Automated Technique for Determining Dissolution and Reaction Rates of Antacids II

Commercial Antacid Products

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Many of the current techniques for evaluating antacids involve metering into a system a quantity of acid at some arbitrary specific rate. This procedure does not allow for distinguishing between rapidly reacting and slowly reacting antacid products. Using the new method described, it is possible to compare automatically the maximum speed at which an antacid product will react with gastric acid. This procedure measures not only the speed of reaction of the antacid but also the rate at which the antacid makes itself available for reaction. Forty-eight commercial antacid preparations are evaluated, encompassing eight liquid, eight effervescent, 21 chewable, and 11 swallowable tablets. Dissolution rates are presented using both hydrochloric acid and simulated gastric juice as titrants. A comparison between the acid-consuming capacities obtained by the U.S.P. procedure *versus* the proposed technique is presented. It is concluded that the proposed method is valuable for evaluating antacid products.

THERE ARE many *in vitro* techniques currently employed for the evaluation of various antacid products (1–12). Even if an investigator were to attempt to combine the more salient features of all these techniques in an effort to produce the ultimate technique, a true and meaningful *in vitro* evaluation of antacid products would still be difficult, if not impossible. Such an *in vitro* technique should, of necessity, include factors such as effect upon digestive processes, effect in producing acid-rebound, effect upon normal gastrointestinal function (diarrhea or constipation), effect upon gastric mucosa—*viz.*, does it increase or decrease irritation (13), initial taste, sucking properties, chewability, after taste, and mouth feel (14). The following criteria should also be subject to assessment by this method: show maximum neutralizing effect in the shortest possible time; should neutralize adequate amounts of gastric acid; should maintain its action during normal period of gastric digestion; any excess of antacid beyond the amount required to neutralize the free gastric acid present should not cause alkalization; should raise the pH of the gastric contents to a level at which pepsin activity is significantly reduced but not totally inhibited; should be palatable after adequate and repeated doses (15); should not produce systemic alkalosis; and finally, should or should not be eructating, as proposed by the manufacturer (16). In view of the above, the investigator might do well to conclude that no single *in vitro* method will ever be able to provide a complete *in vivo* profile of an antacid product.

Many of these previously noted techniques are based upon metering into the system under investigation a quantity of hydrochloric acid at some arbitrary specific rate. These procedures generally do not provide for distinguishing between rapidly reacting and slowly reacting antacid products, *e.g.*, sodium hydroxide, conceivably might be classified as a long-acting antacid by some techniques. Using the proposed Metrohm Combititrator technique, it is possible to compare automatically the maximum speeds at which antacid products make themselves available for reaction with free gastric acid. This procedure measures not only the initial speed of reaction of the antacid but also the over-all rate and duration of action.

It is neither the main intent nor purpose of this paper to introduce a new and novel *in vitro* technique of antacid evaluation which will afford a direct correlation with *in vivo* techniques (13,

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TABLE I.—COMPRESSED ANTACID TABLETS EVALUATED

Sample	Compn.
1	Calcium carbonate and glycine
2	Calcium carbonate and glycine
3	Calcium carbonate and glycine
4	Calcium carbonate, magnesium carbonate, and milk solids
5	Calcium carbonate, magnesium carbonate, and milk solids
6	Calcium carbonate, magnesium hydroxide, and magnesium trisilicate
7	Aluminum hydroxide–magnesium hydroxide
8	Magnesium hydroxide
9	Magnesium hydroxide
10	Sodium bicarbonate
11	Sodium bicarbonate

TABLE II.—CHEWABLE ANTACID TABLETS EVALUATED

Sample	Compn.
12	Calcium carbonate and glycine
13	Calcium carbonate and glycine
14	Calcium carbonate and glycine
15	Calcium carbonate, magnesium carbonate, and milk solids
16	Calcium carbonate, magnesium carbonate, and milk solids
17	Aluminum hydroxide–magnesium hydroxide
18	Aluminum hydroxide–magnesium hydroxide
19	Calcium carbonate, magnesium carbonate, and magnesium trisilicate
20	Calcium carbonate, magnesium carbonate, and magnesium trisilicate
21	Calcium carbonate, magnesium carbonate, and magnesium trisilicate
22	Calcium carbonate, magnesium carbonate, and magnesium trisilicate
23	Aluminum hydroxide
24	Aluminum hydroxide and magnesium hydroxide
25	Aluminum hydroxide and magnesium hydroxide
26	Magnesium trisilicate, magnesium oxide, and calcium carbonate
27	Magnesium carbonate–aluminum hydroxide and calcium carbonate
28	Magnesium trisilicate and aluminum hydroxide
29	Calcium carbonate, magnesium hydroxide, and magnesium trisilicate
30	Dihydroxy aluminum sodium carbonate
31	Magnesium hydroxide
32	Magnesium aluminum silicate

17–25). What is mainly proposed, however, is the introduction of an automated method of antacid analysis which will be of value, with a minimum of effort and skill and a maximum of accuracy, in the comparative evaluation of antacid products. The method, as proposed, could be adapted to perform the following functions accurately and efficiently: (*a*) evaluate new antacid raw materials, (*b*) evaluate combinations of antacid materials in the initial stages of designing a new antacid dosage form, (*c*) compare evaluation of the curve of the new dosage form *versus* the curve of the combination of raw materials, (*d*) use as a control procedure to compare curve of reference standard *versus* those of subsequent production material, and (*e*) use in storage stability testing by comparison of curves of the initial material with those of aged samples.

EXPERIMENTAL

Metrohm Combititrator.—The instrument used in this study, its method of operation and standardization, were discussed thoroughly by Steinberg *et al.* (26).

Procedure.—The Combititrator is standardized and set to perform a pH stat titration at pH 3.0. Two hundred milliliters of distilled water is placed into a jacketed 500-ml. beaker maintained at 37.5 ± 1.0°. Stirring, provided by the magnetic stirrer, was held constant, as outlined in an earlier paper (26). The sample weight (or volume) of the antacid to be tested next is added to the water and the Combititrator immediately activated to start the titration.

As previously noted (26), it was sometimes necessary to operate the Dosigraph manually to prevent overshooting of the pH 3.0 stat point. Manual manipulation was necessary in the case of the effervescent antacid samples *33* through *40* during running of the entire titrations.

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.

Compressed Antacid Tablets.—Eleven different commercially available swallow-type antacids (Table I) were evaluated. All of the Metrohm studies utilized 0.3 *N* hydrochloric acid (Table VII) and 0.3 *N* simulated gastric fluid (Table XI) as the titrants to be tested against one single whole tablet. The U.S.P.–N.F. acid-consuming capacity test result compared favorably with the Metrohm results.

