

If Eq. 7 is integrated:

$$F_{-mA} - F_{0A} = k_m \int_{-m}^0 C_A(x) dx \quad (\text{Eq. 43})$$

This equation means that the flux difference between the drug that enters the epidermis from the stratum corneum and the drug that leaves the epidermis into the aqueous diffusion layer is due to the total amount of metabolism within the epidermis. The relationship between  $F_{0X}$  and  $F_{-mX}$  can be found from Eq. 38 to be:

$$F_{-mX} - F_{0X} = \frac{\kappa'^2}{\kappa} D_X [P (\cosh(\kappa m) - 1) - Q \sinh(\kappa m)] \quad (\text{Eq. 44})$$

where  $P$  and  $Q$  are given by Eqs. 39 and 40, respectively. Finally, from Eq. 8:

$$F_{-mX} - F_{0X} = F_{0A} - F_{-mA} \quad (\text{Eq. 45})$$

$F_{-mX}$  arises because the stratum corneum is permeable to the metabolite,  $X$ , so that  $X$  diffuses back into the donor chamber.

*Limits of High and Low Metabolism*—In the limit of no metabolism when  $\kappa$  tends to zero, Eqs. 37, 38, 41, and 42 become:

$$C_A(x) = \frac{\left[ \frac{1}{D_A/(m+x)} + \frac{1}{P_{SA}} \right] C_A(h) - \left[ \frac{1}{D_A/x} - \frac{1}{P_{aqA}} \right] C_A(-s)}{\frac{1}{P_{aqA}} + \frac{1}{P_{SA}} + \frac{1}{D_A/m}} \quad (\text{Eq. 46})$$

$$C_X(x) = C_X(h) \quad (\text{Eq. 47})$$

$$F_{0A} = F_{-mA} \quad (\text{Eq. 48})$$

$$F_{0A} = \frac{C_A(-s) - C_A(h)}{\frac{1}{P_{aqA}} + \frac{1}{P_{SA}} + \frac{1}{D_A/m}} \quad (\text{Eq. 49})$$

Conversely, in the limit of high metabolism:

$$C_A(s) = 0 \quad (\text{Eq. 50})$$

$$C_X(x) = C_X(h) + F_{0X} \left[ \frac{1}{P_{aqA}} - \frac{x}{D_X} \right] \quad (\text{Eq. 51})$$

$$F_{0A} = -P_{aq} C_A(h) \quad (\text{Eq. 52})$$

$$F_{-mA} = P_{SA} C_A(-s) \quad (\text{Eq. 53})$$

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## ACKNOWLEDGMENTS AND ADDRESSES

Received December 18, 1975, from the *College of Pharmacy, University of Michigan, Ann Arbor, MI 48109*.

Accepted for publication January 14, 1977.

Appreciation is expressed to Mr. J. L. Fox for assistance on the mathematical aspects of diffusion and to Ms. Aurora Calvo for editing and proofreading the manuscript.

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## pH-Stat Titration of Aluminum Hydroxide Gel

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**Abstract** □ The pH-stat titration of aluminum hydroxide gel was evaluated and was affected by pH, temperature, concentration, and ionic strength. Control of these parameters resulted in a highly sensitive and reproducible *in vitro* antacid test. The utility of the pH-stat test was illustrated by monitoring the aging of several carbonate-containing aluminum hydroxide gels and by comparing the antacid properties as measured by the pH-stat titration, the acid-consuming capacity, the Rossett-Rice test, and the test proposed by the Food and Drug Administration Drug Evaluation Panel. The pH-stat titration also was useful for relatively nonreactive aluminum hydroxide gels. The use of sodium fluoride as the reaction medium extended the capability of the pH-stat titration to monitor the aging of chloride-containing gels. The pH-stat titrigram was interpreted in terms of a previously published polymer model of the structure of a chloride-containing aluminum hydroxide gel.

Available *in vitro* antacid tests may be broadly classified as static or dynamic. The acid-consuming capacity test (1), the most widely used static test, determines the total amount of acid neutralized during 1 hr at 37°. The dynamic methods may measure the pH profile during acid neutralization or determine the acid neutralization rate at a constant pH. The test of Holbert *et al.* (2) and the Rossett-Rice test (3) attempt to simulate the stomach and record the pH profile during acid neutralization. Brody and Bachrach (4) first proposed a test that measures the

The acid reactivity of relatively nonreactive gels is believed to be due totally to the chemical neutralization of acid, because the milliequivalents of aluminum ion appearing in solution is the same as the milliequivalents of acid neutralized throughout the pH-stat titration.

**Keyphrases** □ Aluminum hydroxide gel—pH-stat titration evaluated, aging monitored, compared to other tests □ pH-stat titration—evaluated for aluminum hydroxide gel, aging monitored, compared to other tests □ Gels—aluminum hydroxide, pH-stat titration evaluated, aging monitored, compared to other tests □ Aging—aluminum hydroxide gel, monitored with pH-stat titration, compared to other tests □ Antacids—aluminum hydroxide gel, pH-stat titration evaluated, aging monitored, compared to other tests

acid neutralization rate at a constant pH. This test subsequently was automated (5) and recently was correlated with *in vivo* acid neutralization by aluminum hydroxide gel (6).

The Food and Drug Administration (FDA) Drug Evaluation Panel on antacids proposed a test (7) that combines the static approach with the dynamic pH profile.

