DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(13), 1809-1822 (1988)

IN-VITRO EVALUATION OF ANTACID SUSPENSION

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ABSTRACT

Three conceptually different titration procedures are used to evaluate the performance of several antacid suspension products: RIOPAN, RIOPAN PLUS, MAALOX, MAALOX PLUS, AND MYLANTA. When the static acid neutralization capacity test is performed, both RIOPAN and RIOPAN PLUS possess more acid neutralizing capacity, on an equal weight basis, than MAALOX, MAALOX PLUS or MYLANTA. The results of a pH-stat titration test show the RIOPAN products react 10 times faster with acid than other produced based on time to half-neutralization. The dynamic acid neutralizing capacity test (modified Beekman procedure) shows onset of action at pH 3 for the RIOPAN product to be 20 times faster than for MAALOX PLUS and 56 times faster than for MYLANTA. Duration of acid neutralization at pH above 3 for the RIOPAN products is two times longer than for MAALOX or MAALOX PLUS and 1.6 times longer than for MYLANTA.

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INTRODUCTION

The in-vitro performance of antacid formulations can be assessed using various analytical tests. These tests provide information on the neutralizing capacity under both static and dynamic conditions and permit various parameters to be evaluated; characteristics such as total neutralizing capacity, time to attain a specified higher pH value (onset of action), and others result from an in-vitro study of this type. When test conditions are carefully controlled and specified, they can be applied to a variety of market products that would permit a relative evaluation of these products.

The purpose of this study was to evaluate antacid suspensions of marketed products such as RIOPAN, RIOPAN PLUS, MAALOX, MAALOX PLUS, and MYLANTA by the total acid neutralizing capacity test (1), the pH-stat titration method (2,3) and dynamic acid neutralizing capacity test (modified Beekman procedure 4,5).

EXPERIMENTAL

Materials

Commercial antacid suspensions, RIOPAN, RIOPAN PLUS, MAALOX, MAALOX PLUS and MYLANTA were used. To compare lot-to-lot variation and to ensure a true product comparison, six different lots of each product were obtained. The following products were tested:

1. RIOPAN - Lot Nos. 1EEL, 1EEM, 1EEN, 1FB6, 1FC1, 1FCZ;
   Label: each 5 mL contains 540 mg magaldrate
2. RIOPAN PLUS - Lot Nos. 1FB9, 1FLS, 1FLT, 1FLV, 1FLW, 1FLX;
   Label: each 5 mL contains 540 mg magaldrate and 20 mg simethicone
3. MAALOX - Lot Nos. R42, R56, R59, S18, 52308, 55199;
   Label: each 5 mL contains 200 mg magnesium hydroxide and 225 mg aluminum hydroxide
4. MAALOX PLUS - Lot Nos. S38, 51353, 54316, 5527, 56264, 56343;
   Label: each 5 mL contains 200 mg magnesium hydroxide, 225 mg aluminum hydroxide, and 25 mg simethicone
5. MYLANTA - Lot Nos. XO445, XO450, XO456, XO474, XO486, 5184X;
   Label: each 5 mL contains 200 mg magnesium hydroxide, 200 mg aluminum hydroxide and 20 mg simethicone

Static Acid Neutralizing Capacity Test

An acid-neutralizing capacity test method in the USP XX monograph (1) was used as the total acid neutralizing capacity test.

pH-Stat Titration Test

A Radiometer Copenhagen recording titration system was used. It consisted of the pH-meter PHM 84, Titrator TTT 80, Autoburet ABU 80, Titration Assembly TTA 80 and Recorder REC 80. Experimental procedures involved adding 5 mL of the antacid suspension of 50 mL water, equilibration to 37 C, and titration with 1.0 N HCl to maintain a constant pH of 3.0. The pH-stat

titrigram was a graphical representation of mL of 1.0 N HCl added over time. Generated data were stored on an archival disc in the computerized laboratory automation system (CALS)[d] for possible further processing and plotting.

