Syntheses and Evaluation of New High-Capacity Gastric Antacids I

Magnesium Aluminum Oxy Hydroxides

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Three unique, new, highly reactive magnesium aluminum oxy hydroxide (MAOH) polymeric compounds are described. They are prepared by controlled hydrolysis of mixtures of aluminum alcoholates and magnesium alcoholates, hydroxide or oxide in anhydrous media. The white, dense, tasteless, finely divided powders consume 0.1 *N* HCl in the range of 400–450 ml./Gm. *In vitro* antacid evaluation data by (*a*) the Holbert *et al.* procedure, (*b*) Johnson and Duncan method, and (*c*) Bachrach constant pH titration all indicate the three compounds to be up to 50–60 per cent more potent on an equal weight basis than presently known aluminum–magnesium antacid in dry form. All three compounds were evaluated for proteolytic enzyme inhibition properties in the pH range of 2 to 5 using the method of Schaub. They were found to be more strongly antiproteolytic than any aluminum-magnesium antacid similarly tested. The MAOH-21 species has an oral LD_{50} in mice of greater than 6.0 Gm./Kg.

STATISTICALLY, one out of ten of us is destined to suffer from a peptic ulcer (1). The prime objective of ulcer therapy is the prophylactic maintenance of conditions suitable for healing (2). Although other drugs such as anticholinergics are useful adjuncts, the dominant role in the medical management of peptic ulcer is played by gastric antacids (2, 3).

The role is a difficult one, and the requirements for an ideal antacid are very demanding. Important considerations include (*a*) the ability to inhibit gastric proteases which attack mucosal cells and other substrates such as wound healing coagulum in the pH range up to 5.0, (*b*) rapid and high acid consuming properties per unit weight and per unit volume under physiological conditions and in the pH range of 3 to 5, (*c*) high palatability factor with absence of aftertaste and taste fatigue, (*d*) absence of systemic effects such as constipation or laxation also ideally free of sodium, (*e*) new dosage forms which permit continuous antacid–antiproteolytic effect in spite of rapid gastric emptying, and (*f*) reasonable cost.

The advent of colloidal aluminum hydroxide gel in 1934 (4) as a gastric antacid was a big forward step. Some of its shortcomings have been overcome in liquid preparations containing magnesium as well as aluminum hydroxide (5–8). Attempts to overcome the shortcomings of dry blends of aluminum and magnesium hydroxide have included the preparation of codried gels containing sorbitol or glycine (9) and new compounds such as hydrated magnesium aluminate sulfated (HMAS) (10) and hydrated magnesium aluminate (Hallmann patent) (11).

The dry preparations to be described in this paper consume approximately 50–60% more acid per unit weight than presently known aluminum–magnesium antacids. Although calcium–aluminum oxy hydroxides have been prepared, this paper will deal only with the corresponding magnesium compounds.

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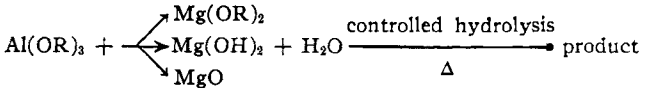
EXPERIMENTAL

Preparation of Magnesium Aluminum Oxy Hydroxides (MAOH).—The three methods which may be used for preparing these compounds are shown in Table I. All three involve the controlled hydrolysis of mixtures of polymeric aluminum alcoholate with either magnesium alcoholate, hydroxide or oxide. All three are carried out in anhydrous media, usually isopropanol, with vigorous agitation. Each product has a constant composition and corresponds to the structural formula shown. Although X-ray diffraction studies have shown the antacids to be essentially amorphous, differential thermal analyses have shown that they are vastly different from mixtures of aluminum and magnesium hydroxide. Furthermore, there is no known or theoretical mixture of aluminum and magnesium hydroxide which can yield such high acid-consuming capacities. The reactions have been designed to yield the maximum number of metal–oxygen–metal bonds for each composition.

Composition and Properties.—The average composition and some of the properties of MAOH's are shown in Table II. They are all dense, white, finely divided, odorless, and tasteless powders free of all foreign anions and cations. The acid-consuming capacity of MAOH-21 is usually about 450 ml. of 0.1 *N* HCl/Gm., whereas the other two are closer to 400.