A sensitive *in vitro* antacid test was needed to study the structure and mechanism of neutralization of aluminum hydroxide gel and to optimize the production of aluminum

**Table I—Effect of Concentration on the pH-Stat Titration of Carbonate-Containing Aluminum Hydroxide Gel<sup>a</sup>**

Reaction Volume, ml	$k_{II}$ , mEq/min	$k_{III}$ , mEq/min	Initiation of Phase III, min	$T_{50}$ , min
11	0.32	0.57	1.3	2.2
22	0.29	0.48	1.5	2.6
33	0.26	0.41	1.8	3.0

<sup>a</sup> Contained 38 mg equivalent  $Al_2O_3$  in all cases.

hydroxide gel and the design of aluminum hydroxide gel dosage forms. The present study was undertaken to evaluate critically the test parameters that affect the pH-stat titration, to establish if the test can be used with non-reactive as well as reactive gels, and to determine if the test possesses sufficient sensitivity and precision to be useful in structural studies.

### EXPERIMENTAL

**Materials**—All chemicals used were either official or reagent grade.

**Aluminum Hydroxide Gel Preparation**—Carbonate-containing aluminum hydroxide gel was prepared by the reaction of aluminum chloride, sodium bicarbonate, and sodium carbonate to a final pH of 6.5 (8). Chloride-containing aluminum hydroxide gels were prepared by the reaction of aluminum chloride and strong ammonia solution to a final pH of 7.0 or 9.2 (8).

**Determination of Acid Reactivity by pH-Stat Titration**—The acid reactivity was measured using an automated pH-stat technique similar to the method described by Steinberg *et al.* (5). A pH meter, a titrator, an autoburet, a titration assembly, and a recorder<sup>1</sup> were used.

An appropriate volume of water was added to the reaction vessel and adjusted to pH 3.0. A volume of aluminum hydroxide gel containing 38 mg equivalent  $Al_2O_3$  was then added. The volume of water was adjusted for each sample to produce a reaction volume of 22 ml. The instrument was set to maintain pH 3.0 by adding 1.0 N HCl from the autoburet and it was activated simultaneously with the sample injection. The recorder plotted milliliters of 1.0 N HCl added *versus* time.

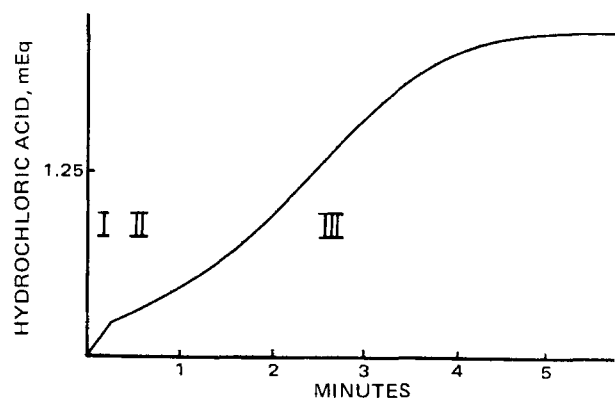
The acid reactivity of the chloride-containing aluminum hydroxide gel also was determined using a sodium fluoride solution as the reaction medium. A 25-ml aliquot of 0.5 N NaF was added to the reaction vessel and adjusted to pH 6.5 with 1.0 N HCl. A gel sample containing 38 mg equivalent  $Al_2O_3$  was added and the instrument was activated to maintain pH 6.5 by the addition of 1.0 N HCl from the autoburet.

**Variables Affecting pH-Stat Titration**—A completely randomized 3<sup>3</sup> factorial study was designed to evaluate the significance of temperature, pH, and stirring speed on the acid reactivity of aluminum hydroxide gel as measured by the pH-stat technique. A freshly precipitated carbonate-containing aluminum hydroxide gel was used. Three levels of each variable were fixed. The temperature levels were 25, 31, and 37°; the pH levels were 2.0, 2.5, and 3.0; and the stirring speeds<sup>2</sup> were 650, 900, and 1400 rpm. The experiment was conducted in 1 day by one operator. Five random replicate trials were determined to estimate the random error.

Three dependent variables,  $T_{25}$ ,  $T_{50}$ , and  $T_{90}$ , were determined from the pH-stat reactivity curves; they were the times required to add 25, 50, and 90%, respectively, of the total 1.0 N HCl needed to neutralize the aluminum hydroxide gel.

**In Vitro Antacid Tests**—The official procedure for the acid-consuming capacity test (1) was followed.

The pH profile during the neutralization reaction was followed by the Rossett-Rice test (3). Seventy milliliters of 0.1 N HCl and 30 ml of water were added to a 400-ml jacketed reaction vessel. When the temperature reached 37°, a 300-mg equivalent  $Al_2O_3$  sample was added. Simultaneously, a pump calibrated to add 0.1 N HCl at a rate of 4 ml/min was activated. A pH meter attached to a recorder provided a record of the time course of the pH during the neutralization reaction. The pH profile is characterized by the lag time, the time to reach pH 3, and the Rossett-Rice time, the time during which the pH is maintained between 3 and 5.



**Figure 1—Characteristic pH-stat titrimogram of carbonate-containing aluminum hydroxide gel showing phases I, II, and III.**

The FDA antacid review panel (7) proposed a two-part *in vitro* test for antacids. The preliminary antacid test measures the pH of the neutralization medium after 10 min. If the pH is 3.5 or greater, the acid-neutralizing capacity test is run. This test measures the amount of acid neutralized in the first 15 min.

**Analytical Procedures**—The equivalent aluminum oxide content of each gel was determined by the ethylenediaminetetraacetic acid titration (1).

The total chloride content of the chloride-containing gels was determined by the Volhard titration (9) after 3 g of gel was dissolved in 15 ml of 6 N nitric acid.

The appearance of aluminum ion during the neutralization of chloride-containing aluminum hydroxide gel was monitored by a modified ethylenediaminetetraacetic acid titration. It was assumed that only the aluminum ion in the neutralization reaction mixture would chelate and that aluminum not released from the gel structure by the neutralization reaction would not be detected. The ethylenediaminetetraacetic acid titration (1) was modified by omitting the addition of acid to dissolve the gel and by not heating the sample drawn from the neutralization reaction. These steps would be likely to increase the amount of aluminum ion in solution by accelerating the neutralization reaction. However, these two changes had no effect on the analysis of a standard aluminum chloride solution because both analytical procedures gave the theoretical aluminum concentration.

