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COMBINATIONS OF ALUMINUM-COORDINATING THERAPEUTIC ADJUVANTS AND ALUMINUM CHELATES AND PROCESS FOR MAKING AND USING THE SAME

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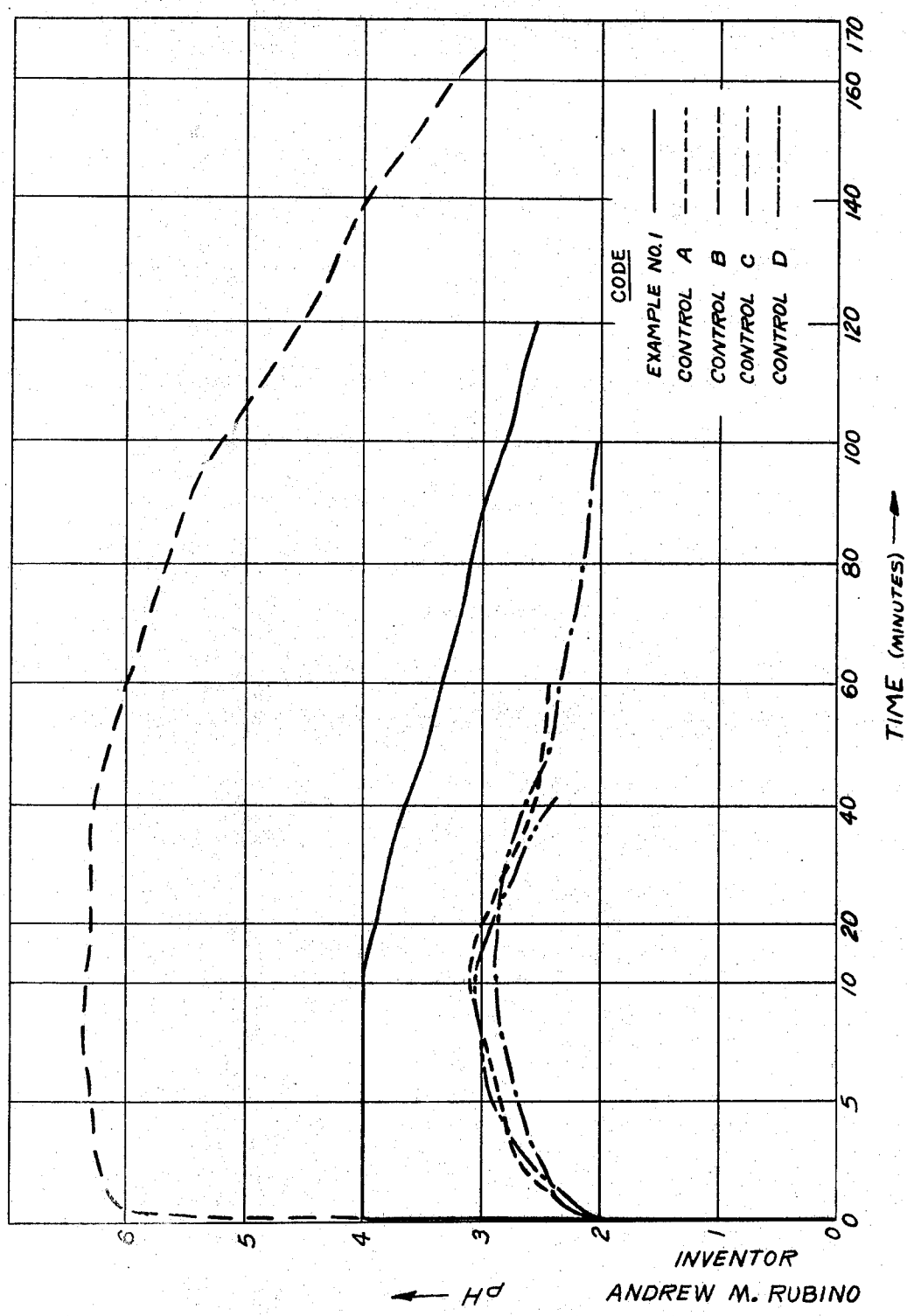

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COMBINATIONS OF ALUMINUM-COORDINATING THERAPEUTIC ADJUVANTS AND ALUMINUM CHELATES AND PROCESS FOR MAKING AND USING THE SAME

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Continuation-in-part of abandoned application Ser. No. 309,612, Sept. 18, 1963. This application July 7, 1967, Ser. No. 651,736

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ABSTRACT OF THE DISCLOSURE

Antacid therapeutic compositions which are orally administered of an aluminum-coordinating therapeutic adjuvant and an aluminum chelate of an alpha or beta hydroxyaliphatic saturated carboxylic acid.

This invention relates to compositions comprising in combination, an aluminum-coordinating therapeutic agent and a nontoxic metal salt of an aluminum hydroxyaliphatic saturated carboxylic acid chelate, to a process for making the same, and to a process for using such compositions therapeutically.

This application is a continuation-in-part of my patent application Ser. No. 309,612 filed Sept. 18, 1963 for: Combination of Aluminum-Chelating Therapeutic Adjuvants and Aluminum Chelates and Process for Making and Using the Same, now abandoned.

In the treatment of many forms of heart disease, ulcers, tuberculosis, rheumatoid arthritis, rheumatic fever, and liver diseases, therapeutic agents such as anticholinergics, antispasmodics, analgesics, sedatives, hypnotics, antituberculosis preparations, antipyretics and diuretics are customarily employed. Many of these, such as the analgesics and antipyretics derived from salicylic acid, for example, aspirin and sodium salicylate, because of their acidity and other factors, cause gastric distress or dyspepsia when taken orally. These side effects are a particular problem in the treatment of patients who have ulcers or who have a predilection for gastric distress upon ingestion of such agents.

Antacids have been used with these therapeutic agents to overcome acidity, but not with complete success. The antacid must, of course, be inert to the therapeutic agent, and effective in its presence. The two components must also be compatible with one another, and with any additional ingredient employed. For convenience in administration of the therapeutic agent (hereinafter referred to as adjuvant), the antacid and the other drug or drugs to be administered should be packaged together without deterioration in their effectiveness over long periods of storage. Preferably, the combination of the therapeutic adjuvant and the antacid should be available not only in liquid form but also in solid form. It should be fast acting, and should produce no deleterious side effects.

However, the antacid-adjuvant combinations available heretofore have not met these ideal requirements satisfactorily. The antacids commonly used, because of cost and compatibility with the adjuvant, have been the magnesium and sodium carbonates and bicarbonates, but these materials are quite alkaline, and are not satisfactory antacids. Many of these conventional antacids tend to increase the pH in the gastric fluids to a level sufficient to cause alkalinosis, while others raise the pH to levels tending to affect the stability of the therapeutic adjuvant or are not sufficiently prolonged in activity to impart sufficient protection. A pH level in the stomach within

the range of from about 3 to about 5 is now generally agreed to be the most comfortable. Magnesium carbonate, for example, produces a pH well beyond the now accepted optimum range of 3 to 5, reaching values as high as 8. This excessive pH, beyond the optimum upper limit of 5, can be maintained for a considerable period. As a result, while pepsin activity is inhibited, the activity of other enzymes capable of causing gastric irritation is promoted. Strongly alkaline materials may in some cases inactivate or break down the therapeutic adjuvants in adjusting the pH to levels in excess of 6 to 7. Obviously the pH buffering range of the antiacid must be tailored to meet the pH requirements of the adjuvant, but most antacids are not capable of modification in this way.

Edwards in The Chemist and Druggist, Dec. 14, 1957, page 647, in discussing the properties of an ideal antacid, has suggested that the nearest approach to the ideal antacid is wet activated alumina gel. Although liquid aluminum hydroxide gel closely approaches the ideal for an antacid, its liquid form makes it inconvenient to use. Also, it is incompatible with therapeutic adjuvants insoluble in or nondispersible with water.

The advantages of the dried alumina gel are obvious. However, dried aluminum hydroxide gel is actually far from an ideal antacid. It exhibits an undesirable lag in its rate of reaction with stomach acids. It does not give a prolonged antacid effect in the optimum pH range, and its antacid properties are severely affected by pepsin. Also, its antacid activity is less than that of the liquid gel, being decreased by the drying, and the reduced activity decreases further with aging. These disadvantages have been noted by Gwilt et al. and other workers in this field. The dry gel therefore is not desirable for use with therapeutic adjuncts in nonaqueous media, the media used in tablets or gelatin capsules.

Aluminum hydroxide gels are particularly prone to have high sodium contents, because of the tendency of the $Al(OH)_3$ to adsorb or occlude sodium or other foreign salts formed as by-products of the reactions by which the antacids are produced. Sodium contents of 2% or more are frequently found. Beekman, Journal of Pharmaceutical Sciences, 51, No. 7, 679–682 (1960), has attempted to produce low sodium content aluminum hydroxide gels, and has succeeded in reducing sodium contents to about 0.02 to 0.3% by substitution of potassium salts for sodium salts in the manufacturing process. However, even these low levels may be too high for some patients.

Further, relative insolubility of the aluminum hydroxide wet gel in the stomach fluids slows its effectiveness. Antacid action is not demonstrated immediately, but instead there is a certain time interval before a sufficient amount of the antacid composition has been dissolved to affect the pH of the stomach. This prevents such compositions from showing their maximum neutralizing effect in the shortest possible time, although they are quite effective in maintaining an optmium pH over a long period of time.

In accordance with the invention, aluminum-coordinating therapeutic adjuvants are combined, usually chemically in a complex or association, with an antacid consisting essentially of a nontoxic metal salt of an aluminum saturated carboxylic acid chelate which is capable of bufflering the acid pH of the adjuvant to within any desired range, such as the optimum range from about 3 to about 5, without overneutralizing to an alkaline pH unless this be desired, and which not only is compatible with the adjuvant but also is capable of solubilizing it in water and in the stomach fluids, as well as in organic solvents such as ethanol, propylene glycol and glycerine. The resulting compositions are as effective in the form of dry solids or in nonaqueous solutions as they are in water

solutions, and hence they can be provided and are effective in any of the desirable forms, including gelatin capsules.

