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(54) Title: LIQUID ANTACID COMPOSITIONS

(57) Abstract

Liquid antacid compositions for neutralizing stomach acid in humans and other animals comprising: (a) calcium carbonate; (b) short chain alkyl esters of p-hydroxybenzoic acid; (c) benzyl alcohol; (d) optionally, but preferably, bis-biguanide compound or a pharmaceutically-acceptable salt thereof; and (e) other excipients. These compositions are further preferably formulated to contain an elevated soluble solids content at a level which will increase the shelf stability of the composition.

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LIQUID ANTACID COMPOSITIONS

BACKGROUND OF THE INVENTION

This invention relates to novel liquid antacid compositions for neutralizing stomach acid in humans and other animals. In particular, it relates to highly efficacious antacid compositions containing calcium carbonate which are aesthetically acceptable and microbially stable.

Pharmaceutical compositions may be produced in a variety of dosage forms, depending upon the desired route of administration of the active material. Liquid suspensions are one preferred dosage form for delivery of antacid active materials which neutralize stomach acid. Liquid antacid suspensions can be generally defined as two-phase systems, wherein a finely divided antacid active, in solid form, is suspended in a liquid medium. These compositions are alkaline, with typical pH values in the range of 7.5 to 9.5.

These compositions must be microbially stable, i.e., resistant to growth of bacteria, molds, and yeast during manufacture. In addition, the compositions must be microbially stable at the time of purchase by the consumer and during the shelf life of the product.

For these reasons, liquid suspension products are typically formulated with preservatives, i.e., compounds having antimicrobial qualities designed to prevent or substantially reduce the growth of microbes in the product. Preservatives known in the art include, for example, alcohols, sorbates, quaternary ammonium compounds, benzoic acid (benzoates) and esters of p-hydroxybenzoic acid (i.e., parabens). However, the preservatives used in liquid antacid products typically impart negative aesthetic qualities to the compositions at the levels used. Such products may have very poor flavor, a chalky and/or numbing mouthfeel, and/or a significant negative after-taste. These aesthetic concerns are particularly important because they may limit consumer acceptability over periods of extended use, thereby limiting consumer compliance with proper treatment regimens.

It has been discovered by the present invention that liquid antacid compositions can be formulated which are microbially stable

and aesthetically pleasing. It is therefore an object of the present invention to provide liquid antacid compositions that are both efficacious and aesthetically pleasing to the consumer. It is also an object of the present invention to provide liquid antacid compositions that are microbially stable during the shelf life of the composition.

These and other objects of the present invention will become readily apparent from the detailed description which follows.

All percentages and ratios used herein are by weight, and all measurements are made at 25 C, unless otherwise specified.

SUMMARY OF THE INVENTION

The present invention relates to liquid antacid compositions. These compositions comprise: from about 5% to about 40% calcium carbonate; from about 0.001% to about 1% short chain alkyl esters of p-hydroxybenzoic acid; from about 0% to about 0.2% bis-biguanide compound or a pharmaceutically-acceptable salt thereof; from about 0.001% to about 5% benzyl alcohol; and from about 60% to about 95% other excipients; and wherein further for those compositions not comprising a bis-biguanide compound, the soluble solids content of the liquid antacid composition is elevated to provide a preservative effect.

The present invention compositions additionally relate to a method for neutralizing excess stomach acid. The method comprises orally administering to a human or lower animal in need of such treatment a safe and effective amount of the liquid antacid composition according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to liquid antacid compositions. These compositions comprise: (a) calcium carbonate; (b) short chain alkyl esters of p-hydroxybenzoic acid; (c) benzyl alcohol; (d) optionally, but preferably, bis-biguanide compound or a pharmaceutically-acceptable salt thereof; and (e) other excipients. These compositions are further preferably formulated to contain an elevated solids content at a level which will increase the shelf stability of the composition.

