optionally comprise a second active agent in addition to cefuroxime. The second active agent can be selected from a group comprising antacid, anticholinergic, antispazmodic, antiemetic, antidiabetic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral, antineoplastic, antiarithmic, antiadrenergic, antiepileptic, anti-parkinson, antiprotozoal, anthelmintic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, tiazolidinedione, biguanide, immunostimulant, immunosuppressant, muscle relaxant, analgesic, psycholeptic, psychoanaleptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamins and minerals, vitamin A, vitamin D and its analogues, vitamin B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

The pharmaceutical tablet formulations of the invention comprising cefuroxime as active agent preferably comprise clavulanic acid as an optional second active agent.

Said tablet formulations can optionally be treated with film-coating agents, for instance sugar-based coating agents, water-soluble film-coating agents, enteric coating agents, coating agents prepared to provide various release properties (such as fast release, slow release, controlled release) or coating compositions comprising any combination thereof.

As sugar-based coating agent, saccharose can be used on its own or optionally with any of the agents such as talc, calcium carbonate, calcium phosphate, calcium sulphate, gelatin, gum arabic, polyvinylpyrrolidone and pullulan or any combination thereof.

The water-soluble film-coating agents can be selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose; synthetic polymers such as polyvinyl acetal diethyl aminoacetate, aminoalkyl methacrylate copolymers and polyvinylpyrrolidone and polysaccharides such as pullulan; or combinations thereof.

The enteric coating agents can be selected from cellulose derivatives such as hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose, cellulose acetate phthalate; acrylic acid derivatives such as methacrylic acid copolymer L, methacrylic acid copolymer LD and methacrylic acid copolymer S; and natural substances such as shellac; or combinations thereof.

When the tablet formulations of the invention are desired to be coated so as to provide a release property such as fast, slow or controlled release, release rate determining polymers that can be comprised in coating composition or pharmaceutical tablet composition can be selected from a group comprising pH dependent polymers, pH independent polymers, swellable polymers, non-swellable polymers, hydrophilic polymers, hydrophobic polymers, and/or one or more hydrophobic substances, sodium alginate, polyactides, polyglycolides, polyactide-co-glycolides, polyactic acids, polyglycolic acids, polyactic acid-co-glycolic acids, polycaprolactone, polycarbonates, polyesteramides, polyanhydrides, polyamino acids, polyorthoesters, polyacetyls, polycyanoacrylates, polyetheresters, polydioxanones, polyalkylene alkylates, polyethylene glycol and polyorthoester copolymers, biodegradable polyurethanes, hydrogels, mixtures and copolymers thereof, high molecular weight water-soluble polymers such as polyethylene oxide, ionic polymers such as carbomer, calcium

carboxy methyl cellulose or carboxy methyl cellulose; non-ionic polymers such as hydroxy propyl methyl cellulose; natural or synthetic polysaccharides such as alkyl celluloses, hydroxy alkyl celluloses, cellulose ethers, nitro cellulose, dextrine, agar, carrageenan, pectin, starch and starch derivatives or mixtures thereof; hydropiylic polysaccharide polimers such as xanthan gum, chitosan; polyvinyls such as cellulosic polymers, methacrylate polymers, methacrylate copolymers, polyvinyl pyrrolidone, polyvinylpyrrolidone- polyvinyl acetate copolymers, polyvinyl alcohol; natural resins such as polyacrylic acids, alginates, gelatin, guar gum; ethyl cellulose, cellulose acetate, cellulose propionate (with high, medium or low molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, polyvinyl acetate, polyvinyl chloride, sodium bicarbonate or combinations thereof.

The preparation method of the formulations of the invention comprises formulating the active agent with an appropriate excipient composition and compressing said formulation in the form of tablets under an appropriate compression force.

A characteristic of the tablet formulations of the present invention is that said tablet formulations comprise cefuroxime as active agent, at least one pharmaceutically acceptable excipient and the tablet compression force used for compressing said formulations in the form of tablets is between 3 kN and 50 kN.

A characteristic feature of the tablet formulations of the present invention is that said tablet formulations comprise cefuroxime as active agent, at least one pharmaceutically acceptable excipient and the tablet compression force used for compressing said formulations in the form of tablets is between 4 kN and 45 kN.

Another characteristic of the tablet formulations of the present invention is that said tablet formulations comprise cefuroxime as active agent, at least one pharmaceutically acceptable excipient and the tablet compression power used for compressing said formulations in the form of tablets is between 5 kN and 40 kN.

The tablet formulations of the invention can be produced in accordance with any of the production methods given below;

1. Mixing cefuroxime as active agent with, if present, the second active agent homogenously and, when necessary, adding at least one of the excipients stated above, treating the mixture optionally with at least one pharmaceutically acceptable lubricant,

compressing this mixture in the form of tablets under an appropriate compression force according to the invention,

2. Wet-granulating the mixture obtained by mixing cefuroxime as active agent with, if present, the second active agent homogenously and, when necessary, adding at least one of the excipients stated above with the granulation solution optionally comprising at least one excipient; drying the obtained granules; treating the mixture optionally with at least one pharmaceutically acceptable lubricant and compressing the granules in the form of tablets under an appropriate compression force according to the invention,
3. Wet-granulating at least one of the excipients stated above with the granulation solution optionally comprising at least one excipient; drying obtained granules; adding cefuroxime and, if present, the second active agent and optionally at least one excipient to the dry granules and mixing them together; treating the granules optionally with at least one pharmaceutically acceptable lubricant and compressing the granules in the form of tablets under an appropriate compression force according to the invention,
4. Dry-granulating the mixture obtained by mixing cefuroxime as active agent with, if present, the second active agent homogenously and, when necessary, adding at least one of the excipients stated above and compressing the obtained granules in the form of tablets under an appropriate compression force according to the invention,
5. In the case that two active agents are used, the production can be made through a method composed of using any of said methods above separately for active agent compositions and combining the obtained formulations together.

