varies even more (6.2%), even with the exclusion of the anomalous capsule No. 4 of low fill weight. Capsule No. 4 may either have a reasonable probability of occurrence or may be a maverick, possibly due to either improper weighing or being the first or last capsule prepared from the lot. Good control practice would demand repeat assays to clarify this.

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Preparation and Properties of New Gastric Antacids V

Aluminum-Magnesium Hydroxide Dried Gels

By STEWART M. BEEKMAN

The preparation of nine aluminum-magnesium hydroxide gels in the Al:Mg atomic ratio range of 2:1, 1:1, and 0.5:1 by a new process is described. The determination of the antacid activity by the modified *in vitro* method of Holbert, Noble, and Grote shows that dried gels stabilized with glycine or sorbitol have antacid characteristics similar to clinically proved liquid aluminum-magnesium hydroxide gel. Blends of the various components separately dried are shown to be relatively ineffective by comparison. The new blends of old antacids are predominantly simple mixtures and not new compounds. Unstabilized dried gels show a substantial aging effect.

In 1944 Rossett and Flexner (1) concluded that mixtures of milk of magnesia with aluminum hydroxide gel were more effective gastric antacids than aluminum hydroxide gel alone. They reached these conclusions as a result of *in vivo* experiments on humans together with extensive clinical experience. They suggested smaller and less frequent doses of the mixtures. They pointed out the avoidance of the undesirable high initial pH rise from the milk of magnesia alone, and the offsetting of the constipating effect of aluminum hydroxide. The outstanding clinical effectiveness of liquid aluminum-magnesium hydroxide gels have been reported by others (2-4) for the treatment of peptic ulcer, hyperacidity, heart burn, spasticity, and gastritis. Properly formulated they are very prompt and prolonged in antacid activity, maintain the gastric pH between 3 and 5, and do not exhibit significant diminution of antacid action on aging.

This investigation had as its purpose the preparation of aluminum-magnesium hydroxide gels in dry form which approaches the antacid activity of the clinically proved fluid gels.

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EXPERIMENTAL

Preparation of Dried Gels.—Three series of aluminum-magnesium hydroxides were prepared. In each series the amount of aluminum to magnesium was varied in the atomic ratios of 2:1, 1:1, and 0.5:1.

The first series (AMH) consisted solely of aluminum and magnesium hydroxide. The second series (AMHG) was formulated to contain approximately 20% of glycine in the dried gel. The third series (AMHS) was prepared to contain 20% of sorbitol.

The method of preparation of all nine dried gels was similar. Highly reactive aluminum hydroxide containing some carbonate and pure gelatinous magnesium hydroxide were separately precipitated, the combined slurries were filtered and washed free of soluble salts, the mixed hydrogels were subjected to highly intensive shear at room temperature and reduced to finely divided powder form by either spray drying or low temperature air drying together with fine pulverizing. Glycine crystals or sorbitol solution was added to the mixed hydrogels before milling.

Physical Properties.—All the dried gels are soft, white, smooth, fine, tasteless, and odorless powders which react readily with gastric strength acid-containing pepsin. The AMH dried gels are somewhat less dense than those containing sorbitol or glycine. The pH of aqueous suspensions of the AMHG series is about 9.0—the others are about 9.6. The carbonate (as CO_2) content ranges from about 5.0 to 12% depending mainly on the method of drying. Dried gels containing glycine or sorbitol are less

TABLE I.—COMPOSITION OF ALUMINUM-MAGNESIUM HYDROXIDE DRIED GELS

Type Designation	Atomic Ratio, Al:Mg	Approximate Analysis Al_2O_3, %	Approximate Analysis MgO, %	Relative Amount per Gm. Aluminum[a] Hydroxide U.S.P., mg.	Relative Amount per Gm. Magnesium Hydroxide N.F., mg.	Relative Amount per Gm. Glycine N.F., mg.	Relative Amount per Gm. Sorbitol, mg.	Ratio Aluminum Hydroxide to Magnesium Hydroxide	Acid[b] Consuming Capacity
F-AMH-21	2:1	39.4	15.8	773	227	...	...	3.4:1	305
F-AMH-11	1:1	32.1	25.6	629	371	...	...	1.7:1	310
F-AMH-12	0.5:1	23.4	37.4	459	541	...	...	0.85:1	314
F-AMHG-21	2:1	31.5	12.6	618	182	200	...	3.4:1	250
F-AMHG-11	1:1	25.7	20.4	504	296	200	...	1.7:1	254
F-AMHG-12	0.5:1	18.7	30.0	367	433	200	...	0.85:1	260
F-AMHS-21	2:1	31.5	12.6	618	182	...	200	3.4:1	250
F-AMHS-11	1:1	25.7	20.4	504	296	...	200	1.7:1	254
F-AMHS-12	0.5:1	18.7	30.0	367	433	...	200	0.85:1	200

