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"IN-VITRO" TESTING OF AN ANTACID FORMULATION WITH PROLONGED GASTRIC RESIDENCE TIME (ALMAGATE FLOT-COAT®)

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ABSTRACT

Dynamic *in vitro* tests were used to study sensitivity to environmental acidity, buffering profile and residence time under simulated gastric conditions of pharmaceutical formulations incorporating the concept of prolonged gastric residence time (Almagate Flot-Coat®). In comparison with classical antacid products the new formulation was shown to have a high antacid potency together with a prolonged *in vitro* gastric residence time.

INTRODUCTION

Classical antacids such as aluminium and magnesium hydroxide gels and co-gels, and crystalline aluminium magnesium hydroxycarbonates

or sulphates such as Hydrotalcite, Almagate and Magaldrate are either rapidly neutralized to water soluble ions (1-3) or sediment to the fundus of the stomach, and are evacuated into the duodenum by normal peristalsis. In the latter case loss of unused drug from its site of action, would be expected if it has not been utilised for immediate neutralisation of acid. Furthermore, the sensation of comfort associated with antacid therapy rarely persists longer than forty minutes after drug intake (4).

An antacid with a prolonged effect would be advantageous, not only enhancing patient compliance but allowing safer administration of higher doses of antacid and covering a wider range of individual acid neutralization needs.

The site of action of antacids is the stomach and standard techniques utilised for formulating sustained release products, where the active principal is slowly released by different mechanisms during gastrointestinal transit, are not applicable for such products. Consequently the concept of a pharmaceutical formulation with a prolonged gastric residence time was developed (5). In this study a selected group of dynamic "in vitro" tests were used to study two pharmaceutical formulations incorporating this concept in comparison with classical antacid products.

MATERIALS

Reagents

Pepsin and hydrochloric acid (analytical grade) were from E. Merck (Germany).

Dosage form samples

Samples of solid antacids were purchased in Spain, and tablets and dry powder sachets (extemporaneous suspension) incorporating

TABLE 1

Brand	Recommended unit dose (1)	Active principles per recommended dose (2)	
Product (A) Dolcopin (Gamir--Rottapharm)	2 tablets	Alginic acid	1 g
		Magnesium aluminium silicate	1 g
		Sodium bicarbonate	0,35 g
		Magnesium trisilicate	0,05 g
Product (B) Flot-Coat® sachets (Almirall Tecnobio)	1 sachet	Almagate (1 g in the form of Almagate Flot-Coat®)	1,5 g
Product (C) Flot-Coat® tablets (Almirall Tecnobio)	1 tablet	Almagate (1 g in the form of Almagate Flot-Coat®)	1,5 g
Product (D) Maalox F (Rorer)	1 or 2 tablets	Aluminium hydroxide	0,8 g
		Magnesium hydroxide	0,8 g
Product (E) Maalox Concent. (Rorer)	1 or 2 tab.	Aluminium hydroxide	1,2 g
		Magnesium hydroxide	0,6 g

(1) According to manufacturer

(2) When two doses are recommended, the amount of active principle(s) given is for the higher dose.

Almagate Flot-Coat ® were formulated in our laboratories. The products used in the present study are shown in the Table 1.

Test samples

The test samples used in all methods were as follows: 2 tablets for products A, D and E; 1 sachet for product B; and 1 tablet for product C.

Instruments

A pH-meter (Radiometer 85, Denmark) fitted with a glass-calomel (KCl) electrode system was used.

The Fordtran and Schaub tests were carried out using an automatic system composed of a pH-meter (Crison 2040) fitted with a liq-glass electrode (Hamilton P/N 238000) and automatic dispenser (microBUR 2030 Crison). The system was controlled and data were collected, by a PC IBM PS/2 (model 30 286) with TMI 302 software (version 1.04).