All components of the present compositions must be pharmaceutically-acceptable. As used herein, a "pharmaceutically-acceptable" component is one that is suitable for use with humans and/or other animals without undue adverse side effects (such as toxicity, irri-

tation and allergic response) commensurate with a reasonable benefit/ risk ratio. The components for use in the present compositions, and the preferred amounts to be utilized, are described in detail hereinafter.

Calcium Carbonate:

The present compositions of the invention contain a safe and effective amount of calcium carbonate as a therapeutically effective antacid active component. Calcium carbonate is effective for neutralizing stomach acid in a human or lower animal. Calcium carbonate typically comprises from about 5% to about 40%, and preferably from about 10% to about 30%, by weight of the present compositions.

Benzyl Alcohol:

The present compositions also comprise benzyl alcohol. Benzyl alcohol is described in more detail in The Merck Index, 10th Edition, published by Merck & Co., No. 1130 (1983), incorporated herein by reference in its entirety. The compositions typically comprise benzyl alcohol at a level of from about 0.001% to about 1%, and preferably from about 0.01% to about 0.5%, by weight of the compositions.

Short Chain Alkyl Esters of p-Hydroxybenzoic Acid:

The present compositions further comprise short chain alkyl esters of p-hydroxybenzoic acid, which are preservatives also known as "parabens", preferably the methyl, propyl, butyl, and ethyl esters of p-hydroxybenzoic acid. These compositions are approved by the Federal Drug Administration as antimicrobial agents for use in foods and pharmaceuticals. Propylparaben, methylparaben, and mixtures thereof are preferred for use in the present antacid compositions. These materials are described in more detail in The Merck Index, 10th Edition, published (1983) by Merck & Co.: No. 7767 ("propylparaben"), No. 5977 ("methylparaben"), No. 3781 ("ethylparaben"), and No. 1556 ("butylparaben"), all incorporated herein by reference in their entirety. These materials are preferably used at levels which reduce or eliminate the negative aesthetics of these parabens in the compositions such that the consumer cannot detect their presence in the present antacid compositions.

The invention compositions typically comprise short chain alkyl esters of p-hydroxybenzoic acid at a level of from about 0.001% to about 0.5%; preferably propylparaben at a level of from about 0.001% to about 0.1%, and methylparaben at a level of from about 0.001% to

about 0.5%, by weight of the compositions. The invention compositions more preferably comprise propylparaben at a level of from about 0.001% to about 0.05%, and methylparaben at a level of from about 0.001% to about 0.3%, by weight of the compositions.

Bis-Biguanide Compounds:

The present antacid compositions optionally, but preferably, may also contain bis-biguanide compounds or the pharmaceutically acceptable salts thereof, at a level of from about 0% to about 0.2%. Bis-biguanide compounds are described in detail in U.S. Patent No. 3,934,002, to Haefele, issued January 20, 1976 (incorporated herein by reference in its entirety).

Chlorhexidine and its pharmaceutically acceptable salts are preferred bis-biguanide compounds that are useful in the present compositions. The term "pharmaceutically acceptable salts", as used herein, means salts of the bis-biguanide compounds which have the same general properties as the compounds from which they are derived, and which are acceptable from a toxicity viewpoint. Preferred salts include the acetate, the hydrochloride, and the gluconate salts. The most preferred bis-biguanide compound is chlorhexidine gluconate. Chlorhexidine, and its gluconate salt, are commercially known and described in The Merck Index, 10th Edition, published by Merck & Co., No. 2057 (1983), incorporated herein by reference in its entirety. Chlorhexidine may be used in the present antacid compositions at a level of from about 0.0001% to about 0.005%, and preferably from about 0.0001% to about 0.002%, by weight of the composition.

Other Excipients:

The compositions of the present invention may also contain other excipients that modify the physical characteristics and/or therapeutic effects of the present compositions. The other excipients must not, however, adversely affect the antacid therapeutic efficacy of the calcium carbonate used in the compositions. The compositions typically comprise from about 60% to about 95%, preferably from about 70% to about 90%, of other excipients by weight of the compositions.