The combination of the therapeutic adjuvant with the chelate antacid, in accordance with the invention, is particularly advantageous as, in the combination, the adjuvant maintains its therapeutic effectiveness for a longer period than it would when administered alone or in combination with the antacids of the prior art. A further advantage is that the chelate antacid-therapeutic adjuvant combinations are, in many instances, more soluble in water than the adjuvant alone, thereby facilitating absorption of the adjuvant by the system.

In the chelate antacids employed in accordance with the invention, the aluminum is chelated in the anionic part of the molecule, by association with the hydroxy group of an alpha or beta hydroxyaliphatic saturated carboxylic acid. Ordinarily, from one-half to all of the coordination positions of the aluminum atom are taken up by reaction with the acid.

In aqueous solution, the nontoxic metal salts of these chelates are in equilibrium with only a very small concentration of aluminum ion. Thus, aluminum is available for antacid activity, which is desirable, but an insufficient amount of aluminum is present to form a salt with the adjuvant, or to precipitate in the form, for example, of aluminum hydroxide, should there be a sufficient amount of hydroxyl ion present to react with the aluminum ion. The amount of aluminum ion in solution is so small that the solubility product of aluminum hydroxide is not exceeded. Indeed, the solubility of the anionic portion including the aluminum ion is so high that even the alkaline earth metal salt is quite water-soluble, corresponding in solubility characteristics to calcium nitrate or calcium chloride, rather than to calcium hydroxide or magnesium hydroxide.

Thus, these chelates are particularly advantageous in the compositions of the invention because of their immediate antacid effect, due to their water solubility. They are immediately soluble in the stomach fluids, and immediately effective as antacids as a result. They impart a sustained antacid effect for a long period of time, due to the slowly released but adequate concentration of aluminum ion provided from the chelate complex. They may also provide a sustained therapeutic effect due to the adjuvant, when the adjuvant is chemically bound or associated with the chelate, because of slow release of the adjuvant. Hence, the compositions of this invention serves as a reservoir, supplying aluminum ion and adjuvant as fast as the available aluminum ion or adjuvant is consumed or dissipated. As a result, one dosage unit of the compositions of this invention can be made to continuously supply aluminum and adjuvant over one and one-half to two hour period, or longer, as required.

Moreover, these antacids can be formulated to yield what ever pH characteristics are required in the final composition within the range from about 3 to about 9. Where desired, the antacid characteristics of the chelate can be adjusted so as to keep the pH of the composition during storage below any critical level and to keep the pH in the stomach upon administration above the hyperacid level. Hence, the antacid chelates may be safely used in conjunction with those therapeutic adjuvants susceptible to breakdown or loss of therapeutic effectiveness at pH values above 5, of the order of 6.5 or more, and they are particularly advantageous for this purpose because of their antacid characteristics which are obtained upon administration in either the wet or dry form.

The nontoxic metal salts of these aluminum hydroxy saturated carboxylic acid chelates used as the antacid component in the compositions of the invention correspond to the empirical formula:

$$M_{m+y}[Al_2(OH)_xCl_y(OOC{-}\underset{\substack{|\\ O-}}{R})_m(OOC{-}R{-}OH)_n]$$

where y, m, n, and x are numbers whose sum is such as to balance the positive valences of the nontoxic metal cation and aluminum, $m+y$ is the total number of gram atoms of the metal cation represented by M in the above formula. The total number of gram molecular weights of the hydroxyaliphatic saturated carboxylic acid is represented by $m+n$. The value of m will ordinarily range from 1 to 3, n from 0 to 3, and y from 0 to 1.5. It will be understood that m and n represent average numbers and need not be integers.

The nontoxic metal cation M is selected from the group consisting of alkali metals, alkaline earth metals, and bismuth. However, sodium is not used where a low sodium content combination is desired, as, for example, in treatment or heart or liver diseases.

R is an aliphatic or hydroxyaliphatic group, the residue of the hydroxyaliphatic saturated carboxylic acid, wherein at least one hydroxy group is alpha or beta to the carboxylic group, and wherein there can be one or a plurality of hydroxy groups. R has at least one hydroxy group and at least one carboxylic acid group for each one of six carbon atoms.

It will be evident from the above that m represents the number of gram molecular weights of hydroxy saturated carboxylic acid in which the hydroxy hydrogen has been neutralized and n the number of gram molecular weights of hydroxy carboxylic acid having an unneutralized hydroxy group. Both where the hydroxy hydrogen is neutralized and where it is not neutralized, the oxygen atom is coordinated directly to the aluminum atom.

In the above formula, the nontoxic metal M is cationic, and the remainder of the molecule enclosed within the brackets is anionic. Thus, the aluminum is entirely in the anionic portion of the molecule.

The value of y in the above formula can be widely varied within the limits indicated. Satisfactory complexes are obtained when the proportion of aluminum to chlorine in the complex is approximately 1.5 to 2.5:1.

It is also possible to formulate complexes in which y is 0, i.e., no chlorine is present. Such complexes are quite satisfactory.

As an example, when y is a positive number and the hydroxy saturated carboxylic acid is lactic acid, the forformula takes on the specific representation:

$$M_m + {}_y[Al_2(OH)_xCl_y(OOC\underset{\substack{|\\ O-}}{C}HCH_3)_m(OOCCHOHCH_3)_n]$$

in which m, n, y, x and M are the same as above. The total of $m+n$ is within the range of 2 to 6, and x is 6 minus $(m^1+n)-y$.

A complex free from chlorine, namely where y equals zero, and incorporating lactic acid has the formula:

$$M_m[Al_2(OH)_x(OOC\underset{\substack{|\\ O-}}{C}HCH_3)_m(OOCCHOHCH_3)_n]$$

As the hydroxy saturated carboxylic acid, any aliphatic carboxylic acid in which the hydroxy group is alpha or beta to the saturated carboxylic acid group can be employed. The acid may contain a plurality of hydroxy groups, provided at least one is in the alpha or beta position, and the acid may also include a plurality of carboxylic acid groups, provided again that at least one hydroxy group is alpha or beta to at least one of the saturated carboxylic acid groups in order that a 5 or 6 membered chelate ring is formed which includes the aluminum ion and the hydroxy saturated carboxylic acid. Typical hydroxy aliphatic acids that can be employed include lactic acid, glycolic acid, gluconic acid, trihydroxy glutaric acid, citryl triglu-conic acid, citryl digluconic acid, citryl monogluconic acid, tartaric acid, malic acid, citric acid, tetrahydroxy adipic acid, and citramalic acid.

It is important to note that the hydroxy saturated carboxylic acid is, in each instance, aluminum-chelating and

[1] m is understood to be divalent.

nontoxic under the conditions of use as well as water-soluble, and soluble in polyhydric alcohols.

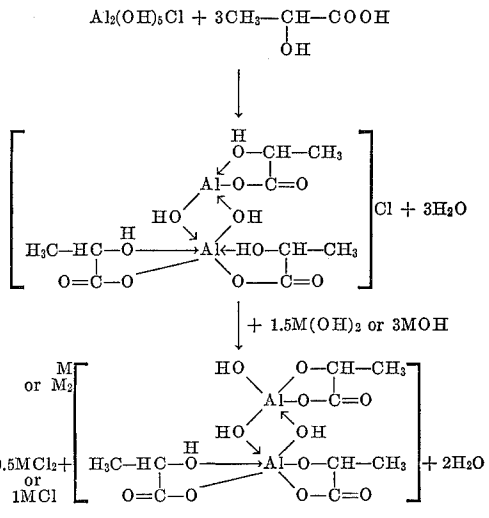
The aluminum chelates used in combination with the therapeutic adjuvant in accordance with the invention are prepared by reacting the aluminum compound with the hydroxy saturated carboxylic acid under carefully controlled conditions. As the aluminum compound in preparing a chlorine-free product, an alkali metal aluminate can be employed, such as sodium or potassium aluminates, or reactive aluminum hydroxide such as in the form of the gel, either dry or wet. Chlorine-containing aluminum chelates are obtained by reaction of the acid with an aluminum chlorhydroxy complex corresponding to the formula:

$$Al_2(OH)_xCl_y$$

in which the sum of x and y is 6, and x and y are each at least 1.

A proportion of acid is employed to establish the best pH level for the finished chelate and is adequate to take up at least 3 up to a total of 6 of the chelating positions of the aluminum, which total 6. The number of positions taken up by one mole of the hydroxy saturated carboxylic acid will depend upon the available chelating groups in the acid. In the case of lactic acid, one mole of the acid will take up 2 coordination positions, to a total of 3 moles per aluminum atom, when all 6 of the coordinating positions of the aluminum atom are taken up. Thus, in the case of lactic acid, from 1.5 to 3 moles of the acid per aluminum atom gives satisfactory results.

For example, 1.5 moles of lactic acid per aluminum atom give the following probable reaction:



In the case of citric acid, if all three of the carboxylic acid groups and the hydroxyl group react, one mole of the acid will take up four coordination positions of each aluminum atom. However, all of these chelating groups need not react, and in this event a greater amount of the acid could be used without fully coordinating the aluminum.

After all of the acid has been chelated with the aluminum, the pH of the composition is adjusted to within the desired range. If the pH is too acid, an alkali metal, an alkaline earth metal or a bismuth hydroxide or carbonate may be added, in the amount required. In some cases, it may be necessary to employ an acid to adjust the pH downwardly.

The chealting reaction can be carried out in any aqueous solution. Ordinarily, water or an aqueous solution of a water-miscible organic liquid such as, for example, any

of the aliphatic alcohols, ethanol, glycerol and propylene glycol can be used. The medium chosen must be one in which the aluminum chelate is soluble.

It is usually necessary to heat the reaction solution at an elevated temperature below the decomposition temperature of the chelate within the range from about 35° C. to the boiling point of the solution to effect the chelation. However, gluconic acid chelates readily at room temperature. Elevated temperatures in particular may be preferred when the aluminum is supplied initially in the form of an aluminum chlorhydroxy-complex, and the chelating acid is lactic acid and citric acid, the heating temperature preferably does not exceed 75° C. The reaction involves first a decomplexing action on the chlorhydroxy complex, in contact with the chelating acid. The chelating acid obtains access to the aluminum, and the aluminum then undergoes chelation, so as to withdraw aluminum ions from the chlorhydroxy complex into the chelating acid complex.

