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(54) Title: FORMULATIONS FOR ORAL SUSPENSIONS COMPRISING ANTIBIOTICS

(57) Abstract: The present invention is related to pharmaceutical formulations comprising cefuroxime axetil and clavulanic acid combinations. Said formulations are characterized in that they are in granule form in order to prepare suspensions.

DESCRIPTION

FORMULATIONS FOR ORAL SUSPENSIONS COMPRISING ANTIBIOTICS

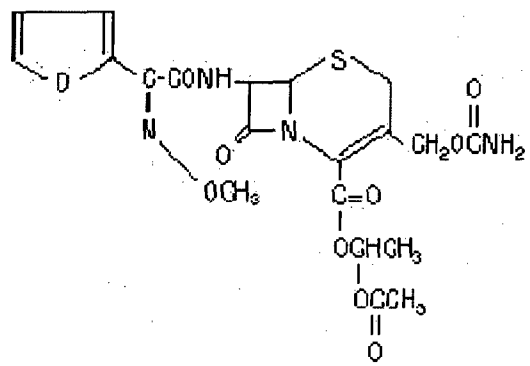
Technical Field

The present invention is related to pharmaceutical formulations comprising cefuroxime axetil and clavulanic acid combinations. Said formulations are characterized in that they are in granule form in order to prepare suspensions.

Prior Art

Cefuroxime has been described for the first time with the application numbered US3974153.

It has been described in said document that cefuroxime was effective in use when treating upper respiratory tract infections such as ear, nose, throat, otitis media, sinusitis, tonsilitis, pharyngitis, sourced from gram negative and gram positive bacteria, lower respiratory tract infections such as pyelonephritis, sistitis, urethritis, skin and soft tissue infections such as pyoderma, and impetigo, and treating diseases such as gonorrhea and lyme.



Formula I

Cefuroxime axetil shown with formula I, can be found in the market in 125mg/5ml and 250mg/5ml oral suspension, granules used to prepare oral suspension and dry powder form. Cefuroxime axetil is a second generation cephalosporin that can be used both orally and with parenteral administration. A member of this group, cefuroxime axetil, which is more active against gram negative bacteria in comparison to first generation

cephalosporin, is used in cases such as severe lower and upper respiratory tract infections, skin infections, otitis media and surgical prophylaxis. Cefuroxime axetil taken orally will be absorbed gastro intestinally and will mix with blood, however as cefuroxime axetil is low in absorption, this will negatively affect bio availability. The reason for this is that cefuroxime axetil has low solubility in water and it also has stability problems.

On the other hand in order to overcome bacterial resistance and to ensure higher antibacterial resistance, tablet forms comprising a beta lactame group cephalosporin antibiotic such as cefuroxime axetil and a beta lactame inhibitor combination such as antibiotics and clavulanic acid are being developed. However in the known state of the art the solubility and stability problems seen in cefuroxime axetil formulations are more in the forefront in tablet formulations comprising cefuroxime axetil and clavulanic acid. The reason for this is that clavulanic acid in the potassium clavulanate form has a hygroscopic structure and as a result it has a high potential for absorbing humectants. For this reason, it is observed that the solubility and stability problems due to the structure of clavulanic acid in formulations comprising cefuroxime axetil and clavulanic acid are quite high.

In the known state of the art it is known that the oral suspension forms containing cefuroxime axetil are higher in bioavailability in comparison to tablet forms and that they are more advantageous for aged patients who are having swallowing difficulty. However the fact that cefuroxime axetil has low dissolution, and that it loses its stability very quickly, leads to more important problems when preparing oral suspension dosage forms when combined with clavulanic acid having a hygroscopic structure.

The inventors, have seen in the studies they have carried out that, the formulations formulated in granule form in order to prepare a suspension comprising cefuroxime axetil and clavulanic acid had the desired viscosity and were stabilized and as a result their bioavailability was high.

The inventors have surprisingly observed that when the formations formulized in a granule form comprising cefuroxime axetil and clavulanic acid, in the case that they contained a suspending agent in the range of 0.05 to 5% by weight, their dissolution increased, they showed the desired viscosity characteristics, they mixed with blood easier and as a result they had high absorbency and bioavailability.

According to this, the first aspect of the present invention is that the formulations formulized in granule form comprising cefuroxime axetil and clavulanic acid also comprised a suspending agent in the range of 0.05 to 5% by weight.
Another characteristic of the formulations prepared suitable to the invention is that they comprise preferably 0.1% to 3%, or more preferably 0.2% to 1% of suspending agent by weight.

