ANTACID PREPARATIONS CONTAINING ACRYLIC ACID POLYMERS AND MAGNESIUM ANTACIDS

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The present application is a continuation-in-part of my copending application, Serial No. 488,422, filed February 15, 1955, now abandoned.

This invention relates to pharmaceuticals and more particularly to a new type of antacid preparation which may be taken in any required amount, without harmful effect, by those who suffer from excess acidity, including persons having ulcers of the stomach or intestines.

A large number of substances are known which will raise the pH of the stomach and thus relieve temporarily the distress which results from hyperacidity. For example, bicarbonate soda is a well known substance of this character. However, this and many other substances have a tendency to raise the pH of the stomach to an excessively high value, soon after they are taken, with the result that the human system promptly reacts to generate more acid to overcome the alkalinity of the stomach. Such acid rebound quickly restores the condition which caused the original distress. Thus if the stomach originally had a pH of 2 or lower, the antacid frequently boosts the pH to a higher range for a brief period but the acid rebound rather quickly brings the pH back to its original low value or even somewhat lower.

Various antacid preparations have been developed which overcome the objectionable acid rebound reaction but these act more slowly in relieving the distress. An example of such a preparation is aluminum hydroxide. This has been found to raise the pH of the stomach to only about 4.5 but it acts relatively slowly and does not bring the pH up to 4 until about 20 to 30 minutes after a usual dose has been taken. Except for the slowness in relieving distress, this preparation provides a desirable antacid effect.

Various buffered antacid preparations have been developed combining the quick action of such substances as bicarbonate of soda and the longer action of such substances as aluminum hydroxide.

However, many previously known forms of antacid preparations have a constipating effect which is particularly serious in the case of persons having ulcers, since they are forced to take an antacid preparation at rather frequent intervals. To offset the constipating action of antacids it has frequently been the practice to take with an antacid preparation some form of active laxative but this has not been found satisfactory, particularly in the case of persons having ulcers or kindred ailments. Most substances having a positive laxative action create distress and irritation which are especially objectionable in ulcer cases.

For example, some produce their effect by irritating the intestinal walls to increase muscular contraction which results in more rapid elimination. In this category fall such substances as cascara sagrada, castor oil, croton oil and phenolphthalein. The irritation which they cause leads to soreness and inflammation of the intestinal tis-
sues. Saline laxatives operate by attracting water into the intestinal tract and thus providing increased volume. In doing so they create irritation of the tissue from which the water is attracted. Laxatives of the emollient type, such as mineral oil and certain vegetable oils, function through their lubricating and dehydration-retarding action. An object to these is to prevent the absorption of oil-soluble materials, such as the oil-soluble vitamins (A, D, E and K) through the intestinal wall. A fourth type of laxative may be classified as bulk laxatives. These include agar-agar, bran, carboxymethylcellulose, methyl cellulose and certain of the vegetable gums. These materials provide bulk by swelling as soon as they come in contact with water. While this action is desirable when confined to the intestinal tract, it produces discomfort and even more serious difficulties when it occurs in the stomach. To avoid this it is usually necessary to add certain ingredients such as glycine or sorbitol, which are gastrointestinal irritants.

A primary object of the present invention has been to provide a new antacid preparation which will give prompt relief from distress due to hyperacidity, will not raise the pH of the stomach above about 5.5, and preferably not above 4.5, so as not to induce acid rebound, and which will not be constipating while imparting no more than a mild bulk laxative action and without requiring the presence of gastrointestinal irritants.

Another object has been to provide a process for the treatment of hyperacidity which does not give rise to constipation or to acid rebound or to discomfort or irritation of the stomach or intestines, and does not interfere with the absorption of desirable nutritive materials into the human system.

It has been discovered that certain mixtures of an antacid, such as the oxide, hydroxide, carbonate, or a hydroxy salt of magnesium with a colloidally water-soluble, crosslinked polymer of acrylic acid in a polymerizable form provide antacid preparations having all of the characteristics desired. For example, if magnesium oxide or magnesium hydroxide is mixed in a dry state with a colloidally water-soluble, crosslinked polymer of acrylic acid the resulting mixture will provide, upon oral administration, the quick-acting effect of the magnesium oxide or hydroxide but will be buffered by the action of the crosslinked acrylic acid polymer so that the pH of the stomach will not be raised appreciably above 5.5, and preferably not above 4.5, and the pH will be maintained below this point for a relatively long period of time when a suitable dose of the preparation is taken. Moreover, as the antacid preparation passes out of the stomach and into the intestines, the crosslinked polymer of acrylic acid will swell and become gelled at the pH present there.

