balance of the blood, (*e*) they exhibit very little diminution of antacid activity on aging, (*f*) they are not adversely affected by pepsin in antacid action, (*g*) they are nonirritating to the gastrointestinal tract, (*h*) they have a desirable mild astringent effect, (*i*) they have minimal constipating or laxative effects, (*j*) they are palatable with very little chalkiness, (*k*) they rehydrate and swell in water to provide a gelatinous, positively charged protective coating for inflamed membranes, and (*l*) they may be produced at moderate cost because of the uncomplicated chemical nature of the compounds employed.

SUMMARY

The preparation of a group of new highly reactive and stable aluminum-magnesium hydroxide gels in powder form has been described. The determination of their antacid activity by a very stringent *in vitro* procedure indicates that they compare favorably with clinically effective liquid aluminum-magnesium hydroxide gels. The dried gels are effective over a wide range of proportions of the two antacid components. The new dried gels which are predominantly simple mixtures and not new compounds approach the ideal for an antacid in dry form.

REFERENCES

(1) Rossett, N. E., and Flexner, J., *Ann. Internal Med.*, **21**, 119(1944).
(2) Rossett, N. E., and Rice, M. L., Jr., *Gastroenterology*, **26**, 490(1954).
(3) Morrison, S., *Am. J. Gastroenterol.*, **21**, 301(1954).
(4) Jankelson, I. R., *Am. J. Digest. Diseases*, **14**, 11(1947).
(5) Beekman, S. M., THIS JOURNAL, **49**, 191(1960).

Preparation and Properties of New Gastric Antacids VI

Low Sodium Aluminum Hydroxide Gel and Dried Gels

By STEWART M. BEEKMAN

The preparation of a new low sodium aluminum hydroxide concentrated gel is described, which when diluted to U.S.P. concentration contains about 0.6 mg. of sodium per 30 ml. The preparation of six new aluminum hydroxide dried gels containing 0.19 to 0.50 mg. of sodium per Gm. is also described. They include an aluminum hydroxide dried gel U.S.P. as well as four combinations with magnesium hydroxide and one with magnesium carbonate. The antacid activity of the various preparations was determined by a very stringent *in vitro* procedure. The activity of the combination dried gels compares favorably with the liquid gel. They are rapid and very prolonged in the optimum pH range of 3 to 5.

RECENT reports (1, 2) in the medical literature have stressed the need for low sodium antacids in liquid and tablet form for the treatment of patients who may have peptic ulcers or bleeding esophogeal varices concomitant with liver or heart disease that may require sodium restriction. Rimer and Frankland (1) who have given this problem detailed study comment that "in prescribing antacids, one may unwittingly violate the first principle of therapeutics and do unnecessary harm to the patients." Bleifer and associates (2) report that "it is obvious that unrestricted use of these materials (antacids) can jeopardize investigative sodium studies as well as therapeutic salt restricted programs."

Rimer and Frankland reported on the analyses of 18 of the most widely used aluminum hydroxide preparations in liquid and tablet form and found that the liquids contain 11.9 to 269.7 mg. of sodium per 30 ml. and from 5.1 to 192 mg. of sodium per 8 tablets. Bleifer, *et al.*, found that four of the popular liquid aluminum hydroxide gels contained 29–39 mg. of sodium per 30-ml. dose. Since the daily dose for patients with acute ulcers may be 500 ml. or more, the amount of sodium ingested from this source alone may be

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500–2500 mg. per day. Many physicians try to restrict the sodium intake from all sources to 210 mg. per day.

The purpose of this paper is to report the results of an investigation which had as its goal the preparation of clinically effective aluminum hydroxide gel and various dried gels with low sodium contents.

EXPERIMENTAL

Aluminum Hydroxide Gel.—A stable, highly reactive aluminum hydroxide was precipitated from the system K_2CO_3-$KHCO_3$-$AlCl_3$ using sodium free aluminum chloride and deionized water. The gel was filtered, washed free of soluble salts, and subjected to high shear at room temperature under aseptic conditions. For the preparation of aluminum hydrogels having uniform physical and chemical properties it is necessary to control many variables carefully including concentration and precise metering of reactants, temperature, degree and type of agitation, reaction rate, method of introducing reactants, pH change, and aging. The resulting snow white, homogeneous hydrogel contains about 9% aluminum hydroxide as aluminum oxide, and when diluted to 4.0% aluminum oxide forms a flowable, slow settling aluminum hydroxide U.S.P. of proper viscosity characteristics. It is designated as type F-1000 LS. Table I shows the analysis of a typical sample diluted to U.S.P. concentration.

