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(54) **COMPOSITION MASQUANT LE GOUT AMER D'AGENTS PHARMACEUTIQUES**

(54) **TASTE-MASKING COMPOSITION OF BITTER PHARMACEUTICAL AGENTS**

(57) A pharmaceutical composition having reduced bitterness consisting of a bitter pharmaceutical agent, a taste-masking component and a pharmaceutically acceptable carrier. The taste-masking component is an alkaline earth metal oxide, an alkaline earth metal hydroxide or an alkaline hydroxide and does not interfere with the activity of the pharmaceutical agent.

ABSTRACT

A pharmaceutical composition having reduced bitterness consisting of a bitter pharmaceutical agent, a taste-masking component and a pharmaceutically acceptable carrier. The taste-masking component is an alkaline earth metal oxide, an alkaline earth metal hydroxide or an alkaline hydroxide and does not interfere with the activity of the pharmaceutical agent.

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TASTE-MASKING COMPOSITION OF BITTER PHARMACEUTICAL AGENTS

Background of the Invention

This invention relates to new and valuable taste-masked pharmaceutical compositions containing an azalide bitter pharmaceutical agent, the compositions being capable of being chewed or imbibed without the production of a bitter taste or aftertaste.

A wide variety of active pharmaceutical agents exhibit the undesirable characteristic of bitter taste production either during or immediately after oral administration. The azalide and erythrolide antibiotics are two particularly bitter tasting classes of pharmaceutical agents, and the azalide azithromycin is among the most bitter pharmaceutical agents known.

The bitter flavor of a bitter pharmaceutical agent in a liquid suspension is inevitably detected during the drinking process or immediately after swallowing. Additionally, the bitter flavor of a bitter pharmaceutical agent in a tablet, capsule, suspension or other oral dosage form may be detected upon administration if the bittering agent is brought into contact with the taste buds as by overlong holding of the dosage form in the mouth, by inadvertent chewing of the dosage form or by some other release of the bitter pharmaceutical agent.

The administration of an oral dosage form is generally the preferred route of administration of many of the pharmaceutical agents recited hereinabove because it provides for easy, low-cost administration. However, patient

compliance can sometimes be a factor when a patient is requested to swallow a tablet, capsule or suspension. Patients give many reasons for their refusal or inability to accept the oral administration of a medicinal such as unattractive presentation, overlarge size, bad taste or simple fear that an unchewed dosage form may catch in the throat. Patients who have difficulties with oral dosage forms often exhibit a gag reflex which effectively prevents oral administration. This problem is common in, but not specific to, children.

It is therefore desirable to formulate azalide pharmaceutical agents in such a way that the above-mentioned problems are overcome. Thus chewable tablets have been developed which have been shown to increase patient compliance in both children and others who have a problem swallowing whole tablets or capsules. However, quite often an azalide pharmaceutical agent is so bitter-tasting that it cannot be tolerated when chewed, and the unpleasant taste or aftertaste imparted by the bittering agent will serve to disincline patients from self-administering the oral dosage form. There is, therefore, a need to mask the taste of azalide bitter pharmaceutical agents such that the bitter flavor is reduced or eradicated from any oral dosage form which may be required for administration.

Conventionally, sweeteners and flavorants have been used in taste-masking. These agents generally work by providing a secondary flavor to the composition which it is hoped will overwhelm any bitter flavor. This technique is

sometimes able to mask mildly bitter pharmaceuticals, but the traditional sweeteners are not effective in masking the bitter flavor of powerfully bitter pharmaceutical agents such as azithromycin.

Alternative approaches which have been used to mask the bitter flavor of certain pharmaceuticals include microencapsulating the unpleasant tasting active agent in a coating of ethyl cellulose or a mixture of ethyl cellulose and hydroxypropyl cellulose or other cellulose derivatives to provide chewable taste-masked dosage forms. These prior art products, however, suffer from the disadvantage that the polymer coating releases the active agent in an inconsistent fashion and may not provide immediate (or timely) release. Further, the use of these cellulose derivatives in and of themselves is quite often insufficient to provide adequate taste-masking of potently bitter active agents such as azithromycin.

