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# ANTACID COMPOSITION AND METHOD OF USING SAME

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The present invention is concerned with an improved, orally administered, prolonged action pharmaceutical preparation. More particularly, the invention is concerned with orally administrable antacid compositions having increased effectiveness due to prolonged gastric retention periods.

The problem of administering pharmaceuticals which have a sustained or long-acting action is well known in the art. While numerous methods are known for sustaining or prolonging the action of many drug substances, available techniques for providing long lasting effectiveness of antacids used in the treatment of gastric hypercidity and ulcers have not been successful. Gastric retention times of most substances are generally not more than 1 to 1½ hours. In some instances, gastric retention times may be as low as 30 minutes. Thus, antacid compositions orally administered and passed to the stomach may reside in the stomach for very short periods of time. As a result, often the antacid agents do not have sufficient retention times in order to provide necessary beneficial effects. Further, much of the ingested dose of antacid may in effect be wasted since it may not remain in the stomach long enough to exert its full acid neutralizing ability. As a specific example, numerous antacid materials only temporarily act to neutralize the stomach acids since they are rapidly discharged from the stomach due to the gastric emptying cycle.

While the prior art has attempted to overcome these difficulties, there still exists a great demand for means for administering orally antacid preparations which have longer retention times and show prolonged effectiveness in the gastric system. The art has heretofore employed multiple dosages of ingredients as a means of overcoming this problem. This solution has obvious difficulties in terms of patient inconvenience and cost, patient forgetfulness, difficulty in administration during sleeping hours, periods of no antacid activity from difficulty in setting dosage cycle, etc. Additionally, ingredients such as antacid pills or tablets coated with substances dissolving at various rates of time are of little value since whether dissolved or not the stomach empties itself of the tablets in a relatively short interval of time and thus their degree of reaction is determined by the gastric emptying cycle rather than the solution rate of their component materials.

In accordance with the present invention, means are taught for overcoming these problems and for forming an orally administerable antacid preparation which exhibits retention times in the stomach for extended periods of time, e.q., over 2 hours. More specifically, the present orally administerable antacid preparation comprises a fatty agent selected from the group consisting of oils and fats, in combination with an antacid.

The fat and/or oil is preferably present in the compositions in amounts, types, etc., such that fat/oil has an aggregate melting point of less than 37° C.

The orally administered antacid compositions of the present invention may take any of a wide variety of forms such as suspensions, emulsions, solutions, tablets, powders, etc., and can be made by any of a number of conventional procedures. Typical formulations of the present invention are described in the examples by way of illustration. The present compositions can contain a wide variety of concentrations of ingredients denoted above. The composition should contain at least an



amount of antacid agent capable of "neutralizing" 20 milliequivalents of hydrochloric acid (200 milliliters of 0.1 N H Cl) to pH 2.5 or above in usual single human dose. This should be combined with at least 2 grams of a fatty agent. The compositions can additionally contain any of a wide variety of well known ingredients such as emulsifiers, antioxidants, binding agents, preservatives, flavors, colors, etc., as is conventional in preparations of this sort.

Examples of conventional antacids are: calcium carbonate, magnesium carbonate, magnesium trisilicate, magnesium hydroxide, aluminum hydroxide, sodium carbonate, magnesium oxide, magnesium hydroxide, sodium bicarbonate, bismuth subcarbonate, dihydroxy aluminum amino acetate, etc. The fat and/or oil component of the present invention should be non-toxic, at least partially digestable, preferably fat and oil of natural origin and especially fats and/or oils with a degree of unsaturation. Normally oily components are preferred because of their lower melting point, i.e., less than 37° C.

The terms "fats" and "oils" are employed to denote esters of higher fat acids and a trihydric alcohol and may be of natural or synthetic origin.

Examples of suitable oils and fats and/or combinations are the following: soy bean oil, safflower oil, palm oil, peanut oil, corn oil, cottonseed oil, coconut oil, sesame, cocoa butter, lard, butter fat, etc.