Rather than use a sample weight of either 1 Gm. of tablet *per se* or an amount equivalent to 1 Gm. of the active ingredients whose concentrations incidentally are not always listed on the label, it was decided to use a single unit of each dosage form. For compressed and chewable antacids, one tablet was used; for effervescent antacids, one tablet, capful, teaspoonful, or package; and for the liquid antacids, 5 ml.

Chewable Antacid Tablets.—Twenty-one different chewable antacid tablets (Table II) were evaluated by the Metrohm against 0.3 *N* hydrochloric acid (Table VIII) and 0.3 *N* simulated gastric fluid (Table XII). A portion of 100-mesh ground tablets, equivalent to the average tablet weight, was used as the sample weight to be tested. In the case of several of the tablets which resisted wetting, it was necessary to prepare first a slurry of the powder in a portion of the water containing 2 drops of polysorbate 20.[1] The slurry then was transferred

[1] Marketed as Tween 20 by the Atlas Chemical Industries, Wilmington, Del.

TABLE III.—EFFERVESCENT ANTACIDS EVALUATED

Sample	
33	Sodium bicarbonate, citric acid, acetaminophen, potassium bromide, acetophetidin, and caffeine
34	Sodium bicarbonate, citric acid, aspirin, and monobasic calcium phosphate
35	Sodium bicarbonate, citric acid, aspirin, and monobasic calcium phosphate
36	Sodium bicarbonate, citric acid, sodium carbonate, and aspirin
37	Sodium bicarbonate and tartaric acid
38	Sodium bicarbonate, citric acid, and monobasic sodium phosphate
39	Sodium bicarbonate, tartaric acid, and potassium sodium tartrate
40	Sodium bicarbonate, tartaric acid, and potassium sodium tartrate

TABLE IV.—LIQUID ANTACIDS EVALUATED

Sample	Compn.
41	Aluminum hydroxide
42	Aluminum hydroxide–magnesium hydroxide
43	Aluminum hydroxide and magnesium trisilicate
44	Aluminum hydroxide and magnesium hydroxide
45	Aluminum hydroxide and magnesium hydroxide
46	Aluminum hydroxide and magnesium hydroxide
47	Magnesium aluminum silicate
48	Magnesium aluminum silicate

TABLE V.—EFFECT OF PAPER SPEED AND TITRANT NORMALITY VARIATION ON METROHM CURVES (ONE WHOLE TABLET *1*)

Time, min.	Paper Speed, HCl Normality			
	Fast, 0.1 *N*	Slow, 0.1 *N*	Fast, 0.3 *N*	Slow, 0.3 *N*
0	0.0	0.0	0.0	0.0
1	19.8		18.4	
2	32.0		31.5	
3	39.1	30.6	38.1	46.5
4	43.0		42.0	
5	45.3		44.2	
6	46.8	43.2	46.1	51.0
7	48.7		47.4	
8	49.9		48.0	
9	50.9	47.8	48.6	52.8
10	51.4		49.1	
11	51.7		49.5	
12	52.0	50.8	50.1	53.2
13	52.2		50.7	
14	52.4		51.1	
15	52.5	51.8	51.4	53.6
18	52.8	52.2	51.8	53.7
21	52.9	52.4	52.0	53.8
24	53.0	52.5	52.2	53.9
27	53.1	52.6	52.4	
30	53.2		52.5	54.0
36	53.3	52.6		54.2
42	53.4	52.8		54.3
48		52.9		
54				
60				

quantitatively to the jacketed beaker and adjusted to give a total volume of 200 ml. Several comparative titrations were performed with and without the polysorbate 20 to determine if it produced any effect on the curve. Results showed that no observable differences could be detected in any case.

Effervescent Antacids.—Eight commercial effervescent antacids (Table III) in the form of tablets, granules, and powders were evaluated. Again 0.3 *N* hydrochloric acid (Table IX) and 0.3 *N* simulated gastric fluid (Table XIII) were used as the titrants. The sample weight used corresponded to the manufacturers' recommended unit dosage form. Although several of the products might be construed to be primarily laxatives, cathartics, or analgesics, according to the manufacturers label claims, they did possess antacid properties and thus were included.

Liquid Antacids.—Eight various liquid antacids (Table IV) were evaluated against 0.3 *N* hydrochloric acid (Table X) and 0.3 *N* simulated gastric fluid (Table XIV). Five-milliliter samples of each preparation were used for the titration to facilitate comparisons.

Feasibility of Proposed Test Method.—In essence, the data presented here provide for feasibility and reproducibility of the proposed test method since the curves outlined in Table V were prepared by four different people. All of the Metrohm curves recorded in Tables VII through XIV were obtained using 0.3 *N* titrants at a slow speed. Results are listed in the more common terms of 0.1 *N* acid, however. To insure that both curves would be identical and that these curves might be used interchangeably, the following experiment was performed. A series of four curves were run by four different persons on a single whole sample *1* tablet using both 0.1 *N* and 0.3 *N* hydrochloric acid at both fast (1.7 cm./min.) and slow (1 cm./10 min.) speeds. The data from the 0.3 *N* acid curves were converted to 0.1 *N* and recorded in Table V along with the directly read 0.1 *N* acid data. Examination of these data shows very good correlation, in spite of the usual tablet-to-tablet variations in properties such as weight, hardness, disintegration time, etc.

Effect of pH Stat Variation.—All titrations in this paper were performed at a pH 3.0 stat point, since this pH generally is considered to be that at which free hydrochloric acid is neutralized (26). Dale and Booth (3) point out that "for certain clinical purposes a final pH range from 4 to 6 may be desirable while for others a pH of 2 to 3 may suffice." In view of this wide range of pH values suggested for antacid evaluation, it seemed advisable to carry out of a series of pH stat titrations covering this range.

