Stokes' law in the derivation of Eq. 2 and that account for the total shear stress which has to be generated in a mixing vessel to cause free suspension of particles. The derivation given by Goyan (8) for the Dankwerts model under laminar flow conditions of stirring relies on a physical model of a particle falling slowly in a liquid medium.

In summary, the multisized particle dissolution profiles point to actual experimental conditions where one may be dealing with a particle-size distribution broad enough to include large particles where $F > 1$ and small particles where $F = 1$. In these circumstances, a simple diffusion model would be inadequate and the Nielsen model in combination with the appropriate distribution function should more successfully predict the dissolution profile.

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Correlation of *In Vitro* and *In Vivo* Methodology for Evaluation of Antacids

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Abstract □ The rate and extent of acid consumption of an antacid suspension and tablet were evaluated by *in vitro* and *in vivo* techniques. Four different test procedures were used to estimate *in vitro* antacid reactivity. *In vivo* effects were determined in the fasted and postcibal states in normal human subjects by a radiotelemetry procedure. The duration of elevation of intragastric pH >3 was in agreement with *in vitro* estimates of total acid consumption of the antacid. There was also good correlation between onset, extent, and duration of *in vivo* antacid activity and a modified *in vitro* Beekman antacid test procedure. There was no significant difference in antacid activity of the tablet or suspension in either *in vitro* or *in vivo* test procedures. A wide variation in antacid activity was observed between subjects and also in the fasted *versus* postcibal states. These studies emphasize the requirements for standardization of antacid products by comparative *in vitro* and *in vivo* evaluations to facilitate individualized dose titration of the antacid in each patient and correlation of the acid secretion rate in various types of GI disease with the antacid dose.

Keyphrases □ Antacids—suspensions and tablets, rate and extent of acid consumption, *in vitro* and *in vivo* evaluations compared □ Acid consumption—rate and extent by antacid suspensions and tablets, *in vitro* and *in vivo* evaluations compared

The Food and Drug Administration (FDA) recently introduced an *in vitro* test (1) to determine the acid-neutralizing rate and acid-consuming capacity of over-the-counter antacid products. FDA also recommended that research be initiated to develop an *in vivo* model to assess antacid activity. Although an *in vitro* test can approximate *in vivo* conditions with respect to acid-consuming capacity, speed and duration of action, and maximum buffering capacity of the antacid, it cannot account for variations in antacid activity due to gastric emptying, changes in the acid secretion rate as seen in the fasting and postcibal states, interaction of antacids with glycoproteins and mucoproteins of gastric juice, coating of the gastric mucosa by antacids, and the effect of antacids on endogenous control of gastric acid secretion (2, 3).

The purpose of the present study was to compare the activity of an antacid tablet and suspension in both *in vitro* and *in vivo* models. Onset of action, maximum buffering capacity, and duration of antacid effect were compared in various *in vitro* systems and in normal human subjects in both the fasting and postcibal states.

EXPERIMENTAL

Methods—Each antacid tablet or 5 ml of suspension contained 200 mg of magnesium hydroxide, 225 mg of aluminum hydroxide, and 250 mg of calcium carbonate. The minimum recommended dose is two tablets (chewed) or 10 ml of suspension.

Total acid-consuming capacity was determined by the USP XVIII procedure (4) and by the OTC antacid test (1). A completely automated Bachrach procedure (5) was developed to determine the rate and extent of acid consumption.

A modified Beekman procedure (6, 7) was developed to determine the onset, duration, and buffering capacity of the antacid and to correlate *in vivo* and *in vitro* results. The modifications were as follows: antacid was added to 50 ml of 0.1 *N* hydrochloric acid at 37.5 ± 1° contained in a jacketed glass vessel provided with a combination pH electrode, agitator, and tubing to introduce the acid and to remove the antacid–acid mixture. The agitator was a paddle-type propeller[1] operated at approximately 400 rpm. Acid was continuously added, and the antacid–acid mixture was continuously removed at the rate of 270 ± 14 ml/hr with a positive displacement tubing pump. A glass reservoir of 0.1 *N* hydrochloric acid was maintained at 37.5 ± 1°. The pH was measured with a combination electrode and standardized pH meter connected to a recorder operating at a chart speed of 20.3 cm (8 in.)/hr.