COMBINATIONS (HAVING AGGREGATE MELTING POINT OF LESS THAN 37° C.)

| | Percent |
|---|---|
| Fats: | |
| Beef tallow | 60 |
| Glyceryl monostearate | 20 |
| Glyceryl mono oleate | 80 |
| Propylene glycol monostearate | 20 |
| Oils: | |
| Safflower oil | 40 |
| Cottonseed oil | 80 |
| Sesame oil | 20 |
| Cottonseed oil | 30 |
| Corn oil | 90 |

The inventor has also found that $C_8^+$ fatty amines and salts of $C_8^+$ fatty amines represent entirely new antacids, and the latter in particular have nearly ideal pH characteristics.

The fatty amine components of the present invention are $C_8^+$ aliphatic hydrocarbons having reactive amino groups of neutralized amino groups. Fatty amines having fewer carbon atoms are normally toxic materials. The fatty amines of the present invention may be straight chained or branched, primary, secondary or tertiary, saturated or unsaturated, etc. Polyamines containing 2 or more primary amine groups, 2 or more secondary amines, 2 or more tertiary amine groups or combinations of primary, secondary and tertiary amino groups within a single molecule can be employed. Examples of suitable diamines include: Cetyl diamine, stearyl diamine and mixtures thereof. The fatty amines as such represent new antacid compositions and are an example where a single material is both the antacid agent and the gastric delaying fatty agent. It is particularly preferred that the fatty amines contain at least one amine group per 30, preferably per 20, carbon atoms and $C_8$ to $C_{22}$ fatty amines are particularly desirable.

Examples of suitable fatty amines are the following:

Saturated—primary—straight chain: cetyl, stearyl, lauryl, myristyl, behenyl amines.

Unsaturated—primary—straight chain (1 double bond): lauroleyl, myristoleyl, palmitoleyl, eracyl amines.

Unsaturated—primary—straight chain (2 or more double bonds): linoleyl, linolenyl amine.

Saturated—secondary—straight chain: dioctyl amine, didecyl amine.

Saturated—primary branched: 3 ethyl-lauryl amine, 3 ethyl, 3 methyl cetyl amine.

Saturated—secondary—branched: diisooctyl amine.

Saturated—teritary—amine: methyl ethyl stearyl amine.

Unsaturated secondary amine: methyl linoleyl amine.

Also useable will be mixtures of amines which are prepared from naturally occurring fats and oils. These fats and oils are generally mixtures of materials of varying composition. Thus, the alkyl chain in the fatty amines will correspond to those of the natural fat from which they are derived. For example:

APPROXIMATE COMPOSITION (PERCENT OF EACH CHAIN LENGTH)

| | $C_8$ | $C_{10}$ | $C_{12}$ | $C_{14}$ | $C_{16}$ | $C_{18}$ | |
|---|---|---|---|---|---|---|---|
| | | | | | | Saturated | Unsaturated |
| Distilled Cocoa Amine [1] | 8 | 7 | 48 | 18 | 9 | 5 | 5 |
| Distilled Tallow Amine [1] | ---- | ------ | ------ | 5 | 30 | 20 | 45 |

[1] Commercially available for example as Adogen 160D, Adogen 170D, respectively from Archer Midland Danidis or Alamine 21D and Alamine 26D, respectively from General Mills, Inc. (Kankakee, Ill.)
Salts made from these are also acceptable.

The salts of the $C_8^+$ fatty amines can also be employed and are normally fatty amine salts of weak acids. They similarly may be salts of mono, di or polyamines and are generally of the same nature as the $C_8^+$ aliphatic amines indicated above. It is particularly desirable to employ water in insoluble salts of $C_8^+$ fatty amines since their water insolubility tends to improve their ability to remain in the stomach and control their rate of reactivity. $C_{10}$ to $C_{18}$ fatty amine salts are particularly desirable. The weak acid salts such as the acetate, fumarates, lactates, are effective as long acting antacids, and the general class of weak acid salts of fatty amines represents new antacid compositions which may be employed as such.