Azithromycin is the generic (United States Adopted Names) name for 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, a broad spectrum antibiotic which has one of the most potently bitter flavors known. Azithromycin is disclosed by Kobrehel et al., U.S. Patent No. 4,517,539. Azithromycin is also known as N-methyl-11-aza-10-deoxo-10-dihydroerythromycin.

The aforementioned bitter taste of azithromycin poses a serious patient compliance problem formulated in an oral dosage form in which the bitter taste is masked or reduced. Currently, azithromycin is being marketed as a non-chewable capsule. This presents a problem for some patients,

as indicated hereinabove.

It is therefore an object of this invention to provide a method of reducing the bitterness of bitter pharmaceutical agents.

Summary of the Invention

The present invention is directed to a pharmaceutical composition having reduced bitterness comprising a pharmaceutically effective amount of an azalide that is a bitter pharmaceutical agent; an alkaline earth metal oxide that is a basic compound in an amount sufficient to reduce bitterness of the bitter pharmaceutical agent; and a pharmaceutically acceptable carrier or diluent.

A preferred group of compounds of this invention comprises the preferred compositions recited hereinabove wherein the alkaline earth metal oxide is magnesium oxide.

Especially preferred within the latter group are the compositions of this invention wherein the azalide is azithromycin or a pharmaceutically acceptable salt thereof.

Advantageously the pharmaceutical composition of this invention further comprises an aldonic acid or a pharmaceutically acceptable salt thereof. A preferred aldonic acid for use in this invention is gluconic acid and an especially preferred embodiment utilizes calcium gluconate.

This invention further embraces a method of reducing the bitterness of a bitter pharmaceutical comprising formulating the bitter pharmaceutical agent as a

pharmaceutical composition as recited hereinabove.

The taste-masked formulations of this invention are capable of being administered either as chewable tablets or as a liquid suspension. In either case, the present compositions provide the substantial benefit that the bitter taste and aftertaste of azalide bitter pharmaceutical agents, particularly azithromycin, is effectively masked such that the patient does not detect the bitter flavor. Further, the taste-masking component of the present invention does not adversely alter intended medicinal effect(s) of the pharmaceutical agent of the composition.

Detail Description of the Invention

The present invention is directed to pharmaceutical compositions having reduced bitterness comprising an azalide bitter pharmaceutical agent, an alkaline earth metal oxide as a taste-masking component and a pharmaceutically acceptable carrier or diluent. The taste-masking component may consist of the basic compound as recited hereinabove alone or in combination with an aldonic acid or a pharmaceutically acceptable salt of an aldonic acid. It is generally preferred that the taste-masking component is a combination of the basic compound and a pharmaceutically acceptable salt of an aldonic acid.

To prepare the pharmaceutical composition of the present invention is a straightforward procedure. The desired pharmaceutical agent is mixed with the taste-masking component and blended well. More specifically, the pharmaceutical agent is mixed with the basic compound selected from the group

consisting of alkaline earth metal oxides. Occasionally it will be desirable to further enhance the taste-masking effects of the composition by the addition of an aldonic acid or a pharmaceutically acceptable salt thereof.

The amount of pharmaceutical agent used will vary depending upon the dosage requirements of the particular pharmaceutical agent being utilized. Generally the amount of the pharmaceutical agent will range from about 10% of the total weight of the composition to about 90% of the total weight of the composition and preferably from about 10% to about 50%. The amount of the basic compound will vary according to the amount of bitter pharmaceutical agent utilized and the degree of bitterness of the bitter pharmaceutical agent. Generally, however, the amount of the basic compound utilized will range from about 1% of the total weight of the composition to about 25% of the total weight of the composition and preferably from about 1% to about 16%. The amount of aldonic acid (or pharmaceutically acceptable salt thereof) utilized will also depend upon the amount of the pharmaceutical agent utilized and upon the degree of bitterness of said pharmaceutical agent. Generally, the amount of aldonic acid (or pharmaceutically acceptable salt thereof) used will range from about 0% to about 25% of the total weight of the pharmaceutical composition. When used, the amount of aldonic acid (or pharmaceutically acceptable salt thereof) used will preferably be from about 5% to about 20%. Generally, the amount of basic compound required is less when used in combination with an aldonic acid (or salt

thereof) and in such cases the preferred amount of the basic compound will range from about 1% to about 10%.

The pharmaceutical composition described hereinabove is sufficient to provide the taste-masking of the azalide class of antibiotics, of which class azithromycin is a member, without forming a complex with any other substance such as a polymer.