The reaction is continued until chelation is substantially complete. From ½ to 5 hours may be required at temperatures of from 60 to 100° C., and correspondingly longer times at lower temperatures. As a test to determine when reaction is complete, no precipitation of aluminum is obtained when a sample of the solution is heated with an ionic precipitant for aluminum, such as ammonia or a sodium hydroxide solution for about a half hour at 70° C.

At the substantial completion of the chelation, the pH of the complex is adjusted to within the range from about 3 to about 9. This makes it possible to adjust the pH in the stomach by an addition of an apropriate amount of the aluminum chelate to maintain any pH within this range as may be required for the specific therapeutic adjuvant to be administered. The pH adjustment as indicated above is normally accomplished by incorporating a sufficient amount of nontoxic alkali metal, alkaline earth metal or bismuth hydroxide or basic salt, such as the carbonates, as for example, sodium hydroxide or carbonate, magnesium, hydroxide or carbonate, or calcium hydroxide or carbonate. The term "carbonate" includes the bicarbonates. The nontoxic metal thus forms a salt with the aluminum chelate, and this salt is water-soluble. In some instances, small quantities of ammonium hydroxide or basic salt can be added in addition to the alkali metal, alkaline earth metal or bismuth compound to more rapidly increase the pH.

These chelates are capable of forming water-soluble complexes, which may be chemical in nature, or merely physical associations, with other aluminum-coordinating compounds, and this property, previously unknown, is utilized in accordance with the invention to form such complexes with aluminum-coordinating therapeutic compounds or adjuvants.

By selection of the appropriate chelate, having the desired number of coordination positions of the aluminum atom taken up by the organic acid, and/or the desired number of chlorine atoms per molecule of the aluminum organic acid chelate and the desired pH buffering range, it is possible to formulate complexes suitable for use with any aluminum-coordinating therapeutic adjuvant. Fer example, a particularly satisfactory anticholinergic composition is comprised of an anticholinergic therapeutic adjuvant, diethyl (2-hydroxyethyl)methyl-ammonium alpha-phenylcyclohexaneglycolate bromide and a lactic acid chelate of the structure indicated above wherein the sum of $m+n$ is in the range of 3 to 5, y is 1 and M is 2 to 2.5. The pH of this comopsition in aqueous solution as well as after administration is maintained below about 7, and this prevents decomposition of this therapeutic adjuvant, which normally occurs at a pH in excess of 7. In the case of acidic therapeutic adjuvants, such as acetyl salicylic acid, para-amino salicylic acid, and nicotine acid, the combination of the therapeutic adjuvant and the chelate prevents the hyperacidity frequently experienced upon ad-

ministration of the adjuvant in its unbuffered state. Although the primary functions of an antacid are to prevent decomposition of the adjuvant in vivo and to prevent hyperacidic discomfort, caution must also be exercised to keep the pH of the composition during storage below the decomposition level and to prevent intra-gastric pH rise above this level after administration.

The therapeutic compositions of this invention comprise the antacid chelates in conjunction with any of the conventional aluminum-coordinating chelating therapeutic agents. An aluminum-coordinating chelating therapeutic agent is one which has available coordination chelation with aluminum at least one coordinating functional group such as: hydroxyl, carbonyl, keto, carboxyl, ester, oxime, amino, imino, pyridyl, amido, sulfonate, and sulfide groups. Some of the adjuvants may possess a multiplicity of such functional groups within the same molecule. If two or more of these groups in proper juxtaposition to each other coordinate simultaneously with aluminum, then 5 or 6 membered chelate rings can be formed to include the aluminum ion therein. These embodiments having 5 or 6 membered chelate rings constitute preferred embodiments, and include by way of example chelate rings comprising acetyl-salicylic acid, mandelic acid, para amino salicyclic acid, nicotinic acid, and salicyclic acid.

The composition of this invention retain undiminished at least that degree of therapeutic effectiveness that each of the components of the composition would display if administered alone, i.e., the antacid effectiveness of the chelate component is undiminished and the therapeutic properties of the adjuvant are retained unimpaired. Indeed, the therapeutic benefits obtained from conventional therapeutic adjuvants may actually be enhanced as a result of the decrease or elimination of hyperacidic discomfort and/or the increase in the duration of their effectiveness and/or the increase of the solubility of the adjuvants obtained with the comopsitions of the invention.

This invention is of particular benefit when the therapeutic agent is sparsely soluble or insoluble in aqueous solution, such as when, for example, the solubility of the therapeutic agent is less than about 0.5 part by weight per 100 parts of water at ambient temperature, since such agents, e.g., salicylic acid, by virtue of their increased solubility when employed as adjuvants in the compositions of this invention, have a greatly increased effectiveness.

Preferred aluminum-coordinating therapeutic agents are the anti-cholinergics, the anti-spasmodics, the analgesics, the anti-pyretics, the sedatives, the hypnotics, anti-tubercular preparations, diuretics, anti-rheumatic fever agents, anti-anemia agents, anti-hypercholesteremia agents and urinary antiseptics which contain the aforesaid functional groups. Examples of anti-cholinergic agents suitable for use in the invention are diethyl (2-hydroxyethyl) methylammonium alpha-phenyl-cyclohexaneglycolate bromide otherwise known as antrenyl bromide; scopolamine methyl bromide; and (3-carbamoyl-3,3-diphenylpropyl) diisopropylmethylammonium iodide, known commercially as isopropamide. Suitable anti-spasmodics are illustrated by 2-diethylaminoethyl diphenylacetate hydrochloride; atropine sulfate; and n-methyl-4-phenyl-4-carbethoxypiperidene hydrochloride (meperidine hydrochloride). The analgesics and anti-pyretics include, for example, aspirin, acetophenetidin, both of which are frequently mixed with citrated caffeine, as well as para amino salicylates, salicylic acid, salicylamide, acetanilide and 4'-hydroxyacetanilide. Typical sedatives and hypnotics include phenobarbital and barbiturate derivatives; scopolamine hydrobromide and 2-monobromisovalerylurea. Examples of the antitubercular preparations are p-amino-salicylic acid and 2-ethylthioisonicotinamide. Diuretics are illustrated by aminophylline. Antirheumatic fever agents such as p-amino benzoic acid (used in conjunction with salicylates) are also within the scope of the invention, as are antianemia agents like ferrous gluconate, and anti-hypercholesteremia agents like incotinic acid, as well as urinary antiseptics such as mandelic acid.

The compositions of this invention are prepared by mixing the nontoxic metal salt of an aluminum hydroxy saturated carboxylic acid chelate or the reactants used in forming such a chelate and the therapeutic adjuvant in a suitable liquid medium in which the chelate is soluble and in which the adjuvant is either soluble or readily dispersible. Water and water-miscible nontoxic inert organic solvents and aqueous solutions thereof, such as, for example, ethanol, glycerol, and propylene glycol are preferred liquid media. Water should be present when the aluminum complex is being formed in situ; in other cases an organic solvent can be used. The mixture is reacted, preferably with agitation, at a temperature within the raneg from about 15° C. to a temperature below the decomposition temperature of the composition, usually not in excess of about 100° C., and preferably from about 35° C. to about 50° C., until a clear solution results. Reaction usually does not require more than one-half hour, but longer heating does no harm unless the adjuvant is heat sensitive.

When the compositions of this invention are made by mixing the adjuvant with the complex forming reactants, i.e., the alpha or beta hydroxy aliphatic saturated carboxylic acid, the aluminum compound, and the nontoxic metal compound, the reaction is carried out under conditions sufficient to ensure the formation of the complex. the conditions necessary for complex formations are set forth above.

The therapeutic compositions of this invention can be administered in liquid form, i.e., in solution or dispersion, or in the solid form. Where desirable, the compositions can be admixed with suitable nontoxic pharmacologically acceptable excipients. Other ingredients can be admixed with the therapeutic compositions of this invention including sweetening agents such as glucose, dextrose or saccharine; lubricants such as magnesium stearate, thickening agents such as starch as well as any necessary preservatives, colorants, flavorants, and the like.

The dosage of the therapeutic compositions of this invention to be administered will depend upon the nature of the therapeutic adjuvant used to prepare the specific composition and will be determined in accordance with the conventional dosage for the particular adjuvant. In general, a sufficient amount of the composition of this invention will be administered to supply the requisite amount of therapeutic agent required for any individual case, as determined by reference to conventional methods and techniques.

The compositions of the invention retain the known therapeutic properties of the adjuvant and the known antacid properties of the chelate antacids without any loss in effectiveness, and hence are used both as therapeutic agents and as antacids in the conventional manner familiar to those skilled in the art.

For convenience, the compositions of this invention can be prepared in dosage unit form such as for example, in the form of an elixir, a powder, as tablets or as capsules. Where a powdered material, encapsulated or not, is desired, the solution prepared as described above may be processed to remove the liquid solvent such as water and produce a solid product. In such instance, the liquid solvent employed should preferably be volatile at a temperature below the decomposition temperature of the composition under atmospheric or reduced pressure. Conventional methods can be employed to remove the reaction medium such as, for example, spray drying or vacuum drying. After drying, the product if not already in powdered form can be pulverized and can be used or encapsulated as such or in admixture with suitable extenders, or tablets may be made therefrom in acccordance with conventional tabletting procedures.

When a therapeutic elixir is desired, the liquid reaction mixture obtained as above can be used directly or it can be diluted with a suitable solvent or other liquid

pharmacologically acceptable excipients and other additives can be employed as indicated above. If desired, the solution obtaiined as above can be dried to obtain a solid material which can then be dissolved or dispersed in a different liquid excipient as required. Non-aqueous solutions of the compositions of this invention are of particular advantage because they can be packaged in soft gelatin capsules. Heretofore antacid-containing therapeutic compositions not be packaged in such capsules.

When the compositions of this invention are prepared in dosage unit form, it is generally desirable that each dosage unit contain from about 0.05 to about 25% by weight of the therapeutic composition. More dilute and more concentrated concentrations can also be employed where necessary.