A series of Metrohm curves were prepared using one whole sample *1* tablet and titrating to pH stat points of 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 using 0.3 *N* hydrochloric acid with slow paper speeds. Results of these tests were quite interesting. (See Table VI.) As the pH stat conditions increase toward pH 5.0, the total acid-consuming capacity decreases while the duration of action increases markedly, and vice versa. Thus it would appear that a manufacturer, using the same antacid raw material, by careful selection of end point, could obtain practically any type of product desired,

TABLE VI.—EFFECT OF pH STAT VARIATION ON METROHM CURVES[a]

Time, min.	pH Stat 1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
0	0	0	0	0	0	0	0	0
3	158.2	81.0	58.3	46.5	22.5	17.1	12.0	10.5
6	161.0	81.3	60.4	51.3	35.2	26.7	18.3	15.4
9	...	81.4	60.9	52.8	43.8	35.2	23.6	19.2
12	...	...	61.0	53.2	44.1	39.0	27.6	22.4
15	...	...	61.2	53.6	46.3	41.4	31.2	25.2
18	...	...	61.3	53.7	46.8	43.3	33.9	27.3
21	...	...	61.4	53.8	47.2	43.8	36.0	29.6
24	...	...	61.5	53.9	47.7	44.7	37.8	31.4
27	...	...	...	...	47.8	45.3	39.3	33.0
30	...	...	...	54.0	48.0	45.3	40.5	34.5
36	...	...	...	54.2	48.2	46.0	42.0	37.0
42	...	...	...	54.3	48.3	46.5	43.4	39.0
48	...	...	...	...	48.4	46.8	44.1	40.5
54	...	...	...	...	...	47.0	44.7	41.8
60	...	...	...	...	...	47.1	45.3	43.0
75	...	...	...	...	...	47.6	46.2	44.6
105	...	...	...	...	...	...	46.5	45.4
120	...	...	...	...	...	...	46.8	46.0
135	...	...	...	...	...	...	...	46.5

[a] One whole tablet *I*; 0.3 *N* HCl; slow speed.

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

Time, min.	Tablet Sample 1	2	3	4	5	6	7	8	9	10	11
0	0	0	0	0	0	0	0	0	0	0	0
3	35.2	30.0	24.0	12.0	7.8	37.5	6.9	13.5	30.9	17.4	30.0
6	47.1	48.0	40.5	32.2	36.8	62.6	11.8	22.5	63.0	25.0	46.5
9	50.0	55.5	51.2	51.3	54.6	7.65	17.8	32.0	79.5	30.0	58.5
12	51.2	60.0	57.0	67.5	68.2	85.5	24.0	39.8	88.8	30.0	58.5
15	51.6	62.7	60.4	80.6	80.2	91.0	33.3	46.6	94.8	31.5	72.8
18	51.8	64.4	63.4	90.9	89.4	95.1	35.1	53.0	98.4	31.5	75.8
21	51.9	65.7	65.6	99.0	97.0	97.8	40.0	58.5	101.4		77.0
24	52.0	66.6	67.5	10.50	133.2	99.8	44.7	133.2	133.2		77.1
27	52.2	67.5	69.3	110.1	108.0	101.0	49.2	67.5	104.4	...	...
30	...	68.0	70.8	114.0	112.2	101.8	53.0	61.2	105.5	...	...
36	...	69.3	72.9	119.6	117.9	103.0	60.0	77.4	107.0	...	...
42	...	70.5	75.0	123.0	121.0	133.5	65.7	81.8	107.7	...	...
48	...	70.8	76.0	125.0	122.7	103.8	70.5	85.2	138.3	...	...
54	...	71.1	77.1	125.8	123.8	104.0	75.0	87.8	108.8	...	...
60	...	71.4	78.0	126.3	124.4	134.1	78.4	89.7	109.0	...	...
75	...	71.6	79.2	126.9	124.6	134.2	85.5	93.0	139.4	...	...
90	...	...	79.8	127.2	124.8	...	93.4	95.0	109.5	...	...
105	...	...	80.4	...	...	...	94.0	96.0	...	...	...
120	...	...	80.7	...	...	...	96.4	96.6	...	...	...
135	...	...	...	...	...	...	98.2	97.0	...	...	...
150	...	...	...	...	...	...	99.6	96.5	...	...	...
165	...	...	...	...	...	...	100.6	...	...	...	...
180	...	...	...	...	...	...	101.4	...	...	...	...
210	...	...	...	...	...	...	102.0	...	...	...	...
240	...	...	...	...	...	...	...	...	...	...	...
270	...	...	...	...	...	...	...	...	...	...	...
300	...	...	...	...	...	...	...	...	...	...	...
330	...	...	...	...	...	...	...	...	...	...	...
360	...	...	...	...	...	...	...	...	...	...	...
390	...	...	...	...	...	...	...	...	...	...	...
420	...	...	...	...	...	...	...	...	...	...	...
Summary of Data											
% of max., 3 min.	67.4	41.9	29.7	9.43	6.2	36.0	6.8	13.8	28.2	55.1	38.9
% of max., 15 min.	98.8	87.6	74.8	63.4	64.2	87.3	29.4	47.8	86.6	100.0	94.4
% of max., 30 min.	100.0	94.9	87.7	89.6	89.9	97.7	52.0	73.0	96.3	...	100.0
% of max., 60 min.	...	99.7	96.6	99.3	99.7	99.9	76.9	92.0	99.6	...	...

[a] Milliliters of 0.1 *N* hydrochloric acid consumed per single whole tablet recorded as a function of time in minutes.

viz., pH 2.0 stat—higher acid-consuming capacity of short duration and pH 5.0 stat—lower acid-consuming capacity of long duration. Conversion of the data to the stomach acid concentration level of 0.0875 *N* would result in even higher acid capacities. Therefore, it would seem that the pharmaceutical chemist by judicious selection of the proper experimental conditions practically should be

