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AN ANALYSIS OF STANDARDS FOR ANTACID SIMETHICONE DEFOAMING PROPERTIES

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ABSTRACT

The US Pharmacopeia XXII standard test method was used to measure the defoaming properties of simethicone antacid products. It was found that two pharmaceutical products did not meet the standards. Differences in defoaming activity were found when a bicarbonate solution was used in place of the acid solution specified by the test, and when the particle size of the tablets was varied. In general, the defoaming properties were reduced in the bicarbonate solution and when particle size was increased. These conditions more accurately reflect physiologic conditions than do the US Pharmacopeia Standards.

INTRODUCTION

The US Pharmacopeia (USP) XXII has set up standards to measure alumina, magnesia, and simethicone antacid defoaming properties as follows:

> Defoaming activity
>
> *Foaming solution*—Dissolve 500 μg of Food, Drug, and Cosmetic (FD&C) Blue No. 1 and 1 g of octoxynol 9 in 100 mL of 0.1 N hydrochloric acid (HCl).
>
> *Procedure*—[NOTE—For each test, employ a clean, unused, 250-mL glass jar.] Transfer a quantity of finely powdered tablets, passed completely through an 80-mesh sieve screen, equivalent to 20 mg of simethicone, to a clean, unused, cylindrical 250-mL glass jar, fitted with a 50-mm cap, containing 100 mL of *foaming solution* that has been warmed to 37 °C.[1]
>
> Cap the jar, and clamp it in an upright position on a wrist-action shaker. Employing a radius of 13.3 ± 0.4 cm (measured from center of shaft to center of bottle), shake for 10 seconds through an arc of 10 degrees at a frequency of 300 ± 30 strokes per minute. Record the time required for the foam to collapse.

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> The time, in seconds, for foam collapse is determined at the instant the first portion of foam-free liquid surface appears, measured from the end of the shaking period.[2]
>
> The defoaming activity time does not exceed 45 seconds.[1]

Although the above standards have been adopted by the US Food and Drug Administration without challenge, several questions can be asked: (1) How many pharmaceutical products meet these specific requirements? (2) Is the method described too sensitive? If so, it would not measure differences from one product to another. (3) Why use 0.1 N HCl with a pH of 1.1? (4) Should a 0.1 N bicarbonate solution with a pH of 8.3 also be used for testing? (5) Does the size of the sieve screen make any difference to the defoaming time?

Using a different method with Alconox® (Alconox Inc, New York, New York)[3] as the foaming agent, many of the commercial pharmaceutical products were found to be ineffective defoaming agents.[4,5] Thus we decided to re-test various products using the method described in USP XXII assuming that all antacid simethicone tablets, although not mentioned, would be required to meet the same standards. We also decided to address some of the above questions by using different sized sieves and a 0.1 N bicarbonate solution.

MATERIALS AND METHODS

The following materials were used: a Burrell wrist-action® shaker #75 (Burrell Scientific, Pittsburgh, Pennsylvania); 250-mL glass jars; 0.1 N HCl produced commercially; Triton® X surfactant (octoxynol 9; Union Carbide Chemical and Plastics Corp, Danbury, Connecticut); various antacid simethicone tablets (Table I) passed through an #80 sieve screen with openings of .0070 in or 180 μm and weighed so that the amount to be tested was equivalent to 20 mg of simethicone; stopwatch; FD&C Blue No. 1; Mettler balance (Mettler Balance-Scientific Products, Evanston, Illinois); and a water bath adjusted to 37 °C. Other sized sieves were used as follows: #20 (with openings of 0.0331 in or 850 μm in diameter); #10 (with openings of 0.787 in or 2.00 mm in diameter); and #5 (with openings of 0.157 in or 4.00 mm in diameter).

A bicarbonate solution, 0.1 N sodium bicarbonate ($NaHCO_3$) with a pH of 8.3, was used in addition to the 0.1 N HCl solution. The simethicone antacid tablets were purchased at a local pharmacy in July 1994; they are listed, along with their expiration dates, in Table I. The target tablet was manufactured in 1979. The target tablet consists of 40-mg simethicone in 360-mg lactose covered with a film coating primarily of inert cellulose

Table I. Products and formulas tested.