To produce an adequate antacid effect it is desirable to provide an excess of substances capable of raising the pH of the stomach, but the character and quantity of these substances employed should not be such as to raise the pH of the stomach for any appreciable length of time above about 5.5, and preferably not above about 4.5, otherwise an objectionable acid rebound will occur which will offset the usefulness of the antacid. It has been found that a crosslinked, colloidally water-soluble polymer of acrylic acid such as defined below is capable of buffering the alkalizing effect of a suitable excess of such substances as magnesium oxide or hydroxide, which in the absence of the crosslinked polymer of acrylic acid would provide an objectionably high pH.

Thus it has been found that if half a gram of magnesium hydroxide or oxide is intermixed with half a gram of a colloidally water-soluble polymer of acrylic acid crosslinked with between about 0.75% and 1.5%, and prefer-
ably about 1.0%, by weight of allyl sucrose, a very desirable antacid effect will be produced. The pH of the stomach will be rather quickly raised from a point below 2 to a point normally between about 4 and 5 and will be maintained at a suitable level for a substantial period of time.

The resins which are contemplated as useful in the present invention are those which include, non-irritating colloidally water-soluble polymers of acrylic acid crosslinked with a polyhydroxy compound having at least 3 and preferably not more than about 8 hydroxyl groups, wherein the hydrogen atoms of at least three hydroxyl groups are replaced with unsaturated aliphatic radicals having two or more carbon atoms. Preferred radicals are those containing from two to four carbon atoms, e.g., vinyl, allyl or crotlyl. These unsaturated radicals may themselves contain other substituents, such as the methyl group. For example, the methallyl radical is useful.

The polyhydroxy compounds useful in the formation of the cross-linking materials contemplated by the present invention preferably contain three or more hydroxyl groups and may include saccharides, for example, mono-, monosaccharides such as glucose, fructose, mannose or galac- tose and disaccharides such as sucrose, maltose, or lactose. Other useful polyhydroxy compounds include polyhydroxy alcohols, such as glycerol, erythritol, dulcitol, mannitol, sorbitol and pentaerythritol. The unsaturated crosslinkers described above are all ethers but I also contemplate the use, as crosslinking materials, of unsaturated esters, such as the triacryl acid ester of glycerol or acrylic acid esters or sucrose having from 3 to 8 acid residues. Unsaturated ether-esters may also be used, but as in the case of unsaturated esters, are not preferred because of their tendency to hydrolyze in aqueous solutions.

The preferred crosslinking compounds are polyallyl sucrose, preferably containing from 5 to 8 allyl groups per sucrose molecule and polyallyl pentaerythritol preferably tetraallyl pentaerythritol.

In each case, the crosslinker preferably comprises from about 0.75% to about 1.5% by weight of the crosslinked material.

The synthetic resins comprising any of the foregoing components are prepared by reacting acrylic acid or a similar monomeric resin-forming material with a crosslinking material, in the presence of a catalyst, under autogenous pressure and in an inert atmosphere to inhibit oxidation. A suitable catalyst, for example, a peroxide, such as benzoyl peroxide or carbonyl peroxide, is used in a concentration of from 0.1% to 2%. The reaction is carried out in the presence of an inert diluent which will not copolymerize with the reactants and which will not result in swelling of the polymerized product. Such diluents preferably should be solvents for the monomers but not for the polymers resulting from the reaction and may include water, alcohol, or saturated aliphatic or aromatic liquid hydrocarbons. Preferred diluents include such liquid hydrocarbons as benzene or toluene. However, solvents for the monomers are not essential, for the reaction may be conducted as an emulsion polymerization although this type of reaction is not preferred. The reaction is an exothermic one and may be carried out with simple agitation in a reactor provided with simple wall-cooling; the temperature being held between 20° C. and 70° C., preferably about 50° C. The reaction temperature is not critical below 50° C., the rate of reaction may be quite slow, whereas if the temperature is allowed to go much above 50° C., the exothermic reaction may proceed too violently. The polymerization is carried out as far toward completion as possible, the time required varying greatly with the reacting materials and other factors. If the reaction is carried out in the presence of an inert diluent as specified above, the progress of the reaction may be followed by periodically sampling the liquid phase and analyzing it for the presence of the free monomer. In such case, the reaction is determined to be complete when the percentage of monomer reaches a minimum concentration. In practice substantially of the monomeric material is converted during the reaction to the polymeric film.

An example of a specific product prepared in accordance with the above procedure is a product made by the B. F. Goodrich Chemical Company and which is designated by the trademark "Carbolopol-944," formerly known as "Goodrite-K-944." This product is a colloidally water-soluble polymer of acrylic acid crosslinked with approximately 1% by weight of allyl sucrose, the latter material having an average of about 5.8 allyl groups per molecule. This product is prepared by mixing the acrylic acid monomer and the allyl sucrose in the presence of a toluene diluent and 1% of benzoyl peroxide and the reaction allowed to proceed to completion at which time the diluent, together with unreacted monomer and catalyst, is removed by filtration and subsequent volatilization from the solid polymeric residue. The polymer thereby obtained is in the form of a white powder having a maximum particle size of about 0.01 mm and a bulk density of about 12 pounds per cubic foot.