[a] Calculated as 51% aluminum oxide. [b] Milliliters 0.1 *N* hydrochloric acid per Gm.

chalky. Spray dried samples have spherical shaped particles and are more free flowing.

Table I shows the composition of the nine aluminum-magnesium hydroxide dried gels as well as typical acid-consuming capacity values.

Infrared Studies.—Rock salt infrared spectra (2 to 15 μ) were run on samples of AMH-21, AMHG-21, AMHS-21, aluminum hydroxide dried gel U.S.P., magnesium hydroxide N.F., glycine N.F., and crystalline D-sorbitol. Nujol and hexachlorobutadiene (HCBD) mulls were made and samples run at capillary thicknesses *vs.* air.

Comparison of the various spectra shows that both AMH-21 and AMHS-21 are simple mixtures. The spectra of AMHG-21 indicates that it is predominantly a simple mixture of the three components, although there is strong evidence of a new glycine derivative—the percentage being fairly small.

Dry Blends.—In order to make a comparison between the antacid activity of the nine dried gels shown in Table I with usual dry blends, it was necessary to prepare nine such blends using aluminum hydroxide dried gel U.S.P., magnesium hydroxide N.F., glycine N.F., and crystalline sorbitol. The blends were made with finely powdered components.

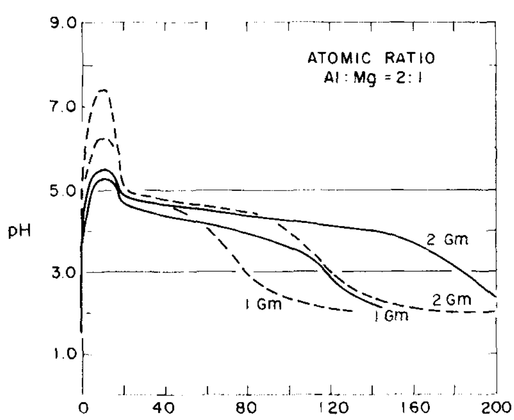

Fig. 1.—Antacid activity of aluminum-magnesium hydroxide dried gel Type F-AMH-21 (—) compared with dry blend of $Al(OH)_3$ U. S. P.-$Mg(OH)_2$ N. F. (- - -). Procedure of Holbert, Noble, and Grote modified.

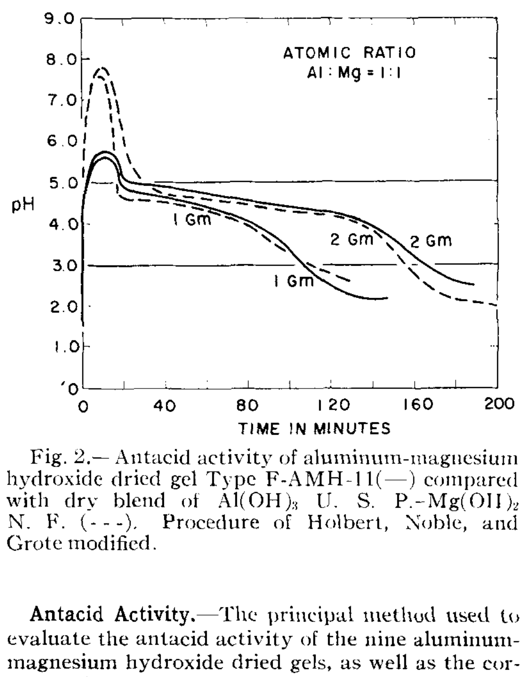

Fig. 2.—Antacid activity of aluminum-magnesium hydroxide dried gel Type F-AMH-11(—) compared with dry blend of $Al(OH)_3$ U. S. P.-$Mg(OH)_2$ N. F. (- - -). Procedure of Holbert, Noble, and Grote modified.