The basic compound of the present invention is an alkaline earth metal oxide. Examples of suitable such basic compounds include, but are not limited to, such compounds as magnesium oxide, calcium oxide and the like. All of these basic compounds of the present invention are readily available.

The aldonic acids used herein are readily available derivatives of sugars such as gluconic acid, mannonic acid, galactonic acid and the like. When the aldonic acid is not readily available, the aldonic acid can be simply prepared utilizing the methods well known to one skilled in the art. Thus the readily available aldose is oxidized with either bromine in water or a weak nitric acid solution to yield the corresponding aldonic acid derivative.

The pharmaceutically acceptable salts of the aldonic acids are prepared by reacting the aldonic acid with an appropriate base, usually one equivalent, in a cosolvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, ethylenediamine, meglumine, benethamine, diethylamine,

piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In some cases, salts can be prepared by mixing a solution of the aldonic acid with a solution of a different salt of the cation (sodium ethylhexanoate, magnesium, or calcium oleate), employing a solvent in which the desired cationic salt precipitates, or can be otherwise isolated by concentration and addition of a non-solvent. Generally, the preferred aldonic acid salts, such as calcium gluconate, are readily available.

The expression "pharmaceutically acceptable salt" is intended to define such salts as the alkali metal salts (e.g. sodium and potassium), the alkaline earth metal salts (e.g. magnesium and calcium), aluminum salts, ammonium salts and salts with organic amines such as benzathine, choline, diethanolamine, ethylenediamine, meglumine, benethomine, diethylamine, piperazine, tromethamine and the like.

The bitter pharmaceutical agents of the present invention include, but are not limited to, such bitter pharmaceutical agents that belong to the azalide class of the antibiotics as azithromycin, and the like. Azithromycin may be prepared by the method recited in Bright, U.S. Patent No. 4,474,468. Azithromycin dihydrate may be prepared by the method recited in International Patent Publication No. WO89/00576.

The composition as described above provides the desired taste-masking characteristics of the present invention. To prepare the tablet or powder form (for constitution) it is often desirable to add other excipients to the above-recited composition. These excipients may include sweeteners, flavorants, binders, stabilizers, plasticizers, pigments, bulking agents and the like.

Sweeteners are sometimes used to impart a pleasant flavor to the taste-masked composition. The sweet flavor imparted by the sweeteners is not altered or reduced by the taste-masking component. The taste-masking component is specific for the taste-masking of bitter agents. Preferred sweeteners include artificial sweeteners such as aspartame, saccharin, cyclamates and the like, including mixture of aspartame and saccharin. Sometimes natural sweeteners such as sucrose, fructose, glucose, sodium glycolate and the other mono- and disaccharides are preferred. Also preferred are mixture of artificial and natural sweeteners, such as the mixture of aspartame and sucrose and other such mixtures. The sweetener comprises about 0.02% to about 75%

by weight of the tablet, depending upon the sweetener used. Of course, the amount of aspartame and saccharin used will generally be much smaller than the amount of the other sweeteners mentioned above and preferably will be less than about 5% of the weight of the tablet to be administered, when used alone.

Flavorants may also be used to improve the flavor of the composition and, as with the sweeteners, the pleasant flavor of the flavorant is not altered or reduced by the taste-masking component of the present invention. The flavorants recited hereinbelow may be used singly or in combination. Preferred flavorants include, but are not limited to, cherry, strawberry, grape, cream, vanilla, chocolate, mocha, spearmint, cola and the like. In general the total amount of flavorant required to elicit satisfactory flavoring of the composition is at most 3% by weight of the pharmaceutical composition.

Binders which may be used in the preparation of tablet forms of the present invention include such binding agents as hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethyl methylcellulose sodium and methylcellulose. The amount of binder used will be dependent upon the nature of the particular pharmaceutical agent which is being manufactured, but generally the amount of binder will not exceed 5% of the total weight of the pharmaceutical composition.

