Automated Technique for Determining Dissolution and Reaction Rate of Antacids I

Instrumentation and Evaluation of Antacid Raw Materials

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Evaluation of antacids *in vitro* is difficult and involves many different antacid attributes. Current methods for evaluating antacids are reviewed. It is concluded that no single method can provide an entire profile of an antacid. A method is presented which determines the fastest rate at which an antacid system can react with acid, presuming gastric acid is always present. A procedure for automating the technique is described which provides a rapid and accurate profile of the dissolution and reaction rate in addition to the total acid-consuming capacity of an antacid system. Data are presented on 27 antacid materials. The results enable comparative judgments to be made regarding the probable value of the antacid. It is concluded that the method provides a quick and important procedure for laboratory evaluation of new antacid materials.

ANY ANTACID literature survey will reveal a large number of methods for determining the onset of reaction, rate of reaction, duration of activity, and total acid-consuming capacity for both antacid materials and commercial products. Many of these methods, while not entirely new, are merely modifications or proposed improvements of existing methods. They generally are designed to provide a more *in vivo*-like atmosphere for the testing of the antacid material under investigation.

The pH range in which a good antacid should buffer the gastric contents has undergone much discussion. A range of pH 3.0 to 5.0 appears to be generally acceptable to most workers in the field; however, the following specific pH ranges have been proposed: 2.0–4.0 (1, 2), 2.4–4.5 (3), 3.0–5.0 (4, 5), 3.0–5.5 (6), 3.5–4.0 (7–10), 3.5–4.5 (11), 4.0–5.5 (12), 4.0–6.0 (13), and 4.0–8.0 (14).

The subject of whether pepsin (*i.e.*, simulated gastric fluid, T.S.) should be included in the testing program also has been the topic of much discussion. Although the use of 0.1 *N* hydrochloric acid is more convenient, somewhere in the evaluation of the test material, an *in vitro* titration should be made using a pepsin-containing titrant. It is generally agreed that neutralization of excess acidity is required for ulcer healing. Excess acidity alone, however, is not solely responsible for the formation of gastric ulcers. Pepsin has been suggested as playing a role in ulcer formation (7) and has been demonstrated in the laboratory by LeVeen (15). Bergman *et al.* (16), in agreement with Persson and Bunke (17), point out that gastric proteolysis on certain substrates (including gastric mucosa) is relatively rapid at pH 3 to 5, which is the ambient pH probably present with most antacid products during therapy. These authors also reconfirm the high antiproteolytic activity of the aluminum ions in solution and point out the lack of such activity with the use of calcium and magnesium ions. Strongly alkaline antacids also were shown to be potent proteolytic inhibitors. When performing any one of the many proposed routine types of hydrochloric acid-consuming tests, however, the acid-consuming capacity of the aluminum antacids normally is reduced by the addition of pepsin, while the sodium, calcium, and magnesium antacids usually are reported to be relatively unaffected.

The foregoing complex picture of some of the considerations of antacid evaluations *in vitro* while being far from complete, nevertheless does serve to point out that the current state of *in vitro* evaluation techniques is an extremely clouded one. It would appear that such complexity and cloudiness conceivably could be utilized advantageously by a potential antacid manufacturer in selecting only those conditions for evaluation which will suit their product most profitably.

Thus, it has been shown that a meaningful evaluation of antacid materials by using any one of the currently employed *in vitro* techniques is at best difficult, if not impossible. The main purpose of this paper is not to introduce the ultimate *in vitro* method of antacid evaluation, but

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TABLE I.—ANTACID CHEMICALS EVALUATED

Sample	Name	Grade	Compn.
1	Aluminum hydroxide dried gel, sample *A*	U.S.P.	51% Al_2O_3 (approx.)
2	Aluminum hydroxide dried gel, sample *B*	U.S.P.	51% Al_2O_3 (approx.)
3	Aluminum hydroxide dried gel, sample *C*	U.S.P.	51% Al_2O_3 (approx.)
4	Aluminum triple precipitate		24.5% Al_2O_3–48.5% $CaCO_3$–20% basic $MgCO_3$
5	Calcium carbonate	Reagent	$CaCO_3$
6	Calcium carbonate	U.S.P.	$CaCO_3$
7	Dihydroxyaluminum aminoacetate, sample *A*	N.F.	$(HO)_2AlOOCCH_2NH_2$
8	Dihydroxyaluminum aminoacetate, sample *B*	N.F.	$(HO)_2AlOOCCH_2NH_2$
9	Dihydroxyaluminum sodium carbonate		$(HO)_2AlOCOONa$
10	Glycine	N.F.	H_2NCH_2COOH
11	Magnesium aluminum silicate, sample *A*		
12	Magnesium aluminum silicate, sample *B*		
13	Magnesium carbonate	U.S.P.	$MgCO_3$
14	Magnesium carbonate–aluminum hydroxide co-dried gel, process A		Al_2O_3:MgO mol. ratio, 2:1
15	Magnesium carbonate–aluminum hydroxide co-dried gel, process B		Al_2O_3:MgO mol. ratio, 2:1
16	Magnesium hydroxide	N.F.	$Mg(OH)_2$
17	Magnesium hydroxy aminoacetate		$HOMgOOCCH_2NH_2$
18	Magnesium oxide, heavy, sample *A*	Reagent	MgO
19	Magnesium oxide, heavy, sample *B*	Reagent	MgO
20	Magnesium oxide, heavy, sample *C*	U.S.P.	MgO
21	Magnesium oxide, light	U.S.P.	MgO
22	Magnesium trisilicate, sample *A*	U.S.P.	$2\ MgO \cdot 3\ SiO_2 \cdot n\ H_2O$
23	Magnesium trisilicate, sample *B*	U.S.P.	$2\ MgO \cdot 3\ SiO_2 \cdot n\ H_2O$
24	Magnesium trisilicate, sample *C*	U.S.P.	$2\ MgO \cdot 3\ SiO_2 \cdot n\ H_2O$
25	Sodium bicarbonate, sample *A*	U.S.P.	$NaHCO_3$
26	Sodium bicarbonate, sample *B*	U.S.P.	$NaHCO_3$
27	Sodium bicarbonate, sample *C*	U.S.P.	$NaHCO_3$

