United States Patent

[11] 3,621,094

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[21] Appl. No. **719,234**
[22] Filed **Apr. 5, 1968**
[45] Patented **Nov. 16, 1971**

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[54] **CONCENTRATED AQUEOUS LIQUID ANTACID COMPOSITIONS CONTAINING CERTAIN PHOSPHATE AND GLUCONATE SALTS**
6 Claims, No Drawings

[52] **U.S. Cl.** **424/128,** 424/127, 424/131, 424/154, 424/155, 424/156, 424/157, 424/158, 424/180, 424/319
[51] **Int. Cl.** **A61k 27/00**
[50] **Field of Search** 424/128, 131, 154, 155, 156, 157, 158, 180, 127, 319

[56] **References Cited**

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ABSTRACT: Pharmaceutically elegant aqueous pharmaceutical suspensions having antacid and antiulcer activity comprising a high concentration of antacid and a combination of calcium phosphate monobasic and a nontoxic alkali metal or alkaline earth gluconate salt such as sodium, potassium, calcium or magnesium gluconate.

CONCENTRATED AQUEOUS LIQUID ANTACID COMPOSITIONS CONTAINING CERTAIN PHOSPHATE AND GLUCONATE SALTS

This invention relates to new pharmaceutically elegant antacid compositions. More specifically, this invention relates to aqueous pharmaceutical suspensions for oral use having antacid and antiulcer properties which contain a high concentration of antacid but which are also pharmaceutically stable and very palatable.

Therapeutically, antacids are used for the treatment of gastric hyperacidity, dyspepsia and peptic ulcers. Antacids have played a major role in the clinical management of peptic ulcers and in appropriate doses to relieve the plain of this condition.

One of the major disadvantages of using the currently available liquid antacid preparations for ulcer therapy is that they necessarily contain a low concentration, approximately 8 percent, of active antacid ingredient. These commercially available antacid preparations are rapidly and readily eliminated from the stomach as it empties. After a 30-minute period not enough antacid remains to provide effective antacid or antiulcer activity. In an attempt to overcome this short duration of action and to obtain a sustained protective effect recent therapy comprises administering the prior art liquid antacid preparations at hourly intervals. Even when these are administered within these frequent hourly intervals the desired therapeutic effect, maintenance of gastric pH above 3.5, is frequently lost between doses. This procedure also makes it difficult, if not impossible, to control the gastric acidity during the sleeping hours.

It is also apparent that because of the low concentration of current liquid antacid preparations this method of therapy, particularly for peptic ulcers, involves the oral administration of continuous and large daily volumes of antacid to keep the gastric contents neutralized. The administration of larger volumes of the commercial liquid antacid suspensions per does has proven very impractical. Most important, it has been demonstrated that increasing the volume of the suspension does not increase the duration of action and produces substantially the same therapeutic effect. Secondly, increasing the volume of antacid per dose would result in a serious personal discomfort and expense.

A further disadvantage is that even commercially available antacid products have well recognized stability problems. One of these is their tendency to coagulate and clump upon standing. Further, the palatability of the prior art liquid antacids is very objectionable, i.e. they have a chalky and astringent taste. These problems are multiplied as the concentration of antacid increase.

It is therefore the object of this invention to provide more concentrated forms of liquid antacid suspensions which are stable and palatable but still provide for prompt and long-acting antacid and antiulcer activity, i.e., antacid and ulcer protection well beyond the normal gastric emptying time and of sufficient duration of effective activity to maintain the gastric contents at a desirable pH between doses.

Unexpectedly the preparations of this invention offer a much more concentrated form of antacid preparation than has been previously available. If such a concentration could be prepared in the vehicle of the prior art antacid preparation it would resemble a slightly damp chalk powder. This invention therefore provides a more convenient, stable and palatable liquid for antacid therapy. The preparation in accordance with this invention can contain as high as 50 percent antacid which represents more than a fivefold increase in concentration over the commercially available liquid antacid preparations.

The novel pharmaceutical preparations of this invention are unique in that they are not only much more concentrated than the commercially available antacid preparations but are also more pharmaceutically elegant. These antacid suspensions are more stable and have improved palatability being free of the gritty, astringent, chalky taste which is so prevalent even with the previously known antacid compositions.

The novel pharmaceutical compositions of this invention are also unique in that they provide for improved concentrated liquid antacid formulations of the type which promptly neutralize gastric acidity and maintain this neutralization over an extended period of time. In accordance with this invention, an improved antacid preparation is provided which increases both the degree and duration of action of the antacid and assures adequate antacid and antiulcer protection between doses. When equal volumes of a representative liquid antacid preparation of this invention and the leading commercial antacid preparation are administered orally in standard tests the preparation of this invention exerts antiulcer activity over twice as long as does the prior art antacid preparation.