TABLE I.—MAGNESIUM–ALUMINUM OXY HYDROXIDES—HIGH-CAPACITY ANTACIDS—METHODS OF PREPARATION



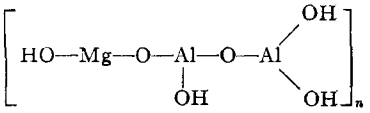
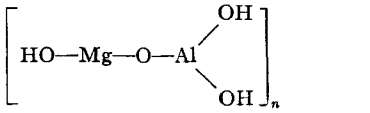
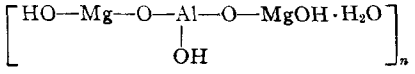
Designation	At. Ratio Al	At. Ratio Mg	Empirical Formula	Possible Structure
A MAOH-21	2	1	$MgAl_2O_6H_4$	
B MAOH-11	1	1	$MgAlO_4H_3$	
C MAOH-12	1	2	$Mg_2AlO_6H_5$	

TABLE II.—MAGNESIUM–ALUMINUM OXY HYDROXIDES—HIGH-CAPACITY ANTACIDS—COMPOSITON AND PROPERTIES

Designation	Al_2O_3, %	MgO, %	CO_3	Cl	SO_4	Na	pH in Water	ACC[a]	App. Density, Gm./ml.
MAOH-21	57.2	22.6	Absent	Absent	Absent	Trace	8.7	420–450	0.55
MAOH-11	43.1	34.1	Absent	Absent	Absent	Trace	8.8	390–400	0.55
MAOH-12	28.9	45.5	Absent	Absent	Absent	Trace	9.0	390–400	0.55

Physical properties: dense, white, tasteless, finely divided powder readily soluble in gastric acid

[a] Acid-consuming capacity = ml. 0.1 *N* HCl per Gm.

TABLE III.—*In Vitro* ANTACID EVALUATION PROCEDURES USED[a]

Method	Description of Method	Gastric Fluid: Vol. Start, ml.	Gastric Fluid: Concn. Start, meq.	Gastric Fluid: Addition Rate ml./hr.	Gastric Fluid: Addition Rate meq./hr.	Gastric Fluid: Replacement Rate, ml./hr.	Gastric Fluid, Compn.
A	Holbert *et al.* modified	150	4.75	120	3.79	120	pH 1.5 HCl 0.0316 *N* 0.20% pepsin
B	Johnson and Duncan, modified by Schaub	150	7.5	120	12.0	120	150 ml. at start 0.05 *N* HCl 0.15% pepsin addition fluid 0.10 *N* HCl 0.15% pepsin
C	Bachrach	Titration at constant pH 3.5					Simulated gastric fluid U.S.P. HCl, 0.0875 *N* pepsin, 0.32% NaCl, 0.20%

[a] Basis, 1.0 Gm.; temp., 37.5°C.; agitation constant.

In Vitro Antacid Evaluation Procedures Used.—Three stringent procedures were used to evaluate the antacid activity of the new MAOH antacids as follows: method *A*, Holbert *et al.* modified, method *B*, Johnson and Duncan as modified by Schaub, and method *C*, Bachrach method. (These are outlined in Table III.)

Method A.—This was carried out essentially as outlined by Beekman (12). It has been very widely used to assess (*a*) the speed of reaction, (*b*) the pH range in which neutralization takes place, and (*c*) the duration of antacid activity. It was never the purpose of this test to be physiological. It is useful for *in vitro* comparison of various antacid materials. Because of the dilute nature of the gastric fluid (0.0316 *N*), the test is a very stringent one.

In order to compare the antacid activity of the new MAOH's with various combinations of aluminum and magnesium hydroxide, it was first necessary to prepare highly reactive aluminum hydroxide gel and magnesium hydroxide paste, thoroughly blending them until homogeneous, air drying at 120°F., and finely pulverizing to 90% less than 44 μ. Samples of codried gels were prepared having Al–Mg atomic ratios of 2:1, 1:1, and 0.5:1. Corresponding dry blends were prepared using aluminum hydroxide dried gel U.S.P. and magnesium hydroxide N.F. powder.

Method *A* was carried out on all nine samples.

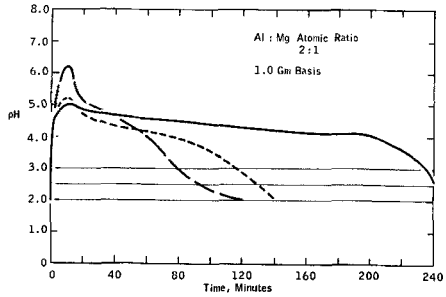


Fig. 1.—*In vitro* evaluation of antacid activity, method *A*. Key: ——, MAOH-21; - - -, magnesium–aluminum hydroxide codried gel; – – –, magnesium hydroxide–aluminum hydroxide dried gel blend.