The exact molecular weight is, of course, unknown but analysis shows that the product has an equivalent weight (molecular weight per repeating unit) of about 77. The minimum molecular weight, as roughly determined from viscosity measurements, is probably about 200,000.

The viscosity of a resin, made in accordance with the foregoing procedure, was determined by the following procedure. A 2.5 gram sample of resin was sifted into 500 ml. of distilled water in a Waring Blender run at low speed and mixed for three minutes. The resulting 0.5% colloidal solution was transferred to a 1 liter beaker and allowed to stand until the foam broke. The pH was then adjusted with ammonium hydroxide to 6.5-7.0, and the solution stirred for 30 seconds at 250 r.p.m. The resulting gel was allowed to stand for one hour at 25° C. and a viscosity test was then run with a modified viscometer using a number 4 spindle at 60 r.p.m.

The above test was repeated eleven times, using for each of the tests a sample from a different lot of resin. The average viscosity was found to be 71±7 poises.

When tested in a manner similar to the procedure described above, one form of the monomer-linked acrylic acid polymer found desirable for use in accordance with the invention gave a pH of 3 and a viscosity of 24.0 centipoises when dispersed to the extent of 1% aqueous sol. When the pH of this colloidal solution or sol was adjusted to about 3.6 with dilute alkali, the viscosity increased to 264.0 centipoises. Upon further increase of the pH to about 4.3 the viscosity increased to about 6,500 centipoises. On increasing the pH to about 6.0, where maximum gelation seems to occur, the resulting gel becomes firm and is so viscous that its viscosity is almost impossible to measure. Upon increasing of pH to above about 9 or 10, the gel again decreases in viscosity. The colloidal gel, derived from the relatively small amount of polyacrylic acid contemplated in accordance with the invention, has the desirable "bulk" properties which provide the non-consisting effect desired. When the pH of the colloidal gel or sol is lowered, the viscosity is observed to decrease. However, when the pH is induced to fall below 3 the viscosity is not materially lowered below 24 centipoises, which was observed at this pH.

One form of the crosslinked acrylic acid polymer containing 1% of allyl sucrose crosslinker desirable for employment in preparing the compositions of the invention is a white dry powder, which does not have a melting point. Instead of melting, it changes color at about 190° C. and becomes quite dark at about 260° C.
Within a relatively wide temperature range the material is stable so that it will withstand autoclaving, and it is not degraded by moderate amounts of acid unless the material is substantially non-toxic, odorless, colorless, and it might be said to have a slightly sour taste. It is bland, causes no irritation and appears to be non-habit forming. When this crosslinked polymer is dispersed in water to the extent of 1% it is found to provide a pH to the solution of approximately 3.

The crosslinked acrylic acid polymers desirable for use in the compositions of the invention are considered to be colloiddally water-soluble, or "sol-forming," and are herein described as such. Although their aqueous sols may contain no suspended matter which settles upon standing, they are not true solutions in the crystalloid sense and may be more accurately described as colloidal suspensions or solutions (sols). While none of the material will settle out upon standing, if subjected to ultra-centrifuging, much of this material, being colloidal in nature, may be separated from its colloidal solution or suspension. These aqueous sols give the characteristic "Tyndall effect" of aqueous colloidal dispersions.

Suitable compositions in accordance with the invention may be obtained by intimately intermixing various quantities by weight of a colloiddally water-soluble, crosslinked polymer of acrylic acid of the character indicated above, and a suitable antacid such as acid, hydroxide, carbonate, or basic salt of magnesium, including the basic carbonate of magnesium known as magnesium abla. In a mixture of the crosslinked polymer of acrylic acid with one of the antacid ingredients, the latter should be in excess of stoichiometric proportions required to react with the crosslinked polymer of acrylic acid. Thus it has been found that the equivalent weight of polyacrylic acid crosslinked with about 1% of allylsucrose, i.e., the average molecular weight per repeating unit in the polymer structure, is 77 and that one equivalent weight of such a polymer chemically combines with ½ mole, i.e., approximately 29 grams of magnesium hydroxide to yield a magnesium salt of the polyacrylic acid. If a greater antacid effect is desired, a larger proportion of the antacid ingredient may be employed. For example, for each gram of the crosslinked polymer of acrylic acid there may be used either 1 gram, 1.5 grams, 2 grams or 3 grams, or more up to 10 grams of the antacid components mentioned, such as magnesium hydroxide. It has been found, however, that if the antacid ingredient is present in too great an excess, as for example in a 16 to 1 ratio by weight, the composition will behave in a manner similar to the straight antacid component. The pH will then increase too rapidly and the buffering action will take place at too high a pH. Therefore, it is not generally desirable to include a higher content of the antacid component than about a 6 to 1 ratio.