The proportions of the nontoxic metal salt of the aluminum carboxylic acid chelate to the therapeutic adjuvant used in preparing the compositions of this invention will depend upon the pH range and the therapeutic activity desired in the final product. There is no upper limit on the quantity of the chelate except that an amount that would cause adverse side effects would not be used. The amount of chelate antacid is at least enough to ensure that the desired pH is obtained. The ratio normally will be within the range from about 20:1 to about 1:20, expressed as the ratio of the total weight of the chelate to the total weight of the therapeutic adjuvant.

The antacid effectiveness of the compositions of the invention is determined by the method of Holbert, Noble and Grote, Journal of the American Pharmaceutical Association (Scientific Edition), 36 149 (1947; 37 292 (1948); 41 361 (1952)), as modified by Steward M. Beekman, 49 191 (1960). In this method, a test sample of antacid is added to 150 ml. of artificial gastric juice consisting of 0.0316 N hydrochloric acid (pH=1.5) containing 2 g. of pepsin N.F. per liter. The artificial gastric juice is maintained at a temperature of 37.5° C. The test procedure is carried out by continuously introducing fresh artificial gastric juice, beginning with the tenth minute of the test period, and removing the antacid-gastric juice mixture by overflow at the rate of 2 ml. per minute. The antacid effect is determined by measuring the pH of the artificial gastric juice during the test period, which is two hours or longer.

The following examples, in the opinion of the inventor, represent the best embodiments of the invention.

EXAMPLE 1

A sodium aluminum lactate chelate (molecular weight ratio lactic acid; aluminum 2.5:1) was prepared as follows: 106 g. of sodium aluminate containing 45% aluminum oxide was dissolved in 450 g. of water and then reacted with 160 g. of an aqueous 80% solution of lactic acid and 135 g. of 58% w./w. sodium lactate solution. The solution was maintained at 40° C. during preparation an dried at 45° C., under vacuum. 25 g. of the dry product was dissolved in 75 g. of glycerine.

Ten grams of acetylsalicylic acid (aspirin) was then added to the glycerine solution of sodium aluminum lactate, and 100 mls. of absolute ethanol was added and the mixture was maintained with stirring at a temperature of 30° C. for about one hour, whereupon a clear solution was obtained containing 5.3% of acetylsalicylic acid and the equivalent of 2.4% Al_2O_3.

For comparison, the following also were tested:

Control A.—1.75 tablets of a commercial preparation containing 5 grains of acetylsalicylic acid and 1.5 grains of magnesium carbonate per tablet, suspended in 9 mls. of water.

Control B.—2 tablets of the same commercial preparation as in Control A, suspended in 9 mls. water.

Control C.—2 tablets of a commercial preparation containing 0.325 g. aspirin, 0.195 g. monocalcium phosphate, 1.95 g. sodium bicarbonate and 1.05 g. citric acid per tablet, suspended in 35 mls. water.

Control D.—1.85 tablets of another commercial preparation, containing 0.3 g. aspirin and 0.15 g. magnesium-aluminum hydroxide mixture per tablet, suspended in 9 mls. water.

The antacid effectiveness of the above solutions, each in a dose containing the equivalent of one gram of acetylsalicylic acid, together with the solution obtained in accordance with Example 1, were determined by the Holbert, Noble and Grote test procedure.

TABLE I

	pH of Artificial Gastric Juice				
		Controls			
	Example 1	A	B	C	D
Time (Minutes):					
0	1.85	1.6	1.5	1.6	1.8
0.25	4.0	2.0	2.05	4.5	2.0
0.5	4.0	2.2	2.13	5.5	2.1
1	4.0	2.3	2.31	6.1	2.25
2	4.0	2.6	2.47	6.2	2.5
3	4.0	2.7	2.55	6.25	2.7
4	4.0	2.8	2.64	6.25	2.8
5	4.0	2.85	2.69	6.30	2.9
6	4.0	2.9	2.75	6.30	2.95
7	4.0	2.95	2.79	6.35	3.0
8	4.0	3.0	2.82	6.35	3.0
9	4.0	3.05	2.87	6.35	3.05
10	4.0	3.1	2.89	6.35	3.05
20	3.9	3.0	2.87	6.30	2.9
30	3.8	2.8	----	6.30	2.7
40	3.65	2.6	2.65	6.25	2.5
50	3.45	2.5	2.45	6.15	----
60	3.35	2.45	2.35	6.0	----
70	3.20	----	2.23	5.85	----
80	3.10	----	2.15	5.65	----
90	3.0	----	2.10	5.50	----
100	2.8	----	2.04	5.20	----
110	2.7	----	----	4.90	----
120	2.55	----	----	4.50	----
130	----	----	----	4.25	----
140	----	----	----	3.95	----
150	----	----	----	3.60	----
165	----	----	----	3.0	----

The above data show that the chelate antacid-therapeutic adjuvants combination in accordance with the invention sustain pH within the desirable range from about 3 to about 5 for approximately 90 minutes. On the other hand, the commercial preparations either produced an excessive initial pH rise (Control C) or did not sustain a pH within the desirable range for more than about 15 minutes (Controls A, B and D). Further, Controls A, B and D do not reach a pH significantly above about 3 at any time, while the combination chelate antacid-therapeutic adjuvant in accordance with the invention maintained a pH within the desired range from within 15 seconds of administration for a total of 1½ hours.

The composition of Example 1 was also tested to determine the duration of the therapeutic effectiveness of the adjuvant in the system as evidenced by the presence of salicylic acid in the urine and blood of test animals after oral administration. The test animals used were Wistar rats weighing approximately 300 grams. These rats were fasted overnight prior to administration of about 3.3 ml./kilo of the undiluted product of Example 1. Urine specimens were collected from 2 rats for 3 days following feeding of the test dose. Blood samples were collected from 7 additional rats at various time intervals ranging from 5 minutes to 48 hours following feeding of the test dose. For comparison, an equal number of rats were fed the same dose of acetyl salicylic acid, U.S.P., in 50% ethyl alcohol.

The following results were obtained:

[Composite results of 7 rats on each sample]

Time after feeding	Sample Obtained in Accordance with Example 1	Sample Consisting of Acetyl Salicylic Acid in 50% Ethanol
5 Minutes	−	−
10 Minutes	−	+
15 Minutes	+	+
20 Minutes	+	+
30 Minutes	+	+
40 Minutes	+	+
50 Minutes	+	+
1 Hour	+	+
2 Hours	+	+
4 Hours	+	+
6 Hours	+	+
7 Hours	+	+
17 Hours	+	−
20 Hours	+	−
24 Hours	+	−
25 Hours	−	−
30 Hours	−	−
48 Hours	−	−

+ Salicylic Acid detected.
− Salicylic Acid not detected.

TABLE III.—PRESENCE OF SALICYLIC ACID IN THE URINE TEST ANIMALS

Sample Obtained in Accordance with Example 1:
Rat No. 1—+ for 2 days.
Rat No. 2—+ for 3 days.
Sample Consisting of Acetyl Salicylic Acid in 50% Ethanol:
Rat No. 1—+ for 2 days.
Rat No. 2—+ for 2 days.

The above results demonstrate that the compositions of the invention retain their therapeutic effectiveness for a longer period than is obtainable with the therapeutic adjuvant alone.

EXAMPLES 2 TO 13

The following examples were performed to demonstrate the effectiveness of the combination of the chelate antacids with the analgesics and antipyretics.

EXAMPLE 2

20 g. acetophenetidin and 250 ml. of ethanol were added to 150 g. of a solution containing 25% of sodium aluminum lactate in glycerine prepared as described in Example 1. This antacid chelate solution contained the equivalent of 4.25% Al_2O_3. The final mixture was agitated at 35° C. for one-half hour under reflux. A clear solution having both antacid and analgesic properties resulted.

EXAMPLE 3

This example represents an analogy to the typical aspirin, acetophenetidin and caffeine type of system frequently used in commercial preparations. 10 g. of citrated caffeine, 20 g. of acetylsalicylic acid were suspended in 300 ml. of absolute ethanol. This was added to 250 g. of the solution containing 25% sodium aluminum lactate in glycerine described in Example 1. This system was maintained at 40° C. for one-half hour under reflux and agitation, whereupon a clear, very light pink solution resulted. The composition displayed the therapeutic effectiveness of the adjuvants and satisfactory antacid properties.

EXAMPLE 4

10 g. of citrated caffeine, 20 g. of 4'-hydroxy-acetanilide and 20 g. of salicylic acid were suspended in a solution of 200 ml. of absolute ethanol and 100 ml. of water. This suspension was added to 250 g. of a 25% solution of the same sodium aluminum lactate solution in glycerine as in Example 1. The system was heated with agitation under reflux at 40° C. for one-half hour, whereupon a clear, light pink solution having antacid, analgesic and antipyretic properties resulted.

EXAMPLE 5

Sodium aluminum chlorohydroxy lactate (8.0% Al_2O_3) was prepared by mixing 218 grams of aluminum chlorhydroxide $Al_2(OH)_5Cl$, 50% aqueous solution, with 100 grams of deionized water and 210 grams of 80% lactic acid, reacting with agitation at 70° C. for 2 hours, and thereafter adding 128 grams of 50% sodium hydroxide solution to adjust the pH to 6.2. The product contained about 5.6% sodium and about 25% lactic acid prior to drying. This represents a lactic acid to aluminum ratio of 1.85 moles of acid to 1.0 gram atoms of aluminum. The sodium aluminum chlorhydroxy lactate was then dried at 45° C., in vacuo, and dissolved in glycerine.

3 g. of acetylsalicylic acid was added to a mixture of 30 ml. of absolute ethanol and 30 g. of a 25% solution of the sodium aluminum chlorhydroxy lactate, prepared as described above, in glycerine. This glycerine solution contained 4.2% Al_2O_3. A clear colorless, analgesic solution was obtained, which was also effective as an antacid. The lower pH sodium aluminum chlorhydroxy chelate complex was employed in order to minimize hydrolysis of the acetylsalicylic acid in the finished preparation, even though the medium is essentially anhydrous.

EXAMPLE 6

10 g. of acetylsalicylic acid was dissolved in 100 ml. of absolute ethanol. This was added slowly with agitation at 30° C. to 100 g. of a 20% magnesium aluminum hydroxy lactate solution in anhydrous glycerine. The mixture of acetylsalicylic acid, ethanol and the chelate antacid solution in glycerine was agitated at room temperature for one-half hour, whereupon a clear solution of antacid, analgesic and antipyretic properties was obtained.