Product Name	Lot No.	Expiration Date	$CaCo_3$ (mg)	$Mg(OH)_2$ (mg)	Magaldrate (mg)	$AlOH_3$ (mg)	Simethicone (mg)	Amount of Tablet Used
Di-Gel® Antacid/Anti-Gas	4C004	3/98	280	128	—	—	20	1
Gelusil® Antacid/Anti-Gas	00624B	2/97	—	200	—	200	25	4/5
Maalox® Plus Antacid/Anti-Gas	95056	4/95	—	200	—	200	25	4/5
Mylanta® Antacid/Anti-Gas	MBF684	7/95	—	200	—	200	20	1
Riopan Plus® Antacid & Anti-Gas	9317	9/95	—	—	480	—	20	1
Riopan Plus® Double Strength Antacid & Anti-Gas	93122	11/95	—	—	1080	—	20	1
Titralac® Plus Antacid	361059	8/95	420	—	—	—	21	1
Tums® Anti-Gas/Antacid	3L06	11/95	500	—	—	—	20	1
Target tablet	PD-0818	1/79*	—	200	—	200	40	1/2

$CaCO_3$ = calcium carbonate; $Mg(OH)_2$ = magnesium hydroxide; $AlOH_3$ = aluminum hydroxide.
Note: Di-Gel® Antacid/Anti-Gas is a registered trademark of Schering Plough Healthcare Products, Liberty Corner, New Jersey; Gelusil® Antacid/Anti-Gas is a registered trademark of Warner Wellcome Consumer Healthcare Products, Morris Plains, New Jersey; Maalox® Plus Antacid/Anti-Gas is a registered trademark of Rhône-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, Pennsylvania; Mylanta® Antacid/Anti-Gas is a registered trademark of Johnson & Johnson–Merck Consumer Pharmaceuticals Co., Fort Washington, Pennsylvania; Riopan® Plus Antacid & Anti-Gas and Riopan® Plus Double Strength Antacid & Anti-Gas are registered trademarks of Whitehall Laboratories, New York, New York; Titralac® Plus Antacid is a registered trademark of 3M, St. Paul, Minnesota; and Tums® Anti-Gas/Antacid is a registered trademark of SmithKline Beecham Consumer Healthcare, Pittsburgh, Pennsylvania.
* Date of manufacture.

material (cellulose acetate phthalate). The outer part of the tablet contains 200-mg magnesium hydroxide and 200-mg aluminum hydroxide. These experiments were conducted between July and September 1994.

We added 500 mg of FD&C Blue No. 1 and 1 g of Triton X to 100 mL of 0.1 N HCl or 100 mL of 0.1 N $NaHCO_3$. The antacid simethicone granules were then passed through the various sieves. These granules were then added to the HCl or $NaHCO_3$ solution that had been previously warmed to 37 °C. The remainder of the test was performed per the USP method. All tests were done in triplicate, and results were averaged. All tests were also compared with a control that showed no significant defoaming activity.

RESULTS

Table II shows results of screens #80, #20, #10, and #5, and differences between the HCl and bicarbonate solutions. In almost all cases, the defoaming action was decreased when $NaHCO_3$ was used in place of HCl. In addition, the smaller the screen size used, the more effective the defoaming activity.

Using HCl and the #80 sieve specified in USP requirements, Riopan Plus® and Riopan Plus® Double Strength failed to meet the 45-second time limit for defoaming activity (both products took 10+ minutes). With a bicarbonate solution and the #80 sieve, these two products along with Maalox® Plus (7+ minutes) failed to meet the criterion. However, although it is not precise, based on numerous chewed samples of antacid simethicone, we estimated that the particle size before swallowing is closer to sieve #5 than #80. Using the #5 sieve and either HCl or $NaHCO_3$, only Di-Gel®, Titralac® Plus, Tums®, and the target tablet met the 45-second defoaming time criterion; Gelusil®, Maalox Plus, Mylanta®, Riopan Plus, and Riopan Plus Double Strength failed to meet the criterion.

DISCUSSION AND CONCLUSIONS

The antacid simethicone tablets used in these experiments were purchased at a local pharmacy. It was not our intent to make a comprehensive study of all the pharmacies and their products. We wished to use material from a fairly typical local pharmacy so that we could determine the effectiveness of the various antacid simethicone tablets that were on the store shelf at the time.

Although the differences in Di-Gel, Titralac Plus, Tums, and the target tablet were not significant, there are still many unanswered questions.

Table II. Defoaming time measured from the end of shaking period until foam collapse (average of three trials).