rather to introduce simply an automated method which can determine the fastest rate at which an antacid system can react with acid, presuming, of course, that acid is always present. Experimental evidence indicates that, based on the use of the Metrohm Combititrator, such a procedure has been developed which will provide a rapid and accurate profile of the dissolution behavior of the antacid system under study in that it is capable of producing a curve which shows the onset of reaction, rate of reaction, duration of action, and total acid-consuming capacity.

EXPERIMENTAL

Metrohm.—The instrument used in the study is the Metrohm Combititrator 3D. It consists of the pH meter model E 300, the Impulsomat E 373, and the Dosigraph E 364 (a recording piston buret) (Fig. 1).

The Impulsomat is equipped with a pulse generator, a variable source for a preselected potential, and elements for adapting the response of the apparatus to a previously defined end point. Upon starting a titration with recording of the curve, the drive for the reference potentiometer is set in motion. As soon as a difference exists between the set point and the actually existing potential as picked up by the electrode chain, the piston buret delivers titrant upon a signal from the pulse generator. Due to the synchronized drive mechanism for the reference potentiometer and recording paper, the time coordinate is directly proportional to the measured value, *i.e.*, pH or *mV*. The recorded diagram thus represents the function pH (*mV*) against milliliters of titrant. One characteristic of this set up is the change of titrating speed with variations of the slope of the curve. The speed is slowest at the end point.

Operating as an automatic titrator set for a preselected end point (pH 3.00), the end point potentiometer is set to the desired value, and the pulse generator sends pulses to the recording motor piston buret until the selected setting is reached. The duration of the pulses is adjusted automatically in accordance with the existing difference at any given moment between the selected end point and the actually existing electrode potential. Sensitive dosing of the titrant thus is assured as the pH-stat

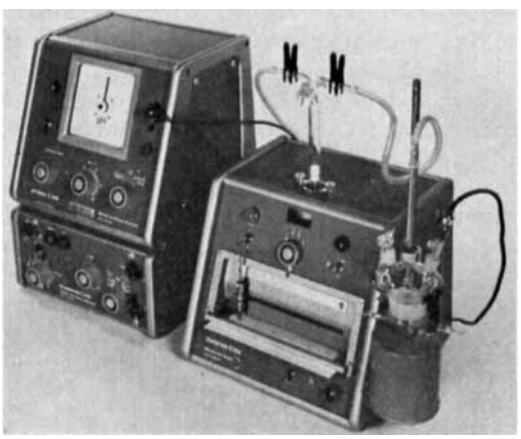

Fig. 1.—Metrohm Combititrator model 3D composed of model E-300 pH meter, model E-373 Impulsomat, and model E-364 Dosigraph.

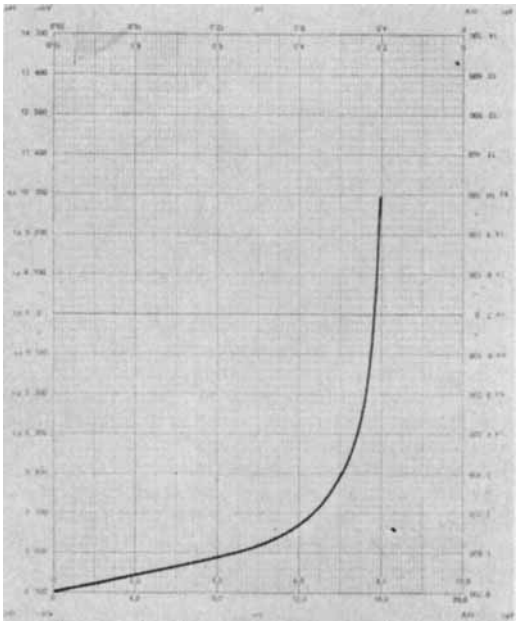

Fig. 2.—Typical Metrohm curve of antacid material as obtained with recording graph paper No. E-364.

point is approached. When pH 3.00 is reached, the apparatus operates as a regulator for maintaining the pH-stat value of the solution.