Dynamic Acid Neutralizing Capacity Test

The modified Beekman method (4) was adopted with some modifications to determine all operating parameters. Antacid (5 mL) was added to 0.1 N HCl (50 mL) at 37 C in a jacketed glass vessel (250 mL) equipped with a combination pH electrode, magnetic stirring bar (25 mm diameter, 7 cm length), and tubing to introduce the acid and to remove the antacid-acid mixture. A glass reservoir of 0.1 N HCl was maintained at 37 C. The pumping in-flow and out-flow were adjusted to be the same rate at 270 mL/hr with a proportioning pump.

Pumping of the continuous flowing system and stirring of the antacid-acid mixture at the rate of 400 rpm were initiated immediately after 5 mL of antacid suspension was introduced with a syringe into the reaction vessel. At the same time pH changes as a function of time were recorded. All information collection, storage, retrieval, plotting and averaging were done with aid of a Hewlett Packard computer.

The modified Beekman procedure (4) uses 15 mL of suspension samples and a paddle stirrer at 400 rpm. Since different antacid

TABLE I

Total Acid Neutralizing Capacity (TANC) of the Six Batches form Each Antacid Suspension

ANTACID	MEAN TANC (mEq/mL)	S.D.	C.V.
RIOPAN	3.11	0.12	4.01
RIOPAN PLUS	2.99	0.11	3.73
MAALOX	2.84	0.14	5.08
MAALOX PLUS	2.85	0.07	2.53
MYLANTA	2.65	0.03	1.29

products have different recommended dosage levels, a uniform volume of approximately 5 mL was used in all cases. Also, a stirring bar, instead of a paddle stirrer, was used; and its rpm was controlled accurately and reproducibility with the aid of a strobe.

RESULTS AND DISCUSSION

Total Acid Neutralizing Capacity

The total acid neutralizing capacity (TANC) of the six batches from each antacid product was measured. The average values of neutralizing capacity (mEq/mL), standard deviations (S.D.) and coefficient of variation (C.V.) are given in Table I.

A statistical comparison of the means was done with two sided t-tests. If a preliminary F-test for equality of variances was significant at the 0.05 level of significance, Satterthwaite's approximation for the degree of freedom was used in the t-test. When RIOPAN is compared to MAALOX, MAALOX PLUS, and MYLANTA, the means are significantly different at the 5% significance level with RIOPAN higher in all cases. When RIOPAN PLUS is compared to MAALOX PLUS any MYLANTA, there again is a statistically significant difference at the 5% significance level with RIOPAN PLUS greater in both cases. RIOPAN PLUS and MAALOX are not significantly different, however. In the same manner, RIOPAN and RIOPAN PLUS are not found to differ significantly from one another.

pH-Stat Titration

pH-stat titrigrams were obtained on each of the six different antacid suspension products; averaged titrigrams are shown in Figure 1. Initial pH of sample, half neutralization time, and acid neutralization capacity (mEq at the end of titration runs) are given in Table II.

A precision assessment was made in order to evaluate fully the pH-stat data and to demonstrate that the techniques, apparatus, and data requisition components under control. Half neutralization time and acid neutralization capacity were the parameters selected for evaluation of RIOPAN. Results of statistical analysis show that the estimate between day variance

