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DESCRIPTION

TECHNICAL FIELD

[0001] The present invention relates to a stable pharmaceutical composition for oral administration of the antibiotic fosfomycin.

BACKGROUND ART

[0002] Fosfomycin trometamol, which chemical name is mono(2-ammonium-2-hydroxymethyl-1,3-propanediol) (2R,cis)-(3-methyloxiranyl)phosphonate, is an antibiotic indicated in the prophylaxis and treatment of uncomplicated acute infections of the lower urinary tract.

[0003] There are some fosfomycin trometamol pharmaceutical compositions for oral administration disclosed in the state of the art.

[0004] The Spanish patent application ES495870 (Zambon, S.p.a.) describes a composition for oral administration in form of sachets containing fosfomycin trometamol, sodium carboxymethylcellulose, lactose, titanium dioxide, orange flavour and sucrose. The sucrose content in this composition, depending on the active substance dosage, changes between 56 and 76 % expressed by weight over the composition total weight.

[0005] Another Spanish patent application, ES2020790 (Zambon Group, S.p.a.), discloses a granulated containing fosfomycin trometamol, saccharine, flavour and sucrose. The sucrose content in this composition comprises 28 % expressed by weight over the composition total weight.

[0006] The Spanish patent application ES2224869 (Zambon Group, S.p.a.) discloses the use of certain basic compounds to stabilize a fosfomycin trometamol pharmaceutical composition. Some compositions described in the examples also mention the use of between 16 % and 22 % of sucrose expressed by weight over the composition total weight.

[0007] The Spanish patent application ES2244333 (Simbec Ibérica, S.L.) discloses a pharmaceutical preparation comprising fosfomycin trometamol, mannitol and/or xylitol and an artificial sweetener selected from the group including acesulfame, aspartame, saccharin, alitame and/or cyclamate. The mannitol and/or xylitol content comprises between 20-40 % expressed by weight over the composition total weight.

[0008] The presence of certain sugars such as sucrose, fructose or glucose in a fosfomycin trometamol pharmaceutical composition can arise in an undesirable colouration due to the reaction between the aldehyde groups of such sugars with the trometamol amine or any other primary amino group present in the composition. Furthermore, the presence of these sugars makes the obtained pharmaceutical composition not suitable for the administration to diabetic patients.

[0009] On the other hand, it is well known in the state of the art that pharmaceutical compositions comprising a sugar derivative such as a sugar alcohol, in particular xylitol, mannitol, sorbitol or mixtures thereof, can cause intestinal problems such as an undesirable laxative effect or abdominals gases.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The present invention relates to a stable solid fosfomycin pharmaceutical composition for oral administration characterised by comprising fosfomycin trometamol, glycine, optionally other pharmaceutically acceptable excipients, and it is substantially free from sugars and sugar alcohols such as sucrose, fructose, glucose, xylitol, mannitol, sorbitol or mixtures thereof.

[0011] By the term "substantially free" it is understood that the sugar or sugar alcohol content is non-existent or so low that fosfomycin pharmaceutical composition of the invention still is stable from colouration, suitable for diabetics and no cause intestinal problems.

[0012] Glycine is a neutral amino acid with a pH value between 5.9 and 6.4 according to the European Pharmacopoeia 6.0.

Glycine does not have any lateral chain; it is the unique amino acid without chiral centre.

[0013] This amino acid has a slight sweet taste that, different from other amino acids with bitter or acid taste, makes it suitable to be used as a diluent in an oral administration pharmaceutical composition. Furthermore, the absence of aldehyde groups on its structure avoids the coloration due to the Maillard reaction with amines making possible to obtain stable from coloration compositions. At the same time, a pharmaceutical composition comprising glycine does not represent any risk for diabetic patients because does not give any glycemic response, and no gastrointestinal problems such as an undesirable laxative effect or abdominal gases are arisen.