When using the high sensitivity range of the pH meter E 300 (total range extending over 2.8 pH units anywhere on the pH scale), a remarkable degree of accuracy can be maintained. The Dosigraph records the position of the buret against time. Two different speeds of the paper advance are available for the purpose of recording fast and slow processes. All comparative evaluations in this paper utilized the Metrohm set to run at the slow speed of 1 cm./10 min. using 0.3 *N* titrant to allow use of the Metrohm recording graph paper (Fig. 2). The use of this combination of 0.3 *N* titrant and slow paper advance is more suitable for obtaining the complete profile of an antacid material. In those instances where it is desired to obtain a picture of the behavior during the first few minutes of reaction, the Metrohm can be outfitted with a roll of recording paper, then set to the fast paper advance speed of 1.7 cm./min. using 0.1 *N* hydrochloric acid as the titrant.

The reaction vessel was controlled at 37.5 ± 1° during each titration. The vessel consisted of a jacketed beaker of approximately 500-ml. capacity. A constant-temperature water bath fitted with a circulator pump attachment provided water to the jacketed reaction vessel. Agitation in the reaction vessel was provided by a variable-speed magnetic stirring system which is built into the Dosigraph portion.

Procedure.—The Combititrator is standardized and set to perform a pH-stat titration at pH 3.0 using the expanded scale. The pH of 3.0 was selected as the stat point since this pH generally is considered to be that at which free hydrochloric acid is neutralized (18–21).

Two hundred milliliters of distilled water is placed into the jacketed beaker, maintained at 37.5°. Stirring is provided by the magnetic stirrer, previously set at a constant speed, which provided for the disintegration of a tablet in the same time as obtained with the U.S.P. disintegration time apparatus. A 0.5-Gm. sample of the antacid raw material then is added to the water and the Combititrator activated to record automatically the volume of 0.3 *N* acid consumed to maintain a pH 3.0-stat condition *versus* time in minutes.

In the majority of cases, the Metrohm was capable of adding the titrant sufficiently fast to maintain a pH of 3.0. Certain extremely fast-acting materials, however, required manual manipulation of the Dosigraph for the first minute or so to prevent accidental overshooting of the pH 3.0 end point.

The capacity of the Dosigraph titrant buret used was 50 ml. (equivalent to 150 ml. of 0.1 *N* hydrochloric acid). In those cases where volumes in excess of 50 ml. of titrant were used, it was necessary to refill the buret. After several practice refills, the operator can perform this task easily within 10 sec. During refilling of the buret, the Dosigraph and Impulsomat are inactivated automatically, leaving only the pH meter recording the pH.

Reagents.—*0.3 N Hydrochloric Acid.*—This was supplied in 5-gal. prestandardized containers by the Hartman-Leddon Co., Philadelphia, Pa.

0.3 N "Simulated Gastric Fluid."—This was equivalent to the U.S.P. XVI test solution and was prepared as follows: sodium chloride, 6.85 Gm.; pepsin, 10.96 Gm.; and 0.3 *N* HCl to make 1000.00 ml.

NOTE: The simulated gastric fluid was made up to 0.3 *N* and both solutions standardized periodically against sodium carbonate using methyl orange indicator.

Antacid Chemicals Evaluated.—Twenty-seven individual samples of antacid chemicals (Table I) were evaluated by three techniques. The Metrohm technique was used to evaluate the chemicals againt 0.3 *N* hydrochloric acid and also 0.3 *N* simulated gastric fluid. The acid-consuming capacities of all chemicals were performed according to recommended U.S.P.–N.F. procedures. Determinations of the acid-consuming capacities of all 27 antacids evaluated showed excellent comparisons between the U.S.P.–N.F. *versus* the Metrohm method. One-half gram samples of the antacid chemicals were tested to maintain the curve on the Metrohm test paper. One-quarter and 1-Gm. samples were tested and found to give correspondingly similar results. In all chemicals tested, the sample weight used was on an "as is" basis and was not corrected for moisture, purity, etc.

Feasibility of Proposed Test Method.—All of the titration curve results in this paper are listed in terms of 0.1 *N* hydrochloric acid. The original Metrohm curves were obtained using 0.3 *N* hydrochloric acid at the slow speed to obtain a complete curve on one sheet of Metrohm recording paper, thus facilitating filing of the curves for future reference use. To insure that the same type of curve was obtained with both normalities of acid and at both the slow (1 cm./10 min.) and the fast (1.7 cm./min.) speeds, a series of four curves were run using 0.5-Gm. samples of antacid *8*. Examina-

TABLE II.—EFFECT OF PAPER SPEED AND TITRANT NORMALITY VARIATION ON METROHM CURVES, SAMPLE *8*

Paper Speed: / HCl Normality:	Fast 0.1 *N*	Slow 0.1 *N*	Fast 0.3 *N*	Slow 0.3 *N*
Time, min.				
0	0.0	0.0	0.0	0.0
1	17.4	17.0	22.5	21.0
2	33.5	30.0	37.5	34.5
3	45.0	44.0	49.5	45.0
4	56.0	57.5	59.2	55.5
5	67.5	65.5	66.8	64.2
6	73.2	71.5	72.0	69.8
7	77.5	76.0	77.0	75.0
8	81.5	79.5	80.2	78.6
9	83.8	82.0	82.5	81.3
10	85.4	84.0	84.0	83.6
11	86.6	85.2	85.4	85.0
12	87.4	86.2	86.4	86.0
13	88.0	87.0	87.2	87.0
14	88.5	87.6	87.6	87.6
15	88.8	88.1	88.0	88.2
18	89.5	88.9	89.0	89.2
21	90.1	89.5	89.7	90.0
24	90.4	89.9	90.0	90.3
27	90.7	90.3	90.3	90.6
30	91.0	90.6	90.6	90.9
36	91.4	91.0	91.0	91.4
42	91.8	91.3	91.5	91.6
48	92.0	91.6	91.8	92.0
54	92.2	92.0	92.1	92.2
60	92.4	92.2	92.4	92.6
75	92.8	92.5	93.0	93.0
90	93.2	92.8	93.3	93.3
105	93.4	93.0	93.4	