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

Time, min.	Tablet Sample 12	13	14	15	16	17	18	19	20	21	22
0	0	0	0	0	0	0	0	0	0	0	0
3	48.6	52.5	49.5	69.0	69.0	45.0	7.8	68.4	93.6	106.5	76.5
6	49.5	60.0	63.0	90.0	88.5	121.5	17.7	83.4	97.0	120.8	94.5
9	49.8	63.0	68.8	99.2	93.0	120.0	32.1	86.8	97.8	128.0	98.4
12	50.1	65.0	72.6	102.7	97.2	172.0	44.2	89.1	98.0	133.5	99.3
15	50.2	66.0	75.0	108.4	100.8	181.0	53.2	92.8	98.1	136.6	99.6
18	50.4	66.4	76.4	111.0	105.0	188.4	60.0	96.6	98.2	138.8	99.8
21	50.6	67.0	77.4	113.0	108.0	195.0	65.0	99.3	98.4	140.1	...
24	50.7	67.4	78.2	114.6	110.0	200.6	69.0	101.8	98.6	141.0	...
27	50.8	67.5	78.9	115.8	112.0	205.5	72.4	103.5	...	141.6	...
30	51.0	67.6	79.5	116.7	113.2	210.0	75.4	105.4	...	142.0	...
36	...	68.0	80.4	117.9	116.1	217.5	80.6	108.6	...	142.5	...
42	...	68.1	81.0	118.8	117.3	223.5	84.3	111.0	...	142.8	...
48	...	68.2	81.8	119.2	118.6	228.8	87.4	112.8	...	143.1	...
54	...	68.4	82.4	119.6	119.4	232.8	90.2	114.3	...	143.2	...
60	...	68.6	83.2	120.0	120.0	236.7	92.6	115.2	...	143.4	...
75	...	68.7	84.8	...	123.0	243.9	96.4	116.4	...	143.7	...
90	...	...	85.5	...	125.2	248.7	99.2	117.0	...	143.8	...
105	...	...	85.9	...	126.8	251.7	101.2	...	...	144.0	...
120	...	...	...	...	127.5	253.6	102.6	...	...	...	...
135	...	...	...	...	127.8	254.8	133.4	...	...	...	...
150	...	...	...	...	128.1	255.4	104.0	...	...	...	...
165	...	...	...	...	128.3	255.9	104.4	...	...	...	...
180	...	...	...	...	...	256.2	104.7	...	...	...	...
210	...	...	...	...	...	...	104.8	...	...	...	...
240	...	...	...	...	...	...	105.0	...	...	...	...
270	...	...	...	...	...	...	...	...	...	...	...
300	...	...	...	...	...	...	...	...	...	...	...
330	...	...	...	...	...	...	...	...	...	...	...
360	...	...	...	...	...	...	...	...	...	...	...
390	...	...	...	...	...	...	...	...	...	...	...
420	...	...	...	...	...	...	...	...	...	...	...
Summary of Data											
% of max., 3 min.	95.3	76.5	57.6	57.5	53.8	17.6	7.4	63.9	94.9	74.0	76.6
% of max., 15 min.	98.4	96.1	87.3	90.3	78.6	70.6	50.7	79.3	99.5	94.8	99.8
% of max., 30 min.	100.0	98.4	92.5	97.3	88.2	92.0	71.8	90.1	100.0	98.6	100.0
% of max., 60 min.		99.9	96.9	100	93.5	92.4	88.2	98.5	...	99.6	...

Time, min.	Tablet Sample 23	24	25	26	27	28	29	30	31	32
0	0	0	0	0	0	0	0	0	0	0
3	11.0	18.4	74.2	168.0	135.8	16.5	84.3	67.5	93.0	47.2
6	17.4	43.5	89.2	183.2	165.0	21.4	93.6	75.0	101.2	61.5
9	26.7	55.5	99.8	189.0	177.0	25.8	98.4	78.0	106.0	67.6
12	39.6	62.7	107.1	191.2	183.8	29.6	100.8	79.5	109.4	71.6
15	55.5	68.0	112.5	192.4	189.0	32.6	102.0	80.1	111.0	74.2
18	73.5	72.3	116.7	193.4	194.2	35.1	102.8	80.6	112.0	76.4
21	93.0	76.0	120.0	194.0	197.8	37.4	103.0	81.0	112.6	77.8
24	111.0	79.5	122.6	194.4	200.0	39.3	103.4	81.2	113.0	79.0
27	129.0	82.5	124.8	194.7	202.5	41.2	103.6	81.3	113.4	80.2
30	146.2	85.2	126.3	195.0	204.4	42.6	103.8	81.4	113.6	81.0
36	175.5	90.0	129.0	195.3	207.2	45.0	104.0	81.6	113.7	82.4
42	197.0	94.0	130.5	195.6	209.0	46.8	...	81.8	...	83.2
48	213.0	97.5	132.0	195.9	210.3	48.2	...	81.9	...	83.8
54	223.5	100.6	132.9	196.2	210.9	49.5	...	81.9	...	84.4
60	231.0	103.0	133.5	196.4	211.5	50.7	...	...	...	84.8
75	241.2	108.2	134.4	196.5	212.6	53.2	...	...	...	85.5
90	245.6	111.8	135.0	196.8	213.3	55.0	...	...	...	86.2
105	247.5	114.4	135.0	197.1	213.8	57.3	...	...	...	87.0
120	248.7	116.6	...	197.4	214.0	58.8	...	...	...	87.4
135	249.3	118.0	...	197.7	...	60.3	...	...	...	87.8
150	249.6	119.0	...	197.8	...	61.6	...	...	...	88.0
165	249.9	120.0	...	198.0	...	62.8	...	...	...	88.5
180	250.2	120.8	...	...	...	63.8	...	...	...	...
210	250.8	122.0	...	...	...	65.8	...	...	...	...
240	251.0	122.8	...	...	...	67.5	...	...	...	...
270	251.1	123.0	...	...	...	68.6	...	...	...	...
300	251.2	...	...	...	...	69.2	...	...	...	...
330	251.4	...	...	...	...	69.8	...	...	...	...
360	251.6	...	...	...	...	70.4	...	...	...	...
390	...	...	...	...	...	70.6	...	...	...	...
420	...	...	...	...	...	71.0	...	...	...	...
Summary of Data										
% of max., 3 min.	4.3	15.0	55.0	84.8	63.5	23.2	81.0	82.4	81.8	53.3
% of max., 15 min.	22.1	55.3	83.3	97.2	88.3	45.9	98.0	97.8	97.6	83.8
% of max., 30 min.	58.1	69.3	93.6	98.5	95.5	60.0	99.8	99.4	99.9	91.5
% of max., 60 min.	91.8	83.7	98.9	99.2	98.8	71.4	100.0	100.0	100.0	95.8

[a] Milliliters of 0.1 *N* hydrochloric acid consumed per single chewable tablet recorded as a function of time in minutes.

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

	Effervescent Sample							
Time, min.	33	34	35	36	37	38	39	40
0	0	0	0	0	0	0	0	0
3	213.3	190.0	197.2	259.2	165.0	161.6	515.1	524.5
6	...	...	...	...	...	...	...	...
9	...	...	...	...	...	...	...	...
12	...	...	...	...	...	...	...	...
15	...	...	...	...	...	...	...	...
18	...	...	...	...	...	...	...	...
21	...	...	...	...	...	...	...	...
24	...	...	...	...	...	...	...	...
27	...	...	...	...	...	...	...	...
30	...	...	...	...	...	...	...	...
Summary of Data								
% of max., 3 min.	100	100	100	100	100	100	100	100
% of max., 16 min.	...	...	...	...	...	...	...	...
% of max., 30 min.	...	...	...	...	...	...	...	...

[a] Milliliters of 0.1 *N* hydrochloric acid consumed per single dose of effervescent antacid recorded as a function of time in minutes.