Antacid Activity.—The principal method used to evaluate the antacid activity of the nine aluminum-magnesium hydroxide dried gels, as well as the corresponding dry blends, was the dynamic, stringent procedure of Holbert, Noble, and Grote modified, which was described in considerable detail in the first paper in this series of *in vitro* studies (5). Samples were evaluated on the basis of 1.0 and 2.0-Gm. dose levels. The results for the various dried gels are plotted in Figs. 1-9.

Effect of Age.—To determine the effect of time on samples of aluminum-magnesium hydroxide dried gels stored in closed glass containers at ambient temperatures, the antacid activity of 1.0-Gm. samples was determined by the Holbert, Noble, and Grote method after 5 months' storage, and compared with values obtained on freshly prepared samples. The criteria used for aging is the total time that a 1.0-Gm. sample maintains the pH above 3.0 when tested by the modified Holbert, Noble, and Grote procedure. The results are shown in Table II.

Comparison with Dry Blends.—The antacid activity of 5-month-old samples of all nine AMH dried gels are compared with corresponding dry blends in Table II also.

Comparison with Liquid Gels.—For comparison

TABLE II.—EFFECT OF TIME ON ANTACID ACTIVITY[a] OF AMH DRIED GELS AND COMPARISON WITH DRY BLENDS

Type Designation	A Age of Sample, months 0 min.	B 5 min.	C Loss in Activity After 5 months, %	D Antacid Activity Corresponding Dry Blend, min.	Increase in Activity of Col. B over Col. D, %
F-AMH-21	142	113	20	68	66
F-AMH-11	142	102	28	97	3
F-AMH-12	135	127	6	128	same
F-AMHG-21	147	140	5	55	155
F-AMHG-11	142	133	6	88	51
F-AMHG-12	140	135	4	107	26
F-AMHS-21	145	134	8	47	185
F-AMHS-11	142	137	4	83	66
F-AMHS-12	150	143	5	105	36

[a] Procedure of Holbert, Noble, and Grote modified (time above pH 3.0 for 1.0-Gm. sample).

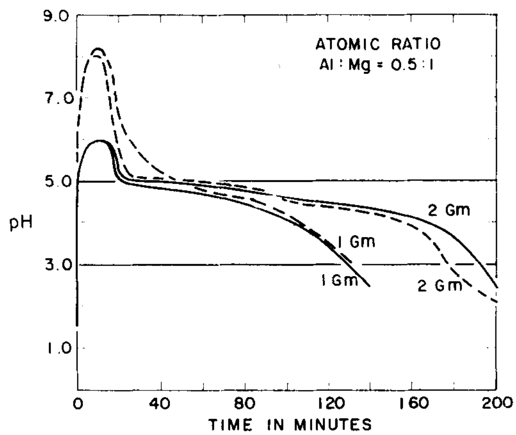

Fig. 3.—Antacid activity of aluminum-magnesium hydroxide dried gel Type F-AMH-12 (—) compared with dry blend of $Al(OH)_3$ U. S. P.–$Mg(OH)_2$ N. F. (- - -). Procedure of Holbert, Noble, and Grote modified.

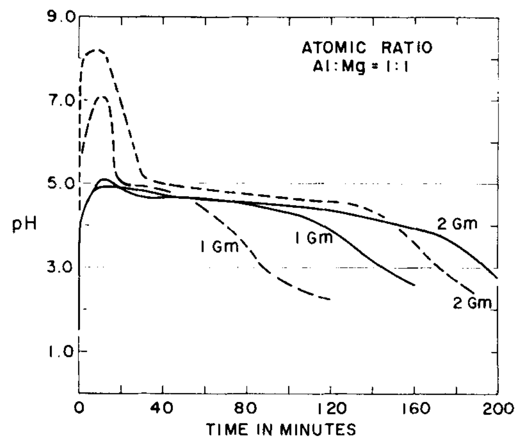

Fig. 5.—Antacid activity of aluminum-magnesium hydroxide-glycine dried gel Type F-AMHG-11 (—) compared with dry blend of $Al(OH)_3$ U. S. P.–$Mg(OH)_2$ N. F.–glycine N. F. (- - -). Procedure of Holbert, Noble, and Grote modified.