The inventors have observed, in the studies they have carried out that, the flow regularity at the stage of preparing formulations comprising a cefuroxime axetil and clavulanic acid combination was insufficient and that this led to negative results when providing weight and dose uniformity. In the formulation studies carried out to overcome this problem it has been observed that the desired flow regularity is obtained in the case that the ratio of cefuroxime axetil to suspending agent is in the range of 40:1 to 15:1, preferably 30:1 to 20:1 by weight; as a result it has been observed that this formulation provides the weight and dosage uniformity desired.

Accordingly another aspect of the formulation subject to the invention is that the cefuroxime axetil: suspending agent ratio is in the range of 40:1 to 15:1 and preferably 30:1 to 20:1 by weight.

The suspending agent that can be used in formulations subject to the invention can be selected from the group of gum Arabic, tragant gum, aliginic acid, carrageenan, carob gum, guar gum, xanthenes gum, gelatine, bentonite, carbomer, methyl cellulose, hydroxy ethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose.

In the formulations according to the invention, sodium carboxymethyl cellulose can be used as a suspending agent.

It is known that the particle size of the active agent used during the formulation development process effects the bioavailability provided from the suspension forms obtained and the dissolution of the granules. According to this, the inventors, have observed in their formulation improvement studies that the cefuroxime axetil's particle size used in the formulation affected the dissolution of granules, formation of agglomeration and the bioavailability provided. In this respect, in the case that cefuroxime axetil having the average particle size between 0.5-10 μm, preferably 1-5 μm is used as an active ingredient, it has been seen that the agglomeration problem of the granules are better solved.

According to this another characteristic of the formulations prepared in compliance with the present invention, is that the particle size of cefuroxime axetil used as an active ingredient is between 0.5-10 μm and preferably between 1-5 μm.

Cefuroxime axetil and clavulanic acid formulations subject to the invention can contain at least one pharmaceutically acceptable excipient in addition to the suspending agent. The pharmaceutically acceptable excipients that can be used in the formulation subject to the invention can be selected from the group of diluents, binders, lubricants, aromatic agents, colorants and sweeteners.

The diluent that can be used in the formulations according to the invention can be selected from the group of calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maktodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc and xylitol.

The binder that can be used in the formulations according to the invention can be selected from the group of ethyl cellulose, gelatine, hydroxyethyl cellulose,

hydroxymethyl cellulose, hydroxypropyl cellulose, hipromellose, magnesium aluminium silicate, methyl cellulose and povidone.

It has been explained in the known state of the art that the ratios of the excipients used in the formulation has an effect on the dissolution of the dosage form. The inventors have noticed during the studies they have carried out, that the diluent found in the formulation increased the dissolution of the granules and improved bioavailability if it is used in the range of 40:1 to 15:1, preferably 35:1 to 20:1 by weight.

According to this, another characteristic of the present invention is that the diluent-binder amount present in the formulation is in the range of 40:1 to 15:1, preferably in the range of 35:1 to 20:1 by weight.

The lubricant that can be used in formulations prepared according to the invention can be selected from the group of calcium stearate, magnesium stearate, sodium sterile fumarate, polyethylene glycol, PEG 6000, polyvinyl alcohol, potassium benzoate, and sodium benzoate.

Preferably magnesium stearate can be used as a lubricant in the formulations subject to the invention.

The colorant that can be used in formulations suitable to the invention can be selected from amount the group of titanium dioxide, chlorophyll, yellow iron oxide, other synthetic iron oxides and beta-carotene.

The sweetener in formulations subject to the invention can be selected from among the group of acesulfame potassium, aspartame, fructose, maltitol, xylitol, saccharin, sodium cyclamate, sucralose and sucrose.

The aromatic agent that can be used in formulations subject to the invention, can be selected from among the group of mint, menthol, mentane, anethole, methyl salicylate, ocalyptole, cinnamon,1-methyl acetate, sage, eugenol, lemons, oxanone, oranges, strawberries, blackberries or a mixture thereof.

In the oral suspension formulations subject to the invention, cefuroxime axetil at the amount of 5-25%, potassium clavulanate at the amount of 2-25%, diluent at the amount of 35-85%, suspending agent at the amount of 1-4%, sweetener at the amount of 0,5-4%, lubricant at the amount of 0,1-4%, aromatic agent at the amount of 0,5-4 and colorant at the amount of 0,005-0,1% by the total weight of the unit dose can be present.

The production method to prepare formulations subject to the invention can comprise the steps of, obtaining a mixture by mixing a part of cefuroxime, potassium clavulanate and lubricant, adding diluents, binders, sweeteners and a suspending agent to said mixture, obtaining granules by compacting the obtained mixture, adding aroma agent and colorant to the obtained granules and mixing said mixture, lubricating the granules with the remaining amount of the lubricant, and then obtaining the final mixture.