[0014] The amount of glycine can be easily determined by a person skilled in the art in order to get a fosfomycin trometamol solid oral pharmaceutical composition by known techniques usual in the state of the art. Generally, the amount of glycine presents in the fosfomycin pharmaceutical composition can comprise between 0.1% and 70 % expressed by weight over the composition total weight. Preferably, the amount of glycine comprises between 20 and 50 % by weight over the composition total weight.

[0015] Optionally, this fosfomycin trometamol pharmaceutical composition comprises one or more sweeteners to improve its palatability. Preferably, the sweetener is selected from the group including sucralose, acesulfame, aspartame, saccharine, alitame, cyclamate, neohesperidine dihydrochalcone, thaumatococcos and mixtures thereof.

[0016] More preferably, the sweetener used to improve the palatability of the pharmaceutical composition comprising fosfomycin trometamol and glycine is sucralose. This compound is between 300 and 1000 times sweeter than sucrose, does not have the aftertaste characteristic of other artificial sweeteners, is not absorbed by the organism and does not present toxicity problems.

[0017] The addition of sucralose to the pharmaceutical composition allows obtain a more pleasant taste using only a small quantity of such a sweetener. The fosfomycin trometamol and glycine pharmaceutical composition of this invention can comprise between 0.0 and 5.0 % of sucralose, preferably between 1.0 and 2.0 % expressed by weight over the composition total weight.

[0018] In a preferred embodiment, the fosfomycin pharmaceutical composition is presented in form of powder or granulates for solution. More preferably the powder or granulates for solution are contained in single dosage sachets for solution.

[0019] Optionally, the fosfomycin pharmaceutical composition further comprises one or more of pharmaceutically acceptable excipients usual in the pharmaceutical industry to obtain oral administration solid compositions, in particular to obtain pharmaceutical compositions in form of powder or granulate for solution.

[0020] Preferably these excipients are selected from the group including glidants such as calcium silicate, magnesium silicate, silicon dioxide, magnesium stearate, magnesium oxide, talc, cellulose, starch or mixtures thereof; binders such as microcrystalline cellulose, pregelatinized starch, copovidone, polyvinylpyrrolidone (povidone), hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydrogenated vegetable oil or mixtures thereof; and/or flavours such as orange, tangerine, lemon, raspberry, strawberry or coconut.

[0021] More preferably, the pharmaceutical composition of the invention further comprises silicon dioxide as glidant, polyvinylpyrrolidone as binder and lemon flavour.

[0022] The pharmaceutical composition of this invention generally contains between 1.9 and 7.5 g of fosfomycin trometamol, corresponding to 1.0 and 4.0 g of fosfomycin expressed as free acid. Preferably, the composition contains between 3.8 g and 5.6 g of fosfomycin trometamol, corresponding to 2.0 and 3.0 g of fosfomycin expressed as free acid.

[0023] The amount of the active ingredient previously mentioned corresponds to between 30 % and 99.9 % by weight over the composition total weight. Preferably, the content of fosfomycin trometamol represents between 50 % and 80 % by weight over the composition total weight.

[0024] The fosfomycin stable solid pharmaceutical composition for oral administration of this invention can be used for the manufacture of a medicament for the treatment or prophylaxis of uncomplicated acute infections of the lower urinary tract.

[0025] Furthermore, the fosfomycin stable solid pharmaceutical composition for oral administration of this invention can be used for the treatment or prophylaxis of uncomplicated acute infections of the lower urinary tract.

[0026] The fosfomycin pharmaceutical composition to this invention can be obtained by methods widely known by the person skilled in the art, in particular by mixing and/or granulation methods.

EXAMPLE: Powder or granulate for solution

[0027] The components are homogeneously mixed and, optionally, granulated by known techniques usual in the state of the art. The solid obtained is dosed in sachets containing the quantity equivalent to 2.0 g or 3.0 g of fosfomycin in acid form.