METHODS

a) Selective reactivity

To the test sample (dispersed through a 840 µm screen) an exactly measured volume (250 ml) of hydrochloric acid (0,1M or 0,05M for test I or II, respectively) was added. The mixture was stirred magnetically for 20 minutes and the pH value of the resulting suspension was noted, the suspension filtered, and the dissolved aluminium content was determined complexometrically. The results are expressed as the ratio (%) of this value to the total aluminium content of the test sample, for both tests I and II.

b) Resistance to simulated gastric emptying (RSGE)

A glass cylinder (4 cm inside diameter, 15 cm height) was used and 0.5 cm from the bottom a glass tap (inside diameter 0,7 cm) was fitted, to allow discharge of liquid in a gastric emptying simulation.

The antacid sample (previously dispersed through a 600 µm screen) was added to 0.1M hydrochloric acid (150 ml) in the glass cylinder. After 15 minutes of gentle magnetic stirring the tap was opened allowing free discharge of the contents of the cylinder (liquid and solids in suspension).

The solids remaining adhered to the glass surface were quantitatively collected with 1M hydrochloric acid (c.a. 225 ml), stirred vigorously during two hours to permit complete dissolution of antacid particles, filtered, transferred to a 250 ml volumetric flask and made up to volume with 1M hydrochloric acid. The concentration of dissolved aluminium in this solution was determined complexometrically. The results are expressed as in paragraph a).

c) Antacid flow performance

The test of Schaub (6) was used, with adaptation to our instrumentation. The sample was added with continuous stirring to USP simulated gastric juice (150 ml) maintained at 37 ± 1°C. After 20 minutes the pH value was recorded (pH max), and immediately a volume of standard USP simulated gastric juice (20.0 ml) was added. Concomitantly a volume of 20.0 ml was removed from the reaction vessel. This process was repeated until the pH value fell below 3. The total amount of gastric juice consumed, and the time of reaction were recorded.

d) Prolonged buffering profile

The test of Fordtran as modified by Browers (7, 8) and adapted to our instrumentation was used. The sample was dispersed

through a 840 μm screen and then suspended in distilled water (100 ml) maintained at 37 ± 1°C with continuous stirring. After 10 minutes triply concentrated USP simulated gastric juice (50 ml) was added, to give a total volume of 150 ml of standard USP simulated gastric juice. After 10 minutes the pH value was recorded (pH at 20 min), and more simulated gastric juice (USP concentration) was added, to pH3. Neutralization was allowed to continue during 5 minutes, and this procedure was repeated until the antacid activity was completely exhausted. The total amount of gastric juice neutralised, its distribution throughout the test and pH variations were recorded.

The test was also carried out with a modified USP simulated gastric juice to which no pepsin had been added.

RESULTS AND DISCUSSION

The results obtained are shown in Tables 2 and 3. The selective reactivity test was carried out in an attempt to define the capability of the products to behave as "on demand antacids", with sensitivity to environmental acidity. Acid neutralisation performance in two different acid concentrations was studied. The final pH value shows that product A has little antacid efficacy, being incapable of reducing the acidity enough to reach pH value 3 under the test conditions. The products B and C reduce acidity to the recommended pH values, independently of differences in ambiental acidity in tests I and II, and act as an "on demand antacids", balancing the dissolution of the antacid component to the neutralization requirement at each acid concentration.

The products D and E function well under the conditions of test I, but in less severe conditions (i.e. in testII) produce an increase of pH to 6.7, even though the amount of aluminium hydroxide dissolved was less than 0,3%, implicating the

TABLE 2. ANTACID PERFORMANCE

Product	USP Acid Neutralization capacity (mmol)	Selective Reactivity I D.Al[4] (%)	I pH	II D.Al[4] (%)	II pH
A	21.0 [1]	51.1	2.33	20.5	2.78
B	42.8 [2]	37.4	4.37	3.6	4.83
C	42.5 [3]	37.0	4.38	3.8	4.87
D	40,6 [1]	6.6	4.84	0.3	6.67
E	40,9 [1]	13.9	4.46	0.2	6.16