In the studies carried out by the inventors in order to improve a method for preparing formulations subject to the invention, the inventors have observed that when a part of the lubricant is mixed with cefuroxime and potassium clavulanate in the first step, and when the remaining part is added to the lubrication process in the last step, the flow regularity of the formulation was improved in comparison to the prior method. When the flow regularity is improved, they have realized that they can obtain uniformity easier than before in comparison to the prior production method.

Formulations subject to the invention can be used in preventing and treating upper respiratory tract infections such as ear, nose, throat, otitis media, sinusitis, tonsilitis, pharyngitis, sourced from gram negative and gram positive bacteria, lower respiratory tract infections such as pyelonephritis, sistitis, urethritis, skin and soft tissue infections such as froncle, pyoderma, and impetigo, and diseases such as gonorrhea and lyme.

Although the below mentioned examples were not given to limit the invention, they have been supplied to further describe the invention:

Example 1: Granule formulations for an oral suspension comprising a cefuroxime axetil – potassium clavulanate combination (Formulation comprising a suspending agent between the range of **0,05 - 5 %**)

Name of component	% amount inside a unit dose
Cefuroxime axetil	18
Potassium clavulanate	10,98
Diluting agent	62,5
Binder	3
Suspending agent	1,5*
Sweetener	1,5
Lubricant	1
Aroma	1,5
Colorant	0,02

* The suspending agent amount is between the limits of 0,05-5%.

In order to prepare the above mentioned formulations, first of all cefuroxime axetil, potassium clavulanate and some of the lubricant is mixed. The diluting agent, binder, sweetener and suspending agent is added to the first mixture and is mixed. The mixture obtained is compacted and granules are obtained. Aromatic agent and colorant is added and mixed to the obtained granules. Finally the mixture is lubricated with the remaining part of the lubricant; thus the final mixture is obtained.

Comparative example 1: Granule formulations for oral suspensions containing Cefuroxime axetil and potassium clavulanate combinations (**Formulation containing more than 5% suspending agent)**

Name of component	% amount inside a unit dose
Cefuroxime axetil	18
Potassium clavulanate	10,98
Diluting agent	58

Binder	3
Suspending agent	6*
Sweetener	1,5
Lubricant	1
Aroma	1,5
Colorant	0,02

* The suspending agent amount is between the limits of 0,05-5%.

In order to prepare the above mentioned formulation first of all a part of cefuroxime axetil, potassium clavulanate and lubricant is mixed. Diluent, binder, sweetener and suspending agent is added to the mixture and mixed. The obtained mixture is compacted and granules are obtained. Aromatic agents, colorant is added to the granules and mixed. Finally the mixture is lubricated with the remaining part of the lubricant and the final mixture is obtained.

Table I. Mixing the dissolution speed of granule formulations for oral suspensions containing a combination of Cefuroxime axetil and potassium clavulanate.

	Cefuroxime axetil		**Potassium Clavulanate**	
	Time (min)	**% Dissolution**	**Time**	**% Dissolution**
Sample 1	10	82	10	92
	20	91	20	95
	30	94	30	96
Comparative example 1	10	78	10	92
	20	86	20	93
	30	89	30	93

The inventors have compared the dissolution speed of granules obtained with formulations which have not been prepared according to the present invention described in the comparative example 1 in their studies and the dissolution speed of granules obtained with formulations prepared according to the present invention in example 1.

The data obtained as a result of this comparison has been shown in Table 1 above. According to these results, the dissolution speed of the granules in example 1 prepared according to the formulations subject to the invention is higher than the dissolution speed of the granules which are not suitable to the formulations subject to the invention according to example 1. It has been observed that according to this, the clavulanic acid granules and cefuroxime axetil used for the preparation of a suspension containing a suspending agent at the rate of 0.05 to 5% by weight had the desired viscosity and dissolution speed and as a result it has been observed that absorbance and bioavailability also increased.

CLAIMS

1. A formulation which has a granule form in order to prepare an acid comprising clavulanic acid and cefuroxime axetil characterized in that it comprises a suspending agent at the rate of 0.05% to 5% by weight.

2. A formulation according to claim 1, characterized in that it comprises a suspending agent at the amount of 0.1 to 3% by weight.

3. A formulation according to claims 1 to 2, characterized in that it comprises a suspending agent at the amount of 0.2 to 1% by weight.