tion of the results listed in Table II show that upon conversion of the data to 0.1 *N* hydrochloric acid, practically identical curves were obtained in all four cases. These results indicate that the two acid normalities and paper speeds, as used in this paper, are interchangeable.

RESULTS

Aluminum Hydroxide Dried Gel.—All three samples show a slow initial onset of acid-consuming activity, with samples *1* and *2* being somewhat faster than *3*. Figures 3 and 4 graphically show that while the presence of pepsin decreases both the initial speed of reaction and the total acid consumed, it does appear to significantly prolong the activity—*viz.*, after 60 min., about 50% reacted with pepsin and 85% without pepsin.

Aluminum Triple Precipitate.—Sample *4* has a rapid onset of activity (presence of calcium and magnesium antacids) and a long duration of activity (presence of aluminum). It is affected only slightly by the presence of pepsin with regard to onset and duration of activity. The two curves excellently demonstrate all the individual moieties of the parent antacid.

Calcium Carbonate.—Both samples *5* and *6* show an extremely rapid onset of activity with a relatively short duration of action. They are essentially unaffected by the presence of pepsin. The reagent grade (*5*) appears to consume more acid than the U.S.P. grade (*6*).

Dihydroxyaluminum Aminoacetate.—The two samples appear to have different initial rates and durations of activity. It is of interest to note that *7* is relatively free from the effects of pepsin, while *8* seems to be affected by its presence.

Dihydroxy Aluminum Sodium Carbonate.—The presence of pepsin seems to have only a slight effect on the duration of activity. The initial rate and total acid-consuming capacity appear to be unaffected.

Glycine.—Although not an antacid *per se*, it performs with and without pepsin as expected. It is of interest to note that, due to the back titration with alkali, glycine has an acid-consuming capacity of 0.0 ml. per Gm. using the U.S.P. test method.

Magnesium Aluminum Silicate.—Both samples *11* and *12* appear to be unaffected by the presence of pepsin. Although the initial rate of activity and total acid-consuming capacities of the two samples are practically identical, there is a definite difference in the durations of activity.

Magnesium Carbonate.—This extremely rapidly reacting antacid chemical behaved as expected both in and without the presence of pepsin.

Magnesium Carbonate–Aluminum Hydroxide Co-Dried Gel.—These two antacid samples (*14* and *15*) both retain their relatively high initial rate of activity and total acid consumption with and without pepsin. Table IV shows the prolongation of activity duration due to the presence of pepsin, showing it to be one of the few aluminum-type antacids not adversely affected by pepsin to a great degree.

Magnesium Hydroxide.—This was one of the more reactive compounds tested and had extremely high initial rate and total capacity. It appears to be affected only slightly by pepsin activity as can be seen under *Summary of Data* in Tables III and IV—*viz.*, after 3 min., 86% was reacted without pepsin and only 65% with pepsin.

Magnesium Hydroxy Aminoacetate.—Sample *17* was medial with respect to its initial rate and

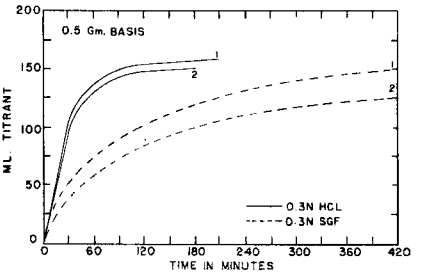

Fig. 3.—Aluminum hydroxide dried gel U.S.P., samples *1* and *2*.

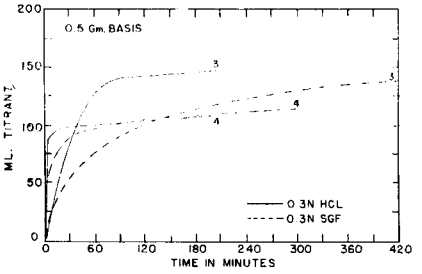

Fig. 4.—Sample *3* aluminum hydroxide dried gel U.S.P. and sample *4* aluminum triple precipitate.