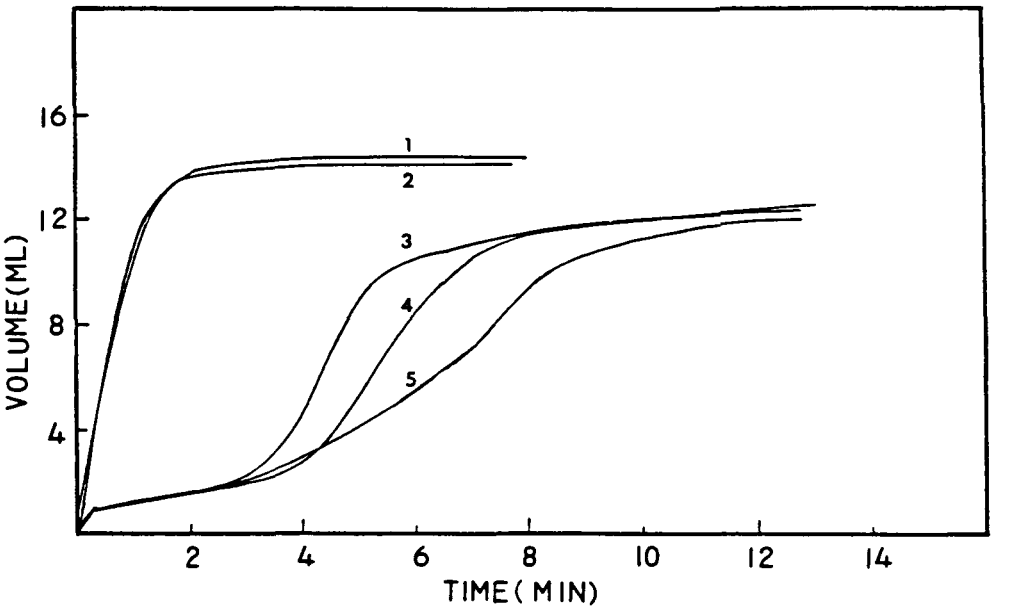

FIGURE 1

pH-stat titrigrams of 5 mL antacid suspensions at pH 3.0 and 37°C. Key: (1), Riopan; (2) Riopan Plus; (3) Maalox; (4) Maalox Plus; (5) Mylanta.

TABLE II

In-Vitro Evaluation of Antacid by pH-Stat Titration Procedure (Mean ± S.D.)

ANTACID	SAMPLE WEIGHT (g)	INITIAL pH	HALF NEUTRALIZATION TIME[a] (min)	ACID NEUTRALIZATION CAPACITY[b] (mEq)
RIOPAN	5.027 ± 0.082	8.90 ± 0.13	0.592 ± 0.209	14.64 ± 0.20
RIOPAN PLUS	5.018 ± 0.004	8.76 ± 0.11	0.456 ± 0.053	14.35 ± 0.18
MAALOX	5.010 ± 0.009	8.06 ± 0.05	4.280 ± 0.206	12.71 ± 0.21
MAALOX PLUS	5.003 ± 0.005	8.14 ± 0.17	5.297 ± 0.493	12.80 ± 0.22
MYLANTA	5.012 ± 0.009	8.18 ± 0.15	6.739 ± 1.217	12.17 ± 0.21

[a] Time to reach half the maximum acid volume required to neutralize the antacid samples

[b] Milliequivalent (mEq) of acid consumed at the end of the titration runs

is zero, and C.V.'s are 7.7% and 0.41% for half-neutralization time and acid neutralization capacity respectively. This level of variability is acceptable for the intended use of this data.

A review of results the pH-stat test permits some conclusions to be drawn as follows:

1. RIOPAN PLUS exhibits the highest product uniformity.
2. MYLANTA exhibits the widest product performance variation between batches.
3. All non-RIOPAN products data show half-neutralization times that range from 4.3 to 6.7 minutes, however, corresponding times are much faster for RIOPAN at 0.59 minutes and for RIOPAN PLUS at 0.46 minutes.

Dynamic Acid Neutralizing Capacity

Six different batches from each of five different products were evaluated using the modified Beekman procedure (4). The pH-time profiles are shown in Figure 2, where each curve represents averaged values of six batches for a given product. Numerical pH and time values extracted from these curves are given in Table III.