The magnesium aluminum hydroxy lactate was prepared by mixing 1000 g. of aluminum hydroxide compressed gel, 10.2% Al_2O_3 with 450 g. of lactic acid, 80% solution and 290 ml. of deionized water. The solution thus formed was heated at a temperature of 60° C. for 2 hours. Thereafter 74.6 g. of magnesium carbonate powder, 42% MgO was added and the mixture was heated for an additional 4 hours at 65° C. to form a clear aqueous solution of magnesium aluminum hydroxy lactate. This solution was dried at 60° C. for 12 hours (in vacuo) to obtain the chelate in the form of a dry solid which was thereafter dissolved in anhydrous glycerine.

EXAMPLE 7

2 g. of salicylamide, 2 g. of 4'-hydroxyanilide, 2 g. of acetophenetidin, and 0.5 g.of citrated caffeine were suspended in a mixture of 10 ml. of water, 30 ml. of absolute ethanol and 10 g. of sorbitol 70% solution. This suspension was added with agitation to 40 g. of a 25% solution of sodium aluminum lactate in glycerine prepared as described in Example 1.

This system was maintained under reflux at 35° C. for one-half hour. A clear, light yellow solution useful as an analgesic antipyretic and antacid resulted.

EXAMPLE 8

25 ml. of a 10% solution of acetylsalicylic acid in absolute ethanol was mixed with 50 grams of a 25% solution of sodium aluminum chlorhydroxy lactate in 99.5% glycerine. The combination was agitated for one-half hour after which a clear solution was obtained, the pH being 7.0. The solution retained the therapeutic properties of the acetylsalicylic acid as well as the antacid properties of the sodium aluminum chlorhydroxy lactate. A 1:10 dilution of this solution in distilled water yielded a pH of 6.2. The sodium aluminum chlorhydroxy lactate used in this example was prepared by mixing 218 g. of aluminum chlorhydroxide $Al_2(OH)_5Cl$, in a 50% aqueous solution, with 120 g. of deionized water and 170 g. of 80% lactic acid, reacting with agitation at 60° C. for two hours, and thereafter adding 128 g. of 50% sodium hydroxide solution to adjust the pH to 8.4. The resultant solution of sodium aluminum chlorhydroxy lactate contained 5.6% sodium, 8.4% Al_2O_3 and had a molar ratio of lactic acid to aluminum of 1.5 to 1. The chelate antacid solution was

then dried at 45° C. in vacuo to obtain a dry solid, which was then dissolved in glycerine.

The chelate antacid-therapeutic adjuvant complex was then aged for six months. At the end of this period the U.S.P. free salicylates analysis showed that the system contained less than one-tenth of 1% free salicylate.

EXAMPLE 9

100 g. of a 25% solution of sodium aluminate lactate in glycerine containing 4.5% Al_2O_3 was mixed with 50 ml. of a 10% solution of aceylsalicylic acid in absolute ethanol. The sodium aluminum lactate was prepared as described in Example 1.

This system was agitated for one-half hour at 30° C. A clear, light yellow solution, useful as an analgesic, antipyretic and antacid, resulted.

EXAMPLE 10

100 g. of the same 25% solution of sodium aluminum lactate in glycerine used in Example 1 was reacted with a solution of 20 g. of salicylic acid in 100 ml. of anhydrous ethanol.

This system was agitated under reflux for one-half hour at 40° C. A faintly pink, clear solution resulted, the pH of which was 6.0. The solution retained the therapeutic properties of the salicylic acid and the antacid properties of the chelate.

EXAMPLE 11

100 g. of the sodium aluminum lactate solution used in Example 1 was reacted with 200 ml. of a solution of 16.5 g. of salicylamide, in 200 ml. of anhydrous ethanol.

This solution was stirred for one-half hour at 35° C. under reflux. A light yellow, clear solution retaining the therapeutic properties of both the adjuvant and the antacid resulted, the pH of which was 7.0.

EXAMPLE 12

(A) 5 ml. of the resulting solution from Example 8 was mixed with 8 ounces of tap water. A clear solution resulted.

This is by way of illustration that the product of the invention may be diluted with the appropriate quantities of water for oral ingestion without precipitation of the active ingredients.

(B) 5 ml. of the resulting solution from Example 9 was diluted with 8 ounces of tap water to form a clear solution to again illustrate that the combinations of the invention will not precipitate on dilution.

(C) 5 ml. of each of the resulting complexes from Examples 10 and 11 were mixed individually with 8 ounces of tap water, and in each case, clear solutions resulted.

EXAMPLE 13

1.0 g. of acetophenetidin was dissolved in 18 ml. of anhydrous ethanol. This solution was reacted with 10 g. of a 25% solution of sodium aluminum lactate in glycerine, as previously described in Example 1.

This system was reacted at 40° C. for one-half hour under reflux. A clear analgesic and antipyretic solution displaying antacid effectiveness resulted, the pH of which was 8.2.

EXAMPLES 14 TO 16

These examples illustrate the combination of the chelate antacids with the anticholinergics.

EXAMPLE 14

10 g. antrenyl bromide (diethyl (2-hydroxyethyl) methylammonium alpha-phenylcyclohexaneglycolate bromide), an anticholinergic, was disoslved in 100 ml. of absolute ethanol. This was stirred into 200 g. of a 25% solution of sodium aluminum lactate in glycerine. A clear, colorless solution having anticholinergic and antacid properties was obtained.

The sodium aluminum lactate-glycerine solutions employed in this example differs from that used in Example 1 in that the solid which was dissolved in glyverine was prepared as in Example 1 except that a greater quantity of lactic acid was employed to achieve an end pH in water of 6.5. This aqueous solution was then vacuum dried to a virtually anhydrous product prior to dissolving it in 99.5% glycerine. This was done to prevent the hydrolytic breakdown of antrenyl bromide, which occurs in solutions above pH 7.

EXAMPLE 15

0.5 g. of the same anticholinergic used in Example 14 together with 1.0 g. of phenobarbital were dissolved in 25 ml. of absolute ethanol. This solution was added to 50 g. of 25% sodium aluminum lactate in glycerine. The sodium aluminum lactate aqueous solution which was dried down to form the solid which was dissolved in glycerine was prepared as previously described in Example 14 in aqueous solution to yield a pH of 6.5. The antacid-therapeutic adjuvant was obtained in the form of a colorless solution which retained, undiminished, the therapeutic properties of both its constituents.

EXAMPLE 16

A 45% solution of magnesium aluminum hydroxy gluconate was prepared as follows: 1000 g. of aluminum hydroxide gel (10.2% Al_2O_3) was reacted with 713 g. of glucono-delta-lactone at 60° C. for 2 hours. At the conclusion of the chelation to form the aluminum hydroxy gluconate, 260 g. of $Mg(OH)_2$ paste, 31% MgO, was added and allowed to react with this solution at 70° C. for 2 hours. A clear, stable aqueous solution of magnesium aluminum hydroxy gluconate was thus obtained. This chelate solution had a pH of 6.5 and contained 5.2% Al_2O_3 and 4.25% MgO.

0.5 g. of the same anticholinergic used in the two preceding examples was dissolved in a mixture of 10 g. of 70% sorbitol solution, 20 g. of distilled water and 50 g. of the 45% solution of magnesium aluminum hydroxy gluconate in water, prepared as described above. A clear solution having antacid as well as anticholinergic properties resulted.

EXAMPLES 17 AND 18

These examples illustrate the combination of the chelate antacids wtih the sedatives and hypnotics.

EXAMPLE 17

25 g. of barbital (5,5-diethyl barbituric acid) was suspended in 200 ml. of absolute ethanol. This was added with agitation to 150 g. of the same sodium aluminum lactate solution used in Example 1.

This system was maintained under reflux for one-half hour at 40° C. A clear, colorless solution having both sedative and antacid properties resulted.

EXAMPLE 18

1.0 g. of phenobarbitial and 1.0 g. of 2-diethylaminoethyl diphenylacetate hydrochloride, an anti-spasmodic, were dissolved in 25 ml. of absolute ethanol. This was added to 30 g. of a 25% solution of sodium aluminum lactate in glycerine.

The sodium aluminum lactate was prepared as described in Example 14 so that it possessed a pH of 6.5 in aqueous solution prior to drying and dissolving in glycerine.

A clear, colorless solution retaining the therapeutic benefits of its three constituents resulted from the combination of ingredients of this example.

EXAMPLES 19 TO 21

These examples illustrate the combination of the antispasmodics with the chelate antacids. (See also Example 18.)

EXAMPLE 19

1.0 g. of adiphenine hydrochloride (2-diethylaminoethyl diphenylacetate hydrochloride) was dissolved in 20 ml. of absolute ethanol. This was added to 50 g. of a solution containing 25% sodium aluminum chlorhydroxy lactate in glycerine. The aluminum chelate was prepared as described in Example 5 and had a pH in water of 6.2 prior to drying and dissolving in glycerine. The therapeutic properties of the anti-spasmodic and the antacid were retained.

EXAMPLE 20

0.3 g. of the same anti-spasmodic used in Example 19 was dissolved in 10 ml. of absolute ethanol. This was added to 10 g. of the same 25% solution of sodium aluminum lactate in glycerine used in Example 1. A clear solution resulted, the pH of which was 8.0. The combination displayed the therapeutic properties of the two therapeutically active ingredients, i.e., the chelate antacid and the anti-spasmodic.

EXAMPLE 21

10 mg. of atropine sulfate was dissolved in 50 g. of a 25% solution of sodium aluminum lactate in glycerine. The antacid chelate was prepared as described in Example 14 and had a pH in water of 6.2 prior to being dried and dissolved in glycerine. A clear solution resulted from the combination of atropine sulfate with the soluble antacid, with the therapeutic effectiveness of neither constituent adversely affected by the combination.

EXAMPLES 22 TO 24

These examples illustrate the combination of the anti-rheumatic fever and anti-tubercular drugs with the chelate antacids.