TABLE III.—METROHM *In Vitro* EVALUATION OF ANTACID ACTIVITY[a]

Time, min.	Antacid Sample 1	2	3	4	5	6	7	8	9
0	0	0	0	0	0	0	0	0	0
3	5.1	5.6	3.3	75.8	99.0	98.7	24.0	45.0	72.0
6	12.0	9.0	6.0	81.6	106.2	101.0	54.0	69.8	96.0
9	21.8	14.4	10.2	85.2	106.8	101.2	71.2	81.3	106.2
12	31.6	21.9	16.2	88.4	...	...	79.0	86.0	110.7
15	41.2	30.9	24.3	91.5	...	...	82.8	88.2	113.1
18	51.0	40.5	33.0	94.2	...	...	84.4	89.2	114.4
21	60.2	50.1	42.8	96.4	...	...	85.5	90.0	115.5
24	69.6	58.6	52.5	100.0	...	...	86.1	90.3	116.0
27	78.4	67.2	62.4	100.2	...	...	86.7	90.6	116.4
30	87.0	74.7	71.2	101.7	...	...	87.0	90.9	116.7
36	102.0	88.2	87.0	103.8	...	...	87.4	91.4	116.8
42	114.0	99.4	100.2	105.4	...	...	88.0	91.6	117.0
48	123.4	109.5	110.2	106.5	...	...	88.6	92.0	117.2
54	130.8	117.4	118.4	107.4	...	...	89.1	92.2	...
60	136.5	124.2	124.5	108.0	...	...	89.6	92.6	...
75	146.0	135.8	134.7	109.2	...	...	90.2	93.0	...
90	150.4	141.4	140.6	109.8	...	...	90.6	93.3	...
105	153.4	144.4	143.7	110.7	...	...	91.0	...	...
120	155.3	146.1	145.5	111.0	...	...	91.4	...	...
135	156.3	147.0	146.6	111.3	...	...	91.5	...	...
150	157.2	147.8	147.2	111.6	...	...	...	...	...
165	157.8	148.2	147.6	111.9	...	...	...	...	...
180	158.2	148.5	148.1	112.2	...	...	...	...	...
210	158.7	...	148.8	112.5	...	...	...	...	...
240	...	...	...	...	...	...	...	...	...
270	...	...	...	...	...	...	...	...	...
300	...	...	...	...	...	...	...	...	...
330	...	...	...	...	...	...	...	...	...
360	...	...	...	...	...	...	...	...	...
390	...	...	...	...	...	...	...	...	...
420	...	...	...	...	...	...	...	...	...
Summary of Data									
% of max., 3 min.	3.2	3.8	2.2	67.4	92.7	97.5	26.2	48.2	61.4
% of max., 15 min.	26.0	20.8	16.3	81.3	100	100	90.5	95.6	96.5
% of max., 30 min.	54.8	50.3	47.8	90.4	...	...	95.1	97.4	99.6
% of max., 60 min.	86.0	83.6	83.7	96.0	...	...	97.9	99.2	100

Time, min.	Antacid Sample 10	11	12	13	14	15	16	17	18
0	0	0	0	0	0	0	0	0	0
3	14.7	51.0	49.5	106.8	67.5	45.0	144.8	42.0	237.8
6	...	63.3	63.2	107.1	102.8	96.0	159.6	63.0	241.0
9	...	68.0	67.8	107.2	126.8	125.2	163.5	71.7	242.2
12	...	70.5	70.0	...	138.4	138.0	165.8	75.8	243.3
15	...	72.2	71.2	...	143.0	143.0	166.8	78.2	244.2
18	...	73.5	72.3	...	144.8	144.6	167.2	79.5	245.0
21	...	74.4	73.2	...	145.2	145.4	167.6	80.4	245.6
24	...	75.3	73.8	...	145.5	145.5	167.7	81.0	246.0
27	...	76.0	74.4	...	...	145.6	167.9	81.3	246.4
30	...	76.5	75.0	...	...	145.8	...	81.6	246.9
36	...	77.6	75.9	...	...	...	...	81.9	247.4
42	...	78.3	76.6	...	...	...	...	82.0	247.8
48	...	78.8	77.2	...	...	...	...	82.2	248.1
54	...	79.2	77.8	...	...	...	...	...	248.4
60	...	79.5	78.3	...	...	...	...	...	248.7
75	...	80.0	79.4	...	...	...	...	...	248.9
90	...	80.4	79.8	...	...	...	...	...	...
105	...	80.7	80.6	...	...	...	...	...	...
120	...	80.8	81.0	...	...	...	...	...	...
135	...	81.0	81.3	...	...	...	...	...	...
150	...	...	81.6	...	...	...	...	...	...
165	...	...	81.9	...	...	...	...	...	...
180	...	...	82.2	...	...	...	...	...	...
210	...	...	82.5	...	...	...	...	...	...
240	...	...	...	...	...	...	...	...	...
270	...	...	...	...	...	...	...	...	...
300	...	...	...	...	...	...	...	...	...

continued overleaf

330	...	...	...	...	...	...	...	...	...
360	...	...	...	...	...	...	...	...	...
390	...	...	...	...	...	...	...	...	...
420	...	...	...	...	...	...	...	...	...
Summary of Data									
% of max., 3 min.	100.0	62.9	60.0	99.6	46.4	30.9	86.2	51.2	95.5
% of max., 15 min.	...	89.1	86.3	100	98.3	98.0	99.3	95.1	98.1
% of max., 30 min.	...	94.4	90.9	...	100	100.0	100	99.3	99.1
% of max., 60 min.	...	98.1	94.9	...	...	...	...	100	99.9