While the pH of the stomach will be raised to a point above about 4 upon taking the compositions of the present invention, the antacid ingredient embodied in it, this will produce some, but not objectionable, bulking of the crosslinked polymer of acrylic acid in the stomach. When the proper dosage of the composition is taken the quantity of the colloiddally water-soluble polymer of acrylic acid present will not be sufficient to create an uncomfortable feeling of fullness. Moreover, the polymer of acrylic acid provides a buffering action which prevents the pH of the stomach from rising substantially above 5.5, and preferably not above 4.5, and while at the latter pH the viscosity of the crosslinked polymer of acrylic acid will be greatly increased, such increase is by no means comparable to the increase in viscosity which results at a pH of 6 or higher. In fact, a beneficial action appears to take place as a result of the increase in viscosity of the crosslinked polymer of acrylic acid component of the composition when the stomach attains a pH of about 4.5. This increase in viscosity tends to retard the discharge of the composition from the stomach through the pylorus into the duodenum. In this way it is more likely that the antacid component of the composition will remain in the stomach long enough to provide its full effect before it passes through the pylorus. As the pH of the stomach drops to a point around 3, which occurs after the antacid component has been spent, through the continual process of generation of hydrochloric acid within the system the crosslinked polymer of acrylic acid will have its viscosity lowered to a point commensurate with that originally attained at a pH of 3. Accordingly, it becomes sufficiently fluid by that time, and even at a somewhat earlier stage, to pass freely through the pylorus. Upon reaching the intestinal region, however, where a pH of 6 or higher is present, the colloiddally water-soluble, crosslinked polymer of acrylic acid will assume the form of a firm gel having an exceedingly high viscosity, which provides the desired bulking and eliminating action. The eliminating action is achieved without irritation of the intestines. Moreover, while the gel or jelly has certain lubricating qualities it does not have the objectionable action of mineral oil, and the like, of preventing the absorption through the intestinal wall of beneficial oil-soluble materials, such as oil-soluble vitamins.

To illustrate the character of the gel formed at a relatively high pH, it may be mentioned that a 1% gel of the colloiddally water-soluble, crosslinked polymer of acrylic acid at a pH of 7 was found to retain its form and water content in the face of centrifugation creating a force equal to 20,000 times that of gravity. It will be readily apparent that a comparatively small amount of the polymer of acrylic acid in this form is sufficient to bring about the bulking action in the intestines necessary to offset the accompanying effect of the antacid ingredient itself.

While the new composition of the invention may, if desired, be taken in liquid form, i.e., as a solution or suspension of the ingredients in a non-aqueous medium such as ethyl alcohol, glycerine, coconut or other edible vegetable oil, this is not ordinarily desirable because of the rather high viscosity of the substance which may result from the elevated pH which may be imparted to the compositions by the antacid component. In the case of magnesium oxide, hydroxide, carbonate or hydroxy salt of magnesium, the gelling of the crosslinked polymer of acrylic acid is not as rapid as with certain other antacids, and, if administered reasonably promptly, liquid compositions employing these magnesium antacids will have time to form a gel. For the same reason it is not ordinarily preferred to provide the new composition in the form of a granulation, to be stirred into a glass of water prior to taking, although if the resulting aqueous composition employs one of the magnesium antacid components described above it will not become appreciably viscous if taken promptly by the user, and may be dispensed in this form. Preferably the composition is taken in the form of a dry tablet. Such a tablet may be produced from the mixture of a colloiddally water-soluble, crosslinked polymer of acrylic acid and an antacid component, such as the oxide, hydroxide, carbonate or hydroxy salt of magnesium, with the addition of suitable binders or tablet-forming constituents, such as gelatin, gum acacia, gum tragacanth, pectin or other vegetable and biological gums. In addition, there may be added inert diluents such as starch, talc, terra alba, and the like, to provide body. By inert diluents I mean substances of the character indicated which are non-toxic and will not react unfavorably with or upon either the human system or the active ingredients of the preparation. It should not have a hydrolytic, decomposing or untoward effect upon the active constituents. The binder employed may also be considered a diluent and should be inert in the same respect.