EXAMPLE 22

10 g. of p-aminosalicyclic acid, an antitubercular agent, was dissolved in 200 ml. of absolute ethanol. This was mixed with a solution of 200 g. of 25% sodium aluminum lactate in glycerine (see Example 1). A clear, light brownish solution resulted, useful as both an anti-tubercular agent and an antacid.

EXAMPLE 23

20 g. p-aminosalicylic acid was suspended in 200 ml. of absolute ethanol and reacted with 200 g. of the sodium lactate of Example 1 dissolved in glycerine (25% solution) for one-half hour at 40° C. under reflux. A clear, dark brown solution having anti-tubercular and antacid properties resulted.

It appears that more p-aminosalicyclic acid dissolves in this system than is normally soluble in a combination of glycerine and alcohol as illustrated by the following control: 20 g. of p-aminosalicyclic acid was suspended in 200 ml. of absolute ethanol. This was then added to 150 g. of 99.5% glycerine. This system was heated under reflux for one-half hour at 40° C. Some solid still remained at the end of this heating cycle.

EXAMPLE 24

15 g. of p-aminobenzoic acid, a drug used in conjunction with salicylates in the treatment of rheumatic fever, was dissolved in 120 ml. of absolute ethanol. This solution was mixed with agitation with 120 g. of the same sodium aluminum lactate solution in glycerine used in the previous Example 1.

This system was heated for one-half hour at 40° C., whereupon a clear, light yellow solution resulted. The pH of this system was 6.0. The product produced in accordance with this example had utility in the treatment of rheumatic fever and displayed antacid characteristics as well.

EXAMPLE 25

5 g. nicotinic acid, an anti-hypercholesteremia agent which causes stomach distress in the absence of buffering, was added to a mixture of 50 ml. of absolute ethanol and 50 g. of the same 25% sodium aluminum lactate solution in glycerine used in Example 1. This was agitated under reflux at 40° C. for one-half hour. A clear, colorless solution resulted which possessed the therapeutic properties of the nicotinic acid and of the antacid as well.

EXAMPLE 26

280 g. of a 45% aqueous solution of magnesium aluminum hydroxy gluconate prepared as described in Example 16 was diluted with 100 ml. of distilled water. 30 g. of nicotinic acid was added to this solution and the mixture was maintained at 40° C. with agitation for one hour. A clear, light yellow solution resulted.

A definite reaction occurred, since the product was water soluble, whereas the solubility of nicotinic acid is less than 2% in water. The nicotinic acid retained its effectiveness as an anti-hypercholesteremia agent. The antacid effectiveness of the chelate was likewise displayed.

EXAMPLE 27

100 mg. of aminophylline, a diuretic, was dissolved in 50 ml. of water. This solution was then mixed with 50 g. of a 45% solution of magnesium aluminum hydroxy gluconate prepared as described in Example 16. A clear solution having both diuretic and antacid properties was obtained.

EXAMPLE 28

2 g. of ferrous gluconate, used in treatment of iron deficiency anemia, was added to a combination of 5 ml. of distilled water, 20 g. of 70% sorbitol solution, and 30 g. of sodium aluminum lactate in glycerine (25% solution—see Example 1). A clear solution having utility in the treatment of iron deficiency anemia as well as antacid properties was obtained.

EXAMPLE 29

A 40% sodium aluminum chlorhydroxy lactate in water was prepared in a manner similar to that described in Example 5 except that a greater amount of sodium hydroxide was added to increase the pH of the chelate complex to 8.5. The chelate antacid complex contained 8.2% Al_2O_3 and had a 1.5:1.0 molar ratio of lactic acid to aluminum, 50 g. of this 40% sodium aluminum chlorhydroxy lactate aqueous solution was mixed with 30 g. of water and 10 g. of racemic mandelic acid, a urinary antiseptic.

This was heated at 50° C. for one hour with agitation under reflux. A clear solution resulted, the pH of which was 4.2. The urinary antiseptic properties of the mandelic acid and the antacid properties of the chelate were displayed by the product.

EXAMPLE 30

100 g. of the same sodium aluminum chlorhydroxy lactate aqueous solution described in Example 29 was mixed with 60 g. of water and 10 g. of racemic mandelic acid and heated under reflux for one hour at 50° C. with agitation. A clear solution resulted, the pH of which was 6.7. This solution had both urinary antiseptic and antacid properties.

The aluminum oxide content of this system was 4.8%. The mandelic acid content was 5.85%.

EXAMPLE 31

Calcium aluminum chlorhydroxy gluconate was prepared by adding 62.9 g. of a 50% aqueous aluminum monochlorohydroxide solution, $Al_2(OH)_5Cl$ and 102.8 g. of glucono-delta-lactone solution, to 35 g. of water. The resulting mixture was heated with agitation at 60 to 75° C. for two hours. There was then added 26 g. of

powdered calcium carbonate and heating and stirring continued for 2.3 hours, yielding a clear solution of calcium aluminum chlorhydroxy gluconate, having a pH of 6.4.

100 g. of the aqueous solution of the antacid chelate, prepared as described above, was added to 5 mg. of scopolamine hydrobromide, a sedative. This mixture was maintained under reflux at 35° C. for ½ hour. A clear solution resulted having utility as a sedative with antacid properties.

EXAMPLE 32

28.3 g. of dried aluminum hydroxide gel, 50% Al_2O_3, was reacted with 100.8 g. of glucono-delta-lactone in 42 g. of water at 75° C. for 3.5 hours. Thereafter, 25.7 g. of calcium carbonate was added and reaction was continued for one hour at 75° C., yielding a clear, aqueous solution having a pH of 5.4. 4 g. of 40% aqueous potassium hydroxide was added to adjust the pH to 6.5. The resulting product, a potassium calcium aluminum hydroxy gluconate, contained 4.65% calcium oxide, 4.35% aluminum oxide, 34.2% gluconic acid and 0.3% potassium. The density of the solution was 26.3° Baumé at 28° C.

100 g. of the aqueous solution of potassium calcium aluminum hydroxy gluconate, prepared as described above, was added to 10 mg. of atropine sulfate. The system was maintained under reflux for ½ hour at 35° C. A clear solution having utility as an anti-spasmodic with antacid properties resulted.

EXAMPLE 33

41.7 g. of aluminum hydroxide dried gel, 50% Al_2O_3, was reacted with 148 g. of glucono-delta-lactone and 62 g. of deionized water for 3.5 hours at 75° C. To this aluminum hydroxide gluconate solution was added 4.6 g. of freshly prepared bismuth hydroxide (75.8% bismuth) and 10 g. of glucono-delta-lactone, and the resulting solution was reacted at 60° C. for 4 hours. At the end of this time, the pH was adjusted to 7 by addition of 108 g. of 40% aqueous potassium hydroxide. A clear, stable, aqueous solution of potassium bismuth aluminum hydroxy gluconate was obtained containing 9.1% potassium, 1% bismuth, 5.4% Al_2O_3, 45.9% gluconic acid and no chlorine.

3 g. of acetylsalicylic acid was added to 100 g. of the chelate solution, prepared as described above. The resulting mixture was agitated at 35° C. for 1 hour under reflux. A clear solution, useful as an analgesic and antipyretic as well as an antacid, was obtained.

EXAMPLE 34

71.6 g. of aluminum monochlorohydroxide,

$$Al_2(OH)_5Cl$$

(50% aqueous solution), 82.6 g. of malic acid and 33 g. of deionized water were mixed and heated with agitation for two hours at 60° C. The pH of the resulting solution was 1.1 and was adjusted to 7.0 by reaction with 159.5 g. of 40% potassium hydroxide at 65° C. for 2.5 hours. The resulting product was a clear, stable, aqueous solution of potassium aluminum chlorhydroxy malate having a potassium content of 13.5%, an aluminum oxide content of 5.46%, a malic acid content of 26.8%, a chlorine content of 1.9%, and a density of 33.0° Baumé at 28° C.

100 g. of the aqueous solution of potassium aluminum chlorhydroxy malate prepared as described above were added to 10 g. of p-aminosalicylic acid. A clear solution was obtained after heating under reflux for 1 hour at 40° C. The product had the therapeutic properties of the antacid chelate and the p-aminosalicylic acid.

EXAMPLE 35

Sodium aluminum hydroxy citrate was prepared by mixing an aqueous solution containing 18.2% sodium aluminate with 95 g. of granular citric acid and heating the mixture with agitation at 60° C. for 0.5 hour. Thereafter, 44.9 g. of a 50% aqueous sodium hydroxide solution was added, yielding a clear stable solution having a pH of 6.5, an aluminum content of 5.1%, a citric acid content of 27% and a sodium content of 3.9%.

100 g. of the aqueous solution of sodium aluminum hydroxy citrate, prepared as described above, was added to 3 g. of acetylsalicylic acid. The resulting mixture was heated under reflux at a temperature of 35° C. for 1 hour, to obtain a clear solution useful as an analgesic, an antipyretic and an antacid.

EXAMPLE 36

Sodium aluminum chlorhydroxy tartrate was prepared by mixing 89.5 g. of aluminum chlorhydroxide with 49 g. of water and 61.9 g. of tartaric acid and reacting at 65° C. for 2 hours. Thereafter, 57.4 g. of aqueous sodium hydroxide was added yielding a clear, stable, aqueous solution of sodium aluminum chlorhydroxy tartrate having a pH of 7.6, an aluminum oxide content of 5.59%, a tartaric acid content of 17.5%, and a sodium content of 4.7%.

100 g. of the water solution of the chelate antacid prepared as described above, were added to 5 g. of salicylic acid and maintained at a temperature of 40° C. for 1 hour under reflux. A clear solution was obtained having the therapeutic properties of the salicylic acid as an analgesic and antipyretic or the antacid effectiveness of the sodium aluminum chlorhydroxy tartrate.

EXAMPLE 37

500 g. of magnesium aluminum hydroxy gluconate, prepared as described in Example 16 was added to 250 ml. of a solution of salicylic acid in absolute ethanol, containing 20 g. of salicylic acid per 100 ml. of solution. The mixture was heated at 40° C. for one-half hour under reflux at which time a clear, slightly pink solution was obtained. The product had the analgesic and antacid properties of the salicylic acid and the magnesium aluminum hydroxy gluconate.