The timer was activated, on addition of the test sample, and the pH values were recorded. The pump was then automatically started, adding 0.1 *N* hydrochloric acid and removing the antacid–acid reac-

[1] Coated with Teflon (du Pont).

Table I—*In Vitro* Evaluation of Antacids by the Bachrach Procedure[a]

Antacid	Initial pH[b]	Initial Neutralization[c], ml of 0.800 *N* HCl in sec: ml	Initial Neutralization[c], ml of 0.800 *N* HCl in sec: sec	End-Point[d], ml of 0.800 *N* HCl in min: ml	End-Point[d], ml of 0.800 *N* HCl in min: min	Acid Consumed at 10 min, ml of 0.800 *N* HCl
Suspension	8.56 ± 0.21	1.80	~75	5.40 ± 0.10	9.3 ± 0.8	5.41 ± 0.11
Tablet	8.66 ± 0.20	1.10	~60	4.90 ± 0.09	13.8 ± 1.9	4.62 ± 0.21

[a] Data are based on samples from five lots of each antacid. Comparable sample sizes of antacids were used (1.20 ml of suspension or 12% of weight of two tablets). All results are expressed as mean ± *SD*. [b] The pH of the antacid. [c] Volume of acid to initially obtain pH 3.5. [d] The end-point was the volume of acid necessary to maintain a pH of 3.5 ± 0.1 for at least 30 sec.

tion mixture. With the automation provided, the apparatus required no further attention until the titration was completed (pH ≤ 3).

The suspension was introduced directly into the reaction vessel with a syringe. Tablets were crushed and handscreened through a No. 20 mesh screen. A three-tablet equivalent, mixed with 15 ml of distilled water to maintain a reaction volume equivalent to the suspension sample size (15 ml), was used.

***In Vivo* Studies**—About 70% of the subjects tested were admitted to the study. The normal male and female subjects had a steady baseline intragastric pH value of less than 1.8 for at least 60 min. This value was confirmed by a baseline test, which followed the same procedures as the studies but substituted 35 ml of water for the dose of antacid.

None of the subjects had active upper respiratory or GI infections, a history of malabsorption disease, milk–alkali syndrome, pernicious anema, achlorhydria, peptic ulcer disease, or liver or kidney dysfunction. Upon confirmation of a steady baseline pH of less than 1.8, subjects were assigned to treatment according to a randomized allocation schedule. Subjects did not recieve any medication known to affect GI secretion or motility for 72 hr prior to each test day.

In the fasting study, subjects did not receive any food or liquids, except water, for a minimum of 8 hr before each test day. In the postcibal study, subjects ate a standard breakfast of 1 cup of dry cereal, 240 ml (8 oz.) of whole milk, 180 ml (6 oz.) of orange juice, sugar to flavor the cereal, and 1 cup of coffee or tea. One hour prior to testing, subjects ate a standard meal of 180 g (6 oz.) of medium-cooked chopped sirloin steak, one lightly toasted bun, and 1 cup of coffee or tea.

At the start of the test, the Heidelberg capsule (8, 9) was activated by immersion in 0.15 *M* sodium chloride at 37° for 5 min. The capsule was standardized with 0.1 *M* glycine–hydrochloric acid buffer, pH 1.0, and 0.1 *M* tromethamine buffer, pH 7.0. The capsule was then attached to a nonwettable surgical string and swallowed with 100–150 ml of water. The position of the capsule was controlled by the thread.

When 10–15 cm of the thread had passed through the esophagogastric junction, as indicated by the appearance of a pH reading of below 3 in the stomach, the thread was taped to the cheek. The position of the capsule in the stomach was confirmed by observation of a continuous baseline pH of less than 1.8 for 30 min. Free movement of the capsule in the stomach was confirmed by moving the string 2–4 cm without a significant interruption in the pH recording signal.