Time, min.	Antacid Sample 19	20	21	22	23	24	25	26	27
0	0	0	0	0	0	0	0	0	0
3	222.0	213.0	218.6	10.5	12.4	28.2	60.5	61.8	61.2
6	236.2	231.3	221.0	14.4	18.3	36.8	...	...	...
9	239.0	238.8	221.7	17.2	24.0	42.0	...	...	...
12	240.3	241.8	222.2	20.1	29.2	45.6	...	...	...
15	241.2	243.0	222.4	22.6	33.8	48.0	...	...	...
18	241.6	243.8	222.8	25.2	37.5	49.8	...	...	...
21	242.1	244.0	222.9	27.4	39.0	51.2	...	...	...
24	242.4	...	223.0	30.0	42.8	52.0	...	...	...
27	242.7	...	...	32.1	45.0	53.0	...	...	...
30	242.9	...	...	34.2	46.4	53.7	...	...	...
36	243.0	...	...	37.5	48.8	54.4	...	...	...
42	243.2	...	...	40.0	50.2	55.2	...	...	...
48	243.3	...	...	41.8	51.3	55.6	...	...	...
54	...	...	...	43.4	52.0	56.0	...	...	...
60	...	...	...	44.7	52.8	56.2	...	...	...
75	...	...	...	46.5	53.7	56.7	...	...	...
90	...	...	...	48.0	54.4	57.0	...	...	...
105	...	...	...	49.0	54.8	57.4	...	...	...
120	...	...	...	49.8	55.0	...	...	...	...
135	...	...	...	50.4	...	...	...	...	...
150	...	...	...	50.8	...	...	...	...	...
165	...	...	...	51.3	...	...	...	...	...
180	...	...	...	51.4	...	...	...	...	...
210	...	...	...	51.8	...	...	...	...	...
240	...	...	...	52.0	...	...	...	...	...
270	...	...	...	...	...	...	...	...	...
300	...	...	...	...	...	...	...	...	...
330	...	...	...	...	...	...	...	...	...
360	...	...	...	...	...	...	...	...	...
390	...	...	...	...	...	...	...	...	...
420	...	...	...	...	...	...	...	...	...
Summary of Data									
% of max., 3 min.	91.2	87.3	98.0	20.2	22.5	49.1	100	100	100
% of max., 15 min.	99.1	99.6	99.9	43.4	61.4	83.6	...	...	...
% of max., 30 min.	99.8	100	100	65.8	84.4	93.5	...	...	...
% of max., 60 min.	100	...	...	85.9	96.0	97.9	...	...	...

[a] Milliliters of 0.1 *N* HCl consumed per 0.5 Gm. antacid material recorded as a function of time in minutes.

duration of activity. Its antacid activity is unaffected by pepsin.

Magnesium Oxide.—These four samples (*18*, *19*, *20*, and *21*) were by far the most active antacids tested in this paper. Similar to the curves of magnesium hydroxide, the initial rates of reaction were diminished somewhat in the presence of pepsin. However, the duration of action and the total acid-consuming capacity were unaffected by pepsin. As was noted with calcium carbonate (samples *5* and *6*), the reagent grades of magnesium oxide generally yielded higher acid-consuming capacities and longer durations of activity than did the U.S.P. grades. Similarly, the heavy grade appears to have a higher acid-consuming capacity than does the light grade.

Magnesium Trisilicate.—All of the three samples tested showed similar total acid-consuming capacities irrespective of the presence of pepsin. In fact, all of the samples basically were unaffected by the presence of pepsin. Initially, however, there was an observable increase in the initial rate of reaction in the presence of pepsin. A careful examination of the three curves in Tables III and IV shows that there are slight but definite differences in the initial rate and duration of action of the compound supplied by three different sources.

TABLE IV.—METROHM *In Vitro* EVALUATION OF ANTACID ACTIVITY[a]

Time, min.	Antacid Sample 1	2	3	4	5	6	7	8	9
0	0	0	0	0	0	0	0	0	0
3	4.5	6.0	2.2	67.5	106.4	99.3	27.0	34.5	75.0
6	7.4	8.0	3.3	76.8	107.4	100.8	47.0	57.0	94.5
9	10.8	10.2	4.8	80.6	107.6	...	62.2	70.0	103.4
12	15.4	13.2	8.6	83.0	107.7	...	72.4	77.1	108.3
15	20.4	16.5	14.2	85.1	107.8	...	78.8	81.0	111.3
18	25.2	20.0	21.0	86.7	...	...	82.5	83.6	113.2
21	29.7	24.0	28.4	88.2	...	...	84.6	85.0	114.3
24	34.2	26.4	34.8	90.0	...	...	86.0	86.0	115.3
27	38.6	31.5	41.1	90.8	...	...	86.7	86.7	116.1
30	42.9	34.8	46.6	92.0	...	...	87.3	88.2	116.7
36	50.6	41.1	56.1	94.1	...	...	88.0	88.6	117.4
42	58.0	46.6	63.4	95.9	...	...	88.5	88.8	117.9
48	64.2	51.2	69.6	97.4	...	...	89.0	...	118.0
54	70.2	55.5	74.6	98.7	...	...	89.4	...	118.2
60	75.0	59.2	79.0	99.8	...	...	90.0	...	118.4
75	85.2	67.5	87.3	102.0	...	...	90.2	...	118.5
90	92.7	73.8	93.8	104.0	...	...	90.4	...	...
105	99.0	79.4	99.0	105.5	...	...	90.9	...	...
120	104.0	84.0	103.2	106.8	...	...	91.4	...	...
135	108.4	88.5	106.8	107.9	...	...	91.5	...	...
150	112.5	92.1	110.0	108.8	...	...	...	...	...
165	115.8	95.7	112.8	109.5	...	...	...	...	...
180	118.8	98.7	115.2	110.3	...	...	...	...	...
210	124.0	104.2	120.0	111.2	...	...	...	...	...
240	129.2	109.4	123.4	111.5	...	...	...	...	...
270	133.0	113.1	125.1	111.9	...	...	...	...	...
300	136.6	116.6	129.2	112.2	...	...	...	...	...
330	139.8	119.4	131.2	...	...	...	...	...	...
360	142.5	121.6	133.2	...	...	...	...	...	...
390	145.0	123.6	135.0	...	...	...	...	...	...
420	147.0	125.6	136.5	...	...	...	...	...	...
Summary of Data									
% of max., 3 min.	3.1	4.8	1.6	60.1	98.7	98.5	29.5	38.8	63.3
% of max., 15 min.	13.9	13.2	10.4	75.8	100	100	86.1	91.2	93.9
% of max., 30 min.	29.2	27.7	34.1	82.0	...	...	95.4	99.3	98.5
% of max., 60 min.	51.0	44.2	57.9	88.9	...	...	98.4	100	99.9