A still further advantage of the concentrated antacid composition of this invention is due to its high concentration. It eliminates the necessity of administering large daily volumes of antacid to obtain a therapeutic effect. The frequency of administration is greatly diminished when using the concentrated pharmaceutical composition of this invention.

The novel pharmaceutical composition of this invention comprises an aqueous suspension comprising a high concentration of antacid and a combination of calcium phosphate monobasic and a pharmaceutically acceptable, nontoxic alkali earth or alkali metal gluconate especially sodium, potassium, magnesium or calcium gluconate. Most advantageously, the aqueous suspension will comprise the antacid in combination with calcium phosphate monobasic and calcium gluconate. It has been unexpectedly discovered that the addition of calcium phosphate monobasic and at least one of the above-noted gluconate salts permit a much higher concentration of antacid in an aqueous suspension than has previously been possible. The employment of the combination of these additives has the further added advantage in that it not only produces an aqueous suspension of an antacid having a high concentration but it also provides for a palatable and stable preparation. The presence of calcium phosphate monobasic and a gluconate salt in the aqueous vehicle effectively prevents the suspended antacid from clumping or caking at the bottom of the container thus insuring proper dosage by simple shaking before use.

It has been discovered that these additives must be present in combination in order to achieve the advantages of stability and palatability noted above. If either the monobasic calcium phosphate or one of the disclosed gluconate salts is employed alone to prepare a concentrated aqueous antacid suspension the resulting composition will slowly thicken, then solidify into a nonpourable mass. When these additives are used in combination the resulting concentrated antacid suspension results in the described pharmaceutically elegant preparation.

Advantageously, the monobasic calcium phosphate and the alkali gluconate salt, preferably calcium gluconate, will each be present in an amount of from about 0.5 percent to about 7.0 percent by weight/volume of the liquid suspension. Most advantageously, the calcium phosphate monobasic and calcium gluconate will each be present in an amount of from about 2.0 percent to about 5.0 percent by weight/volume of the liquid suspension. The total concentration of the additives will be present in an amount of about 3 percent to about 10 percent.

By the term high concentration of antacid is meant that the antacid ingredient is present up to about 50 percent weight/volume. Preferably, the antacid 50 present from about 25 percent to about 50 percent weight/volume, most advantageously from about 30 percent to about 45 percent weight/volume. Of course, lower concentrations of antacid can be used in the described vehicle of this invention if one desires a conventional antacid preparation of increased elegance.

The antacid employed may be any of the conventional antacids well known to the art. For example, the antacid may be calcium carbonate, magnesium oxide, magnesium trisilicate, magnesium carbonate, aluminum hydroxide, bismuth subcarbonate, dihydroxy aluminum aminoacetate, bismuth alu-

minate, aluminum oxyhydroxide, sodium bicarbonate, magnesium hydroxide, sodium carbonate and aluminum phosphate or combinations thereof such as, for example, aluminum hydroxide-magnesium hydroxide glycine dried gel and aluminum hydroxide-magnesium carbonate codried gel.

The above aqueous concentrated antacid suspensions are made following the techniques described hereafter. When are made following the techniques described hereafter. When necessary, any desired pharmaceutically compatible adjuvant used in liquid preparations by those skilled in the art may be employed. For example, preservatives such as methylparaben, or propylparaben, flavoring agents such as oil of orange, lemon-lime flavors, raspberry flavor, cola flavors, mint flavors or the combination of these flavors or any solubilizing agent such as glycerin or propylene glycol may be employed. Further, antispasmodic agents, tranquilizers or other medicaments can be optionally included in the preparation.

The invention will be further clarified by the following specific examples. These examples are not limiting but are used to make obvious to one skilled in the art the full practice of the method of this invention.

EXAMPLE 1

Ingredients	Amount
Aluminum hydroxide, NF	18.90 gm.
Magnesium hydroxide, NF	11.07 gm.
Precipitated calcium carbonate, USP	7.50 gm.
Cetyl dimethyl benzyl ammonium chloride	0.01 gm.
Glycine	9.00 gm.
Calcium cyclamate	0.30 gm.
Calcium phosphate monobasic	3.75 gm.
Calcium gluconate	2.00 gm.
Hydroxypropyl	0.12 gm.
Antifoam emulsion	0.01 gm.
Peppermint flavor	0.10 ml.
Water, USP qs	ad 100.00 ml.