Ultrafiltration and centrifugation procedures were tried to separate the unreacted solids in the reaction mixture prior to the aluminum assay. These methods were not satisfactory due to the time required for the separation and the rapid aging characteristics of the chloride-containing aluminum hydroxide gel. Thus, the modified ethylenediaminetetraacetic acid titration, which did not require a separation step, was used. Freshly precipitated gel, 20 ml, accurately weighed, was diluted with 20 ml of water, and the pH-stat reactivity was determined at pH 3.0. A 25.0-ml buret was used to deliver 1.0 N HCl from the autoburet. During the neutralization reaction, six 2.0-ml samples were withdrawn at various times and analyzed for aluminum ion by the modified ethylenediaminetetraacetic acid titration.

For X-ray analysis, a gel sample was air dried at room temperature and ground to a fine powder with an agate mortar and pestle. Powder specimens were prepared using aluminum McCreery mounts. The diffraction pattern was recorded<sup>3</sup> from 6 to 30° 2 $\theta$  under the following conditions:  $CuK\alpha$  radiation, 40 kv, 20 mamp, 500 Hz full scale, and 2°/min scan speed.

IR spectra<sup>4</sup> were obtained by air drying a 0.10-ml gel sample on a zinc sulfide<sup>5</sup> window. The concentration on the window was 0.3 mg of aluminum oxide/cm<sup>2</sup>.

### RESULTS AND DISCUSSION

**Measurement of Acid Reactivity of Carbonate-Containing Gels**—Figure 1 is a characteristic pH-stat neutralization curve of a completely reactive carbonate-containing aluminum hydroxide gel. The neutralization reaction appears to be composed of three phases: an initial rapid phase (I), a slow zero-order period (II), and a more rapid terminal

<sup>1</sup> A pH meter PHM 26, titrator TTT II, autoburet ABU 12 (2.5 ml), titration assembly TTA 3, and recorder SBR 2; Radiometer, Copenhagen, Denmark.

<sup>2</sup> Stirring speed was measured by a stroboscope; Strobotac, General Radio Co., Cambridge, Mass.

<sup>3</sup> Norelco, Phillips Electronic Instruments, Mount Vernon, N.Y.

<sup>4</sup> Model 421, Perkin-Elmer Corp., Norwalk, Conn.

<sup>5</sup> Irtran 2, Eastman Kodak Co., Rochester, N.Y.

**Table II—Effect of Ionic Strength of Reaction Medium on pH-Stat Titration of Carbonate-Containing Aluminum Hydroxide Gel**

Reaction Medium	Ionic Strength	$k_{II}$ , mEq/min	$k_{III}$ , mEq/min	Initiation of Phase III, min	$T_{50}$ , min
Distilled water	0	0.206	0.367	2.2	3.5
0.2 M NaCl	0.20	0.397	0.481	1.7	2.3
0.4 M NaCl	0.40	0.543	0.610	1.0	1.8
0.6 M NaCl	0.60	0.568	0.657	0.9	1.7
0.8 M NaCl	0.80	0.657	0.735	0.8	1.5
1.0 M NaCl	1.00	0.694	0.806	0.7	1.4
0.037 M AlCl <sub>3</sub>	0.222	0.357	0.471	1.7	2.2
0.1 M AlCl <sub>3</sub>	0.60	0.555	0.644	0.8	1.6
0.2 M AlCl <sub>3</sub>	1.20	0.610	0.749	0.7	1.4

zero-order phase (III). In Fig. 1, phase II begins at 0.23 min and phase III begins at 1.5 min. The acid neutralization rate during phase I is very rapid and exceeds the capability of the autoburet to add compensating acid. Thus, the total volume of acid neutralized during phase I can be measured, but no rate measurements are possible.

The specially prepared computer program evaluated neutralization rate periods II and III by simple linear regression. The output consisted of the two zero-order rate constants ( $k_{II}$  and  $k_{III}$ ), the linear correlation coefficients, the *F*-test ratio, the percent aluminum oxide based on total acid neutralized, and the time for the initiation of phase III. This time was computed from the intersection of the  $k_{II}$  line with the  $k_{III}$  line by using simultaneous equations from linear regression analysis of the two neutralization rate periods.

A second approach used to evaluate the pH-stat titrations was to determine the time required to add 50% ( $T_{50}$ ) of the total 1.0 N HCl needed to neutralize the aluminum hydroxide gel. This approach is limited to completely reactive aluminum hydroxide gels.

**Variables Affecting pH-Stat Titration**—Analysis of variance of the 3<sup>3</sup> factorial design experiment, using the three-way interaction as the error term (10), indicated that pH and temperature were significant at the 0.5% level. There was also a significant pH-temperature interaction. Stirring speed was not a significant main effect within the range of stirring speeds available with the titration assembly. The critical factors of pH and temperature can be controlled easily during the titration, resulting in a highly reproducible test. Conditions were standardized using pH 3.0, 25°, and 900 rpm.

The neutralization reaction proceeds faster as the concentration of equivalent aluminum oxide in the sample is increased (Table I). The concentration of the reacting medium was, therefore, standardized at 38 mg equivalent Al<sub>2</sub>O<sub>3</sub>/22 ml. This concentration was chosen because 2.235 mEq (89.4% of the volume of 1.0 N HCl available in the 2.5-ml buret) would be neutralized if the equivalent aluminum oxide reacted stoichiometrically with hydrochloric acid.