To assess the reproducibility and precision of the test procedure, two parameters were selected: the maximum pH level and the time at or above pH 2. The variance component estimates were obtained from three batches of RIOPAN assayed on each of four

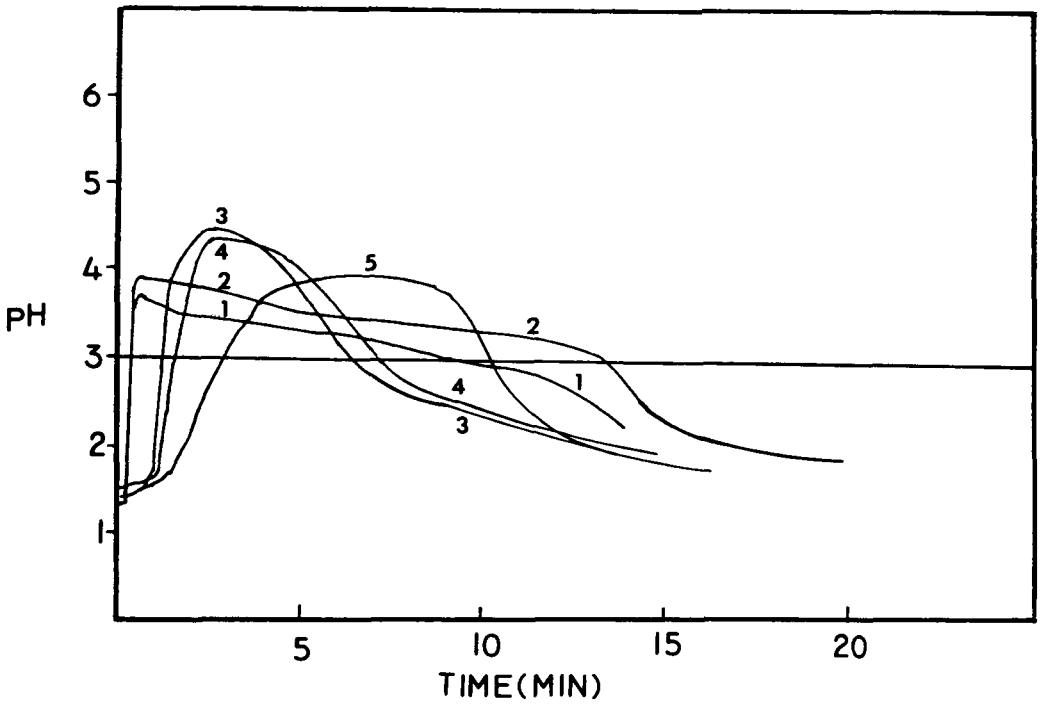

FIGURE 2

Plots of pH against time for modified Beekman procedure. Key: (1) Riopan; (2) Riopan Plus; (3) Maalox; (4) Maalox Plus; (5) Mylanta.

days. The within-day and between-day variance components were estimated using a two-way analysis of variance where the batch effect was fixed and the day was a random effect. The sum of between-day and within-day variance components gave estimated total C.V. of 1.5% and 13.7% for maximum pH and time greater than or equal to that required for reaching pH 2 respectively. This variability was acceptable.

TABLE III

In-vitro Evaluation of Antacid by Modified Beekman Procedure (Mean ± S.D.)

ANTACID	SAMPLE WEIGHT (g)	MAXIMUM pH REACHED	MAXIMUM pH (min.)	TIME TO REACH pH 3 INITIALLY (min.)	TIME ABOVE pH 3 (min.)
RIOPAN	5.36 ± 0.08	3.68 ± 0.08	0.37 ± 0.15	0.05 ± 0.01	11.1 ± 2.32
RIOPAN PLUS	5.35 ± 0.08	3.89 ± 0.08	0.42 ± 0.06	0.04 ± 0.01	13.1 ± 0.35
MAALOX	5.16 ± 0.10	4.52 ± 0.17	2.45 ± 0.42	0.89 ± 0.15	5.19 ± 0.62
MAALOX PLUS	5.33 ± 0.08	4.51 ± 0.71	3.07 ± 0.96	1.27 ± 0.34	5.45 ± 0.52
MYLANTA	5.44 ± 0.06	4.00 ± 0.04	6.62 ± 0.71	2.52 ± 0.53	7.50 ± 0.68

TABLE IV
Inferential Statistical Analysis for Modified Smyth Test: - Significance Level of Two Sided t-test Comparing Means*