The composition may also contain a pigment which may be used to improve the appearance of the tablet since an attractive coloration imparted by a pigment can sometimes improve patient compliance. Generally the particle size of the pigments will be between five and ten micrometers, when said pigment is used. Pigments such as titanium dioxide, iron oxide and various other color pigments, including vegetable dyes, may be used. The shelf-life of light sensitive or otherwise unstable pharmaceutical agents can often be improved by the stabilizing effects of pigments and opacifiers. When pigments or opacifiers are used, it is sometimes preferred that non-ionic plasticizers such as polysorbate 60, polysorbate 80, polyvinyl pyrolidone, propylene glycol and the like be used if the use of a plasticizer is desired.

In many embodiments of this invention it may be desirable to add a diluent or bulking agent to the composition. Acceptable diluents useful in embodiments of the present invention include dextrose, sorbitol, sucrose, lactose and mannitol, urea, salts, for example potassium chloride, sodium chloride, salts of phosphate, gelatin, starch, the natural and synthetic cellulose derivative including, for example methyl-, ethyl-, propyl-, hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxypropyl methyl cellulose,

silica, polyvinyl alcohol, polyvinylpyrrolidone and stearic acid and its salts for example magnesium stearate, among others. Generally, the type and amount of diluent or bulking agent is dependent upon the physicochemical characteristics of the pharmaceutical agent being formulated. The diluent generally comprises from about 0.1% to about 95% by weight of the composition and preferably comprises between about 10% to about 35% by weight of the composition.

The preparation of the pharmaceutical composition can be accomplished by utilizing any one of a wide variety of different prior art methods well known to one of ordinary skill in the art, generally without employing extraordinary methods such as melt-granulation and heat-granulation. Preferably, the active pharmaceutical agent is mixed with the taste-masking component, sweeteners and other excipients and blended in a blender. The blend is added to a solution of a binder or bulking agent such as hydroxypropyl cellulose in water in a wet-massing apparatus (such as a Hobart* Model A200T Mixer). Generally it is preferable to add the blend to the aqueous solution in portions. Following each addition of blend, the contents are mixed thoroughly by the wet-massing apparatus until a wet-massing endpoint is achieved. The wet-massing endpoint is detected by visual examination, as is understood by one of ordinary skill in the art.

The wet-massed granulation obtained from the wet-massing step is dried and the dried blend is generally processed further by sizing the granulation through a mill and placing the sized granulation in a blender. At this point any flavorants which may be desired are added, with blending. Any other excipient which is desired but which has not already been added is generally added at this point.

After this final blend the composition is ready to be

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placed into its final dosage form. If the dosage form is simply a powder which is to be constituted into a liquid suspension by the pharmacist or other qualified person, the preparation is complete. Furthermore, the wet-massed granulation step is optional when a suspension dosage form is desired. If the final dosage form is to be a chewable tablet, the composition prepared as recited above is transferred to a tablet press (such as a Manestry* F3 Tablet Press). The size of the tablet will be determined by the amount of the pharmaceutical agent which it is desired to dispense with each dosing, and will vary depending upon the potency of the individual pharmaceutical agent. Generally, for azithromycin, the size of the tablet will be from about 250 mg to about 1500 mg and the amount of active agent present in the tablet will be from about 100 mg to about 500 mg.

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Administration of the formulations of the present invention is achieved according to the normal oral mode of administration, that is, the tablets are placed in the mouth, chewed and then swallowed. The tablets may be ground up and mixed with, placed in or sprinkled on cereal, ice cream or other foods or drinks and then ingested. Alternatively, the tablets may be swallowed whole, if preferred, without chewing or admixing. When a reconstitutable form of the composition is administered as a liquid suspension, said suspension is generally simply imbibed. Alternatively said suspension may be mixed with foods and drinks if preferred, as recited hereinabove for tablets.

The term azalide, when used herein, means any semi-synthetic erythromycin derivative containing a nitrogen atom as part of the ring system. (See, for example, Bright et al., *Journal of Antibiotics*, 1988, 41, 1029-47).

The following examples are given by way of illustration and are not to be construed as a limitation in any way of this invention, many variations of which are possible within the scope thereof.