4. A formulation according to claims 1 to 3, characterized in that the cefuroxime axetil: suspending agent ratio in the formulation is in the range of 40:1 to 15:1 by weight.

5. A formulation according to claim 4, characterized in that the rate of cefuroxime axetil: suspending agent ratio in the formulation is in the range of 30:1 to 20:1.

6. A formulation according to claims 1 to 5, characterized in that, the suspending agent used in the formulation can be selected from among the group of gum Arabic, tragant gum, aliginic acid, carrageenan, carob gum, guar gum, xanthenes gum, gelatine, bentonite, carbomer, methyl cellulose, hydroxy ethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose.

7. A formulation according to 6, characterized in that the suspending agent used inside the formulation is sodium carboxymethylcellulose.

8. A formulation according to claims 1 to 7, characterized in that the cefuroxime axetil used in the formulation has an average particle size between 0.5-10 μm.

9. A formulation according to any of the preceding claims, characterized in that the pharmaceutically acceptable excipients that can be used in the formulation can be selected from the group of diluent, binder, lubricant, aromatic agent, colorant, and sweetener.

10. A formulation according to claim 9, characterized in that; the diluent is selected from among the group of calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maktodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc and xylitol.

11. A formulation according to claim 9, characterized in that the binder is selected from among the group of ethyl cellulose, gelatine, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hipromellose, magnesium aluminium silicate, methyl cellulose and povidone.

12. A formulation according to claim 9 to 11, characterized in that the diluent: binder ratio within the formulation is in the range of 40:1 to 15:1 by weight.

13. A formulation according to claim 9, characterized in that, the lubricant is selected from the group of calcium stearate, magnesium stearate, sodium sterile fumarate, polyethylene glycol, PEG 6000, polyvinyl alcohol, potassium benzoate, and sodium benzoate.

14. A formulation according to claim 9, characterized in that, the colorant is selected from among the group of titanium dioxide, chlorophyll, yellow iron oxide, other synthetic iron oxides and beta-carotene.

15. A formulation according to claim 9, characterized in that, the sweetener is selected from among the group of acesulfame potassium, aspartame, fructose, maltitol, xylitol, saccharin, sodium cyclamate, sucralose and sucrose.

16. A formulation according to claim 9, characterized in that, the aromatic agent is selected from among the group of mint, menthol, mentane, anethole, methyl salicylate, ocalyptole, cinnamon,1-methyl acetate, sage, eugenol, lemons, oxanone, oranges, strawberries, blackberries or a mixture thereof.

17. A formulation according to any of the preceding claims, characterized in that said formulation can comprise cefuroxime axetil at the amount of 5-25%, potassium clavulanate at the amount of 2-25%, diluent at the amount of 35-85%, suspending agent at the amount of 1-4%, sweetener at the amount of 0,5-4%, lubricant at the amount of 0,1-4%, aromatic agent at the amount of 0,5-4 and colorant at the amount of 0,005-0,1% by the total weight of the unit dose.

18. A method for producing the formulation according to any of the preceding claims, characterized in that; it comprises the steps of:

- obtaining a mixture by mixing a part of cefuroxime, potassium clavulanate and lubricant,
- adding diluents, binders, sweeteners and a suspending agent to said mixture,

- obtaining granules by compacting the obtained mixture,
- adding an aroma agent and colorant to the obtained granules and mixing said mixture,
- lubricating the granules with the remaining amount of the lubricant, and then
- obtaining the final mixture.

19. A method according to claim 18, characterized in that in the first step of said method used to prepare the formulation, a part of the lubricant is mixed with cefuroxime and potassium clavulanate and in the final step the remaining amount of the lubricant is added into the lubricating process.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K31/424 A61K31/546 A61K45/06
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2011/152806 A1 (BILGIC MAHMUT [TR]) 8 December 2011 (2011-12-08)	1-6,9-17
Y	page 5, last paragraph; example 3	7,8,18, 19

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Y	example 39	7,8,18, 19

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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

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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

"&" document member of the same patent family

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

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PCT/TR2013/000328

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KITTIPONGPATANA O S ET AL: "Development of suspending agent from sodium carboxymethyl mungbean starches", DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 32, no. 7, 1 August 2006 (2006-08-01) , pages 809-820, XP009088270, ISSN: 0363-9045, DOI: 10.1080/03639040500529978 page 818, left-hand column, last paragraph -----	7
Y	WO 98/35672 A1 (SMITHKLINE BEECHAM LAB [FR]; SMITHKLINE BEECHAM SA [ES]; SMITHKLINE BE) 20 August 1998 (1998-08-20) page 5, lines 19-20; examples 1,2 -----	7,8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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