Aluminum Hydroxide Dried Gel.—Aluminum hydroxide gel similar to that described above was carefully dried by low temperature circulating air and pulverized to a finely divided form. The resulting soft, white, bulky powder meets the requirements for a fairly reactive aluminum hydroxide dried gel U.S.P. It is also designated as type F-1000 LS. The analysis of a typical sample is seen in Table I.

Aluminum-Magnesium Hydroxide Dried Gels.—Low sodium magnesium hydroxide was precipitated, mixed with low sodium aluminum hydroxide gel, combined with either glycine or sorbitol, subjected to intensive mixing, and reduced to dry powder form. Four different dried gels were prepared. Two were stabilized with glycine and two with sorbitol. The preparations were made with Al:Mg atomic ratios of 2:1 and 1:1. In Table I the analyses of typical samples are shown.

Aluminum Hydroxide-Magnesium Carbonate Dried Gel.—Magnesium carbonate gel was prepared by the low temperature precipitation in the system K_2CO_3-$MgCl_2$, intimately combined with low sodium aluminum hydroxide gel, and the resulting mixture spray dried to finely divided form. The analysis of a typical sample of this dried gel which is designated as Type F-MA11-LS may be seen in Table I.

Sodium Content.—The sodium content of the various samples was determined by means of a Beckman model B spectrophotometer with flame attachment. The results are also shown in Table I.

Antacid Activity.—The acid consuming capacity (ACC) values for all samples are shown in Table I. Since all samples were completely soluble in 0.1 *N* hydrochloric acid at 37.5°, the ACC values are approximately equivalent to the amount of aluminum and/or magnesium present in the various products.

Reheis and Mutch reaction velocity values (3) were determined on all samples. They were seen to be rapidly reactive. The least reactive was the aluminum hydroxide dried gel U.S.P.

The principle method of measuring the antacid activity was the modified Holbert, Noble, and Grote procedure previously described, using an automated apparatus developed for the purpose. Figure 1 shows the results on 5, 10, and 15-ml. samples of an aluminum hydroxide gel U.S.P., Type F-1000 LS. In Fig.2 the antacid activity of new and 4-month-old samples of an aluminum hydroxide dried gel U.S.P., Type F-1000 LS is plotted on the basis of 1.0 Gm. Figure 3 shows the results obtained on 1.0-Gm. samples of the two aluminum-magnesium hydroxide glycine dried gels. The data for the two aluminum-magnesium hydroxide sorbitol dried gels is seen in

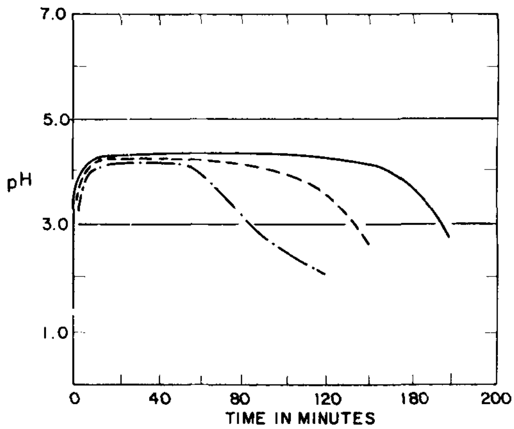

Fig. 1.—Antacid activity of low sodium aluminum hydroxide gel U.S.P., type F-1000LS. ——, 15 ml.; - - -, 10 ml.; -·-·, 5 ml., procedure of Holbert, Noble, and Grote modified.

TABLE I.—ANALYSIS OF TYPICAL SAMPLES OF LOW SODIUM ALUMINUM HYDROXIDE GELS AND DRIED GELS

Type Designation	Al_2O_3, %	MgO, %	Glycine, %	Sorbitol, %	CO_2, %	Na, %	Acid Consuming Capacity[c]
F-1000-LS[a]	4.0	...	...	..	1.7	0.0019	22.6
F-1000-LS[b]	52.1	...	...	..	10.5	0.019	302
F-AMHG-21LS	33.4	12.6	19.1	..	7.1	0.019	264
F-AMHG-11LS	28.2	21.6	19.5	..	7.1	0.029	279
F-AMHS-21LS	32.9	13.7	...	20	6.8	0.029	253
F-AMHS-11LS	27.0	22.8	...	20	6.7	0.029	271
F-MA11-LS	38.1	9.5	...	..	22.1	0.05	272

[a] Aluminum hydroxide gel U.S.P. [b] Aluminum hydroxide dried gel U.S.P. [c] Milliliters 0.1 *N* hydrochloric acid per Gm.