The excipents, in addition, optionally but preferably are present in the invention compositions at a level which provide an elevated soluble solids content in the composition to enhance microbial stability. Excipients useful in providing an elevated soluble solids content include, for example, glycerin, sorbitol, propylene glycol,

mannitol, glucose, sucrose, dextrose, and mixtures thereof. The elevated soluble solids preferably comprise from about 15% to about 40%, more preferably from about 20% to about 40%, by weight of the composition.

The invention compositions also preferably contain a suspension system comprising one or more compounds which maintain the calcium carbonate in an essentially uniform aqueous suspension at typical conditions of storage and use. Such suspension systems, suspension agents, and methods for their use include those well known in the art. See, for example, M. Pernarowski, "Solutions, Emulsions and Suspensions" Remington's Pharmaceutical Sciences (A. Osol, editor, 15th Edition, 1975), incorporated herein by reference. Suspension agents useful in the present compositions include xanthan gum, guar gum, cellulose gums, cellulose gum derivatives, magnesium aluminum silicate, carboxy vinyl polymers such as carbopol, and mixtures thereof. The suspension agents typically comprise from about 0.1% to about 1%, and preferably from about 0.15% to about 0.35%, by weight of the antacid compositions.

The present compositions also may contain a humectant, such as glycerin and sorbitol, which provides a benefit as a mixing aid and helps to modify the Water Activity ("Aw") of the compositions. Glycerin is preferred and commercially available in food grade quality. Glycerin typically comprises from about 1% to about 15%, and preferably from about 3% to about 10%, by weight of the antacid compositions.

A safe and effective amount of simethicone is also a preferred therapeutically active component in the present antacid compositions. Simethicone is a mixture of dimethyl polysiloxanes and silica gel suitably purified for pharmaceutical use and is therapeutically effective as an antiflatulent. Simethicone is described in more detail in The Merck Index, 10th Edition, published by Merck & Co., No. 8374 (1983), incorporated herein by reference in its entirety. The present antacid compositions typically comprise simethicone at a level of from about 0.1% to about 2%, and preferably from about 0.3% to about 1.0%, by weight of the composition.

The present compositions also most preferably comprise one or more sweetening agents. These include materials such as: water-soluble sweetening agents such as monosaccharides, disaccharides, and

polysaccharides including, for example, xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof; water-soluble artificial sweeteners such as the soluble saccharin salts, e.g., sodium or calcium saccharin salts, cyclamate salts, acesulfam-K and the like, and the free acid form of saccharin; or dipeptide based sweeteners such as L-aspartyl-L-phenylalanine methyl ester and materials described in U.S. Pat. No. 3,492,131 and the like. In general, the amount of sweetener is primarily a matter of taste preference and will vary with the sweetener selected and with the ingredients in the composition being prepared; except that as noted hereinbefore some of these materials may also be present at an elevated level to provide an elevated soluble solids content in the composition to enhance the microbial stability of the composition.

Preferred in the present compositions is a non-nutritive artificial sweetener such as saccharin, and/or a sugar component such as sucrose. Particularly preferred sweetening agents are sucrose and sorbitol. The present compositions comprise from about 5% to about 40% of one or more sweetening agents, and more preferably from about 10% to about 35% of one or more sweetening agents by weight of the antacid compositions.

Preferred other excipients useful in the invention compositions also include colorants, flavorants, other pharmaceutical actives (including other antacid agents), and/or coolants. Preferred coolants in the antacid compositions are N-ethyl-p-menthane-3-carboxamide (known commercially as "WS-3"), 3-1-menthoxypropane-1,2-diol (known commercially as "TK-10"), and mixtures thereof. These coolants are described in PCT Patent Application Publication No. WO 92-17164, to Upson et al., published October 15, 1992. TK-10 is also described in U.S. Patent 4,459,425 to Amano et al., issued July 10, 1984; and WS-3 is also described in U.S. Patent 4,136,163 to Watson et al., issued January 23, 1979. The disclosures of all three of these patent publications are incorporated by reference herein in their entirety.