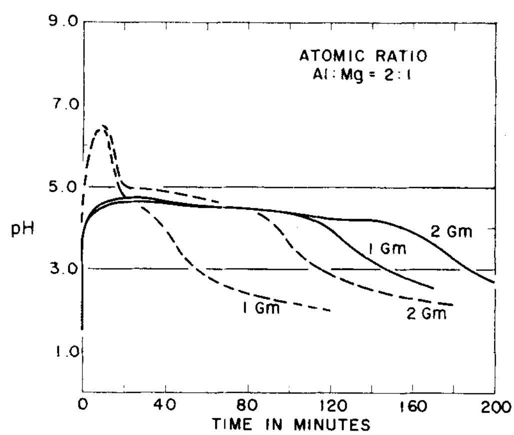

Fig. 4.—Antacid activity of aluminum-magnesium hydroxide-glycine dried gel Type F-AMHG-21 (—) compared with dry blend of $Al(OH)_3$ U. S. P.–$Mg(OH)_2$ N. F.–glycine N. F. (- - -). Procedure of Holbert, Noble, and Grote modified.

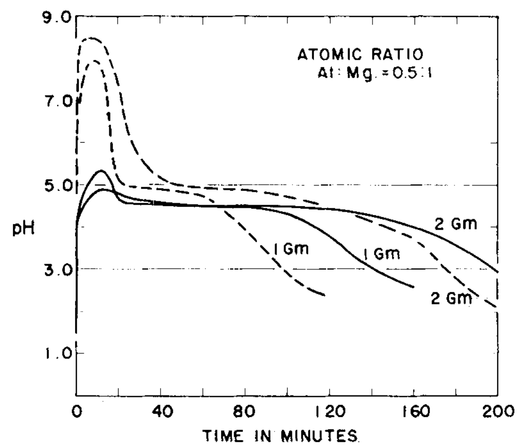

Fig. 6.—Antacid activity of aluminum-magnesium hydroxide-glycine dried gel Type F-AMHG-12 (—) compared with dry blend of $Al(OH)_3$ U. S. P.–$Mg(OH)_2$ N. F.–glycine N. F. (- - -). Procedure of Holbert, Noble, and Grote modified.

purposes the antacid activity data by the modified Holbert, Noble, and Grote method is plotted in Fig. 10 for 5, 10, and 15-ml. samples of a very reactive liquid aluminum-magnesium hydroxide gel having an Al:Mg atomic ratio of 1:1.

RESULTS

From consideration of the antacid activity data for the various aluminum-magnesium hydroxide dried gels and dry blends which are plotted in Figs.

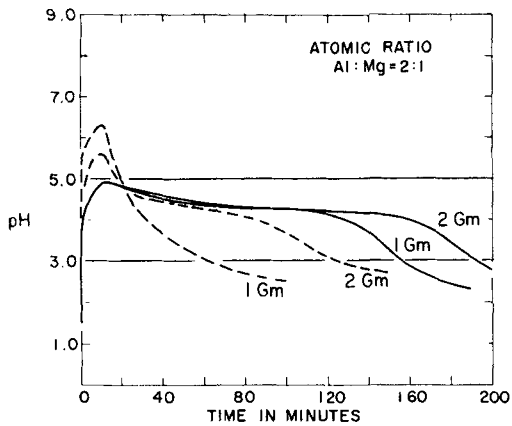

Fig. 7.—Antacid activity of aluminum-magnesium hydroxide-sorbitol dried gel Type F-AMHS-21 (—) compared with dry blend of $Al(OH)_3$ U. S. P.–$Mg(OH)_2$ N. F.–sorbitol (- - -). Procedure of Holbert, Noble, and Grote modified.

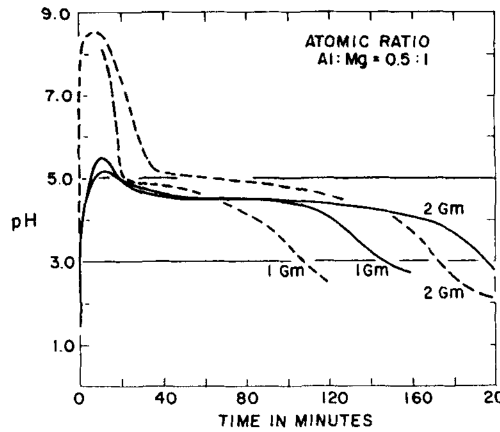

Fig. 9.—Antacid activity of aluminum-magnesium hydroxide-sorbitol dried gel Type F-AMHS-12 (—) compared with dry blend of $Al(OH)_3$ U. S. P.–$Mg(OH)_2$ N. F.–sorbitol (- - -). Procedure of Holbert, Noble, and Grote modified.