Time, min.	Antacid Sample 10	11	12	13	14	15	16	17	18
0	0	0	0	0	0	0	0	0	0
3	15.4	58.4	50.7	106.5	60.0	40.5	108.8	45.8	187.5
6	...	65.4	63.9	107.1	88.5	73.5	135.8	64.5	229.5
9	...	68.6	68.4	...	106.5	96.0	150.0	73.2	238.5
12	...	70.8	70.5	...	118.5	108.8	158.2	77.4	241.4
15	...	72.3	71.6	...	125.7	116.2	162.0	79.6	242.7
18	...	73.5	72.6	...	130.2	121.2	164.0	80.7	243.8
21	...	74.6	73.3	...	133.2	124.5	165.2	81.3	244.5
24	...	75.3	74.0	...	135.4	127.0	165.8	81.8	245.2
27	...	76.0	74.6	...	137.2	129.0	166.2	81.9	245.8
30	...	76.6	75.0	...	138.4	130.5	166.4	82.0	246.3
36	...	77.6	76.0	...	140.6	132.4	166.5	82.2	247.0
42	...	78.3	76.6	...	142.2	134.2	...	...	247.5
48	...	78.9	77.6	...	143.0	135.4	...	...	248.0
54	...	79.4	78.0	...	144.0	136.5	...	...	248.4
60	...	79.6	78.4	...	144.8	137.6	...	...	248.7
75	...	80.2	79.4	...	146.2	139.2	...	...	249.0
90	...	80.6	80.1	...	147.2	140.2	...	...	249.2
105	...	80.8	80.6	...	148.2	141.0	...	...	...
120	...	81.0	80.9	...	148.6	141.8	...	...	...
135	...	...	81.0	...	149.2	142.4	...	...	...
150	...	...	81.3	...	149.7	142.8	...	...	...
165	...	...	81.6	...	150.0	143.2	...	...	...
180	...	...	81.8	...	...	143.6	...	...	...
210	...	...	81.9	...	...	144.0	...	...	...
240	...	...	...	...	...	...	...	...	...
270	...	...	...	...	...	...	...	...	...
300	...	...	...	...	...	...	...	...	...

continued overleaf

330	...	...	...	...	...	...	...	...	...
360	...	...	...	...	...	...	...	...	...
390	...	...	...	...	...	...	...	...	...
420	...	...	...	...	...	...	...	...	...
Summary of Data									
% of max., 3 min.	100	72.1	61.9	99.4	40.0	28.1	65.3	55.7	75.2
% of max., 15 min.	...	89.2	87.4	100	83.8	80.7	97.3	96.8	97.4
% of max., 30 min.	...	94.6	91.6	...	92.3	90.6	99.9	99.8	98.8
% of max., 60 min.	...	98.3	95.7	...	96.5	95.6	100	100	99.7

Time, min.	Antacid Sample *19*	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*
0	0	0	0	0	0	0	0	0	0
3	192.0	180.0	202.5	12.0	15.0	33.0	60.6	62.1	62.0
6	229.5	222.8	217.0	15.6	23.2	40.5	...	...	...
9	242.2	239.0	220.0	18.9	30.0	45.0	...	...	...
12	246.0	244.2	221.4	21.6	35.7	48.0	...	...	...
15	246.3	246.6	222.3	24.3	40.0	50.0	...	...	...
18	246.4	247.5	223.0	27.0	43.2	51.3	...	...	...
21	246.6	247.8	223.2	29.7	45.4	52.5	...	...	...
24	246.8	248.0	223.5	32.1	47.6	53.2	...	...	...
27	247.0	248.1	223.6	34.2	48.9	53.7	...	...	...
30	247.2	...	223.8	36.3	49.8	54.3	...	...	...
36	247.4	...	224.1	39.4	51.4	55.0	...	...	...
42	247.5	...	224.4	41.8	52.8	55.5	...	...	...
48	...	...	...	43.6	53.4	55.8	...	...	...
54	...	...	...	45.0	54.0	56.1	...	...	...
60	...	...	...	46.2	54.4	56.4	...	...	...
75	...	...	...	48.0	55.2	56.7	...	...	...
90	...	...	...	49.4	55.5	...	...	...	...
105	...	...	...	50.4	...	...	...	...	...
120	...	...	...	51.0	...	...	...	...	...
135	...	...	...	51.4	...	...	...	...	...
150	...	...	...	52.0	...	...	...	...	...
165	...	...	...	52.4	...	...	...	...	...
180	...	...	...	52.6	...	...	...	...	...
210	...	...	...	53.1	...	...	...	...	...
240	...	...	...	...	...	...	...	...	...
270	...	...	...	...	...	...	...	...	...
300	...	...	...	...	...	...	...	...	...
330	...	...	...	...	...	...	...	...	...
360	...	...	...	...	...	...	...	...	...
390	...	...	...	...	...	...	...	...	...
420	...	...	...	...	...	...	...	...	...
Summary of Data									
% of max., 3 min.	77.6	72.6	90.2	22.6	27.0	58.2	100	100	100
% of max., 15 min.	99.5	99.4	99.1	45.8	72.1	88.2	...	...	...
% of max., 30 min.	99.9	100	99.7	68.4	89.7	95.8	...	...	...
% of max., 60 min.	100	...	100	87.0	98.0	99.5	...	...	...