Fosfomycin trometamol	63 %
Glycine	32 %
Sucralose	1.3 %
Lemon flavour	1.4 %
Silicon dioxide	0.1 %
Polyvinylpyrrolidone	2.2 %
Total	100 %

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- [ES495870 \[0004\]](#)
- [ES2020790 \[0005\]](#)
- [ES2224869 \[0006\]](#)
- [ES2244333 \[0007\]](#)

Patentkrav

1. Stabil fast farmaceutisk fosfomycinsammensætning til oral administration

kendetegnet ved at omfatte

a) fosfomycintrometamol,

5 b) glycin og

c) eventuelt andre farmaceutisk acceptable excipienser,

og hvor indholdet af sukkere og sukkeralkoholer valgt fra saccharose, fructose, glucose, xylitol, mannitol, sorbitol og blandinger deraf i sammensætningen er ikke-eksisterende eller så lav at den farmaceutiske fosfomycinsammensætning
10 stadig er stabil fra farvning, egnet til diabetikere og ikke forårsager intestinale problemer.

2. Farmaceutisk sammensætning ifølge krav 1, **kendetegnet ved** yderligere at omfatte mindst en farmaceutisk acceptabel sødemiddel.

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3. Farmaceutisk sammensætning ifølge krav 2, **kendetegnet ved at** sødemidlet er valgt fra gruppen bestående af sucralose, acesulfam, aspartam, saccharin, alitam, cyclamat, neohesperidin-dihydrochalcon, thaumatococcus og blandinger deraf.

20 **4.** Farmaceutisk sammensætning ifølge krav 3, **kendetegnet ved at** sødemidlet er sucralose.

5. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav, **kendetegnet ved** at omfatte andre farmaceutisk acceptable excipienser
25 såsom glittemidler, bindemidler, smagsstoffer eller blandinger deraf.

6. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav, **kendetegnet ved** at omfatte, udtrykt ved vægt over sammensætningens totalvægt:

30 a) mellem 30% og 99,9% fosfomycintrometamol,

b) mellem 0,1 og 70% glycin, og

c) eventuelt andre farmaceutisk acceptable excipienser i en tilstrækkelig mængde til at fuldende de 100% af sammensætningens totalvægt.

5 **7.** Farmaceutisk sammensætning ifølge krav 6, **kendetegnet ved** at omfatte, udtrykt ved vægt over sammensætningens totalvægt:

a) ca. 63% fosfomycintrometamol,

b) ca. 32% glycin, og

10 c) eventuelt andre farmaceutisk acceptable excipienser i en tilstrækkelig mængde til at fuldende de 100% af sammensætningens totalvægt.

8. Farmaceutisk sammensætning ifølge krav 6 eller 7, **kendetegnet ved** at omfatte, udtrykt ved vægt over sammensætningens totalvægt:

a) mellem 30% og 99,9% fosfomycintrometamol,

15 b) mellem 0,1 og 70% glycin,

c) mellem 0,0 og 5,0% sødemiddel, og

d) eventuelt andre farmaceutisk acceptable excipienser i en tilstrækkelig mængde til at fuldende de 100% af sammensætningens totalvægt.

20 **9.** Farmaceutisk sammensætning ifølge krav 8, **kendetegnet ved** at omfatte, udtrykt ved vægt over sammensætningens totalvægt:

a) ca. 63% fosfomycintrometamol,

b) ca. 32% glycin,

c) ca. 1,3% sucralose,

- d) ca. 0,1% siliciumdioxid,
- e) ca. 2,2% polyvinylpyrrolidon, og
- f) ca. 1,4% citronsmagsstof.

5 **10.** Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav, **kendetegnet ved** at være pulver eller granulat til opløsning.

11. Farmaceutisk sammensætning ifølge krav 10, **kendetegnet ved at** pulveret eller granulatet til opløsning er opløseligt i vand.

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12. Den stabile faste farmaceutiske fosfomycinsammensætning ifølge et hvilket som helst af de foregående krav, til anvendelse i profylakse og/eller behandling af ukomplicerede akutte infektioner i det nedre urinrør.

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