Examples of suitable acid groups include those derived from the following acids: acetic, fumaric, lactic, adipic, malic, aspartic, carbonic, malonic, glycolic, glutaric, itaconic, tartaric, succinic, etc. Acceptable acids used may be poly functional acids in which one or more carboxylic groups are reacted with the amine function. Acceptable acids preferably will have an ionization constant (ionization constant for first acidic function if poly acid) of less than $2.0 \times 10^{-3}$ if amine is fully reacted with acid (no free residual amino groups). Partial neutralization of the fatty amine with stronger acids will give acceptable materials providing the administered dose is increased to account for the decreased number of residual free and reactive amino groups.

Preferred free amines should also have limited solubility in water and in gastric fluids (approximate pH 1.2) in order to control reactivity and initial pH rise in Holbert test. Thus oleyl amine actually raises pH higher than ideal (oleyl amine HCl is $H_2O$ soluble) while stearyl amine (lower solubility in acid) does not have initial pH as high. Rate of reaction can therefore be controlled by selection of amines and amine salts with requisite solubility. Some solubility and/or miscibility is required however in order to get reasonable rate of acid neutralization.

Examples of fatty amine salts of particular value with regard to acting as antacids are: stearyl diamine diacetate, cetyl diamine monoacetate, lauryl amine lactate, oleyl diamine monoacetate, oleyl diamine diadiptate, behenyl amine aspartate, N-coco trimethylene diamine monofumarate.

Amine salts have advantage over free amines since inherent alkalinity is reduced. Irritation potential to mucous membranes is lessened. However, some slight loss in acid neutralizing ability is sustained in salts of free amines.



As noted previously, both the $C_8^+$ fatty amines and $C_8^+$ weak acid salts of fatty amines represent new antacid compositions which are particularly effective due to their increased stomach retention times. Prior art antacids did not stay in the stomach long enough to fully neutralize gastric acids, e.g., being emptied into the intestines in 20 minutes to an hour. These new antacid compositions show substantially longer antacid activity since they remain in the stomach for extended intervals, e.g., over 2 hours. Thus, these compositions can prove to be highly effective with regard to relieving normal stomach acidity as well as being an effective means for reducing stomach ulcers since they neutralize the source of the difficulty, i.e., gastric acid, for extended periods of time. Moreover, the fatty amine salts in particular show unusual benefits as antacids since they maintain a pH of about 2.5 to 5.5 for an extended period of time. pH's within this range are generally recognized to be best for the treatment of peptic ulcers and gastric hyperacidity and are generally considered characteristic of "ideal antacids." Further, the fatty amine salts show additional advantages in that increased dosages of the fatty amine salts merely go to prolonging their period of effectiveness at the ideal pH range, whereas increased dosages of conventional antacids normally will increase the pH range beyond that desired. Thus the possibility of "acid rebound" (compensatory secretion of additional gastric acid if pH of stomach is raised much above pH 6.0) is greatly reduced. Since exact strength and amount of gastric acid is rarely known, conventional antacids can be administered at times of little or no hyperacidity and result in high gastric pH and "acid rebound." As noted previously, these weak acid salts may be employed alone or combined with conventional antacid substances to increase the total acid consuming activity of the product. Thus, they may be combined with conventional antacids such as magnesium carbonate, magnesium trisilicate, magnesium oxide and/or hydroxide, sodium bicarbonate, calcium carbonate, etc. This combination offers particular advantages in that lower doses of the fatty amine salt may be used without detracting from the total acid consuming ability of the product. Also these weak acid salts may be combined with fat-oil such as safflower, cottonseed, corn oil which can act to improve palatability and reinforce gastric retention ability. Conventional antacids and/or free fatty amines may be included in these products. Mixtures of fatty amine salts may also be combined with free amines of the same or different chain length and types with or without the addition of conventional antacid agents and/or fat-oil.

The various aspects and modifications can be made more readily apparent by reference to the following description and accompanying examples.