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

	Liquid Antacid Sample							
Time, min.	41	42	43	44	45	46	47	48
0	0	0	0	0	0	0	0	0
3	12.0	41.2	42.3	57.0	18.8	54.0	52.5	46.5
6	30.0	69.0	50.2	75.0	46.5	71.7	64.2	69.3
9	63.8	127.5	56.5	106.5	59.1	79.2	68.7	76.8
12	81.8	148.4	60.2	124.4	84.0	84.0	71.2	80.1
15	86.0	149.2	66.0	128.1	121.5	87.0	73.4	82.4
18	87.4	149.6	70.0	130.5	123.2	89.4	74.6	83.8
21	92.2	149.7	73.6	132.2	123.3	90.9	75.9	85.0
24	94.5	149.0	76.5	133.2	123.6	92.1	77.0	86.0
27	96.0	150.0	77.2	134.0	123.9	93.0	78.0	87.0
30	97.0	...	80.6	134.7	124.0	93.6	79.2	87.8
36	98.6	...	83.1	136.5	124.2	94.4	80.8	89.0
42	99.4	...	84.6	136.5	124.4	94.5	82.4	89.7
48	100.2	...	85.8	137.0	...	94.6	83.4	90.3
54	101.0	...	86.7	137.4	...	94.8	84.2	90.8
60	101.9	...	87.3	137.7	...	95.0	84.9	91.2
75	102.3	...	88.8	138.4	...	...	86.0	91.8
90	...	...	89.7	139.0	...	...	86.7	92.2
105	...	...	93.4	139.4	...	...	87.3	92.7
120	...	...	91.4	139.6	...	...	87.8	93.3
135	...	...	91.6	140.0	...	...	88.2	...
150	...	...	...	140.2	...	...	88.5	...
165	...	...	...	140.6	...	...	88.8	...
180	...	...	...	140.7	...	...	89.0	...
210	...	...	...	141.0	...	...	89.2	...
240	...	...	...	...	...	...	...	...
270	...	...	...	...	...	...	...	...
300	...	...	...	...	...	...	...	...
330	...	...	...	...	...	...	...	...
390	...	...	...	...	...	...	...	...
420	...	...	...	...	...	...	...	...
Summary of Data								
% of max., 3 min.	11.7	27.5	46.2	40.4	15.1	56.8	58.9	50.0
% of max., 15 min.	84.0	99.5	72.0	90.9	97.7	91.6	82.3	88.6
% of max., 30 min.	94.8	100.0	88.0	95.5	99.7	98.5	88.8	94.4
% of max., 60 min.	99.6	...	95.3	97.7	100.0	100.0	95.2	98.0

[a] Milliliters of 0.1 *N* hydrochloric acid consumed per 5 ml. of liquid antacid recorded as a function of time in minutes.

able to produce the ideal antacid as outlined in his company's preselected advertising claims. In view of both the large quantities and dollar volumes of antacid products sold yearly and in agreement with Dale and Booth (3), it would appear that more exacting official standardized test procedures should be issued.

Acid-Consuming Capacity.—The acid-consuming capacities of all test products were performed using techniques based upon U.S.P.–N.F. procedures *versus* the Metrohm procedure. Comparisons between these methods generally showed good agreement in the case of short-acting products. In those instances where the duration of action is very long,

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

Time, min.	Tablet Sample 1	2	3	4	5	6	7	8
0	0	0	0	0	0	0	0	0
3	19.5	39.8	30.0	37.5	13.5	30.0	4.2	12.0
6	41.4	49.2	45.0	57.0	30.8	61.5	8.1	21.0
9	45.4	53.7	54.4	74.6	49.5	80.2	13.5	30.0
12	46.0	56.7	61.5	88.0	67.5	90.4	19.2	39.0
15	46.5	59.0	66.0	98.4	81.6	96.4	24.3	46.8
18	47.0	60.6	69.3	106.5	93.0	100.0	29.4	53.7
21	47.6	62.1	72.0	114.0	102.0	101.7	34.0	60.0
24	48.0	63.3	74.0	119.2	108.3	102.8	38.0	65.4
27	48.8	64.5	75.4	122.6	113.7	103.5	42.0	70.5
30	49.4	65.2	76.5	124.5	117.6	103.8	45.4	74.4
36	49.8	66.6	78.0	126.9	123.4	104.2	51.3	81.0
42	50.2	67.5	79.0	128.1	127.2	104.6	56.0	86.0
48	50.6	68.4	79.8	128.7	130.2	104.7	59.7	90.0
54	50.8	69.0	80.2	129.2	132.4	104.8	63.0	92.6
60	51.0	69.3	...	129.3	133.8	105.0	65.4	95.0
75	...	70.0	...	129.4	135.3	105.2	70.0	98.1
90	...	70.5	...	...	135.6	...	73.5	99.4
105	...	70.6	...	...	135.9	...	76.0	100.2
120	...	70.8	...	...	...	...	78.3	100.5
135	...	...	...	...	...	...	80.1	...
150	...	...	...	...	...	...	82.0	...
165	...	...	...	...	...	...	83.6	...
180	...	...	...	...	...	...	84.9	...
210	...	...	...	...	...	...	87.3	...
240	...	...	...	...	...	...	90.0	...
270	...	...	...	...	...	...	92.0	...
300	...	...	...	...	...	...	93.9	...
330	...	...	...	...	...	...	95.6	...
360	...	...	...	...	...	...	96.8	...
390	...	...	...	...	...	...	97.8	...
420	...	...	...	...	...	...	98.8	...
Summary of Data								
% of max., 3 min.	38.2	56.2	37.4	29.0	9.9	28.5	4.3	11.9
% of max., 15 min.	91.2	83.3	82.3	76.0	60.0	91.6	25.1	46.6
% of max., 30 min.	96.9	92.1	95.4	96.2	86.5	98.7	46.9	74.0
% of max., 60 min.	100.0	97.9	100.0	99.9	98.4	99.8	67.6	94.5

[a] Milliliters of 0.1 *N* simulated gastric fluid consumed per single whole tablet recorded as a function of time in minutes.

the Metrohm results are usually somewhat lower since all titrations were stopped at 420 min. To insure that these lowered results were completely a function of time, it was decided to run a Metrohm titration to completion, *i.e.*, no addition of titrant over a 15-min. period. The result should then be the same as that obtained by the U.S.P.–N.F. method.

Effect of Testing Multiples of Unit Dosage Forms.—Table XV shows the effect of testing one, two, three, and four whole sodium bicarbonate tablets (sample *9*). As might be expected, the effects appear to be directly additive.