The subject remained in an upright seated position during the test. The pH of the gastric content was telemetered continuously by a belt antenna positioned around the upper abdomen and connected to the receiver and recorder. A steady baseline pH of less than 1.8 for 30 min was required for the subject to continue the study on each test day. In a randomized, crossover design, subjects were given either three antacid tablets (which the subject chewed) followed by 20 ml of water or 15 ml of antacid suspension followed by 10 ml of water. Administration of a corresponding volume of water had no significant effect on intragastric pH.

The onset of antacid activity, maximum pH, and duration of antacid activity (pH >3) were determined by direct observation. Intragastric pH was monitored until it returned to a steady baseline value for at least 20 min. The capsule was then retrieved, checked for standardization, and discarded.

Each subject underwent 1 test day with the antacid suspension and 1 test day with the antacid tablets; test days were separated by 2–7 days. Analyses of variance for a crossover design (10) were performed to compare the duration of activity of the tablets to the suspension in the fasting and postcibal studies.

Table II—*In Vitro* Evaluation of Antacids by the Modified Beekman Procedure[a]

Antacid	Maximum pH Reached	Time to Maximum pH, min	Time to Reach pH 3 Initially, min	Time above pH 3, min
Suspension	5.62–5.70	5.0–7.5	Immediate	26.5–27.5
Tablet	5.72–6.10	2.5–5.0	Immediate	25.5–28.0

[a] Data are based on samples from five lots of each antacid. Comparable sample sizes of antacids were used (15 ml of suspension or three tablets).

RESULTS

***In Vitro* Tests**—The total acid-consuming capacity was 36.4 ± 0.6 mEq/0.1 *N* HCl with two tablets or 10 ml of suspension, as determined by the USP procedure (4). The acid-neutralizing capacity, as measured by the OTC procedure (1), at the minimum recommended dose of two tablets or 10 ml of suspension was 34.1–35.7 or 32.6–39.5 mEq, respectively. The results of the Bachrach titration are shown in Table I; the modified Beekman test results are listed in Table II.

***In Vivo* Tests**—The antacid activity of the suspension and tablets, as determined by the Heidelberg capsule telemetering technique in the fasting and postcibal states, is shown in Table III. Twenty-two normal male and female volunteers, 21–45 years old, completed the fasting study. All subjects had a baseline pH of less than 1.8 for 30 min prior to antacid administration.

On the 1st test day, subjects randomly received either three antacid tablets or 15 ml of antacid suspension (11 received tablets and 11 received suspension). The crossover was then completed on another test day. No statistically significant difference was observed between the tablet or the suspension for rate of onset, peak pH, and duration of antacid activity. The range of duration of antacid activity was 8–121 min in the fasting state.

Twenty-two normal male and female volunteers (20 of whom participated in the fasting study) completed the postcibal study. Just as in the fasting study, all of the subjects in the postcibal study had a baseline pH of less than 1.8 for 30 min prior to antacid administration. On the 1st test day, the subjects randomly received either three antacid tablets or 15 ml of antacid suspension (12 received suspension and 10 received tablets). The subjects then completed the crossover on another test day. No statistically significant difference was observed between the tablets or the suspension for rate of onset, peak pH, and duration of antacid activity. The range of duration of antacid activity was 2–48 min.

In contrast to a previous report (11), no significant problems were encountered in the standardization and performance of the Heidelberg capsules.

DISCUSSION

Fordtran *et al.* (3) recommended that the dose of an antacid should be determined by its neutralizing capacity. They showed direct correlation of an *in vitro* test and *in vivo* neutralization of gastric acid by antacid suspensions following a standard meal. The *in vitro* test measured the capacity of the antacid to neutralize acid over 2 hr; the *in vivo* evaluation was performed by following intragastric pH in intubated subjects who received the antacid 1 hr after a standard meal.