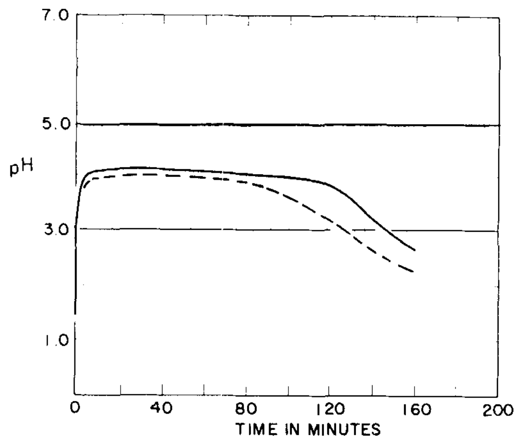

Fig. 2.—Antacid activity of low sodium aluminum hydroxide dried gel U.S.P., Type F-1000LS, basis 1.0 Gm. Age of sample: ——, 4 days; - - -, 4 months. Procedure of Holbert, Noble, and Grote modified.

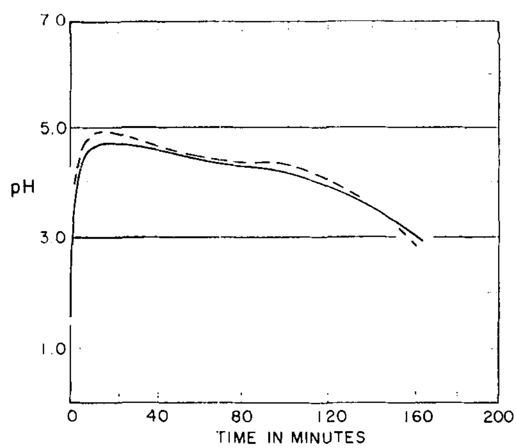

Fig. 3.—Antacid activity of two low sodium aluminum-magnesium hydroxide glycine dried gels, basis 1.0 Gm. ——, F-AMHG-11LS; - - - F-AMHG-21LS. Procedure of Holbert, Noble, and Grote modified.

Fig. 4. Lastly, the antacid activity of the F-MA11-LS dried gel is seen in Fig. 5.

In Table II the antacid characteristics of the various low sodium dried gels are compared on the basis of 1.0-Gm. dose levels. The data is derived from the time-pH curves shown in Figs. 2–5.

RESULTS

Aluminum Hydroxide Gel.—The data presented show that a concentrated aluminum hydroxide gel may be prepared which when diluted to U.S.P. concentration of 4.0% aluminum oxide contains about 0.6 mg. of sodium per 30 ml. It can be seen that a massive 500-ml. daily dose would add only 10 mg. of sodium to the dietary intake, and hence could not be expected to cause edema or ascites in heart or liver disease patients. The gel is prepared from nonsodium reactants and should add less than two cents to the manufacturing cost of a standard 12-oz. bottle of liquid antacid.

Aluminum Hydroxide Dried Gels.—The sodium content of the various dried gels is seen in Table I to vary from 190 to 500 p.p.m. which would add, e.g., only 1 to 2.5 mg. of sodium for 8–10-gr. tablets. As might be expected from data presented in previous papers (3–5) in this series of *in vitro* studies, the aluminum hydroxide dried gels containing either magnesium carbonate or magnesium hydroxide stabilized with glycine or sorbitol exhibit antacid activities which are similar to reactive liquid aluminum hydroxide gel. The aluminum hydroxide dried gel U.S.P. type F-1000 LS prepared as above was much more reactive than most aluminum hydroxide dried gels U.S.P. that we have evaluated by our automated *in vitro* technique. However, after 4 months' aging it had declined in initial speed of reaction some 25%, and 14% in duration of antacid action above pH 3.0.

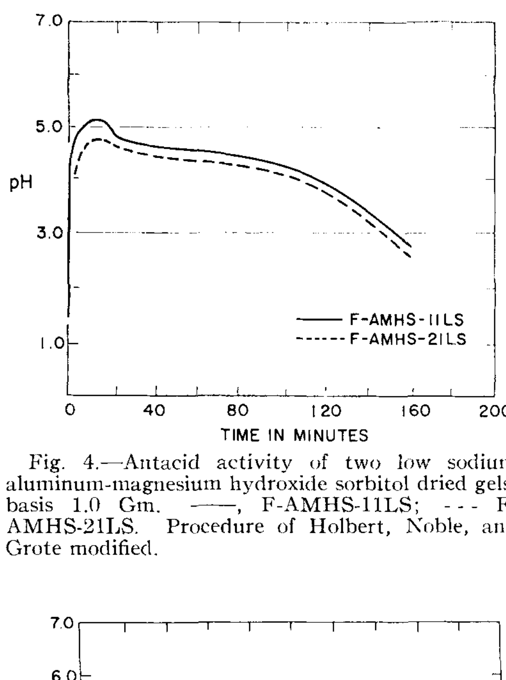

Fig. 4.—Antacid activity of two low sodium aluminum-magnesium hydroxide sorbitol dried gels, basis 1.0 Gm. ——, F-AMHS-11LS; - - - F-AMHS-21LS. Procedure of Holbert, Noble, and Grote modified.