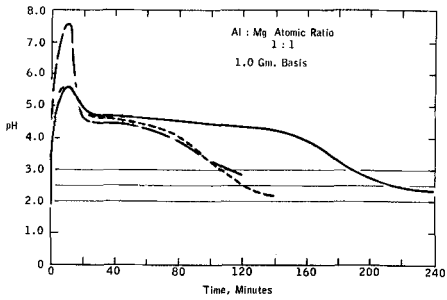


Fig. 2.—*In vitro* evaluation of antacid activity, method *A*. Key: ——, MAOH-11; - - -, magnesium–aluminum hydroxide codried gel; – – –, magnesium–aluminum hydroxide dry blend.

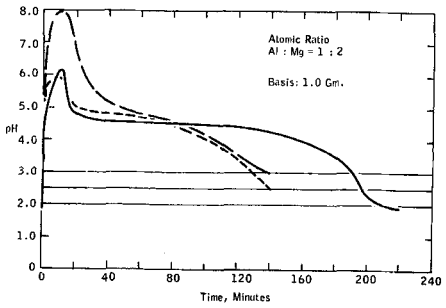


Fig. 3.—*In vitro* evaluation of antacid activity, method *A*. Key: ——, MAOH-12; - - -, magnesium–aluminum hydroxide codried gel; – – –, magnesium–aluminum hydroxide dry blend.

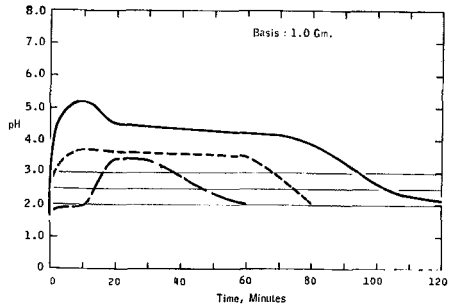


Fig. 4.—*In vitro* evaluation of antacid activity, method *B*. Key: ——, MAOH-21; - - -, aluminum hydroxide–magnesium carbonate codried gel; – – –, aluminum hydroxide dried gel U.S.P.

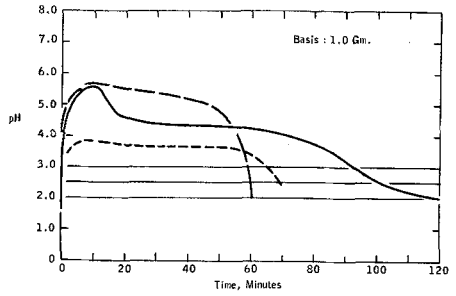


Fig. 5.—*In vitro* evaluation of antacid activity, method *B*. Key: ——, MAOH-11; - - -, dihydroxy aluminum sodium carbonate—DASC; – – –, calcium carbonate, U.S.P.

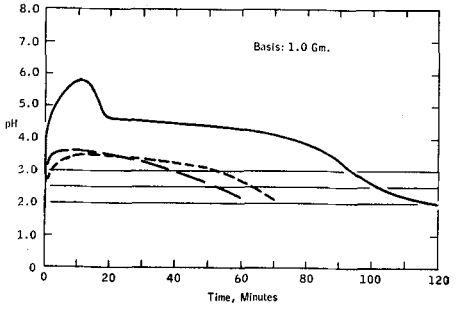


Fig. 6.—*In vitro* evaluation of antacid activity, method *B*. Key: ——, MAOH-12; - - -, hydrated magnesium aluminate sulfated—HMAS; – – –, aluminum hydroxide–magnesium trisilicate codried gel.

The data are plotted in Figs. 1–3. It can readily be seen that the duration of time above pH 3.0 for the new MAOH antacids is from 61 to 98% greater than the corresponding codried aluminum–magnesium hydroxide gels. They are also very prompt in initial reaction.

Method B.—In 1962–1963, Schaub published three papers (13–15) on the antacid–antiproteolytic properties of antacids. The methodology was similar to method *A*, except that he selected stronger titrants to more closely parallel the time–pH data obtained by Rossett and Flexner (6) in humans using 1.0 Gm. of calcium carbonate and sodium bicarbonate as the test substance. Figures 4–6 show the results with the three MAOH antacids compared with some other widely used antacids in powder form. The duration of time above pH is 36% greater than the next best substance tested.