EXAMPLE 38

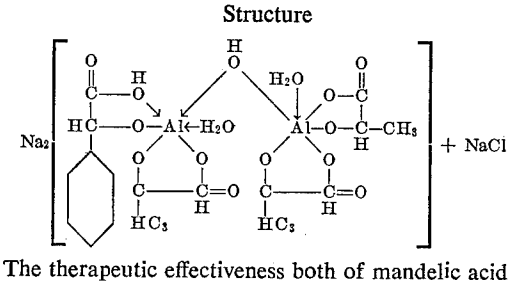
12 g. d-l-mandelic acid was suspended in 100 g. sodium aluminum chlorhydroxy lactate aqueous solution (8.2% Al_2O_3) prepared as described in Example 5. The system was heated at 40° C. for one hour with agitation. A clear solution resulted, the pH of which was 5.5.

30 g. of this solution was dried at 45° C. in an air circulating oven for 35 hours to yield 13 g. of a cream-colored amorphous-in-appearance solid. This solid was soluble in water in the same original proportions, (13 g. solid+17 H_2O).

Composition

	Percent
Al_2O_3	17.2
Al	8.5
Lactic acid	48
Mandelic acid	24.8
Sodium	11.5

Structure



The therapeutic effectiveness both of mandelic acid and

of the aluminum acid chelate was displayed by this compound.

EXAMPLE 39

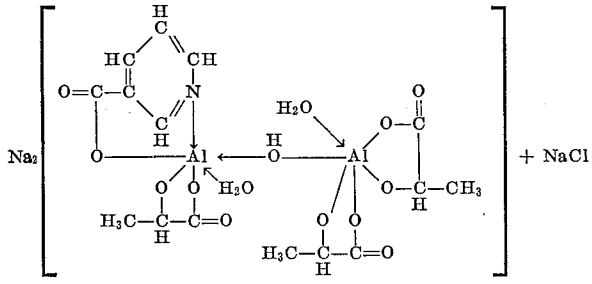
10 g. nicotinic acid was suspended in and reacted with 100 g. of sodium aluminum chlorhydroxy lactate solution (8.2% Al_2O_3) prepared as described in Example 5. The system was agitated for one hour at 40° C. A clear solution having a pH of 5.3 resulted.

The solution was dried in an air circulating oven for 40 hours at 45° C. 45 g. of solution yielded 21.2 g. of an off-white solid.

Composition

	Percent
Na	10.85
Nicotinic acid	19.5
Al_2O_3	15.8
Lactic acid	42.5

Structure



The product displayed the therapeutic effectiveness both of nicotinic acid and of the aluminum antacid.

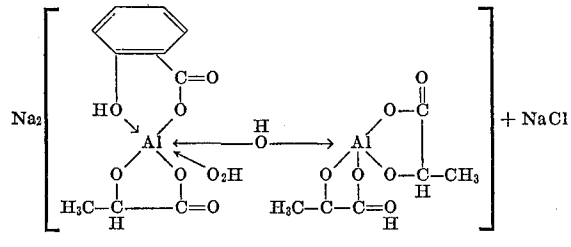
EXAMPLE 40

13.8 g. salicylic acid, U.S.P., and 125 g. sodium aluminum chlorhydroxy lactate (8.2% Al_2O_3) prepared as described in Example 5 were heated to 55° C. and maintained at 55° C. for one-half hour. A light pink clear solution resulted. The solution was dried for 45 hours at 45° C. in an air circulating oven. A light pink solid resulted, amorphous in appearance, which readily dissolved in water to form a solution in the same concentration as was originally present.

Composition

	Percent
Al_2O_3	21
Na	14.2
Lactic acid	56.3
Salicylic acid	28.5

Structure



The product displayed in the therapeutic effectiveness both of salicylic acid and of the aluminum antacid.

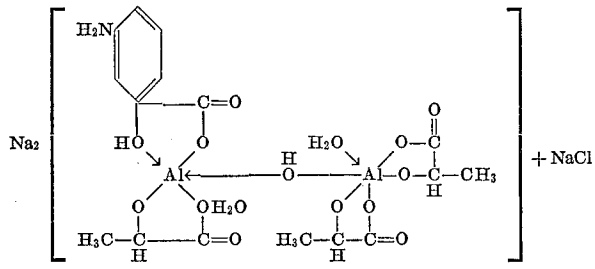
EXAMPLE 41

15.3 g. p-amino salicylic acid was heated at 60° C. for one hour in a solution of 125 g. of sodium aluminum chlorhydroxy lactate (8.2% Al_2O_3) prepared as described in Example 5. A clear brown solution resulted. 40 g. of this solution was dried for 45 hours at 45° C. in an air circulating oven. 14 g. of a light tan solid were recovered. This dissolved in H_2O to form a clear solution of the original proportions.

Composition

Al_2O_3	20.8
Na	14.15
p-Amino salicylic acid	31.2
Lactic acid	56.5

Structure



The product possessed the therapeutic effectiveness of both the p-amino salicylic acid and the aluminum antacid.

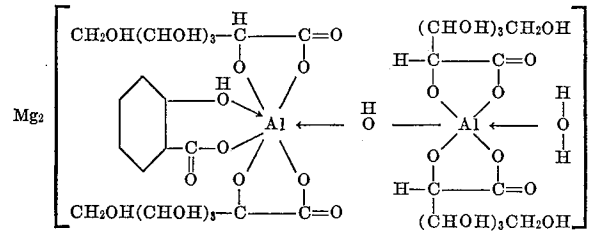
EXAMPLE 42

8 g. salicylic acid was reacted with 25 ml. of water and 100 g. magnesium aluminum hydroxy gluconate prepared in a manner similar to that described in Example 16 but having the following analysis: 47.3% gluconic acid, 5.95% Al_2O_3, 4.2% MgO and a pH of 7.3. Reaction was carried out at 40° C. for one hour. A clear light pinkish-yellow solution resulted, with a pH of 5.4. This solution was dried for about 80 hours at 45° C. in an air circulating oven. 50 g. of solution yielded 24.5 g. of a light pink solid, which dissolved freely in water in original solution proportions.

Composition

	Percent
Al_2O_3	9.15
MgO	6.4
Gluconic acid	72.2
Salicylic acid	12.2

Structure



The product displayed the therapeutic properties of the aluminum antacid and the salicylic acid.

EXAMPLE 43

The antacid-buffer complex, magnesium aluminum hydroxy gluconate was prepared according to the first paragraph of Example 16. Example 23 was then followed using this magnesium aluminum hydroxy gluconate as a substitute for the sodium aluminum lactate of Example 23. This yielded a magnesium aluminum hydroxy gluconate salicylate complex containing 7.86 weight percent salicylate.

Blood levels in rats were compared in accordance with the procedure set forth below for non-complexed salicylic acid and for the complexed magnesium aluminum hydroxy gluconate salicylate complex. The method that was followed was:

Each preparation was suspended in 1% pectin vehicle in an appropriate concentration to result in a final dose of 50 mg./kg. body weight of salicylate, or para-amino salicylate (see Example 44). The suspensions were administered by gavage to male rats of the Holtzman strain. The volume administered was maintained constant at 0.5 ml./100 grams body weight in all experiments.

Blood samples were taken by cardiac puncture from groups of three rats, each, at the following times after drug administration: 0.5, 1.5, 3, 5, 7, 16 and 24 hours, for each of the preparations tested. In addition, blood samples from one group of 10 untreated rats served as a baseline control. In all instances the blood samples were anticoagulated with citrate and centrifuged to obtain the plasma. These plasma samples were then stored at −20° C. until assay. The salicylate content of these plasmas was determined fluorometrically by the method of Dr. S. Udenfriend as reported in "Fluorescence Assay in Biology and Medicine," Academic Press Incorporated, New York, New York, 1962.

Duplicate analyses were done on each plasma sample. In each case there was good agreement between the values so that only the average value is reported below.

A modification of the Udenfriend method was made to include three separate solvent and buffer extractions rather than one in order to facilitate maximum drug recovery from the plasma samples. Two drug standards of 5 and 10 mg. of either salicylic or para-amino salicylic acid were added to plasmas for routine quantitative control of the fluorometric procedure.

Quantitation of the salicylate content of control, standard or test plasmas was made by use of a Farrand spectrofluorometer.

The results of these plasma level determinations are set forth below:

Salicylic Acid, mg./100 ml. of Plasma

	Hours After Drug Administration						
	.5	1.5	3	5	7	16	24
Rat No.:							
1	25.4	26.4	32.0	25.2	20.6	7.0	2.0
2	20.0	36.0	25.0	26.2	20.2	6.0	2.5
3	21.6	29.2	26.0	28.6	25.2	4.0	2.0
Average	22.3	30.5	27.7	26.6	22.0	5.7	2.2

Salicyclic Acid Complex, mg./100 ml. of Plasma

	Hours After Drug Administration						
	.5	1.5	3	5	7	16	24
Rat No.:							
1	19.7	17.7	25.3	29.1	23.4	6.0	2.0
2	27.3	23.0	33.1	25.3	24.4	4.0	2.0
3	19.3	23.8	34.6	26.5	29.3	6.0	2.0
Average	18.8	21.5	31.7	27.0	25.8	5.3	2.0

EXAMPLE 44

Magnesium aluminum hydroxy gluconate para-amino salicylate complex was prepared according to Example 22, but substituting magnesoium aluminum hydroxy gluconate prepared according to Example 16 for the sodium aluminum lactate of Example 22 to yield a complex containing 11.77 weight percent para-amino salicylate. The blood levels in rats were compared in accordance with the procedure set forth in Example 43 with non-complexed para-amino salicylic acid to yield the results shown below:

Para-Amino Salicylic Acid, mg./100 ml. of Plasma

	Hours After Drug Administration						
	.5	1.5	3	5	7	16	24
Rat No.:							
1	8.9	12.8	17.2	13.9	6.9	7.4	4.8
2	8.4	13.4	13.9	11.1	7.2	4.5	4.5
3	10.7	14.5	7.8	5.6	5.9	5.1	3.4
Average	9.3	13.6	13.0	10.2	6.7	5.7	4.2

Para-Amino Salicylic Acid Complex, mg./100 ml of Plasma Q

	Hours After Drug Administration						
	.5	1.5	3	5	7	16	24
Rat No.:							
1	3.3	17.8	17.8	8.9	12.0	9.2	6.7
2	4.4	15.0	14.0	14.5	10.4	8.9	5.6
3	6.7	17.8	15.8	15.6	8.9		5.6
Average	4.8	16.9	15.8	13.0	10.4	9.1	5.9

EXAMPLE 45

Magnesium aluminum hydroxy gluconate mandelate containing 25.8 weight percent mandelate was prepared according to Example 29, except for the substitution of magnesium aluminum hydroxy gluconate prepared by Example 16 for the sodium aluminum chlorhydroxy lactate of Example 29. The aforesaid complex was compared with mandelic acid in respect to the blood levels in rats by the procedure of Example 43 except that in place of the salicylate assay methods referred to in Example 43 the mandelic acid assays were performed by the colorimetric method as described by Drs. A. J. Zimmer and D. C. Lee-Huyck as reported in "Pharmaceutical Analysis," edited by Takeru Higuchi and Einar Brochmann-Hanssen, published 1961 by Interscience Publishers, N.Y.