The ionic strength of the reaction medium also affects the pH-stat titration. Table II shows that the neutralization reaction proceeds more rapidly as the ionic strength is increased. Distilled water was selected as the reaction medium, although the ions generated during the neutralization reaction caused a slight change in ionic strength during the titration. The complete neutralization of 38 mg of aluminum oxide/22 ml

**Table IV—Effect of pH on Acid Neutralization Rate**

pH	$T_{50}$ , min		
	Aluminum Hydroxide Gel <sup>a</sup>	Sodium Bicarbonate <sup>b</sup>	Calcium Carbonate <sup>c</sup>
2.0	0.5	0.05	0.1
2.5	1.0	—	—
3.0	2.2	0.10	0.1
3.5	3.2	—	—
4.0	7.2	0.10	0.2
4.5	NR <sup>d</sup>	—	—
5.0	NR <sup>e</sup>	0.25	2.9
6.0	NR <sup>e</sup>	0.70	26.2
7.0	NR <sup>e</sup>	4.5	NR <sup>f</sup>

<sup>a</sup> Contained 38 mg of aluminum oxide. <sup>b</sup> Contained 185 mg of sodium bicarbonate. <sup>c</sup> Contained 110 mg of calcium carbonate. <sup>d</sup> Thirty-eight percent reacted in 160 min. <sup>e</sup> No appreciable reaction. <sup>f</sup> Twenty-four percent reacted in 160 min.

by hydrochloric acid will result in an ionic strength of 0.15. The effect of the continuously changing ionic strength caused by the neutralization reaction could be minimized by using a sodium chloride or aluminum chloride solution as the reaction medium.

The reproducibility of the pH-stat titration of aluminum hydroxide gel under fixed conditions of pH 3.0, 25°, 900 rpm, and 38 mg of aluminum oxide/22 ml of water was determined by 10 replicate pH-stat titrations of a carbonate-containing gel containing 3.52% equivalent aluminum oxide. The mean values for  $k_{II}$  and  $k_{III}$  were 0.172 and 0.317 mEq/min with standard deviations of 0.005 and 0.017, respectively. The initiation of phase III occurred at 2.4 ± 0.1 min. The  $T_{50}$  was 3.9 ± 0.1 min. These results indicate that the parameters affecting the pH-stat titration can be controlled and that it is a sensitive, reliable, and highly reproducible technique for monitoring the acid reactivity of aluminum hydroxide gel.

**Comparison of *In Vitro* Antacid Tests**—The sensitivity and reproducibility of the pH-stat titration suggest that it may be more useful than present *in vitro* tests in detecting differences in the acid neutralization rate of aluminum hydroxide gel. The *in vitro* tests were compared by monitoring the aging of a laboratory carbonate-containing aluminum hydroxide gel and by examining one laboratory carbonate-containing gel and two commercial gels of different ages.

The data in Table III for Gel 1 indicate that the pH-stat titration is capable of detecting changes in the acid neutralization rate on a daily basis. The time for 50% neutralization increased from 3.7 to 7.2 min over 10 days. The acid-consuming capacity test, the Rossett-Rice time, and the FDA antacid review panel test were insensitive to the changes occurring in the gel structure. The lag time in the Rossett-Rice test did increase from 0.1 to 0.2 min during the 10 days. However, this parameter, although suggesting a structural change, is not capable of monitoring daily changes in acid reactivity of the gel.

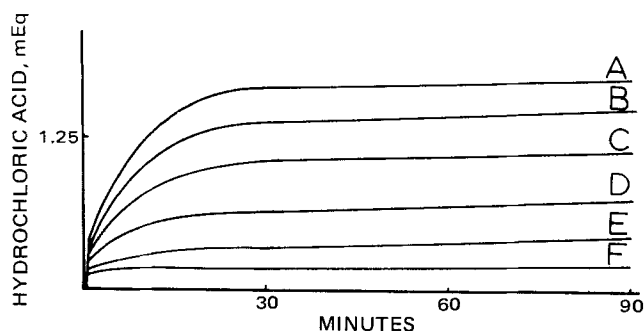
The utility of the pH-stat titration also is seen when three aluminum hydroxide gels, ranging in age from 3 to 33 months, are compared. The  $T_{50}$  values for Gels 2, 3, and 4 (Table III) were 11.2, 24.8, and 46 min, respectively, and were directly related to age.

The acid-consuming capacity measures the milliliters of 0.1 N HCl neutralized by 1 g of gel in 1 hr at 37°. Using this parameter, it is difficult to compare gels of different equivalent aluminum oxide content. The acid

**Table III—Comparison of *In Vitro* Antacid Tests**

Gel, % Al <sub>2</sub> O <sub>3</sub>	Age	Acid-Consuming Capacity Test			FDA Antacid Review Panel Test <sup>a</sup>				
		0.1 N HCl Consumed per Gram of Gel, ml	0.1 N HCl Consumed per Gram of Aluminum Oxide, ml	Theoretical Acid-Consuming Capacity, %	Rossett-Rice Test <sup>a</sup>		pH of Preliminary Antacid Test	Hydrochloric Acid Neutralized in 15 min, mEq	pH-Stat Titration <sup>b</sup> $T_{50}$ , min
					Rossett-Rice Time, min	Lag Time, min			
1 <sup>c</sup> , 3.3	1 day	20.34	616.4	104.8	30.0	0.1	4.1	18.5	3.7
1, 3.3	2 days	20.34	616.4	104.8	30.0	0.1	4.1	18.5	3.9
1, 3.3	3 days	20.34	616.4	104.8	30.0	0.1	4.1	18.5	4.4
1, 3.3	6 days	20.34	616.4	104.8	30.0	0.15	4.1	18.5	5.4
1, 3.3	7 days	20.34	616.4	104.8	30.0	0.15	4.1	18.5	5.8
1, 3.3	9 days	20.34	616.4	104.8	30.0	0.2	4.1	18.5	6.6
1, 3.3	10 days	20.34	616.4	104.8	30.0	0.2	4.1	18.5	7.2
2 <sup>c</sup> , 4.1	3 months	25.65	625.6	106.4	29.2	0.4	4.0	18.5	11.2
3 <sup>d</sup> , 4.2	21 months	25.22	600.5	102.1	29.0	1.5	3.9	16.9	24.8
4 <sup>d</sup> , 5.2	33 months	30.99	596.0	101.4	26.3	2.4	3.8	16.9	46.0