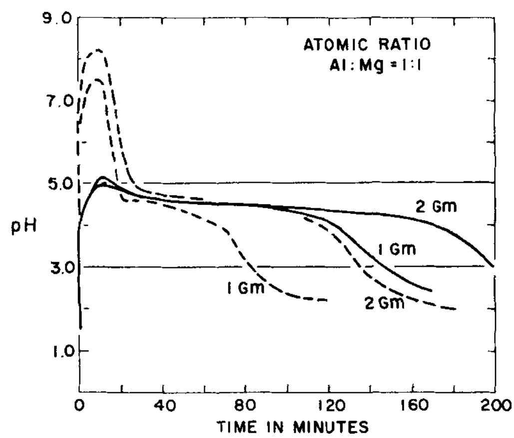

Fig. 8.—Antacid activity of aluminum-magnesium hydroxide-sorbitol dried gel Type F-AMHS-11 (—) compared with dry blend of $Al(OH)_3$ U. S. P.–$Mg(OH)_2$ N. F.–sorbitol (- - -). Procedure of Holbert, Noble, and Grote modified.

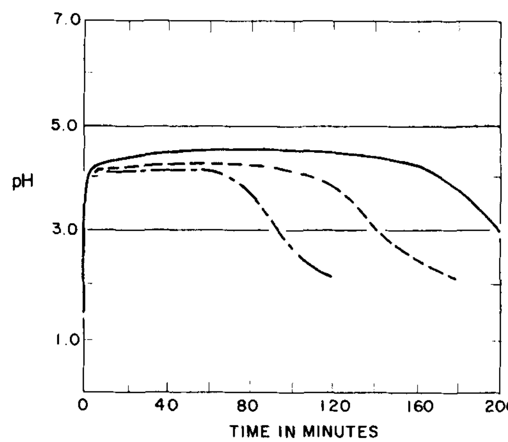

Fig. 10—Antacid activity of liquid aluminum magnesium hydroxide gel. Procedure of Holbert, Noble, and Grote modified. —, 15 ml.; - - -, 10 ml.; — — —., 5 ml.

1–9 and compared in Table II, one may draw several conclusions as follows: (*a*) Aluminum-magnesium hydroxide dried gels prepared by the new process described are much more prolonged in antacid activity in the optimum pH range of 3 to 5 than corresponding dry blends containing the same basic components in the same proportions. They also do not cause such a high undesirable initial rise in pH. (*b*) Unstabilized aluminum-magnesium hydroxide dried gels in the Al to Mg atomic ratio range of 2:1 and 1:1 show a fairly substantial diminution in antacid activity after 5-months' aging. This is a characteristic also of aluminum hydroxide dried gel U.S.P. Acid consuming capacity tests do not show this aging effect. (*c*) Glycine and sorbitol are both excellent stabilizers of the complex aluminum-magnesium hydroxide gel micellar structures during the desiccation process. On freshly prepared samples AMHG and AMHS dried gels have about the same antacid activity as an equal weight of unaged, unstabilized AMH dried gel, although they contain only 80% as much aluminum and magnesium hydroxide. When 5-month-old samples of all dried gels are compared on an active ingredient basis, the AMHG and AMHS dried gels in the Al:Mg ranges of 2:1 and 1:1 are 55–62% more active and 29–33% when the Al:Mg ratio is 0.5 to 1.

DISCUSSION

Aluminum-magnesium hydroxide dried gels AMHG and AMHS approach the theoretical requirements for an ideal antacid in dry form because of the following factors: (*a*) they are very rapid in raising the pH of gastric juice to the optimum pH range of 3 to 5, (*b*) they have extremely long periods of times of reaction in this optimum range, (*c*) the high initial rise in pH characteristics of similar materials dry blended is avoided, (*d*) they are nonsystemic and hence cannot upset the acid-base 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.

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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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