Effect of Aging on Metrohm Curve.—One of the uses proposed earlier for the Metrohm was in the field of antacid stability. Due to the extreme sensitivity of the technique, it was felt that it would be ideal in observing the effects of storage on onset and initial rates of reaction, etc. To demonstrate this proposal, samples of tablet *1*, contained in open bottles, were stored at 100, 120, and 100°F/80% relative humidity for 1 week. At the end of the aging period, one whole tablet from each storage station was tested by the proposed Metrohm technique (0.3 *N* hydrochloric acid, slow speed). Results of these studies are recorded in Table XVI. Examination of the table will show that, even after an extremely short aging period of 1 week, the technique was sensitive enough to show significant effects of aging on the tablet. It is readily apparent that as the storage conditions become more severe (*a*) the duration of activity increases, (*b*) the initial rate of reaction decreases, and (*c*) no effect was observed on the total acid-consuming capacity, since it is a simple calcium carbonate–glycine tablet.

RESULTS

Compressed Tablets.—Tablet *7* appeared to be the only one severely affected by pepsin, as might be expected with aluminum hydroxide present. It was interesting to note the slight increase in acid-consuming capacity with tablets *4* and *5* in the presence of pepsin, probably due to titration of amino acids split off from the protein by the pepsin. It was pointed out that initial reaction rate of magnesium hydroxide is decreased by the presence of pepsin (26), and this held true in tablets *6*, *8*, and *9* containing magnesium hydroxide. Although the initial rate of magnesium trisilicate is increased by pepsin, the quantity present was most likely not significant enough to produce any effect on tablet *6*. The sodium bicarbonate tablets *10* and *11* behaved exactly as one would expect.

Chewable Tablets.—Most of these tablets behaved as one might predict. The calcium carbonate–glycine tablets (*12*, *13*, and *14*) were quite

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

Time, min.	Tablet Sample 12	13	14	15	16	17	18	19	20	21	22
0	0	0	0	0	0	0	0	0	0	0	0
3	48.0	52.5	52.5	102.0	114.0	37.5	9.0	94.5	94.5	94.5	84.8
6	52.5	59.1	63.8	124.5	130.4	123.8	23.2	103.6	97.8	112.5	94.5
9	52.8	61.8	67.5	129.3	132.9	146.2	39.0	108.8	98.2	122.8	98.7
12	53.0	63.3	70.5	131.6	133.6	156.0	50.2	111.4	98.4	129.0	99.7
15	53.1	64.1	73.2	132.4	134.0	161.0	57.3	113.0	98.6	133.5	100.4
18	53.3	64.8	74.7	133.0	134.2	164.2	62.4	114.2	...	137.0	100.5
21	53.4	65.6	76.0	133.5	134.4	166.2	66.3	115.4	...	138.9	100.6
24	53.6	66.3	77.1	134.0	134.6	168.3	69.2	115.6	...	140.6	100.8
27	53.6	67.1	77.7	134.1	134.7	169.2	71.6	115.8	...	141.4	...
30	53.7	67.8	78.3	134.2	134.8	170.2	73.5	...	...	142.2	...
36	53.7	69.5	79.5	134.4	135.0	171.9	76.4	...	...	143.0	...
42	53.9	70.2	80.2	...	...	173.2	78.4	...	...	143.6	...
48	...	70.8	80.8	...	...	174.6	80.2	...	...	143.7	...
54	...	71.1	81.4	...	...	175.8	81.3	...	...	143.8	...
60	...	71.2	81.9	...	...	176.8	82.4	...	...	144.0	...
75	...	71.7	82.5	...	...	179.7	84.3	...	...	144.3	...
90	...	72.2	83.2	...	...	182.0	86.0	...	...	144.4	...
105	...	...	83.6	...	...	184.5	87.3	...	...	...	...
120	...	...	83.8	...	...	186.6	88.6	...	...	...	...
135	...	...	...	...	...	188.7	90.0	...	...	...	...
150	...	...	...	...	...	190.6	91.4	...	...	...	...
165	...	...	...	...	...	192.4	92.6	...	...	...	...
180	...	...	...	...	...	194.6	93.8	...	...	...	...
210	...	...	...	...	...	198.0	95.7	...	...	...	...
240	...	...	...	...	...	201.4	97.5	...	...	...	...
270	...	...	...	...	...	204.4	99.3	...	...	...	...
300	...	...	...	...	...	207.0	100.8	...	...	...	...
330	...	...	...	...	...	209.6	102.2	...	...	...	...
360	...	...	...	...	...	212.0	103.5	...	...	...	...
390	...	...	...	...	...	214.8	104.7	...	...	...	...
420	...	...	...	...	...	217.5	105.8	...	...	...	...
Summary of Data											
% of max., 3 min.	89.1	72.7	62.6	75.9	84.4	17.2	8.5	81.6	95.8	65.4	84.1
% of max., 15 min.	98.5	88.8	87.3	98.5	99.2	74.0	54.1	97.6	100.0	92.4	99.6
% of max., 30 min.	99.6	93.9	93.4	99.8	99.8	78.2	69.4	100.0	...	98.4	100.0
% of max., 60 min.	100.0	98.6	97.7	100.0	100.0	81.3	78.3	...	...	99.7	...