<sup>a</sup> Sample contained 300 mg equivalent Al<sub>2</sub>O<sub>3</sub>. <sup>b</sup> Sample contained 38 mg equivalent Al<sub>2</sub>O<sub>3</sub>. <sup>c</sup> Laboratory gel. <sup>d</sup> Commercial product.



**Figure 2**—The pH-stat titrgram of a chloride-containing aluminum hydroxide gel precipitated at pH 9.2 and aged at 25°. Key: A, 15 min; B, 1.5 hr; C, 2.5 hr; D, 4 hr; E, 6.5 hr; and F, 24 hr.

reactivity of different gels could be compared more accurately if the milliliters of 0.1 N HCl that react with 1 g of equivalent aluminum oxide were expressed. Another alternative that would make the acid-consuming capacity test more useful for studying gels of different equivalent aluminum oxide content would be to calculate the percent theoretical acid-consuming capacity assuming that 6 moles of hydrochloric acid react with 1 mole equivalent aluminum oxide. As seen in Table III, the milliliters of hydrochloric acid consumed per gram of gel is confounded by the different equivalent aluminum oxide content of Gels 2, 3, and 4. A comparison is possible using either milliliters of 0.1 N HCl consumed per gram of equivalent aluminum oxide or percent theoretical acid-consuming capacity. Both parameters indicate a decrease of 5% in acid-consuming capacity between the 3- and 33-month gels.

The Rossett-Rice data also indicate that a slight difference in acid reactivity existed among Gels 2, 3, and 4 directly related to their ages. The lag time seems to be the most sensitive indicator since it increased from 0.4 to 2.4 min.

The FDA antacid review panel test showed that less than a 10% difference in acid reactivity existed among Gels 2, 3, and 4 and that the 21- and 33-month gels were virtually identical.

It is evident that the pH-stat titration is the most sensitive approach for determining changes in acid reactivity occurring as aluminum hydroxide gel ages as well as the *in vitro* acid reactivity differences between aluminum hydroxide gels. This sensitivity to structural changes in aluminum hydroxide gel makes the pH-stat titration a powerful tool for structural studies and for optimizing the production of aluminum hydroxide gel and the design and manufacture of aluminum hydroxide gel dosage forms.

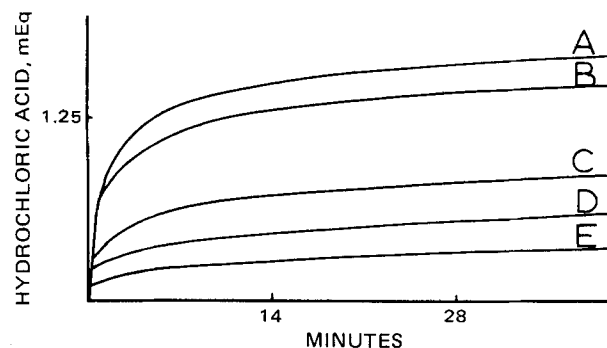
**Effect of pH on Neutralization Rate**—The neutralization rate of carbonate-containing aluminum hydroxide gel was inversely related to

**Table V**—Change in pH-Stat Titrgram during Aging at 25° of Chloride-Containing Aluminum Hydroxide Gel Precipitated at pH 9.2

Age	Phase A, %	Phase B, %	Phase C, %	$k_B$ , mEq/min	$k_C$ , mEq/min
15 min	17.4	54.4	28.2	$9.73 \times 10^{-2}$	$1.15 \times 10^{-3}$
1.5 hr	14.0	44.9	41.1	$9.50 \times 10^{-2}$	$1.35 \times 10^{-3}$
2.5 hr	11.5	35.5	53	$8.58 \times 10^{-2}$	$1.03 \times 10^{-3}$
4 hr	8.5	19.5	72	$7.25 \times 10^{-2}$	$1.35 \times 10^{-3}$
6.5 hr	7.9	4.1	88	$3.15 \times 10^{-2}$	$1.50 \times 10^{-3}$
24 hr	5.7	1.1	93.2	$0.45 \times 10^{-2}$	$1.10 \times 10^{-3}$

**Table VI**—Change in Hydroxyl Exchange during Aging at 25° of Chloride-Containing Aluminum Hydroxide Gel Precipitated at pH 9.2

Age	Phase a, %	Phase b, %	$k_b$ , mEq/min
4 hr	67.9	32.1	$4.57 \times 10^{-3}$
8 hr	57.9	42.1	$5.07 \times 10^{-3}$
1 day	31.0	69.0	$4.86 \times 10^{-3}$
2 days	18.0	82.0	$4.79 \times 10^{-3}$
7 days	8.4	91.6	$4.77 \times 10^{-3}$



**Figure 3**—The pH-stat titrgram of a chloride-containing aluminum hydroxide gel precipitated at pH 9.2 and aged at 25°. Reaction medium was 0.5 N NaF at pH 6.5. Key: A, 4 hr; B, 8 hr; C, 1 day; D, 2 days; and E, 7 days.