EXAMPLE 1

Azithromycin Chewable Tablet #1

Sucrose (1433.216 g), azithromycin dihydrate (530.784 g, 13.4% of total composition), mannitol (1200 g), pregelatinized starch (200 g) and magnesium oxide (280 g, 7.0% of total composition) were placed in a blender and blended for 15 minutes. The blend was passed through a sieve and blended for another 15 minutes. To a wet massing machine's vessel was added a 10% w/w solution of hydroxypropyl cellulose (prepared by adding 40 g of hydroxypropyl cellulose to 360 g of warm (60°C) water with stirring) and the blend was added in four equal portions with the mixer operating on slow speed. After each addition, the contents were mixed thoroughly to reach a wet granulation endpoint. The wet granulated blend was transferred to polyethylene-lined trays and dried at 50°C. The dried blend was further granulated to size by passing through a mill. The granulated blend was then transferred to a blender and blended for five minutes. To the blend was added aspartame (100 g), artificial cherry flavor (32.000 g), artificial cream flavor (32.000 g) and artificial strawberry flavor (32.000 g) and the mixture was blended for ten minutes. To the blend was added magnesium stearate (120.000 g) and the mixture was further blended for five minutes. The contents of the blender were removed from the blender and compressed using a tablet press. This procedure yielded 4000 one gram tablets, each containing 125 mg of azithromycin.

EXAMPLE 2

Azithromycin Chewable Tablet #2

Azithromycin dihydrate (1619.870 g, 60% of total composition), F.D. and C. Red #40 (1.125 g), magnesium oxide (309.757 g, 11.5% of total composition), calcium gluconate (46.4160 mg, 1.7% of total composition) and sodium starch glycolate (139.248 g) were combined in an eight quart "V" blender and blended for 30 minutes. The blend was passed through a Fitzpatrick* JT Comminutor fitted with a #0 plate (0.027 inch opening) at medium speed with the hammers forward. The mixture was then returned to the blender and blended for an additional thirty minutes. The blend was transferred to an eight quart Hobart* Planetary Mixer (Model C-100) and mixed at the slow (#1) setting. During mixing, the mixture was wet massed by the addition of 450 g of hydroxypropyl cellulose solution (prepared by adding 45 g of hydroxypropyl cellulose to 405 g of warm (60°C) water with stirring). Water (108 g) was added and

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the mixture was mixed for ten minutes. An additional 85 g of water was added to the granulation to achieve the endpoint. The mixer was continued at the slow setting for an additional five minutes to granulate the mass. The wet mixture was transferred to a polyethylene-lined tray and heated at 50°C in a forced air over overnight (16 hours). The dried mass was passed through a Fitzpatrick* JT Comminutor fitted with a #2A plate (0.093 inch opening) at slow speed with the knives forward. The granulation was transferred to an eight quart "V" blender, flavors were added and the flavored granulation was blended for thirty minutes. Magnesium stearate (45 g) was added and the mixture was blended for five minutes. The mixture was compressed into tablets to achieve a final tablet weight of 750 mg ± 3%.

EXAMPLE 3

Azithromycin Suspension #1

Sucrose (1433.216 g), azithromycin dihydrate (530.784 g), mannitol (1200 g), pregelatinized starch (200 g) and magnesium oxide (280 g) were placed in a blender and blended for 15 minutes. The blend was passed through a sieve and blended for another 15 minutes. To the blend was added aspartame (100 g), artificial cherry flavor (8.000 g), artificial cream flavor (8.000 g) and artificial strawberry flavor (8.000 g) and the mixture was blended for ten minutes. To the blend was added magnesium stearate (30.000 g) and the mixture was further blended for five minutes. The contents of the blender were removed from the blender and packaged for constitution with water.

EXAMPLES 4 - 15

Using substantially the same procedure as recited in Example 1, but utilizing the differing amounts of azithromycin dihydrate and magnesium oxide recited (as percentages of the total composition) hereinbelow, the following examples were prepared.

EXAMPLE	PERCENT AZITHROMYCIN	PERCENT MgO
4	21.4	3.5
5	35.7	1.7
6	35.7	3.4
7	35.7	6.9
8	30.6	16.0
9	13.4	6.5

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10	13.4	7.5
11	26.5	7.0
12	26.5	14.0
13	31.8	6.5
14	13.1	6.5
15	13.1	1.6

EXAMPLES 16 - 29

Using substantially the same procedure as recited in Example 2, but utilizing the differing amounts of azithromycin dihydrate, magnesium oxide and calcium gluconate recited (as percentages of the total composition) hereinbelow, the following examples were prepared.