The results of these plasma level determinations are set forth below:

Mandelic Acid, mg./100 ml. of Plasma

	Hours After Drug Administration						
	.5	1.5	3	5	7	16	24
Rat No.:							
1	13.4	21.7	20.7	5.8	15.3	9.9	0.0
2	13.4	40.8	17.5	14.4	11.6	9.9	0.0
3	11.1	21.9	12.4	20.5	7.8	3.7	0.0
Average	12.6	28.1	16.9	13.6	11.6	7.8	0.0

Mandelic Acid Complex, mg./100 mg. of Plasma

	Hours After Drug Administration						
	.5	1.5	3	5	7	16	24
Rat No.							
1	35.8	49.5	16.0	25.5	8.7	11.9	0.0
2	15.1	42.9	26.9	10.2	10.8	3.3	0.0
3	22.4	39.1	33.0	11.1	12.0	7.6	0.0
Average	24.4	43.8	25.3	15.6	10.5	7.6	0.0

The complexes of Examples 43 through 46 were tested in vitro according to the procedure of Holbert, Noble & Grote, modified as described in Beekman, Journal of the American Pharmaceutical Association, Scientific Edition, vol. XLIX, No. 4, April 1960, pp. 191 et seq.

Tests performed according to the Beekman modified Holbert, Noble and Grote method as described on page 18 of the specification yielded the following:

Assay	Example 43— Magnesium aluminum gluconate-salicylate complex solution	Example 44— Magnesium aluminum gluconate-p-aminosalicylic complex solution	Example 45— Magnesium aluminum gluconate-mandelate complex solution
Percent Medicament	[1] 2.32%	[2] 2.9%	[3] 8.47%
Percent Ethanol by volume	11.8	29	10.6
Percent Al_2O_3	2.53	2.1	2.45
Percent MgO	0.524	0.436	0.51
Percent Gluconate	13.9	11.5	13.4
Recommended dose, ml.	26	65	24

In Vitro Buffering Evaluation

	pH		
	Example 43	Example 44	Example 45
Time (min.):			
0	1.65	1.5	1.60
1	3.95	3.55	3.45
5	3.0	3.75	3.45
10	4.0	4.75	3.45
20	3.95	4.75	3.40
30	3.95	4.75	3.40
40	3.9	4.25	3.35
50	3.85	4.15	3.30
60	3.80	4.05	3.25
70	3.75	4.05	3.20
80	3.70	4.0	3.15
90	3.65	3.95	3.10
100	3.55	3.90	3.05
110	3.45	3.80	3.00
120	3.35	3.70	2.95
130	3.3	3.80	2.90
140	3.2	3.80	2.85
150	3.1	3.65	2.75
160	3.0	3.55	2.70
170	2.9	3.45	2.60

[1] Salicylic acid.
[2] p-Amino-salicylic acid.
[3] Mandelic acid.

The above examples demonstrate the wide flexibility and advantages of the combination of the chelate antacids and the therapeutic adjuvants in the compositions of this invention. The pH in the stomach can be controlled to within the optimum range for the specific therapeutic adjuvant over long periods, thereby ensuring that administration of the therapeutic adjuvants will not cause gastric distress and discomfort to the patient. Unlike previous antacid adjuvant complexes, there is little or no likelihood of excessively high pH, e.g., sufficient to cause alkalinosis or breakdown of the adjuvant following administration of even massive doses of the chelate antacid-therapeutic adjuvant combinations. Also, by prolonging the effectiveness of the adjuvant, less frequent doses may be required. By enhancing the solubility of those adjuvants which are only slightly soluble in water the combination can greatly increase the flexibility with which these therapeutic adjuvants can be administered.

Because the compositions of this invention are water-soluble and contain no carbonate ion, little or no gas will be liberated by the neutralization of the antacids. Thus, one of the problems associated with the adjuvant antacid complexes of the prior art is avoided. Fuchs in Drug and Cosmetic Industry, 64, 692 (1949) indicates that the carbonates and bicarbonates can release carbon dioxide gas nearly instantaneously during the neutralizing action and states that this is an undesirable characteristic for an antacid. The compositions of this invention in contradistinction to the prior art products release little or no gas during the period of acid neutralization and buffering.

The complexes of this invention are stable and retain their therapeutic, neutralizing and buffering effectiveness over an extended period of time irrespective of whether they are stored in the liquid or solid forms.

I claim:

1. An antacid therapeutic composition consisting essentially of an aluminum-coordinating therapeutic adjuvant selected from the group consisting of acetylsalicylic acid, salicylic acid, para-amino salicylic acid, and mandelic acid and an aluminum chelate of an organic acid selected from the group consisting of alpha hydroxyalkyl saturated carboxylic acids and beta hydroxyalkyl saturated carboxylic acids, the chelate in aqueous solution having a pH within the range from about 3 to about 9, and corresponding in composition to the empirical formula:

$$M_{m+y}[Al_2(OH)_xCl_y(OOC{-}R)_m(OOC{-}R{-}OH)_n]$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O{-}$$

where y, m, n and x are numbers whose sum balances the positive valences of the metal M and aluminum, $m+y$ represents the total number of gram atoms of the metal M, $m+n$ represents the total number of gram molecular weights of the hydroxyalkyl saturated carboxylic acid, m is within the range from 1 to 3, n is within the range from 0 to 3, y is within the range from 0 to 1.5, M represents a nontoxic metal selected from the group consisting of alkali and alkaline earth metals and bismuth, and R represents the residue of the hydroxyalkyl saturated carboxylic acid and has at least one hydroxy group and at least one saturated carboxylic acid group for each 1 to 6 carbon atoms, the aluminum chelate being in an amount to maintain the pH of artificial gastric juice as determined by the Holbert, Noble and Grote test method to within the range from about 3 to about 9 for at least one hour, the ratio of the total weight of the chelate to the total weight of the therapeutic adjuvant being within the range from about 20:1 to about 1:20.

2. An antacid therapeutic composition in accordance with claim **1** consisting of sodium aluminum lactate acetyl salicylate complex.

3. An antacid therapeutic composition in accordance with claim **1** consisting of magnesium aluminum hydroxy gluconate salicylate complex.

4. An antacid therapeutic composition in accordance with claim **1** consisting of magnesium aluminum hydroxy gluconate para-amino salicylate complex.

5. An antacid therapeutic composition in accordance with claim **1** consisting of magnesium aluminum hydroxy gluconate mandelate complex.

6. A process for preparing an antacid therapeutic composition having a pH in aqueous solution within the range from about 3 to about 9, which comprises reacting an aluminum compound selected from the group consisting of the alkali metal aluminates, the reactive aluminum hydroxides, and the aluminum chlorhydroxy complexes corresponding to the formula: $Al_2(OH)_xCl_y$ in which the sum of x and y is 6, and x and y are each at least 1 in the presence of water with a chelating hydroxy alkyl saturated carboxylic acid selected from the group consisting of alpha hydroxy alkyl saturated carboxylic acids and beta hydroxy alkyl saturated carboxylic acids in a proportion stoichiometrically calculated to take up at least three up to a total of six of the coordinating positions of the aluminum, at a temperature at which the reaction proceeds, until no precipitation of aluminum is obtained when a sample of the solution is heated with an ionic precipitant for aluminum and adding an aluminum-coordinating therapeutic adjuvant selected from the group consisting of acetylsalicylic acid, salicylic acid, para-amino salicylic acid, and mandelic acid, the ratio of the total weight of the chelate to the total weight of the therapeutic adjuvant being within the range from about 20:1 to about 1:20.

7. A process for maintaining the pH of gastric juice in the stomach within the range from about 3 to about 6 for at least one hour in the presence of an aluminum-coordinating therapeutic adjuvant, which comprises orally administering a therapeutically effective amount of an aluminum chelate of an organic acid selected from the group consisting of alpha hydroxyalkyl saturated carboxylic acids and beta hydroxyalkyl saturated carboxylic acids, corresponding in composition to the empirical formula:

$$M_m + {}_y[Al_2(OH)_xCl_y(OOC{-}R)_m(OOC{-}R{-}OH)_n]$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O{-}$$

where y, m, n and x are numbers whose sum balances the positive valences of the metal M and aluminum, $m+y$ represents the total number of gram atoms of the metal M, $m+n$ represents the total number of gram molecular weights of the hydroxyalkyl saturated carboxylic acid, m is within the range from 1 to 3, n is within the range from 0 to 3, y is within the range from 0 to 1.5, M represents a nontoxic metal selected from the group consisting of alkali and alkaline earth metals and bismuth, and R represents the residue of the hydroxyalkyl saturated carboxylic

acid and has at least one hydroxy group and at least one saturated carboxylic acid group for each one to six carbon atoms, in combination with an aluminum-coordinating therapeutic adjuvant selected from the group consisting of acetylsalicylic acid, salicylic acid, para-amino salicylic acid, and mandelic acid, the ratio of the total weight of the chelate to the total weight of the therapeutic adjuvant being within the range from about 20:1 to about 1:20.

No references cited.

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U.S. Cl. X.R.

424—231, 232, 233, 234, 235