PRODUCT PAIR FOR COMPARISON	MAXIMUM pH REACHED (min.)	TIME TO MAXIMUM pH (min.)	TIME TO REACH pH 3 (min.)	TIME ABOVE pH3 (min.)
RIOPAN VS. MAALOX	LT** 0.0001	LT 0.0001	LT 0.0001	0.001
RIOPAN VS. MAALOX PLUS	LT 0.0001	0.0009	0.0003	0.002
RIOPAN VS. MYLANTA	LT 0.0001	LT 0.0001	LT 0.0001	0.01
RIOPAN VS. RIOPAN PLUS	0.0002	0.46	0.07	0.08
RIOPAN PLUS VS. MAALOX	0.0002	LT 0.0001	LT 0.0001	LT 0.0001
RIOPAN PLUS VS. MAALOX PLUS	0.0002	0.001	0.0003	LT 0.0001
RIOPAN PLUS VS. MYLANTA	0.0014	LT 0.0001	LT 0.0001	LT 0.0001

* A two sample t-test was used to compare Riopan with each of the other antacid products. If a preliminary F-test for equality of variances was significant at the 0.05 level, Satterthwaite's approximation for the degree of freedom was used in the t-test.
** LT - less than

The mean values in Table III are compared for significance using a two-sided t-test. The inferential statistical analyses for this comparison were performed on the following product pairs: Both RIOPAN and RIOPAN PLUS are compared to MAALOX, MAALOX PLUS and MYLANTA. Results of analyses are given in Table IV.

Results shown in Table III allow the following conclusions supported by inferential statistics shown in Table IV:

1. RIOPAN reaches pH 3 in 0.05 minutes or about 18 times faster than MAALOX (0.89 min.), 25 times faster than MAALOX PLUS (1.27 min.), and 50 times faster than MYLANTA (2.52 min.).
2. RIOPAN PLUS reaches pH 3 in 0.04 minutes or about 22 times faster than MAALOX, 32 times faster than MAALOX PLUS, and 63 times faster than MYLANTA.
3. RIOPAN maintains cell pH at or above pH 3 for 11.1 minutes or about 2 times as long as MAALOX and MAALOX PLUS, and 1.5 times as long as MYLANTA.
4. RIOPAN PLUS maintains cell pH at or above pH 3 for 13.1 minutes or about 2.5 times as long as MAALOX and MAALOX PLUS, and about 1.7 times as long as MYLANTA.
5. None of the RIOPAN or RIOPAN PLUS batches reach pH 4, whereas six each of the MAALOX and MAALOX PLUS and three of the MYLANTA samples attain pH level.

SUMMARY

1. A statis acid neutralization capacity test shows that the RIOPAN products tested possess more acid neutralization

capacity, on an equal weight basis, than MAALOX, MAALOX PLUS or MYLANTA.

2. Results of a pH-stat titration test demonstrate that half-neutralization time for RIOPAN products is about 10 times faster than for the other products.
3. The dynamic acid neutralizing capacity test (modified Beekman procedure) shows that the onset of action (as measured by time to pH 3) for RIOPAN products is about 20 times faster than for MAALOX PLUS and 56 times faster than for MYLANTA.

Duration of acid neutralization (as measured by time at or above pH 3) for RIOPAN products is two times longer than for MAALOX or MAALOX PLUS, and 1.6 times longer than for MYLANTA.

ACKNOWLEDGEMENT

The authors wish to acknowledge Dr. Earl Nordbrock for reviewing of this manuscript.

FOOTNOTE

a. RIOPAN and RIOPAN PLUS - Ayerst Laboratories, Rouses Point, NY
b. MAALOX and MAALOX PLUS - William H. Rorer, Fort Washington, PA
c. MYLANTA - Stuart Pharmaceuticals, Wilmington, DE
d. Computer Automated Laboratory System (CALS), Computer Inquiry System, Inc., Waldwick, NJ

e. HP Computer Model 100, Hewlett-Packard, Inc., Palo Alto, CA

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