As a typical example of a tablet formed in accordance with the invention, there may be thoroughly intermixed 36 parts of colloiddally water-soluble polymer of acrylic acid crosslinked with 1% of allylsucrose, 36 parts of mag-
nesium oxide, and 3 parts of pectin, all determined by weight. After thorough mixing of these ingredients they may be triturated with a mixture of chloroform and acetone. After thorough mixing the composition is dried and the chloroform and acetone are driven off by heat in a drying oven. Subsequently 25 parts, by weight, of the diluent, such as starch, may be mixed with the other ingredients. The resulting mixture may then be pressed into tablets of suitable size.

A suitable dosage of the above tablet composition is that which will contain .5 gram of the crosslinked polymer of acrylic acid and .5 gram of magnesium oxide. Therefore, a tablet having the composition suggested above will weigh 1.39 grams. If desired, each tablet may be made to contain 0.7 gram of the composition and 2 such tablets may be taken as an appropriate dose. It will be understood that the amount of the composition to be taken as a dose may be varied in accordance with the circumstances. In severe cases of hyperacidity a larger amount of the preparation may be taken as a single dose, or the tablets may be taken at more frequent intervals than in milder cases. In general it may be said that from 1 to 4 of the 0.7 gram tablets may be taken as a single dose.

Tablets containing magnesium hydroxide and the colloidal water-soluble, crosslinked polymer of acrylic acid in the ratio of about 3 parts to 1 by weight are preferred. Thus, the preferred tablet composition is in accordance with the present invention contains the following composition for each tablet.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium hydroxide</td>
<td>0.300</td>
</tr>
<tr>
<td>Gelatin</td>
<td>0.015</td>
</tr>
<tr>
<td>Polymer of acrylic acid crosslinked with 1% by weight of allyl sucrose (Carbopol-934)</td>
<td>0.100</td>
</tr>
</tbody>
</table>

Total weight of tablet 0.415

If desired, cornstarch may be added to the above formulation in the amount of 0.069 gram to give a tablet weighting of 0.484 gram. The tablets may be compounded in the same manner as in the first example, the gelatin performing the same function as the pectin of the first example. It is convenient to administer two of these tablets as an average dose, although the dose may be varied as desired.

The crosslinked acrylic acid polymers utilized in the above-described tablet formulations are initially in the form of very finely divided powders having a high electrostatic charge, the latter fact making accurate determination of size distribution of the polymer particles quite difficult to obtain by reason of the tendency of the charged particles to fly apart and to adhere to handling apparatus. This tendency also makes it extremely difficult to use the untreated polymer powder in the formulation of pharmaceutical preparations.

Therefore, the present invention contemplates the use in pharmaceutical anticid preparations of a crosslinked polymer of acrylic acid which has been subjected to steam to agglomerate the resin and to vitiate the effects of the electrostatic charge carried by the polymer in its initial finely divided form.

For example, a polyacrylic acid resin, crosslinked with allyl sucrose and produced as described herein, was placed in a shallow tray in an enclosed housing and treated with steam at a dry bulb temperature of 210° F. and a wet bulb temperature of 190° F., for 45 minutes, after which time the wet bulb temperature was reduced to 100° F. and heating was continued at a dry bulb temperature of 200° F. for another 80 minutes.

The resin subjected to the steaming process is chemically unchanged but is physically agglomerated into a porous cake which is then milled. The product of the milling procedure is screened and the material having a particle diameter less than 40 mesh (0.015 inch) is retained for subsequent formulation. This material has a particle size distribution as shown in the following table:

<table>
<thead>
<tr>
<th>Mesh No.</th>
<th>Inches</th>
<th>Microns</th>
<th>Percent Retained On Sieve</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>0.0685</td>
<td>457</td>
<td>1</td>
</tr>
<tr>
<td>80</td>
<td>0.0498</td>
<td>348</td>
<td>15</td>
</tr>
<tr>
<td>100</td>
<td>0.0399</td>
<td>249</td>
<td>25</td>
</tr>
<tr>
<td>115</td>
<td>0.0349</td>
<td>187</td>
<td>30</td>
</tr>
<tr>
<td>greater than 115</td>
<td></td>
<td></td>
<td>smaller than 0.0099...</td>
</tr>
<tr>
<td>less than 124</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In contrast to the relatively large particle size of the steamed and milled polymer, the particle size of the allyl sucrose crosslinked polymer of acrylic acid, when produced by a process such as that described hereinabove, is from about 10 to about 50 microns.

Despite the increased particle size of the treated polymer, the bulk density of the latter is much greater than that of the untreated polymer. This is of great advantage in formulating pharmaceutical products for oral administration, for increase of bulk density results in decreased volume per dose required.

Illustrative of the mentioned change in bulk density of polymer, an untreated allyl sucrose crosslinked with acrylic acid polymer was loosely filled into a volume of 1 cc. The polymer weighed 0.210 gram. A similar test of the same polymer after steam treatment and milling resulted in a loose bulk density of 0.591 gram per cc.