The following examples illustrate compositions of the present invention and their preparation. They illustrate that the present orally administrable pharmaceutical preparations may take any of a wide variety of forms, i.e. suspensions, solutions, emulsions, pills, etc.

*Example 1*

An antacid composition is formed simply by employing a 10 g. dosage of a fatty amine such as stearyl amine. The dosage can vary from lower limits of about 5 grams.

*Example 2*

The composition of 1 is flavored with 0.01 w./w. percent of Peppermint Oil, U.S.P.

| | Wt. percent |
|---|---|
| Stearyl amine | 99.99 |
| Peppermint Oil, U.S.P. | 0.01 |

The oil of peppermint is blended with the stearyl amine to give a flavored, soft, waxy, solid. The composition can be administered as such in single oral human doses of approximately 5–30 grams.

*Example 3*

15 g. of stearyl amine is admixed at 55° C. with 10 g. of cottonseed oil. The resulting mixture is stirred and cooled to room temperature. The composition is a prolonged action antacid, used in 10–45 gram dosages. The composition of Example 3 may be formulated to include 0.1% of ascorbyl palmitate as antioxidant.

*Example 4*

10 g. of oleyl amine acetate is employed alone as an antacid. The composition of Example 4 may be formulated with 0.2% ascorbyl palmitate or alpha tocophenol as anti-oxidant and 0.02% Orange Oil, U.S.P., as flavor.

*Example 5*

The oleyl amine acetate, i.e., fatty amine acetate, of Example 4 is employed in conjunction with 10 g. of stearyl amine lactate or 10 g. of peanut oil as an antacid.

*Example 6*

An antacid emulsion composition is prepared by adding 10 g. of oleyl amine or distilled coco amine with 100 mg. of sodium lauryl sulfate and thereafter adding sufficient water to make the total composition 50 g. The resulting admixture is subjected to agitation. The composition may be preserved by addition of 0.2% propyl para amino benzoic acid.

*Example 7*

An antacid preparation is prepared by mixing 6.5 grams aluminum hydroxide-magnesium carbonate Dried Gel—Type F–MA–11 (Reheis, Inc.) and 20 g. of cottonseed oil. The resulting composition is an antacid of prolonged acting characteristics.

*Example 8*

A composition as per Example 7 using safflower oil and including 0.1% ascorbyl palmitate as antioxidant and 0.01% spearmint oil as flavor.

*Example 9*

The composition of Example 8 but including 5 grams of cetyl diamine difumarate.

*Example 10*

Antacids as in Example 8 but including 7 grams of n-dodecenyl-n-trialkyl methyl amine or 7 grams of n-lauryl-n-tri alkyl methyl amine which are commercially available under the names of LA–1 and LA–2, respectively, and sold by Rohm and Haas.

*Example 11*

500 mg. of magnesium trisilicate is admixed with 15 g. of distilled tallow amine or distilled tallow amine aspartate or amine acetate. The resulting admixture is an improved antacid.

*Example 12*

The composition of Example 11 is admixed with 150 mg. of an emulsifying agent and suspending agent, e.g., sorbitan mono oleate or sodium lauryl sulfate; and sufficient water is added to make the total composition 30 g. The admixture is subjected to agitation and represents an improved antacid in suspension form.

*Example 13*

Composition of Example 12 plus 0.5% methyl cellulose as auxiliary suspending agent.

*Example 14*

15 grams of lauryl amine acetate is warmed to 55° C. and mixed with 15 grams of powdered sucrose. The resulting mixture is ground to a powder and used as an antacid with prolonged effectiveness.



*Example 15*

Composition of Example 14 with addition of 5 grams of cocoa butter and 0.1% oil of orange and 0.2% propyl para amino benzoate.

*Example 16*

10 grams of aluminum hydroxide-magnesium carbonate dried oil—Type F–MA–11 is blended with a mixture of 7 grams of cocoa butter and 3 grams of corn oil. The resulting solid is used as a prolonged acting antacid.