The present compositions typically comprise WS-3 at a level of from about 0.001% to about 0.05%, and TK-10 at a level of from about 0.0001% to about 0.1% by weight of the composition. Colorants and flavorants preferably comprise from about 0.01% to about 1% by weight

of the composition.

The compositions of this invention may also contain during the manufacturing process antiseptic agents useful in this process as sanitization aides, but which degrade shortly after making the compositions. Typically these agents are used at levels to provide at least about 5 ppm of the agent in the composition during the manufacturing process, and preferably at a level of at least about 300 ppm. Preferred are hydrogen peroxide, chloramine, and hypochlorite and its salts (e.g., calcium; sodium; potassium). Such materials are described, for example, in Disinfection, Sterilization and Preservation 3d (S. Block ed., 1983), incorporated by reference herein.

Finally, the invention compositions also preferably contain a buffering agent. Buffering agents useful herein include, for example, citric, fumaric, malic, adipic, citric, and tartaric acids and mixtures thereof. Buffering agents typically comprise from about 0.05% to about 0.5% by weight of the present compositions.

Method of Treatment

The present invention compositions additionally relate to a method for neutralizing excess stomach acid. The method of treatment herein comprises orally administering to a human or lower animal in need of such treatment a safe and effective amount of a liquid antacid composition according to the present invention.

The term "safe and effective amount", as used herein, means a quantity of the calcium carbonate-containing liquid antacid composition sufficient to yield the desired antacid efficacy without undue adverse side effects (such as toxicity, irritation or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific safe and effective amount will, obviously, vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), and the specific formulation and optional components employed. However, a patient in need of such treatment will typically receive from about 500mg to about 8000mg of calcium carbonate daily.

The following examples further demonstrate and describe embodiments with the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as

a limitation of the present invention as many variations thereof are possible without departing from the spirit and scope.

EXAMPLE 1

Components	Weight %
USP Water	54.656
Methylparaben	0.05
Propylparaben	0.01
Xanthan Gum	0.12
Guar Gum	0.09
Calcium carbonate	12.38
Antifoam C[a)]	1.27
Sucrose	15.0
Sorbitol	11.0
Glycerin	5.0
Benzyl Alcohol	0.2
Citric Acid	0.15
Coolant	0.00888
Flavor	0.0645
Colorant	0.0014

a) 30% Simethicone sold by Dow Corning.

This composition is prepared by first mixing a portion of the glycerin and all of the benzyl alcohol and heating to 65°C, followed by slowly adding and mixing together the methylparaben and propylparaben. The resulting mixture is added with mixing to a preformed mixture of water, xanthan gum, and guar gum until a uniform mixture is obtained. Then the following ingredients are added slowly in the order: remaining glycerin, sorbitol, Antifoam C, calcium carbonate, citric acid, and sucrose. The flavors and coolants are separately combined and then slowly added to the other ingredients.

Ingestion by a person in need of antacid treatment of 1 tablespoon of this composition delivers 1950 mg of calcium carbonate effective for neutralizing the stomach acid of the person in need of the treatment.

EXAMPLE 2

Components	Weight %
USP Water	58.61
Methylparaben	0.15

Propylparaben	0.04
Xanthan Gum	0.12
Guar Gum	0.09
Calcium Carbonate	22.61
Antifoam C[a)]	2.32
Sucrose	7.5
Sorbitol	3.0
Saccharin Sodium	0.035
Glycerin	5.0
Benzyl Alcohol	0.2
Citric Acid	0.25
Flavor	0.0645
Coolant	0.00888
Chlorhexidine Gluconate	0.001
Colorant	0.0014

a) 30% Simethicone sold by Dow Corning.

Example 2 is prepared by a method similar to that described in Example 1.