The polymers treated as described may be readily handled without the undesirable effects experienced with the untreated polymer powder. Thus, when the treated polymers are used, the anticid compositions described hereinabove may be easily formulated by merely mixing all of the ingredients together and subjecting the mixture to the necessary tableting pressure.

An anticid tablet so produced possesses a remarkable superiority over tablets in which the untreated polymers are incorporated. This superiority is manifested in a firmer tablet, having a greatly reduced tendency to crumble, and in a drastically reduced disintegration time when placed in an aqueous solution.

Various tests have been conducted to demonstrate the effectiveness of the new anticid compositions and their superiority over other forms of anticid preparations. For example, 1 gram of magnesium carbonate added to 50 cc. of water with constant stirring has been subjected to the periodic addition 1 normal hydrochloric acid in 2 cc. increments. It has been found that upon the addition of the first increment of hydrochloric acid the pH has dropped from its initial value of about 8.5 to about 5.5. It then climbed rapidly at first and then more slowly for about 10 minutes until it leveled off at a pH of about 8.25. At this time a further increment of the acid was added and substantially the same drop and subsequent climb in pH occurred. Additional 2 cc. increments of 1 normal hydrochloric acid were added at 10-minute intervals with very similar results up to the point at which 16 cc. had been added. Upon the addition of each successive increment the maximum pH gradually became lower, while the minimum pH fluctuated to a certain extent. Upon the addition of the next increment of acid, making a total of 18 cc., the pH dropped to about 2.25 and then climbed to a point slightly over 3.0. On adding a further increment of the acid the pH dropped to about 1.5 and remained at that level.

Similar results were noted upon the addition of 2 cc. increments of 1 normal hydrochloric acid to a suspension of 1 gram of magnesium hydroxide in 50 cc. of water. However, this suspension showed a somewhat greater variation of pH and the pH climbed more rapidly after each decline following the addition of an increment of acid. Moreover, it leveled off more quickly at the higher pH so that increments of acid were added at
The pH of this suspension dropped to about 3.5 upon the addition of the first 2 cc. increment of acid and then climbed to 10.4. Upon the addition of 32 cc. of acid in such increments at 5-minute intervals the pH dropped to about 2.25 and then was restored to about 7.5. Upon the addition of 2 more cc. of acid the pH dropped to 2.0 and was then restored to 4.5, while upon the addition of 2 more cc. of acid, for a total of 36 cc., the pH dropped to about 1.75 and remained at that value.

As contrasted with the foregoing tests, a mixture of magnesium hydroxide and a colloidal water-soluble, crosslinked polymer of acrylic acid (Carbopol-934) in equal amounts by weight and totaling 5 grams in 50 cc. of water gave a somewhat similar pattern, but with a maximum pH of 4.5 and a minimum of about 2 until 16 cc. of 1 normal hydrochloric acid had been added at 5-minute intervals in 2 cc. increments. Upon the addition of the last increment of the total of 16 cc. of acid the pH dropped from 5.0 to 1.75 and remained at that level. The cobalt in pH from the low level to the high level following the addition of each increment of acid was more uniform than in the case of magnesium hydroxide alone, and in no case did the maximum pH exceed a value of about 4.5.

To determine the relative speeds of action and ultimate neutralizing effect of various antacid materials, 1 gram of each was suspended in 50 cc. of water, and to this was added at one time a certain number of cubic centimeters of 1 normal hydrochloric acid, the quantity so added to each suspension being about two-thirds of the amount previously determined as tending to exhaust the neutralizing action of the particular antacid material. 32 cc. of acid were added to a suspension of magnesium oxide, and this was found to climb within 1 minute to a pH of about 9. The same amount of acid added to a suspension of magnesium hydroxide was found to raise the pH within 2 minutes to about 5 and then more gradually to about 6.5. This required about 10 minutes. 20 cc. of acid was added to the magnesium carbonate, and the pH climbed within 2 minutes to about 4.8 and then gradually climbed to about 5.2 over a period of 20 minutes. A suspension of a mixture of 5 gram magnesium hydroxide and 5 gram of colloidal water-soluble, crosslinked polymer of acrylic acid (Carbopol-934) in 50 cc. of water, upon having 16 cc. of the 1 normal hydrochloric acid added to it, was found to provide a uniform rise in pH from about 1.4 to about 3.5 within 7 minutes, and then a more gradual rise in pH to about 4 over a total period of 20 minutes.

Other experiments were conducted with different mixtures of magnesium hydroxide and a crosslinked polymer of acrylic acid (Carbopol-934), in which the proportions of the two ingredients varied, showed rather similar patterns to be followed upon the addition of 2 cc. increments of 1 normal hydrochloric acid to a suspension of 1 gram of each in 50 cc. of water.