The results of Piper and Fenton (12) are also in agreement with the

Table III—Evaluation of the *In Vivo* Antacid Activity of Antacid Tablets and Suspension

State	Antacid[a]	Distribution of Peak pH[b]				Duration[c], min	
		≥7	6.0–6.9	5.0–5.9	3.0–4.9	pH >3	pH >1.8
Fasting	Tablet	15[d]	7	0	0	43 ± 6 (12–121)	49 ± 5 (19–127)
	Suspension	21	1	0	0	44 ± 5 (8–100)	56 ± 6 (14–114)
Postcibal	Tablet	8	6	7	1	28 ± 3 (6–45)	38 ± 3 (6–55)
	Suspension	7	7	6	2	29 ± 3 (2–48)	41 ± 3 (2–64)

[a] Onset of antacid effect (pH >3) was <1 min in all cases. [b] Maximum pH reached after antacid administration (number of subjects = 22). [c] Time of intragastric pH >3 or pH >1.8 (baseline value) (mean ± *SEM* with range of values in parentheses). [d] Number of subjects, *i.e.*, 15 of 22 subjects had pH ≥7.

Fordtran *et al.* (3) observation in that a standard dose of antacid does not exist due to the variable response of patients to antacids. Significant differences in the *in vitro* acid-consuming capacity of various antacid tablets and suspensions and the overall superiority of suspensions has been reported (3, 12, 13). The chewable antacid tablets utilized were formulated (14) to provide an equivalent rate, duration, and extent of *in vitro* acid neutralization as the suspension.

A definite correlation was shown between the total acid-consuming capacity, as measured by the USP or OTC procedures, and the duration of *in vivo* neutralization of gastric acid. The total acid-consuming capacity and *in vivo* neutralization of antacid tablets and suspension were equivalent. However, these *in vitro* tests do not provide any data on the onset, rate, or duration of acid neutralization. The Bachrach titration provides data on the rate of acid consumption and total antacid capacity. Although *in vitro* data from this titration predicted that the suspension would be slightly better than the tablet with respect to onset and neutralization capacity, this result was not observed *in vivo*.

The modified Beekman test provided an excellent correlation with *in vivo* observations in the postcibal state. This *in vitro* test predicted an immediate onset of action, maximum pH between 5.6 and 6.1 in 3–8 min, and a 25–27-min duration of antacid effect. *In vivo* tests showed an immediate onset of action, maximum pH between 5 and 7 in about 5 min, and a 28 ± 3-min duration of intragastric pH >3.

Fordtran and coworkers (3, 15) recommended that maximum neutralization of gastric acid could be accomplished by administering the antacid 1 hr after meals, in contrast to the fasting state. Their results were based on studies using a standard morning meal of 150 g of broiled ground meat, two pieces of toast, and 180 ml of water. They concluded that the combined buffer capacity of the meal and antacid and the increased retention of antacid in the stomach at this time accounted for a longer duration of acid neutralization in the postcibal (3 hr) than in the fasted (20–40 min) state in duodenal or gastric ulcer patients.

The protocol used in this study more closely paralleled normal eating habits and utilized a different test meal, inclusive of a standard morning breakfast, midmorning coffee, and coffee with the midday test meal in normal subjects. Antacid was administered about 1.5 hr after the meal, at which time the intragastric pH was less than 1.8 for 30 min. The longer duration of antacid activity in the fasting state than in the postcibal state is in agreement with the increased rate of postcibal gastric acid secretion (16). However, the combined buffering capacity of the meal and the antacid should result in a 2-hr interval with the intragastric pH greater than 1.8. There was also considerable subject-to-subject variation in antacid activity in both the fasting and postcibal states due to the normal variation in the rate of gastric acid secretion and gastric emptying time.

These results are in agreement with the conclusions of the OTC antacid review panel (1) and other investigators (3, 12, 13) in that: (*a*) the rate and extent of acid-consuming capacity of antacid products are not alike[2], (*b*) the required dose of antacid not only varies between subjects but during each subject's day, and (*c*) additional *in vivo* studies are required to substantiate and correlate *in vitro* acid neutralization results.

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