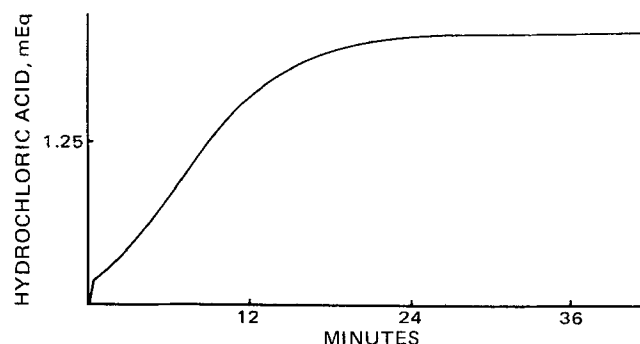
the pH-stat end-point in the pH range below 4 (Table IV). Aluminum hydroxide gel did not react with acid to any appreciable extent above pH 4.0. It is interesting to compare the behavior of aluminum hydroxide gel to the effect of pH on the neutralization of sodium bicarbonate and calcium carbonate. Sodium bicarbonate reacted very rapidly, even up to pH 7 (Table IV). Calcium carbonate also reacted very rapidly at pH's up to 5. The reaction still proceeded above pH 5 but at a slower rate.

These data suggest that aluminum hydroxide gel will only neutralize acid in the stomach or duodenum where the pH is below 4. In comparison, sodium bicarbonate and calcium carbonate are capable of reacting with acid throughout the GI tract. Since ulcers and hyperacidity problems are localized in the stomach and duodenum, the pH-reactivity pattern of aluminum hydroxide gel seems well suited for antacid therapy.

**Measurement of Acid Reactivity of Chloride-Containing Gels**—The study of the acid reactivity of chloride-containing aluminum hydroxide gels presents additional problems due to the relatively non-reactive nature of the gel, the rapid change in reactivity during aging, and the possible adsorption of acid by the gel in addition to the chemical neutralization of acid. As seen in Fig. 2, the freshly precipitated chloride-containing gel precipitated at a final pH of 9.2 was still reacting after 1 hr at pH 3.0 and had not reached the theoretical 2.235 mEq of hydrochloric acid required for a 38-mg equivalent  $Al_2O_3$  sample. The neutralization rate decreased rapidly as the gel aged. After 1 day at 25°, the gel was virtually unreactive since only 7% of the theoretical amount of acid was neutralized during 1 hr.

The pH-stat titrgram (Fig. 2) consists of three phases: an initial immediate reaction (A), followed by a slower zero-order phase (B) and a very slow terminal zero-order phase (C). The neutralization curve can be characterized by the fraction represented by each phase obtained by extrapolation of the linear portion of each phase and by  $k_B$  and  $k_C$ , the zero-order rate constants for phases B and C, respectively. The acid neutralization rate exceeded the speed of the autoburet during phase A. Thus, the total volume of acid neutralized during phase A could be determined but rate measurements for phase A were not possible.

The kinetic parameters for the aging at 25° of the chloride-containing gel precipitated at a final pH of 9.2 are given in Table V. The amounts of phases A and B decreased during aging until both fractions were virtually absent at 24 hr. Phase C increased during aging until it accounted for 93.2% of the gel after 24 hr. The rate of change for each fraction was greatest during the first 4-6 hr following precipitation. The rate constant



**Figure 4**—The pH-stat titrgram of a chloride-containing aluminum hydroxide gel precipitated at pH 7.0 and aged 20 min at 25°.

**Table VII—Change in pH-Stat Titrigram during Aging at 25° of Chloride-Containing Aluminum Hydroxide Gel Precipitated at pH 7.0**

Age	Phase 1, %	Phase 2, %	Phase 3, %	Phase 4, %	$k_2$ , mEq/min	$k_3$ , mEq/min	$k_4$ , mEq/min
20 min	7.8	15.4	69.6	7.2	$9.13 \times 10^{-2}$	$14.7 \times 10^{-2}$	$9.2 \times 10^{-4}$
5 days	4.5	11.5	55.9	28.1	$2.50 \times 10^{-2}$	$4.98 \times 10^{-2}$	$8.8 \times 10^{-4}$
12 days	3.0	9.2	41.3	46.5	$1.48 \times 10^{-2}$	$3.38 \times 10^{-2}$	$10.0 \times 10^{-4}$
21 days	2.0	2.9	34.3	60.8	$1.00 \times 10^{-2}$	$1.63 \times 10^{-2}$	$12.0 \times 10^{-4}$
45 days	1.5	0	27.5	71.0	0	$0.55 \times 10^{-2}$	$8.6 \times 10^{-4}$
80 days	0	0	7.0	93.0	0	$0.43 \times 10^{-2}$	$10.1 \times 10^{-4}$

for phase B decreased with age while  $k_C$  remained constant during aging, although the slow zero-order reaction accounted for an increasingly larger portion of the gel.

Based on the changes in the pH-stat titrigram during aging, it was hypothesized that the gel, when initially precipitated, was composed of hydroxyaluminum polymers (11, 12). Free hydroxyls on the surface of the polymers are readily accessible, react immediately with acid, and are seen in the titrigram as phase A. Small polymer units represent phase B and react relatively rapidly with acid. Larger polymers, which form an ordered structure, are responsible for the slow neutralization rate seen in phase C. During aging, the small polymers coalesce to form more highly ordered structures and the surface hydroxyls are incorporated into the gel structure as the polymer grows. This model is consistent with the behavior of the gel studied because phase C increased during aging while phases A and B decreased. After 24 hr of aging, the gel appeared to consist of a small number of accessible hydroxyls and an ordered hydroxyaluminum polymer which reacts with acid at a very slow rate. Thus, the pH-stat titrigram provides information useful in structural studies of aluminum hydroxide gel.