Thus, in the case of a mixture of 3 parts by weight of magnesium hydroxide to 1 part by weight of the 1% polyallyl sucrose crosslinked polymer of acrylic acid, 1 gram of the mixture was added to 50 cc. of water. An initial pH of about 5.5 was obtained and 2 cc. of 1 normal hydrochloric acid was added. The pH immediately dropped to about 1.75 and climbed, in 5 minutes to about 4.7. Additional 2 cc. increments of acid were added at 5-minute intervals. In each instance the pH dropped to about 1.75 upon addition of the acid and then rose slowly to a maximum value which was, after each successive addition of acid, somewhat lower than the preceding maximum pH. This procedure was repeated until a total of 24 cc. of 1 normal acid were added, at which point the pH remained constant at a value of about 2.

Experiments were also conducted with 1½ to 1 and 2 to 1 parts by weight of magnesium hydroxide to the same crosslinked polyacrylic acid. In each case, the addition of the increments of hydrochloric acid were made promptly after the preparation of the aqueous suspensions and prior to the formation of appreciable quantity of the magnesium salt of the crosslinked polyacrylic acid. Comparisons of the results of these experiments and also the results of the experiments utilizing the 1 to 1 and 3 to 1 ratios of magnesium hydroxide to the crosslinked polymer showed that the mixtures with the higher magnesium hydroxide contents establish a somewhat higher pH after periods of 5 minutes following the addition of each increment, but, as already noted, the maximum pH was about 4.7 for the mixture containing 3 parts of magnesium hydroxide to 1 part of the crosslinked polymer. The other mixtures had somewhat lower maximum pH values. Also, it was found that the mixtures with higher magnesium hydroxide contents served to restore the pH to a higher value more quickly.

The effectiveness of the crosslinked acrylic acid polymer in buffering an antacid solution may be illustrated by repeating the tests set forth above but using other materials which might be utilized in antacid or other similar pharmaceutical preparations as substitutes for the polymers contemplated by the present invention.

For example, an antacid composition was prepared by mixing 3 parts by weight of magnesium hydroxide and 1 part by weight of carboxymethyl cellulose. 1 gram of this mixture was added to 50 cc. of water and a pH of about 10.5 was obtained. Upon the addition of 2 cc. of 1 normal hydrochloric acid, the pH dropped to about 3.5 and then rose rapidly to about 9.5 in about 12 seconds. Additional 2 cc. increments of acid were added at 5-minute intervals and in each case the pH dropped to between 2.5 and 3.5 and rapidly rose in a matter of seconds to a maximum somewhat lower than the preceding maximum pH. This procedure was continued until a total of 24 cc. of 1 normal acid were added, at which point the pH remained constant at about 3.

Comparison of this test with those in which the polymers contemplated by this invention were used vividly illustrates the remarkable superiority of the latter over carboxymethyl cellulose in their ability to buffer the antacid solutions, hence to prevent the undesirable "acid rebound" which occurs in the human stomach when compositions of the antacid are administered.

Other materials, such as various ion-exchange resins, pectin acid and algic acid have been investigated with a view to their possible utility as components of antacid compositions in place of the polymers described herein.

No such other material has been found effective.

While I do not wish to be bound to any theory by which the antacid compositions according to the present invention produce the superior results which may be obtained, it appears that the results are due in part to a buffering and sequestering action by the crosslinked polymer of acrylic acid upon the normally alkaline antacid components which lowers the normal pH obtained with these substances and retards the formation of alkaline salts of the crosslinked polymer of acrylic acid. Consequently, no excessive alkalinity is produced which results in an unwanted acid rebound. Hence under conditions of hyperacidity in the stomach, the customary tendency of these alkaline antacid components to drastically increase the pH of the stomach while the excess hydrochloric acid in the stomach is being neutralized is eliminated. When the antacid compositions of the present invention are placed in plain water, without hydrochloric acid, the pH of the resulting aqueous suspension will increase upon standing for a short period of time (of about 5 to 10 minutes) until the pH is in the alkaline range. This is believed to indicate salt formation between the antacid component and the polymer of acrylic acid. The alkaline salts of the crosslinked polymer of acrylic acid does not have the property of buffering the stomach in the range below a pH of 5.5, and preferably below 4.5, which is
one of the desirable properties of the compositions of the present invention.

While a number of embodiments of the invention have been described in considerable detail and various modifications have been suggested, it will be understood that various other modifications and embodiments may be made within the scope of the appended claims.

What is claimed is:

1. A pharmaceutical antacid preparation comprising a colloidally water-soluble polymer of acrylic acid cross-linked with polyallyl sucrose, and a non-toxic antacid selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium. 11. A pharmaceutical antacid preparation according to claim 1 wherein the antacid is magnesium hydroxide.