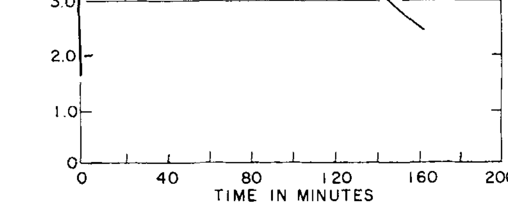

Fig. 5.—Antacid activity of low sodium aluminum hydroxide-magnesium carbonate dried gel type F-MA11-LS, basis 1.0 Gm. Procedure of Holbert, Noble, and Grote modified.

TABLE II.—COMPARISON OF ANTACID ACTIVITY[a] OF VARIOUS LOW SODIUM ALUMINUM HYDROXIDE DRIED GELS

Sample	Time to Reach pH 3.0, sec.	Max. pH	Total Time above pH 3.0, min.
F-1000-LS age, 4 days	180	4.1	145
F-1000-LS age, 4 months	450	4.0	125
F-AMHG-21 LS	45	4.7	160
F-AMHS-21 LS	45	4.7	140
F-AMHG-11 LS	40	4.9	153
F-AMHS-11 LS	38	5.2	150
F-MA11- LS	10	4.6	145

[a] Data from time-pH curves for 1.0-Gm. samples. Procedure of Holbert, Noble, and Grote modified.

DISCUSSION

Nature of Aluminum Hydrogels.—The low sodium antacids prepared in this study compare favorably in all important properties with similar preparations manufactured with sodium salts. The nature of aluminum hydrogels are such that they readily adsorb foreign cations and anions from the systems in which they are made. Many of these ions are strongly bound and are not readily desorbed by washing copiously with pure water. Nor is it entirely desirable to do so, since their excellent antacid action and stability depends in large measure on the nature and amount of these adsorbed impurities.

Economics and Demand for Low Sodium Gels.—The substitution of potassium salts for sodium salts requires some minor changes in their manufacturing process particularly in the precipitation step and adds to the raw material cost because they are heavier in molecular weight and higher in price than sodium salts. Since other costs such as processing, container, shipping, etc., are similar for both systems, the price of low sodium products to the pharmaceutical manufacturer probably should not exceed 25% of the prices for present sodium-containing aluminum hydroxide gels.

One important variable is the potential volume for such low sodium products. As Bleifer, *et al.* (2), point out "the small concentrations of sodium present are in no way contraindicated in the overwhelming majority of cases in which antacid therapy is needed."

It may be uneconomical for manufacturers to make and pharmacists to stock both regular and low sodium grades. It is possible that a demand will be made in the future for sodium content statements on labels of all antacids destined for therapeutic use.

SUMMARY

1. A new concentrated aluminum hydroxide gel has been prepared which contains about 19 p.p.m. of sodium when diluted to U.S.P. strength of 4.0% aluminum oxide. The physical properties of the gel such as viscosity, settling characteristics, taste, and color are excellent. The antacid activity characteristics were determined by a very stringent *in vitro* procedure and seem to compare well with usual high sodium aluminum hydroxide liquid preparations similarly tested.

2. The preparation of six new aluminum hydroxide dried gels containing 190 to 500 p.p.m. of sodium is described. Four co-dried mixtures of aluminum hydroxide with magnesium hydroxide and glycine or sorbitol as well as a co-dried blend with magnesium carbonate are seen to have antacid characteristics similar to liquid aluminum hydroxide gels. An aluminum hydroxide dried gel U.S.P. with fairly good antacid properties is also described.

REFERENCES

(1) Rimer, D. G., and Frankland, M., *J. Am. Med. Assoc.*, **173**, 995(1960).
(2) Bleifer, K. H., Belsky, J. L., and Bleifer, D. J., *New Engl. J. Med.*, **261**, 604(1959).
(3) Beekman, S. M., THIS JOURNAL, **49**, 191(1960).
(4) Beekman, S. M., *ibid.*, **50**, 571(1961).
(5) Beekman, S. M., *ibid.*, **50**, 577(1961).