The gel precipitated at pH 9.2 contained 0.067 mole of chloride/mole of aluminum. This low level of chloride had little effect on the stability of the gel or on the neutralization reaction.

Little information concerning further changes in the gel structure is available after 6.5 hr of aging by use of the pH-stat titration. Edge hydroxyls in aluminum hydroxide are quickly replaced by fluoride, and structural hydroxyls are also replaced but at a slow rate (13). The exchange of fluoride for hydroxyl causes a pH increase, which can be monitored by pH-stat titration at pH 6.5.

Figure 3 shows the pH-stat titrigrams of the chloride-containing gel precipitated at a final pH of 9.2 using 0.5 N NaF as the reaction medium. The gel appeared to react in two phases: an immediate reaction that exceeded the capability of the autoburet to add compensating acid (a) and a slower zero-order reaction (b). The kinetic parameters for this series of titrigrams are given in Table VI. The rate of the slow zero-order reaction did not change as the gel aged, although the proportion of structural hydroxyls increased as the gel aged and the amount of edge hydroxyls decreased. X-ray and IR analyses (14) indicate that bayerite initially forms but that gibbsite is the final crystalline phase.

This behavior, when titrated in the presence of fluoride, agrees with the postulated hydroxyaluminum polymer model. The use of sodium fluoride extends the usefulness of the pH-stat titration in the study of the development of order in aged and nonreactive aluminum hydroxide gel.

The chloride-containing aluminum hydroxide gel precipitated at a final pH of 7.0 contained 0.37 mole of chloride/mole of aluminum and aged

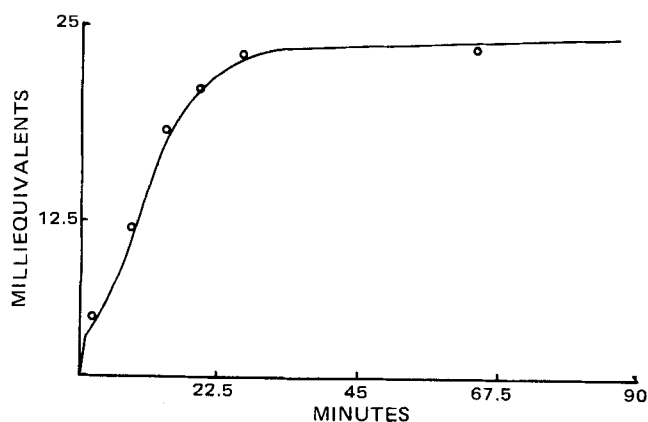
at a slower rate than the gel precipitated at pH 9.2. In addition, the pH-stat titrigram appeared to be composed of four phases: 1, an immediately reactive fraction; 2, a zero-order phase; 3, a more rapid zero-order phase; and 4, a terminal, very slow zero-order phase. Figure 4 shows the pH-stat titrigram of a freshly precipitated chloride-containing gel at pH 7.0. The kinetic parameters for the aging of this gel are given in Table VII. During aging, phases 1 and 2 disappeared. After 21 days, phase 2 was no longer present. Phase 1 was not present in the 80-day titrigram. At this point, the gel was almost completely composed of the very slow reacting fraction. X-ray and IR analyses (14) indicate that order is developing in the gel which ultimately produces gibbsite. It is interesting that the rate constant for the final slow zero-order phase did not change as the gel aged and had approximately the same value as the rate constant for the slow, terminal phase of the chloride-containing gel precipitated at pH 9.2 (Table V).

The difference in the aging rate of the chloride-containing gels is believed to be due to the stabilizing effect of chloride ions in inhibiting the development of order. The pH 9.2 gel contained 0.067 mole of chloride/mole of aluminum while the pH 7.0 gel contained 0.37 mole of chloride/mole of aluminum. The initial three phases of the pH-stat titrigram of the pH 7.0 gel are similar to the carbonate-containing gel, except the chloride-containing gel at pH 7.0 appears to contain some highly ordered material (phase 4) not seen in the carbonate-containing gel. Thus, the gel that contained a significant amount of chloride reacted more rapidly and did not lose reactivity as rapidly as the pH 9.2 gel. However, the chloride ion was not as effective as the carbonate ion in stabilizing the gel and facilitating the neutralization reaction.

**Adsorption of Acid by Chloride-Containing Gels**—The appearance of the aluminum ion in solution during the neutralization of a freshly precipitated pH 7.0 chloride-containing aluminum hydroxide gel was determined. Figure 5 shows the experimentally determined milliequivalents of the aluminum ion produced during neutralization. The solid line is the pH-stat titration curve expressed as milliequivalents of acid added. The mean  $\text{OH}^-/\text{Al}^{3+}$  ratio for six samples analyzed throughout neutralization was  $2.63 \pm 0.19$ . This result compares favorably with the previously reported  $\text{OH}^-/\text{Al}^{3+}$  ratio for the gel of 2.55 (11). This behavior suggests that chemical reaction totally accounts for acid neutralization by the slowly reactive aluminum hydroxide gels. If physical adsorption of acid were an important neutralization mechanism, then acid neutralization without a concomitant generation of the aluminum ion would be expected. As shown in Fig. 5, the physical adsorption of acid is insignificant when compared to the amount neutralized following chemical reaction.

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**Figure 5**—Appearance of aluminum ions during pH-stat titration of a chloride-containing aluminum hydroxide gel precipitated at pH 7.0. Key: —,  $\text{H}^+$  consumed; and  $\text{O}$ ,  $\text{Al}^{3+}$  released.

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#### ACKNOWLEDGMENTS AND ADDRESSES

Received September 15, 1976, from the \**Industrial and Physical*

*Pharmacy Department and the †Department of Agronomy, Purdue University, West Lafayette, IN 47907.*

Accepted for publication January 17, 1977.