[a] Milliliters of 0.1 *N* simulated gastric fluid consumed per 0.5 Gm. antacid material recorded as a function of time in minutes.

Sodium Bicarbonate.—Samples *25*, *26*, and *27*, provided by three manufacturers, had identical curves in every respect, and all were totally unaffected by the presence of pepsin.

Aluminum Phosphate and Bismuth Subcarbonate.—Both of these chemicals proved to be inactive when tested *via* the proposed Metrohm technique. A U.S.P. based acid-consuming capacity test confirmed these findings.

DISCUSSION

In general, the results obtained through use of the curves from the Metrohm titrations compare favorably with those obtained by use of existing methods. It was of interest to note the effect of pepsin on the various antacids. The sodium and calcium antacids were unaffected by the presence of pepsin, while the aluminum antacids were affected rather severely. The magnesium antacids, however, appeared to be affected by pepsin in several ways. Those antacids with a high initial rate of reaction (*8*, *16*, *18*, *19*, *20*, and *21*) showed an initial decrease in the presence of pepsin, while those with a low initial rate (*22*, *23*, and *24*) showed an initial increase with pepsin. In so far as durations of activity and total acid-consuming capacities were concerned, the only observable trend in either type appeared to be a slight decrease in the duration of activity in those antacids with a low initial rate

(*i.e.*, *22*, *23*, and *24*). The behavior of those complex antacids containing both magnesium and aluminum moieties could be predicted somewhat, based on the knowledge of the mole ratios of aluminum *versus* magnesium present in the parent antacid.

SUMMARY

1. A comparative *in vitro* procedure, based on the the use of the Metrohm Combititrator, has been proposed which provides a simple, rapid, and accurate method for determination of the complete profile of an antacid system. A curve is obtained from which one can determine the initial onset of reaction, rate of reaction, duration of action, and the total acid-consuming capacity.

2. A comparative correlation has been made to show the interchangeability of the method to utilize either 0.1 *N* or 0.3 *N* hydrochloric acid with either slow or fast paper speeds. The use of 0.3 *N* hydrochloric acid with slow paper speeds is recommended as a means of recording all the data for the profile of an antacid on a single sheet of recording paper to facilitate storage of and future reference to the curves.

3. *In vitro* evaluations of 27 antacid materials have been studied by use of Metrohm technique.

4. The effect of pepsin on the titration of the various antacids with 0.3 *N* hydrochloric acid has been studied. Results from titrations of calcium, sodium, and aluminum antacids are consistent with previously reported findings in the literature. Metrohm curves of magnesium antacids, while being consistent in comparison with their own classes, are erratic in their behavior in the presence of pepsin, unlike previously reported work which claimed magnesium compounds to be unaffected by pepsin.

5. Careful evaluations of the Metrohm curves show variations between various grades of the same antacid. Indeed, significant variations between the same grade of an antacid supplied by different manufacturers become readily apparent. In agreement with Dale and Booth (22), such variations in U.S.P.–N.F. antacid materials suggest the need for more exact test procedures to insure uniformity.

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Notes

Natural Occurrence of 2-Hydroxyxanthone

By R. A. FINNEGAN and P. L. BACHMAN*

2-Hydroxyxanthone has been isolated from the seeds of *Mammea americana* L. and identified by spectroscopic and melting point comparisons of the phenol and its derivations with synthetic samples. This is believed to be the simplest xanthone yet encountered in nature.

VARIOUS PARTS of the mamey tree (*Mammea americana* L.) have attracted scientific attention for many years, and the results of previous chemical examinations have been recently summarized (1). The structures of three rather closely related phenolic polysubstituted coumarins, mammein (2), mammeisin (3), and mammeigin (4), have been elucidated previously, as has the nature of the wax (mamey wax) which was isolated from the seed oil (1). The continuing chemical investigation of mamey seed extracts has led to the discovery and identification of yet another phenolic constituent. The present article is an account of this work.

The benzene extract of ground mamey seeds, which had been extracted previously with isohexane, was partitioned in the usual manner into acidic,

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