Time, min.	Tablet Sample 23	24	25	26	27	28	29	30	31	32
0	0	0	0	0	0	0	0	0	0	0
3	10.6	24.0	72.8	177.8	179.2	15.8	69.0	45.8	109.8	40.5
6	14.8	52.5	87.4	189.0	187.0	21.0	84.8	57.3	112.0	58.8
9	18.6	61.5	95.8	192.8	190.5	24.2	93.0	63.8	112.8	67.8
12	24.0	66.0	100.5	194.2	192.8	27.3	97.2	68.0	113.2	73.2
15	29.4	69.0	104.0	194.8	194.2	30.2	99.4	70.4	113.6	76.5
18	36.2	71.0	106.5	195.4	195.0	32.8	100.8	72.3	113.7	78.8
21	42.0	72.3	108.8	195.8	195.8	35.0	101.4	73.5	...	80.4
24	50.2	73.6	110.2	195.9	196.5	36.9	101.8	74.6	...	81.8
27	57.8	74.6	111.4	196.1	197.2	38.6	102.2	75.3	...	82.8
30	65.2	75.3	112.6	196.2	197.7	40.0	102.3	75.9	...	83.7
36	81.2	76.5	114.4	196.4	198.8	42.3	102.6	76.8	...	85.0
42	94.5	77.2	115.8	196.5	199.5	44.1	102.8	77.2	...	86.0
48	106.5	78.0	177.2	196.5	200.2	45.6	102.9	77.7	...	86.7
54	118.6	78.4	118.2	196.6	201.0	47.0	103.0	78.2	...	87.0
60	127.8	79.0	119.2	196.8	201.8	48.0	103.2	78.4	...	87.4
75	147.0	79.8	120.9	197.0	203.0	50.2	103.5	78.8	...	88.0
90	161.7	80.8	122.2	197.2	234.0	52.0	103.6	...	...	88.5
105	173.2	81.6	123.4	197.4	205.0	53.7	...	...	...	88.8
120	182.4	82.4	124.4	197.6	205.8	55.0	...	...	...	89.1
135	189.9	83.0	125.7	197.7	206.8	56.1	...	...	...	89.4
150	196.2	83.8	126.2	197.8	207.6	57.2	...	...	...	89.7
165	201.0	84.6	126.8	198.0	208.4	58.2	...	...	...	89.8
180	205.4	85.4	127.4	...	208.8	59.2	...	...	...	90.0
210	216.0	86.8	128.2	...	210.0	61.0	...	...	...	...
240	218.7	88.0	128.7	...	211.5	63.3	...	...	...	...
270	222.9	89.4	129.2	...	212.2	65.0	...	...	...	...
300	226.8	90.4	129.4	...	213.0	66.2	...	...	...	...
330	230.7	91.8	129.7	...	214.2	67.5	...	...	...	...
360	232.6	93.0	130.2	...	215.2	68.4	...	...	...	...
390	235.5	94.2	130.5	...	216.3	69.3	...	...	...	...
420	237.6	95.1	...	...	217.2	70.5	...	...	...	...
Summary of Data										
% of max., 3 min.	4.4	25.2	55.8	89.7	82.5	22.4	66.6	58.1	96.6	45.0
% of max., 15 min.	12.4	72.6	79.7	98.4	89.4	42.8	95.9	89.3	99.0	85.1
% of max., 30 min.	27.4	79.2	86.3	99.1	91.0	56.7	98.7	96.3	100.0	93.0
% of max., 60 min.	53.8	83.1	91.3	99.4	92.9	68.0	99.6	99.5	...	97.1

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

Time, min.	Effervescent Sample 33	34	35	36	37	38	39	40
0	0	0	0	0	0	0	0	0
3	213.9	193.5	199.6	259.8	165.0	160.5	514.0	517.0
6	...	197.0	...	...	...	...	...	.
9	...	...	...	...	...	...	...	...
12	...	...	...	...	...	...	...	...
15	...	...	...	...	...	...	...	...
18	...	...	...	...	...	...	...	...
21	...	...	...	...	...	...	...	...
24	...	...	...	...	...	...	...	...
27	...	...	...	...	...	...	...	...
30	...	...	...	...	...	...	...	...
Summary of Data								
% of max., 3 min.	100.0	98.2	100.0	100.0	100.0	100.0	100.0	100.0
% of max., 15 min.	...	100.0	...	...	...	...	...	...
% of max., 30 min.	...	...	...	...	...	...	...	...

[a] Milliliters of 0.1 *N* simulated gastric fluid consumed per single dose of effervescent antacid recorded as a function of time in minutes.

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

Time, min.	Sample 41	42	43	44	45	46	47	48
0	0	0	0	0	0	0	0	0
3	16.2	36.0	37.5	50.2	24.0	52.0	48.8	59.7
6	23.2	58.5	45.4	60.8	42.0	68.2	60.0	66.2
9	35.7	69.4	50.7	84.4	50.6	75.8	64.5	69.2
12	51.8	91.5	54.6	113.2	55.4	80.7	66.4	71.0
15	66.4	124.5	58.2	122.8	61.5	84.0	68.0	72.3
18	76.3	139.5	61.2	126.8	70.8	86.2	69.2	73.2
21	81.3	141.0	64.0	129.4	86.0	87.8	70.2	74.1
24	84.4	141.8	66.4	131.0	103.2	89.2	71.0	75.0
27	86.6	142.2	69.0	132.3	114.6	90.0	71.8	75.9
30	87.9	142.5	71.6	133.4	118.0	90.4	72.4	76.5
36	90.2	143.0	75.8	134.8	118.8	90.8	73.8	77.7
42	92.1	143.6	79.5	136.2	119.4	90.9	74.8	78.8
48	93.4	143.8	82.5	137.3	119.7	91.2	75.8	79.5
54	94.8	144.0	84.6	137.8	120.0	91.2	76.5	80.1
60	96.0	144.2	86.6	138.8	120.2	91.4	77.2	80.7
75	98.4	144.4	89.7	140.0	120.3	91.5	78.4	81.4
90	99.8	144.9	91.8	141.0	120.4	...	79.5	81.9
105	100.8	145.0	93.3	142.2	120.6	...	80.0	82.6
120	101.7	145.2	94.4	142.8	...	...	80.4	82.8
135	102.4	...	95.2	143.6	...	...	80.4	82.8
150	103.2	...	96.0	144.0	...	...	80.7	83.0
165	103.6	...	96.6	144.3	...	...	...	...
180	104.2	...	97.2	...	...	...	...	...
210	105.0	...	98.1	...	...	...	...	...
240	106.5	...	99.3	...	...	...	...	...
270	107.0	...	100.0	...	...	...	...	...
300	107.6	...	100.8	...	...	...	...	...
330	108.0	...	101.4	...	...	...	...	...
360	...	...	...	...	...	...	...	...
390	...	...	...	...	...	...	...	...
420	...	...	...	...	...	...	...	...
Summary of Data								
% of max., 3 min.	15.0	24.8	36.9	34.8	19.9	56.8	60.5	71.9
% of max., 15 min.	61.5	85.7	57.4	85.1	51.8	84.3	84.3	87.1
% of max., 30 min.	81.4	98.1	70.6	92.4	97.8	98.8	89.7	92.1
% of max., 60 min.	88.9	99.3	85.4	96.2	99.9	99.9	95.7	97.2

[a] Milliliters of 0.1 *N* simulated gastric fluid per 5 ml. of liquid antacid recorded as a function of time in minutes.

unaffected by pepsin. Tablets *15* and *16*, containing the milk solids, again proved to give interesting results because the acid-consuming capacity was higher in the presence of pepsin, most probably due to the splitting of the milk proteins by the pepsin. Due to the fine particle size used in this series, the effect was more pronounced than noted when a whole compressed tablet was used. All of the aluminum hydroxide-containing tablets (*17*, *18*, *23*, *24*, *25*, *27*, and *28*) generally showed a decrease in acid-consuming capacity and an increase in duration of action. The calcium and magnesium carbonates–magnesium trisilicate series of tablets (*19* through *22*) were unaffected by the presence of

TABLE XV.—EFFECT OF TESTING MULTIPLES OF UNIT DOSAGE FORMS[a]

Sample Size, No. of Whole Tablets, Time, min.	One Tablet	Two Tablets	Three Tablets	Four Tablets
	Titrant Consumed, ml.			
0	0	0	0	0
3	13.5	24.6	36.0	46.5
6	23.1	42.6	64.5	84.0
9	29.6	55.5	83.7	110.7
12	33.0	63.2	94.2	124.5
15	33.8	66.0	96.3	127.5
18	33.9	66.3	...	127.7
21	...	...	...	...