Supported in part by a David Ross Fellowship (to N. J. Kerkhof) and an American Foundation for Pharmaceutical Education Fellowship (to R. K. Vanderlaan).

This report is Journal Paper 6431, Purdue University Agricultural Experiment Station, West Lafayette, IN 47907.

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## Role of Carbonate in Acid Neutralization of Aluminum Hydroxide Gel

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**Abstract** □ The role of carbonate in the acid neutralization of a carbonate-containing aluminum hydroxide gel was studied. The pH-stat neutralization reaction was comprised of three phases: an initial, immediately reacting phase; a slow, zero-order phase; and a terminal, fast zero-order phase. The evolution of carbon dioxide and the appearance of aluminum ions were monitored during neutralization. Acid neutralization is believed to occur predominantly at the aluminum-carbonate bond during the slow phase of neutralization. The reaction of structural carbonate disrupts the gel structure and increases the porosity and surface area of the gel. The diffusion of acid into the gel structure is facilitated and accelerates the neutralization rate, as seen in the final phase of the pH-stat titrations. This behavior of carbonate is probably responsible for the rapid and complete neutralization of acid generally observed with carbonate-containing aluminum hydroxide gel.

**Keyphrases** □ Aluminum hydroxide gel—acid neutralization, pH-stat titration, role of carbonate □ Gels—aluminum hydroxide, acid neutralization, pH-stat titration, role of carbonate □ Acid neutralization—aluminum hydroxide gel, pH-stat titration, role of carbonate □ pH-stat titration—aluminum hydroxide gel, acid neutralization, role of carbonate □ Carbonate—role in acid neutralization of aluminum hydroxide gel, pH-stat titration □ Antacids—aluminum hydroxide gel, acid neutralization, pH-stat titration, role of carbonate

Carbonate is an integral part of the aluminum hydroxide gel structure (1). The presence of carbonate in the gel structure contributes to gel stability (2), probably by inhibiting polymerization of the hydroxylaluminum particles and retarding the development of a highly ordered structure. In addition to enhanced stability, carbonate-containing aluminum hydroxide gels usually exhibit a faster acid neutralization rate than is observed in gels stabilized by other anions such as chloride or sulfate (2). The objective of this investigation was to determine the mechanism of acid neutralization in carbonate-containing aluminum hydroxide gels.

#### EXPERIMENTAL

**Materials**—All chemicals used were either official or reagent grade.

**Aluminum Hydroxide Gel Preparation**—Carbonate-containing aluminum hydroxide gel was prepared by the reaction of aluminum chloride, sodium bicarbonate, and sodium carbonate to a final pH of 6.5 (2).

**Analytical Procedures**—The equivalent aluminum oxide content was determined by the ethylenediaminetetraacetic acid titration (3). The acid reactivity was measured using an automated pH-stat method (4).

The carbonate content of the gels was analyzed by a gasometric displacement technique (5) using a Chittick apparatus<sup>1</sup>. The results are expressed as the ratio of millimoles of carbon dioxide evolved to millimoles of aluminum in the gel.

A specially designed glass reaction vessel, with a polytef head and methyl methacrylate top, was fabricated to study the evolution rate of carbon dioxide from the carbonate-containing aluminum hydroxide gels during neutralization with 1.0 N HCl. The reaction assembly consisted of a glass reaction vessel and an airtight head and top, which sealed the system and served as a holder for the electrodes, the titrant delivery tube, and the gas outlet tube connected to the Chittick apparatus.

The glass reaction flask was made of 45-mm o.d. × 100-mm Pyrex glass tubing. The wall thickness was 1.92 mm. The reaction vessel was fabricated with a flat bottom to facilitate the use of a standard 2.54-cm polytef-coated magnetic stirring bar.

The reaction head was fabricated from a 5.08-cm polytef rod (Fig. 1). The bottom side was machined to 41-mm diameter to fit inside the reaction vessel. A groove for a 3.175 × 41.275-mm o.d. O-ring was machined in the circumference of the bottom lip so that a tight press fit was obtained when the reaction vessel was forced over the O-ring.

Appropriately sized holes were drilled through the head to allow the insertion of the electrodes, the titrant delivery tube, and the gas outlet tube. A clear methyl methacrylate top was machined to the same pattern as the head. Eight holes were drilled in the top and threaded in the head to accept binding-head machine screws. The O-rings were fitted over the electrodes, the titrant delivery tube, and the gas outlet and were placed between the top and the head. The openings in the top and head were beveled to compress the O-rings and to seal the head when the machine screws were tightened.

An injection port was included in the reaction head. An appropriately sized hole was machined in the head to accept a high-pressure liquid chromatographic septum.

The reaction vessel, head, and top were combined with the pH-stat titrator and the Chittick apparatus. The sealed reaction vessel replaced the decomposition flask of the Chittick apparatus, and the 25-ml pH-stat autoburet replaced the glass buret.

The following procedure is used to monitor the evolution of carbon dioxide during the neutralization of a sample containing 380 mg equivalent Al<sub>2</sub>O<sub>3</sub> by 1.0 N HCl at pH 3.0. Transfer an appropriate volume of liquid gel, accurately weighed, into the decomposition reaction vessel. Secure the reaction vessel to the reaction head assembly. With the stopcock open to the atmosphere, adjust the leveling bulb to bring the displacement solution to 20.0 ml above the zero mark. Let the system stand 1–2 min to allow the temperature and pressure within the apparatus to equilibrate to room conditions. Then close the stopcock to the atmosphere. Lower the leveling bulb until the level reads zero on the measuring buret.

Using a glass syringe fitted with a 7.62-cm, 22-gauge needle, insert the needle through the injection port septum and slowly add 20.0 ml of

<sup>1</sup> Sargent-Welch Scientific Co., Skokie, Ill.