The cetyl dimethyl benzyl ammonium chloride is dissolved in 65 ml. of water. The aluminum hydroxide, magnesium hydroxide and glycine are evenly suspended in the solution. The calcium gluconate and calcium phosphate monobasic are then added. The calcium carbonate, hydroxypropyl methylcellulose and antifoam are also added to the suspension with gently agitation. The flavor is added and the suspension is brought to the desired volume by the addition of sufficient water.

EXAMPLE 2

Ingredients	Amount
Aluminum hydroxide, NF	22.70 gm.
Magnesium hydroxide, NF	13.28 gm.
Precipitated calcium carbonate, USP	9.00 gm.
Cetyl dimethyl benzyl ammonium chloride	0.01 gm.
Calcium cyclamate	0.03 gm.
Calcium phosphate monobasic	3.00 gm.
Calcium gluconate	3.00 gm.
glycerin	10.50 ml.
Lemon-lime flavor	0.01 ml.
Water, USP qs	ad 100.00 ml.

The cetyl dimethyl benzyl ammonium chloride is dissolved in 65 ml. of water. The aluminum hydroxide and magnesium hydroxide are evenly suspended in the solution. The calcium gluconate and calcium phosphate monobasic are added with agitation, then the calcium carbonate, calcium cyclamate and glycerin are added to the suspension with gentle agitation. The flavor is then added and the suspension is brought to the desired volume by the addition of sufficient water.

EXAMPLE 3

Ingredients	Amount
Aluminum hydroxide, NF	27.5 gm.
Methylparaben	0.045 gm.
Propylparaben	0.020 gm.
Propylene glycol	5.00 ml.
Calcium phosphate monobasic	3.00 gm.
Sodium gluconate	2.50 gm.
Imitation wintergreen	0.25 ml.
Purified water qs	ad 100.00 ml.

Aluminum hydroxide is evenly suspended in 65 ml. of water and the calcium phosphate monobasic and sodium gluconate are added. The parabens are dissolved in the propylene glycol with the aid of heat and added to the suspension. The flavor is then added and the suspension is brought to the desired volume by the addition of sufficient water.

EXAMPLE 4

Ingredients	Amount
Aluminum hydroxide, NF	28.00 gm.
Magnesium carbonate, NF	5.10 gm.
Cetyl dimethyl benzyl ammonium chloride	0.01 gm.
Calcium cyclamate	0.30 gm.
Calcium phosphate monobasic	3.75 gm.
Magnesium gluconate	2.00 gm.
Hydroxypropyl methylcellulose	0.12 gm.
Peppermint flavor	0.05 ml.
Water, USP	ad 100.00 ml.

The cetyl dimethyl benzyl ammonium chloride is dissolved in 65 ml. of water. The aluminum hydroxide and magnesium carbonate are evenly suspended in the solution. The magnesium gluconate and calcium phosphate monobasic are added with agitation, then the hydroxypropyl methylcellulose and calcium cyclamate are added to the suspension with gentle agitation. The flavor is then added and the suspension is brought to the desired volume by the addition of sufficient water.

What is claimed is:

1. A pharmaceutically elegant liquid pharmaceutical composition for oral use comprising from about 25 percent to about 50 percent of a solid antacid material comprising aluminum hydroxide, magnesium hydroxide, calcium carbonate, magnesium oxide, magnesium trisilicate, magnesium carbonate, bismuth subcarbonate, dihydroxy aluminum aminoacetate, bismuth aluminate, aluminum oxyhydroxide, sodium bicarbonate, sodium carbonate, aluminum phosphate, glycine or combinations thereof suspended in an aqueous vehicle containing from about 0.5 percent to about 7.0 percent weight/volume of monobasic calcium phosphate and at least one of sodium, potassium, calcium or magnesium gluconates the total concentrations of phosphate and gluconate being from about 3 percent to about 10 percent.

2. The pharmaceutical composition of claim 1 wherein the gluconate salt is calcium gluconate.

3. The pharmaceutical composition of claim 1 wherein the antacid is present from about 30 percent to about 45 percent weight/volume and the monobasic calcium phosphate and calcium gluconate are each present in an amount of from about 2.0 percent to about 5.0 percent.

4. The pharmaceutical composition of claim 2 wherein the antacid is magnesium hydroxide, aluminum hydroxide, magnesium carbonate, calcium carbonate or combinations thereof.

5. The pharmaceutical composition of claim 1 in which the antacid is at least one of aluminum hydroxide, magnesium carbonate or calcium carbonate.

6. The pharmaceutical composition of claim 1 in which the essential ingredients in the aqueous vehicle comprise about 19 percent aluminum hydroxide, about 11 percent magnesium hydroxide, about 7.5 percent calcium carbonate, about 3.7percent calcium phosphate monobasic, and about 2 percent calcium gluconate.

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