Method C.—This method is very useful for determining the rapidity and duration of reactivity up to some arbitrary time such as 60 min. Since the titration based on 1.0 Gm. of test substance is carried out at pH 3.5, at which point there is no free hydrochloric acid in the physiological sense, it is a most stringent procedure. It can not be used by itself because it does not indicate the pH

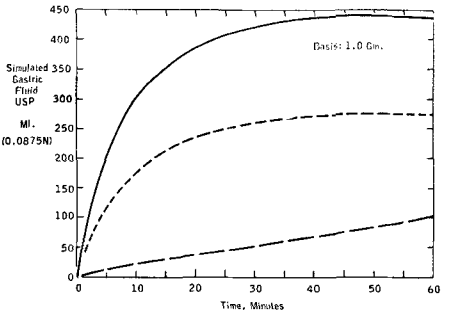


Fig. 7.—*In vitro* evaluation of antacid activity, method *C;* Bachrach constant pH 3.5. Key: ——, MAOH-21; - - -, aluminum hydroxide–magnesium carbonate codried gel; – – –, aluminum hydroxide dried gel U.S.P.

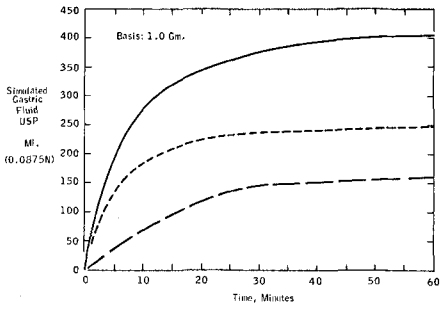


Fig. 8.—*In vitro* evaluation of antacid activity, method *C;* Bachrach constant pH 3.5. Key: ——, MAOH-11; - - -, dihydroxyaluminum sodium carbonate—DASC; – – –, dihydroxyaluminum aminoacetate—DAA.

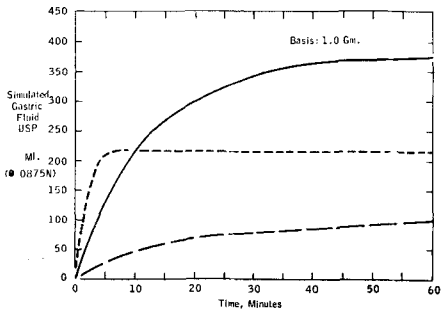


Fig. 9.—*In vitro* evaluation of antacid activity, method *C;* Bachrach constant pH 3.5. Key: ——, MAOH-12; - - -, calcium carbonate U.S.P.; – – –, magnesium trisilicate U.S.P.

range in which it buffers with an excess antacid present. The method is carried out as described by Hinkel *et al.* (16). To make the Bachrach procedure more stringent, simulated gastric fluid U.S.P. standardized at (0.0875 *N*) is used as the titrant. One-hour Bachrach figures are very useful for comparing the potential capacities of various antacids.

The data obtained by method *C* are plotted in Figs. 7–9 on all three MAOH antacids together with corresponding data on some of the better known dry antacids. The data show, for example, that 1.0 Gm. of MAOH-21 will neutralize 57% more acid than 1.0 Gm. of aluminum hydroxide–magnesium carbonate codried gel. When compared on an equal volume basis, this increases to about 100% because of the apparent density differences of the two powders. Thus, the new compositions are up to twice as potent on an equal volume basis.

Antiproteolytic Properties.—To determine the inhibition of gastric proteolytic enzymes at pH ranges up to 5.0, the method of Schaub (13–15) was used. This was based on a procedure used by Bateson (17) which was adapted from a method of West *et al.* (18) for the determination of uropepsin. The test is based on the coagulation time of casein in fresh homogenized milk and is carried out in an acetate buffer system at pH 4.9 and 13°. Before assessing antacids, it is necessary to construct a calibration curve relating coagulation time with pepsin N.F. solutions of known concentration. The relationship between pepsin concentration and coagulation time may be expressed by the formula

$$K = \frac{\log T_2 - \log T_1}{\log cP_2 - \log cP_1}$$

where K = inclination constant, cP_1 = pepsin concentrations which yields time, T_1, and cP_2 = pepsin concentration which yields time, T_2. Bateson (17) reported that the inclination constant K is similar for pepsin of different effectiveness, and hence, the calibration curves of different pepsin samples yield a family of parallels.