[a] Sample *10*; 0.1 *N* HCl; slow speed.

pepsin, as essentially were the remaining tablets evaluated. It was interesting to note the exceptionally high initial rates of reaction afforded to tablet *26* by the presence of magnesium oxide. Tablet *27* almost achieved this high initial rate through the sole use of aluminum hydroxide–magnesium carbonate codried gel and calcium carbonate. Both exhibited a moderately long duration of action.

Effervescent Antacids.—These antacids are, for the most part, completely water soluble and as such naturally have the highest initial rate of reaction and the shortest duration of action. Tables IX and XIII represent, in essence, simply a pH 3.0 stat titration of a water-soluble buffer with 0.3 *N* hydrochloric acid.

Liquid Antacids.—Most of the liquid antacids evaluated were observed to be fairly reactive initially with a moderate duration of action in most cases. Since all of the liquids tested contained an aluminum antacid material, a check with the results of similar type chewable antacids shows relatively little differences in the per cent of activity released at 3 min.; however, the liquids exhibit a higher percentage at the 15-min. level. A study of the summary of data in Tables X and XIV shows that pepsin has a slight retarding effect on the over-all rate and duration of reaction and little effect on the initial rate. There are significant differences in the product-to-product rates, however. As expected, liquids *47* and *48*, containing no aluminum hydroxide, are the least affected.

DISCUSSION

In this paper, the authors have endeavored to propose an automated comparative method of evaluating antacids based on utilization of the Metrohm Combititrator run at pH 3.0 stat conditions. The method produces a curve capable of showing the onset of reaction, initial and over-all rate of reaction, duration of action, and acid-consuming capacity.

To demonstrate its accuracy and feasibility, curves were prepared by several people of a sample compressed tablet under varying Metrohm conditions. Test results indicated an excellent correlation. The method has also been used to show the effect of variation of pH stat conditions upon the type of curve that is obtained.

Forty-eight antacid products were evaluated by the method. Results of the curves obtained from the titrations were generally in good agreement with those obtained through the use of other methods. The Metrohm curves also gave an excellent indication of the acid-consuming power of the product. In the case of extremely slow-reacting products, it was demonstrated that continuing the titration for additional time periods will provide for the correct acid-consuming capacity.

Remembering that this method is based upon the premise that it will titrate all the antacid that makes

TABLE XVI.—EFFECTS OF AGING ON COMPRESSED TABLETS *via* METROHM EVALUATION

Storage Conditions Length of Storage	100°F. 7 Days	120°F. 7 Days	140°F. 7 Days	100°F./80% R. H. 7 Days
One Whole Tablet, Sample No.	*1*	*1*	*1*	*1*
Time, min.				
0	0	0	0	0
3	27.0	24.0	22.5	15.0
6	42.0	43.0	37.8	30.9
9	47.6	46.5	44.6	39.3
12	49.9	49.5	47.3	43.8
15	51.0	50.7	48.9	46.8
18	51.5	51.4	49.8	49.1
21	52.0	51.8	50.5	50.6
24	52.2	52.0	50.7	51.4
27	52.4	52.3	50.9	52.0
30	52.5	52.5	51.0	52.5
36	52.7	52.7	51.4	52.9
42	52.8	52.8	51.7	53.2
48	52.9	52.9	52.0	53.5
54	53.0	53.0	52.3	53.7
60	...	53.2	52.5	53.8
75	...	...	...	54.0
90	...	...	...	...
Summary of Data				
% of max., 3 min.	50.9	45.1	42.9	27.7
% of max., 15 min.	96.2	95.3	93.1	86.6
% of max., 30 min.	99.2	98.6	97.1	97.2
% of max., 60 min.	100.0	100.0	100.0	99.6

itself available down to a pH of 3.0, it is no surprise that the effervescent antacids possessed an extraordinarily high onset and initial rate of reaction. Because they are water soluble, their duration of action could be measured in terms of less than 1–3 min. The compressed tablets as a class were the slowest in reacting, due mostly to the fact that the quantity of antacid available for reaction was directly related to the disintegration time of the tablet. A surprising feature of the experimental work was that there was so little difference between the liquid antacids and the chewable tablets with regard to their general over-all behavior. Of course, the liquids were more reactive over the first 15 to 30 min. than their compressed counterparts; however, the rates initially were quite similar. This fast initial rate may have been due, in part, to the fact that the compressed tablets were ground and screened 100 mesh prior to analysis. This seemed to be advisable as a means of standardizing the technique. So many papers simply refer to crushed, ground, or powdered tablets (2–4, 12, 15) to be used in the evaluation. These are vague terms; crushed may mean 8 mesh to one investigator and 200 mesh to another. Again, there is a need for official guidance in the technique for evaluating antacids.

SUMMARY

1. An automated method has been developed which will comparatively evaluate the maximum speed at which an antacid can react with gastric acid and the rate at which an antacid makes itself available for reaction. The curves obtained from the method also indicate the duration of action and acid-consuming capacity of the antacid system.

2. A procedure was developed to evaluate antacid products using the Metrohm Combititrator operating at slow speed with a 0.3 *N* titrant. Results of a comparative correlative study showed that the same results are obtained, irregardless of whether fast or slow paper speeds are used with either 0.1 *N* or 0.3 *N* titrant.

3. Certain of the tablets possessed extraordinarily long durations of action; *i.e.*, after 420 min., the theoretical quantity was still not released. A study was made to determine whether the Metrohm technique would be quantitative. In the case cited, a time period of 1440 min. was required to obtain a completed reaction.

4. The data presented appear to justify the proposal of the Metrohm technique as an extremely valuable tool in the *in vitro* study of the effect of aging on antacid products. The current work shows the method to be sufficiently accurate and sensitive enough to detect unusually small differences.

5. Forty-eight different antacid preparations were evaluated using the currently proposed Metrohm Combititrator technique. Generally, the effervescent antacids were the most reactive, next the liquids, followed closely by the chewable tablets. The swallow-type whole tablets were significantly slower than their chewable counterparts.

6. Due to the wide variance in product-to-product evaluation of the same type of antacid, the need for establishment of official protocols was suggested.

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