Product Name	#80 Sieve		#20 Sieve		#10 Sieve		#5 Sieve	
	HCl	$NaHCO_3$	HCl	$NaHCO_3$	HCl	$NaHCO_3$	HCl	$NaHCO_3$
Di-Gel® Antacid/Anti-Gas	4 s	8 s	8 s	12 s	8 s	14 s	11 s	28 s
Gelusil® Antacid/Anti-Gas	5 s	17 s	20 s	10+ min	10+ min	10+ min	10+ min	10+ min
Maalox® Plus Antacid/Anti-Gas	14 s	7+ min	10+ min	10+ min	10+ min	10+ min	10+ min	10+ min
Mylanta® Antacid/Anti-Gas	12 s	26 s	15 s	10+ min	24 s	10+ min	10+ min	10+ min
Riopan Plus® Antacid & Anti-Gas	10+ min	10+ min	10+ min	10+ min	10+ min	10+ min	10+ min	10+ min
Riopan Plus® Double Strength Antacid & Anti-Gas	10+ min	10+ min	10+ min	10+ min	10+ min	10+ min	10+ min	10+ min
Titralac® Plus Antacid	7 s	12 s	9 s	27 s	8 s	43 s	11 s	24 s
Tums® Anti-Gas/Antacid	2 s	3 s	2 s	3 s	2 s	3 s	2 s	5 s
Target tablet	2 s	9 s	2 s	2 s	5 s	4 s	9 s	6 s

HCl = hydrochloric acid; $NaHCO_3$ = sodium bicarbonate.

Note: DiGel® Antacid/Anti-Gas is a registered trademark of Schering Plough Healthcare Products, Liberty Corner, New Jersey; Gelusil® Antacid/Anti-Gas is a registered trademark of Warner Wellcome Consumer Healthcare Products, Morris Plains, New Jersey; Maalox® Plus Antacid/Anti-Gas is a registered trademark of Rhône-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, Pennsylvania; Mylanta® Antacid/Anti-Gas is a registered trademark of Johnson & Johnson–Merck Consumer Pharmaceuticals Co., Fort Washington, Pennsylvania; Riopan® Plus Antacid & Anti-Gas and Riopan® Plus Double Strength Antacid & Anti-Gas are registered trademarks of Whitehall Laboratories, New York, New York; Titralac® Plus Antacid is a registered trademark of 3M, St. Paul, Minnesota; and Tums® Anti-Gas/Antacid is a registered trademark of SmithKline Beecham Consumer Healthcare, Pittsburgh, Pennsylvania.

We assume that the USP based its standardization requirements on some resemblance to physiologic conditions. Admittedly, it is extremely difficult to duplicate exact physiological conditions in vitro to test defoaming action of various agents. However, we think it important to at least try to produce an environment that somewhat reflects physiological conditions. The #5 sieve is much closer to the size of the tablet particles after chewing than the #80 sieve, which is essentially a very, very fine particle. Furthermore, we must consider that gas in the gastrointestinal tract exists in two places: the stomach with an average fasting pH of 3.0 for men and 3.8 for women[6] and the small bowel with a pH between 7 and 8.[7] Thus 0.1 N HCl with a pH of 1.1 is a little low. More importantly, a bicarbonate alkaline solution should be used as a part of the test. Why shake the experimental contents in a wrist-action shaker? When one swallows an antacid simethicone tablet after it has been chewed, there is no shaking in the stomach, only mild peristalsis. Furthermore, most of the distressing gas in the gastrointestinal tract that leads to cramps and bloating is in the small bowel or colon—not in the stomach. Finally, what is the relationship of age of the simethicone antacid tablets to defoaming activity? Based on previous work, admittedly using a different test, it has been demonstrated that there is a significant deterioration of defoaming properties with age of the antacid simethicone mixture.[2,4,5] Additional studies are in progress to assess the aging effect on defoaming using the USP method. The target tablet, manufactured in 1979, was included in this study to show that this particular preparation has shown no deterioration in defoaming properties over 15 years.

We concluded from our study that simethicone antacid tablet defoaming properties are less effective in bicarbonate solution, and that the particle size of simethicone antacid tablets being tested has a significant effect on defoaming time—the larger the size the less effective the defoaming activity.

It is our recommendation that the USP revise its standards to take into consideration the differences in pH in the stomach and small bowel and take into consideration the differences in size produced by chewing compared with that produced by forcing the preparation through a small sieve.

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