2. The pharmaceutical antacid preparation according to claim 1 wherein the antacid is magnesium oxide.

3. The pharmaceutical antacid preparation according to claim 1 wherein the antacid is magnesium carbonate.

4. A pharmaceutical antacid preparation according to claim 1 wherein the antacid is magnesium sulphate.

5. A pharmaceutical antacid preparation comprising a non-toxic colloidally water-soluble polymer of acrylic acid crosslinked with a polyhydroxy compound wherein the hydrogen atoms of at least 3 hydroxyl groups are replaced with unsaturated aliphatic radicals, and a non-toxic antacid selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium. 11. A pharmaceutical antacid preparation comprising a non-toxic colloidally water-soluble polymer of acrylic acid crosslinked with a polyhydroxy alcohol wherein the hydrogen atoms of at least 3 hydroxyl groups are replaced with unsaturated aliphatic radicals, and a non-toxic antacid selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium.

6. A pharmaceutical antacid preparation comprising a non-toxic colloidally water-soluble polymer of acrylic acid crosslinked with a polyhydroxy compound wherein the hydrogen atoms of at least 3 hydroxyl groups are replaced with unsaturated aliphatic radicals having from 2 to 4 carbon atoms, and a non-toxic antacid selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium.

7. A pharmaceutical antacid preparation comprising a non-toxic colloidally water-soluble polymer of acrylic acid crosslinked with a substituted polyhydroxy compound having at least 3 double bonds available for crosslinking purposes, and a non-toxic antacid selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium, said polymer having been subjected to the action of steam to form a porous cake, said cake then having been dried and milled to a predetermined particle size.

8. A pharmaceutical antacid preparation comprising a non-toxic colloidally water-soluble polymer of acrylic acid crosslinked with an unsaturated ester having at least 3 double bonds available for crosslinking purposes, and a non-toxic antacid selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium.

9. A pharmaceutical antacid preparation comprising a non-toxic colloidally water-soluble polymer of acrylic acid crosslinked with an unsaturated saccharide ether having at least 3 double bonds available for crosslinking purposes, and a non-toxic antacid selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium.

10. A pharmaceutical antacid preparation comprising a colloidally water-soluble polymer of acrylic acid crosslinked with from about 0.75% to 1.5% of polyallyl sucrose and magnesium hydroxide, the crosslinked polymer and the magnesium hydroxide being present in a ratio of 1 part by weight of the former to about 1 to 6 parts by weight of the latter.

12. A pharmaceutical antacid preparation comprising a non-toxic colloidally water-soluble polymer of acrylic acid crosslinked with a polyhydroxy compound wherein the hydrogen atoms of at least 3 hydroxyl groups are replaced with allyl groups and a non-toxic antacid selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium.

13. A pharmaceutical antacid preparation comprising a non-toxic colloidally water-soluble polymer of acrylic acid crosslinked with a polyhydroxy alcohol wherein the hydrogen atoms of at least 3 hydroxyl groups are replaced with unsaturated aliphatic radicals, and a non-toxic antacid selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium.

14. A pharmaceutical antacid preparation comprising a colloidally water-soluble polymer of acrylic acid crosslinked with from about 0.75% to about 1.5% of polyallyl succrose and magnesium hydroxide, the crosslinked polymer and the magnesium hydroxide being present in a ratio of 1 part by weight of the former to about 1 to 6 parts by weight of the latter.

A method of treating hyperacidity which comprises administering a suitable quantity of a composition comprising a non-toxic colloidally water-soluble polymer of acrylic acid crosslinked with a polyhydroxy compound wherein the hydrogen atoms of at least 3 hydroxyl groups are replaced with unsaturated aliphatic radicals having from 2 to 4 carbon atoms, and a pharmaceutical suitably stable substance of the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium.

17. A method of treating hyperacidity which comprises administering a suitable quantity of a composition comprising a colloidally water-soluble polymer of acrylic acid crosslinked with from about 0.75% to about 1.5% of polyallyl succrose, and an amount of a non-toxic antacid substance selected from the group consisting of the oxide, hydroxide, carbonate and hydroxy salts of magnesium, said non-toxic antacid substance ranging from an equal amount by weight up to 6 times the weight of said polymer of acrylic acid.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 2,912,358

Ludwig A. Staib, Jr.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 1, line 36, for "bring" read — brings —; column 4, line 5, after "substantially" insert — all—; column 5, line 29, for "abla" read — alba —; column 9, line 54, for "inredients" read — ingredients —.

Signed and sealed this 26th day of April 1960.

(SEAL)
Attest:

KARL H. AXLINE
Attesting Officer

ROBERT C. WATSON
Commissioner of Patents