The pharmaceutical composition of the invention can be used for upper respiratory tract infections such as otorhinolaryngological infections, otitis media, sinusitis, tonsillitis, pharyngitis; lower respiratory tract infections such as pyelonephritis, cystitis and urethritis; skin and soft tissue infections such as furuncle, pyoderma, impetigo; in the prophylaxis and treatment of gonorrhea and lyme diseases caused by gram positive and gram negative bacteria.

The examples below are given to explain the pharmaceutical compositions of the invention and the preparation methods thereof; the scope of the invention cannot be limited to these examples.

EXAMPLE

1. Film-Coated Tablet Formulation

	Amount % in unit dose
Cefuroxime axetil	64 %
Diluent	18 %
Disintegrant	10 %
Binder	2.5 %
Glidant	3.5 %
Coating agent	2 %

The production method to be applied for the tablet formulations to be prepared according to the formulation given above is as follows;

1. Dry-mixing cefuroxime axetil, diluent, sweetener and disintegrant,
2. Wet granulating the mixture with the granulation solution composed of solvent and binder,
3. Drying the granules and treating them with glidant and coating them with a solution comprising coating agent,
4. Compressing the obtained mixture in the form of tablets under a compression force of 15 kN.

CLAIMS

1. A pharmaceutical tablet formulation comprising cefuroxime as active agent with at least one pharmaceutically acceptable excipient, characterized in that
   - tablet hardness value of said tablet formulation is between 3 and 50 kP.
   - tablet compression force used for tablet compression is between 3 and 50 kN.
2. The pharmaceutical tablet formulation according to claim 1, characterized in that tablet hardness value of said tablet formulation is between 4 and 40 kP.
3. The pharmaceutical tablet formulation according to claims 1 and 2, characterized in that tablet hardness value of said tablet formulation is between 5 and 30 kP.
4. The pharmaceutical tablet formulation according to claims 1-3, characterized in that the tablet compression force used for tablet compression is between 4 and 45 kN.
5. The pharmaceutical tablet formulation according to claims 1-4, characterized in that the tablet compression power used for tablet compression is between 5 and 40 kN.
6. The pharmaceutical tablet formulation according to any of the preceding claims, characterized in that said tablet formulation is in the form of any of tablet, effervescent tablet, film-coated tablet, enteric-coated tablet, orodispersible tablet, water-soluble tablet, extended-release tablet, modified-release tablet, delayed-release tablet dosage forms.
7. The pharmaceutical tablet formulation according to any of the preceding claims, characterized in that cefuroxime is in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations thereof in terms of chemical structure; and in amorphous or crystalline forms or combinations thereof in terms of polymorphic structure.
8. The pharmaceutical tablet formulation according to claim 7, characterized in that cefuroxime is in the form of pharmaceutically acceptable cefuroxime axetil.
9. The pharmaceutical tablet formulation according to any of the preceding claims, characterized in that at least one pharmaceutically acceptable excipient to be used with cefuroxime is selected from the group comprising diluent, lubricant, glidant, binder, effervescent couple composed of at least one effervescent acid and at least one effervescent base, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent.

10. The pharmaceutical tablet formulation according to any of the preceding claims, characterized in that said tablet formulation comprises cefuroxime in the range of 0.1-99.9% by weight.

11. The pharmaceutical tablet formulation according to any of the preceding claims, characterized in that said tablet formulation comprises cefuroxime in the range of 1-99% by weight.

12. The pharmaceutical tablet formulation according to any of the preceding claims, characterized in that said tablet formulation comprises cefuroxime in the range of 5-95% by weight.

13. The pharmaceutical tablet formulation according to any of the preceding claims, characterized in that said tablet formulation comprises at least a second active agent, in addition to cefuroxime, selected from a group comprising antacid, anticholinergic, antispazmodic, antiemetic, antidiabetic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral, antineoplastic, antiarithmic, antiadrenergic, antiepileptic, anti-parkinson, antiprotozoal, anthelmintic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, tiazolidinedione, biguanide, immunostimulant, immunosuppressant, muscle relaxant, analgesic, psycholeptic, psychoanaleptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamins and minerals, vitamin A, vitamin D and its analogues, vitamin B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000018

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 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, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 342 470 A1 (PHARMATHEN SA [GR] ORBUS PHARMA INC [CA]) 10 September 2003 (2003-09-10)	1-12
Y	example 2 claims 1-14	13

X	US 2005/079213 A1 (TAN MA TERESA Y [PH] ET AL) 14 April 2005 (2005-04-14)	1-12
Y	examples 3,4	13

X	WO 2005/018618 A1 (KOREA UNITED PHARM INC [KR]; YANG GEUN-WOO [KR]; GIL YOUNG-SIG [KR]; H) 3 March 2005 (2005-03-03)	1-12
Y	examples	13

X,P	EP 2 510 922 A1 (SANOVEL ILAC SANAYI VE TICARET ANONIM SIRKETI [TR]) 17 October 2012 (2012-10-17) example	1-12

☐ 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

"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)

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2013/000018

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