Ingestion by a person in need of antacid treatment of 1 tablespoon of this composition delivers 3900 mg of calcium carbonate effective for neutralizing the stomach acid of the person in need of the treatment.

WHAT IS CLAIMED IS:

1. A liquid antacid composition comprising:
   a) from 5% to 40% calcium carbonate;
   b) from 0.001% to 1% short chain alkyl esters of p-hydroxybenzoic acid;
   c) from 0.001% to 5% benzyl alcohol;
   d) from 0% to 0.2% bis-biguanide compound or a pharmaceutically-acceptable salt thereof; and
   e) from 60% to 95% other excipients;

   and wherein further for those compositions not comprising a bis-biguanide compound, the soluble solids content of the liquid antacid composition is elevated to provide a preservative effect.

2. The composition according to Claim 1 further comprising simethicone.

3. The composition according to Claim 1 or 2 wherein the short chain alkyl esters of p-hydroxybenzoic acid are selected from the group consisting of propyl esters, methyl esters, and mixtures thereof.

4. The composition according to Claims 1-3 comprising chlorhexidine.

5. A liquid antacid composition comprising:
   a) from 10% to 30% calcium carbonate;
   b) from 0.001% to 1% short chain alkyl esters of p-hydroxybenzoic acid selected from the group consisting of methyl, propyl, butyl, and ethyl esters of p-hydroxybenzoic acid, and mixtures thereof;
   c) from 0.01% to 2% benzyl alcohol;
   d) from 0% to 0.2% bis-biguanide compound or a pharmaceutically-acceptable salt thereof; and
   e) from 70% to 90% other excipients;

   and wherein further for those compositions not comprising a bis-biguanide compound, the soluble solids content of the liquid antacid composition is elevated to provide a preservative effect.

6. The composition according to Claim 5 further comprising from 0.1% to 2% simethicone.

7. The composition according to Claim 5 or 6 wherein the short chain alkyl esters of p-hydroxybenzoic acid are selected from the group consisting of from about 0.001% to about 0.2% propyl ester, from about 0.001% to about 0.5% methyl ester, and mixtures thereof.

8. The composition according to Claims 5-7 comprising chlorhexidine gluconate.

9. A liquid antacid composition comprising:
   a) from 10% to 30% calcium carbonate;
   b) from 0.001% to 1% short chain alkyl esters of p-hydroxybenzoic acid selected from the group consisting of methyl and propyl esters of p-hydroxybenzoic acid, and mixtures thereof;
   c) from 0.01% to 2% benzyl alcohol;
   d) from 0.0001% to 0.005% chlorhexidine or a pharmaceutically-acceptable salt thereof; and
   e) from 70% to 90% other excipients;

   and wherein further the soluble solids content of the liquid antacid composition is elevated within the range of from 20% to 40% by weight of the composition to provide a preservative effect.

10. The composition according to Claim 9 wherein the excipients which are soluble solids comprise glycerin, sorbitol, propylene glycol, mannitol, glucose, sucrose, dextrose, and mixtures thereof.

11. The composition according to Claim 1-10 further comprising from about 0.1% to about 2% simethicone.

12. The composition according to Claim 1-11 comprising chlorhexidine gluconate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/04176

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/00

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)
IPC 5 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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FR,A,2 595 249 (UNIVERSITE BORDEAUX II) 11 September 1987 see the whole document	1,3-5,7, 9,10
Y	JOURNAL MONDIAL DE PHARMACIE, vol.12, no.4, October 1969 pages 321 - 29 T. J. MCCARTHY 'the influence of insoluble powders on preservatives in solution' see the whole document	1,3-5,7, 9,10
A	DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, vol.13, no.9, 1987, NEW YORK pages 1429 - 46 E. VANHAECKE, ET AL. 'A comparative study of the effectiveness of preservatives in twelve antacid suspensions' see the whole document	2,6,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
1 August 1994	5. 08. 94

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INTERNATIONAL SEARCH REPORT

information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-2595249	11-09-87	EP-A,B 0242244	21-10-87