In carrying out the method, a sample is withdrawn from the reaction cell as outlined in method *B*. It is quickly filtered, and 1 ml. is added to 4 ml. acetate buffer (pH 4.9) and 3 ml. water all cooled to 13.0°. At time zero, the milk buffer is added to the sample which is agitated at 13° until coagulation takes place. The time of coagulation is noted. The latter may range from 2 to 800 sec. The method is very sensitive, and hence all equipment used must be scrupulously clean.

A comparison of 1.0 Gm. of MAOH antacids with other well-known antacids in dry form is

TABLE IV.—COMPARISON OF ANTIPROTEOLYTIC ACTIVITIES OF MAGNESIUM–ALUMINUM OXY HYDROXIDES WITH VARIOUS ANTACID CHEMICALS[a]

Antacid	Duration of Anti-proteolytic Activity of 90–100%, min.
MAOH-21	100
MAOH-11	100
MAOH-12	100
Aluminum hydroxide–magnesium carbonate codried gel	74
Aluminum hydroxide dried gel U.S.P.	90
Magnesium trisilicate U.S.P.	27
Dihydroxy aluminum sodium carbonate	74
Dihydroxyaluminum aminoacetate	100
Calcium carbonate U.S.P.	23
Hydrated magnesium aluminate sulfated	60
Bismuth subcarbonate U.S.P.	0

[a] Basis, 1.0-Gm. sample; procedure, method of Schaub.

shown in Table IV. The comparison is based on the total time in minutes that the per cent residual active pepsin is maintained at 10% or less, starting with 150 mg. of pepsin N.F. per ml. of gastric fluid.

All three MAOH samples maintained this condition for 100 min. or more. It was matched only by 1 Gm. of dihydroxyaluminum aminoacetate.

Toxicity Studies.—A preliminary report on the oral administration in mice of MAOH antacid type MAOH-21 prepared by the pharmacology department, Chattanooga Medicine Co., reveals the following information: (*a*) oral LD_{50} in mice = greater than 6.0 Gm./Kg.; (*b*) doses of 0.1–6.0 Gm./Kg. orally are not laxative in mice; and (*c*) single doses of 0.1, 3.0, and 6.0 Gm./Kg. orally produce no immediate signs of toxicity, nor was any gross pathology seen at sacrifice 21 hr. following administration.

DISCUSSION

From the foregoing *in vitro* performance data, one might conclude that if there is such a thing as an ideal antacid substance, the various magnesium–aluminum oxy hydroxides approach it. The high-capacity per unit volume makes possible smaller tablets for a given dose, provision for greater amounts of excipients, or higher-capacity single-dose tablets. MAOH antacids must not be wetted with water with which it reacts and degrades. Granulation can be carried out with anhydrous alcohol.

MAOH antacids are not compatible with water, but liquid suspensions can be prepared with other suitable nonaqueous fluids such as propylene glycol or glycerol. Thirty grams of MAOH-21 suspended in 100 Gm. of glycerol yielded a flowable suspension which had a neutralizing potency of 150 ml. 0.1 *N* HCl per ml. of suspension. Sucking-type slowly-melt-away tablets or pastilles are possible due largely to the bland taste and high potency of the new MAOH polymeric compounds.

The *in vivo* performance of MAOH in humans will be reported at a later date.

SUMMARY

1. The preparation and properties of three new highly reactive MAOH polymeric antacids were described. These are new chemical entities not heretofore described.

2. The acid consuming capacity per gram ranges from 400–450 ml. 0.1 *N* HCl per Gm.

3. *In vitro* evaluation of antacid properties by three stringent techniques shows that they outperform any known aluminum–magnesium antacid by a wide margin.

4. All three MAOH antacids were found to be powerful inhibitors of gastric proteolytic enzymes in the pH range of 2.0 to 5.0.

5. Preliminary oral toxicity studies on mice revealed an LD_{50} of greater than 6.0 Gm./Kg. and the absence of laxative or gastrointestinal blockage in single or repeated doses up to 6.0 Gm./Kg. per day.

6. Improved antacid tablets are possible with the MAOH antacid as well as high-potency liquids and new dosage forms.

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