*Examples 17–20*

The following examples illustrate the acid neutralizing ability of fatty amines and the most desirable pH characteristics of the acid salts of fatty amines and illustrate their use as antacids.

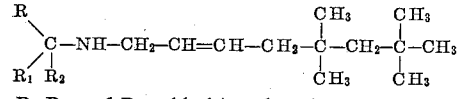
The antacid characteristics were determined by the method of Holbert, Noble and Grote, Journal of the American Pharmaceutical Association, 36, 149 (1947); 37, 292 (1948). In this method, a test sample of the antacid is added to 150 ml. of pH 1.4 hydrochloric acid containing 2 g. of pepsin N.F. per liter (artificial gastric juice) at 37½° C. 20 ml. of the artificial gastric juice is withdrawn every 10 minutes and replaced with an equal volume of fresh gastric juice. The antacid effect is determined by measuring the pH of the artificial gastric juice during the test period.

Two samples of fatty amine and two samples of fatty amine salts were tested by this procedure and were found to have the following antacid characteristics.

The following samples were employed:

(1) 8 grams of N-lauryl-N-trialkyl methyl amine available as LA–2 from Rohm and Haas, Inc. (chemical type same as below without double bond).

(2) 10 grams of N-dodicenyl-N-trialkyl methyl amine available as LA–1 from Rohm and Haas, Inc. (chemical type is



where R, $R_1$ and $R_2$=11–14 carbons).

(3) 12 grams distilled primary hydrogenated tallow amine acetate available as Alamac H26D from General Mills, Inc.

(4) 10 grams of distilled oleyl amine acetate as available from Armour and Company as Armac C.

TABLE I.—ANTACID CHARACTERISTICS (pH)

| Sample | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Time, minutes: | | | | |
| 0 | 1.4 | 1.4 | 1.4 | 1.4 |
| 10 | 4.9 | 4.5 | 4.0 | 4.1 |
| 20 | 4.8 | 4.6 | 4.2 | 4.1 |
| 30 | 4.7 | 4.5 | 4.2 | 4.0 |
| 40 | 4.5 | 4.5 | 4.1 | 4.0 |
| 50 | 4.3 | 4.4 | 4.1 | 4.0 |
| 60 | 4.1 | 4.4 | 4.0 | 3.9 |
| 70 | 3.9 | 4.3 | 3.9 | 3.8 |
| 80 | 3.6 | 4.2 | 3.8 | 3.7 |
| 90 | 3.5 | 4.0 | 3.6 | 3.4 |
| 100 | 3.3 | 3.8 | 3.5 | 3.3 |
| 110 | 3.1 | 3.8 | 3.3 | 3.0 |
| 120 | 3.0 | 3.7 | 3.1 | 2.9 |
| 130 | 2.8 | 3.5 | 3.0 | 2.7 |
| 140 | 2.7 | 3.1 | 2.8 | 2.5 |
| 150 | 2.6 | 3.0 | 2.8 | 2.2 |
| 160 | 2.5 | 2.8 | 2.6 | 2.0 |
| 170 | 2.1 | 2.6 | 2.3 | 1.8 |
| 180 | 2.0 | 2.5 | 2.0 | 1.7 |

As shown in Table I, compositions comprising fatty amines and fatty amine salts are highly effective as antacid compositions. The compositions maintained a pH within the range of 4.9 to 2.5 for over 2 hours (in doses tested). This pH range is well known in the art to be highly desirable for antacid compositions and is generally considered the optimum to ensure adequate relief for hyperacidity without over alkalization.

*Examples 21–23*

The following examples illustrate the particular effectiveness of salts of $C_8^+$ fatty amines with regard to their antacid ability. It illustrates that increasing the dosage of such materials merely increases the duration of their action within the desirable pH range of 2.5 to 5.5 without materially affecting their peak pH's. Thus, the compositions will be extremely long acting, the desired time period of their action being readily controlled by change of their dosage.

All tests were run in the same manner as Examples 17-20, employing the Hobert, Noble and Grote procedure.