EXAMPLE	% AZITHROMYCIN	% MgO	% CaGLUCONATE
16	21.4	4.1	11.0
17	13.3	2.5	13.7
18	13.3	6.5	7.0
19	13.1	1.5	16.5
20	31.8	3.1	16.5
21	31.4	4.6	16.5
22	31.5	6.2	16.5
23	59.0	9.5	6.6
24	59.0	11.5	23.5
25	71.0	13.8	9.2
26	71.0	13.8	8.5
27	71.0	13.8	5.4
28	71.0	13.8	7.4
29	72.0	13.8	6.2

EXAMPLES 30 - 34

Azithromycin Suspension

Azithromycin was mixed with magnesium oxide and the mixture was suspended in 50 mL of water to afford an oral suspension.

EXAMPLE	AZITHROMYCIN (mg)	MgO (mg)
30	600	20.65
31	500	103
32	500	51.63
33	500	25.81
34	500	12.91

EXAMPLES 35 - 39

Azithromycin, magnesium oxide and calcium gluconate were mixed and suspended in water (50 mL) to afford an orally administrable suspension.

EXAMPLE	AZITHROMYCIN (mg)	MgO (mg)	CALCIUM GLUCONATE (mg)
35	300	15.5	165.3
36	300	65	165.3
37	300	16	165.3
38	300	35	165.3
39	300	46.5	165.3

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A pharmaceutical composition having reduced bitterness, comprising:

a pharmaceutically effective amount of an azalide;

an alkaline earth metal oxide in an amount sufficient to reduce bitterness of the azalide; and

a pharmaceutically acceptable carrier,

wherein the composition is obtained without employing a melt-granulation or heat-granulation.

2. A composition according to claim 1 wherein the alkaline earth metal oxide is magnesium oxide.

3. A composition according to claim 1 or 2, wherein the azalide is azithromycin.

4. A composition according to any one of claims 1 to 3, additionally comprising an aldonic acid or a pharmaceutically acceptable salt thereof.

5. A composition according to claim 4 wherein the aldonic acid occurs as a pharmaceutically acceptable salt.

6. A composition according to claim 5 wherein the aldonic acid salt is calcium gluconate.

7. A method of reducing the bitterness of a bitter pharmaceutical agent comprising formulating the pharmaceutical

agent as a pharmaceutical composition according to any one of claims 1 to 6, without employing a melt-granulation or heat-granulation.

8. **A pharmaceutical composition in a dosage form adapted for oral administration, which comprises:**

(a) an azalide in an amount of 10 to 90% by weight of the composition,

(b) an alkaline earth metal oxide in an amount within the range of from 1 to 25% by weight of the composition, the said amount being sufficient to reduce bitterness of the azalide, and

(c) a pharmaceutically acceptable carrier suitable for the oral administration,

wherein the azalide is present in the composition without forming a complex.

9. A composition according to claim 8, wherein the alkaline earth metal oxide is magnesium oxide.

10. A composition according to claim 8 or 9, wherein the azalide is azithromycin dihydride.

11. A composition according to claim 8, 9 or 10, which is a chewable taste-masked solid formulation.

12. A composition according to any one of claims 8 to 11, which further comprises an aldonic acid or a pharmaceutically acceptable salt thereof in an amount of up to

25% by weight of the composition.

13. A composition according to claim 12, which comprises calcium gluconate as the pharmaceutically acceptable salt.

14. A composition according to any one of claims 1 to 6 or any one of claims 8 to 13, which further comprises 0.02% to 75% (based on the composition) of a sweetener.

15. A composition according to any one of claims 1 to 6 or any one of claims 8 to 14, which further comprises a binder in an amount of up to 5% by weight based on the composition.

16. A composition according to claim 15, wherein the binder is selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethyl methylcellulose sodium and methylcellulose.

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17. A composition according to any one of claims 1 to 6, which is obtained by a method involving a wet-massing granulation.

18. A process for preparing a pharmaceutical composition which comprises a sweetener and a binder in addition to the ingredients defined in any one of claims 1 to 6, which process comprises:

blending the azalide, the alkaline earth metal oxide, the sweetener and the carrier in a blender;

adding the blend to a solution of the binder in water in a wet-massing apparatus and thoroughly mixing the resulting mixture until a wet-massing endpoint is achieved, to obtain a wet-massed granulation; and

drying and sizing the wet-massed granulation.

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