TABLE II.—ANTACID CHARACTERISTICS (pH)

| Sample | 1<br>Oleyl Amine Acetate, 10 grams | 2<br>Oleyl Amine Acetate, 15 grams | 3<br>Oleyl Amine Acetate, 20 grams |
|---|---|---|---|
| Time, min.: | | | |
| 0 | 1.4 | 1.4 | 1.4 |
| 10 | 4.1 | 4.8 | 4.8 |
| 20 | 4.1 | 4.8 | 4.8 |
| 30 | 4.0 | 4.7 | 4.8 |
| 40 | 4.0 | 4.1 | 4.7 |
| 50 | 4.0 | 4.1 | 4.5 |
| 60 | 3.9 | 4.0 | 4.3 |
| 70 | 3.8 | 3.8 | 4.0 |
| 80 | 3.7 | 3.8 | 3.8 |
| 90 | 3.4 | 3.8 | 3.8 |
| 100 | 3.3 | 3.5 | 3.6 |
| 110 | 3.0 | 3.4 | 3.5 |
| 120 | 2.9 | 3.0 | 3.4 |
| 130 | 2.7 | 3.0 | 3.4 |
| 140 | 2.5 | 3.0 | 3.4 |
| 150 | 2.3 | 2.9 | 3.2 |
| 160 | 2.0 | 2.9 | 3.2 |
| 170 | 1.8 | 2.8 | 3.0 |
| 180 | 1.7 | 2.7 | 2.9 |
| 190 | | 2.6 | 2.9 |
| 200 | | 2.5 | 2.7 |
| 210 | | 2.5 | 2.7 |
| 220 | | | 2.6 |
| 230 | | | 2.6 |
| 240 | | | 2.5 |

Various modifications of the present invention will be suggested to those skilled in the art.

Having described the present invention, that which is sought to be protected is set forth in the following claims.

I claim:

1. An orally administrable antacid composition comprising: a fatty agent being an ester of a higher fat acid and a trihydric alcohol, and an antacid chemical agent, said composition containing, per single human dose, sufficient antacid agent to neutralize at least 20 milliequivalents of hydrochloric acid to a pH of at least 2.5, and to maintain a pH of at least 2.5 for at least two hours as measured by the method of Holbert et al., and at least 2 grams of fatty agent.

2. The composition of claim 1 wherein said fatty agent has a melting point of less than 37° C.



3. A method for relieving acidity which comprises orally administering to a human the composition of claim 1.

4. The composition of claim 1 wherein said fatty agent is selected from the group consisting of soy bean oil, safflower oil, palm oil, peanut oil, cottonseed oil, cocoanut oil and sesame, cocoa butter, lard and butter fat.

5. A method for relieving acidity which comprises orally administering to a human the composition of claim 4.

6. An orally administrable antacid composition comprising an aqueous emulsion of a fatty agent having a melting point of less than 30° C., said fatty agent being an ester of a higher fat acid and a trihydric alcohol, and an antacid chemical agent, said composition containing, per single human dose, sufficient antacid agent to neutralize at least 20 milliequivalents of hydrochloric acid to a pH of at least 2.5, and to maintain a pH of at least 2.5 for at least two hours as measured by the method of Holbert et al., and at least 2 grams of fatty agent.

7. A method for relieving acidity which comprises orally administering to a human the composition of claim 6.

8. An orally administrable long acting antacid composition comprising an antacid agent selected from the group consisting of calcium carbonate, magnesium carbonate, magnesium trisilicate, magnesium hydroxide, aluminum hydroxide, sodium carbonate, magnesium oxide, sodium bicarbonate, bismuth subcarbonate, and dihydroxy aluminum amino acetate, said composition containing, per single human dose, sufficient antacid to neutralize at least 20 milliequivalents of hydrochloric acid to a pH of at least 2.5, and to maintain a pH of at least 2.5 for at least two hours as measured by the method of Holbert et al.; and at least 2 grams of an ester of a higher fat acid and a trihydric alcohol.

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