[1] : 2 tablets
[2] : 1 sachet
[3] : 1 tablet
[4] : Dissolved aluminium

TABLE 3. DYNAMIC ANTACID PROFILES

Product	RSGE (%)	Flow Antacid Performance		
		pH max	Time (min)	Vol. (ml)
A	33,2	3,68	48	73
B	40,8	5,50	152	247
C	47,3	5,71	150	244
D	27,4	6,64	96	166
E	20,1	6,65	81	137

(continued)

magnesium hydroxide component as the cause of excess alkalinity.

Significant differences are detected in the potential of each sample to adhere to glass surfaces, and as expected products C and B exhibited the highest resistance in the simulated gastric emptying experiment. These results are more striking since the test measures the aluminium content of the material adhering to the walls of the vessel and products B and C contain less aluminium (150 mg) than do products A, D and E (231, 220 and 342 mg respectively).

The correlation of "in vitro" methods of evaluating antacid efficacy with "in vivo" performance are controversial. Obviously, dynamic methods would be preferred, and are mandatory when reaction kinetics must be observed to support claims based on prolonged "in vitro" antacid activity. In this

TABLE 3. (Cont.)

Prolonged Buffering Profile									
Time [1] to pH = 3 (min)		Time [1] to pH = 6 (min)		Time [1] over pH = 6 (min)		pH at 10 min[1]		Acid Neutralized (mmol)	
PP[2]	PA[3]	PP[2]	PA[3]	PP[2]	PA[3]	PP[2]	PA[3]	PP[2]	PA[3]
0,76	1,61	-	-	-	-	3,38	3,45	21,7	19,5
0,76	1,22	-	-	-	-	4,90	4,64	43,0	42,1
0,59	0,95	-	-	-	-	5,00	4,74	42,5	41,6
0,78	1,34	2,32	2,56	25,18	10,38	6,95	6,75	36,4	41,3
0,66	1,73	2,56	3,98	20,00	10,28	6,86	6,30	36,9	40,9

1 : After gastric juice input
2 : Pepsin present
3 : Pepsin absent

sense the results obtained in Fordtran's test are informative as they show the profile of acid consumption of the different samples during the reaction period of three hours (Fig. 1). Higher acid neutralization capacity extending over a period of more than two hours was measured for products B and C. These products also neutralize a considerable amount of acid (ca. 24 mmol) in the first hour, continue neutralising acid in the second hour (ca. 17 mmole acid) after which antacid activity is negligable. Products A, D and E only neutralize acid in the first hour. The particular galenical formulation of products B and C confers extended antacid reactivity while maintaining the complete availability of its active principle, as demonstrated by the agreement between the total acid neutralized in the test of Fordtran and the USP acid neutralisation capacity (Tables 2 and 3).

The acid neutralization profile is a fundamental parameter defining an antacid drug's performance, however, the test should be carried out under conditions which most closely resemble those occurring "in vivo". An antacid formulation must bring the pH of the media within the now generally accepted range 3-6 (9, 10), rapidly, reversibly inhibit digestive enzymes and avoid a rebound effect. If Fordtran's test is carried out in the absence of pepsin all of the products continue to neutralise acid for up to 4 hours (Fig. 2). Under more natural conditions, in the presence of pepsin, the pharmaceutical formulations B and C are long acting without allowing the pH to exceed 6. The pH values attained with products D and E surpass this value, whereas product A brings the pH just above the minimum value 3 (Fig. 1 and Table 3). Special concern was focused on the ability of the products to maintain a long duration of activity without loss of potent initial neutralization strength permiting the immediate relief of the patient's symptoms. All the products tested rapidly increase the pH to 3 (Table 3), but product D and E raised the pH to 6 within 2 to 3 minutes, and maintained the pH above 6

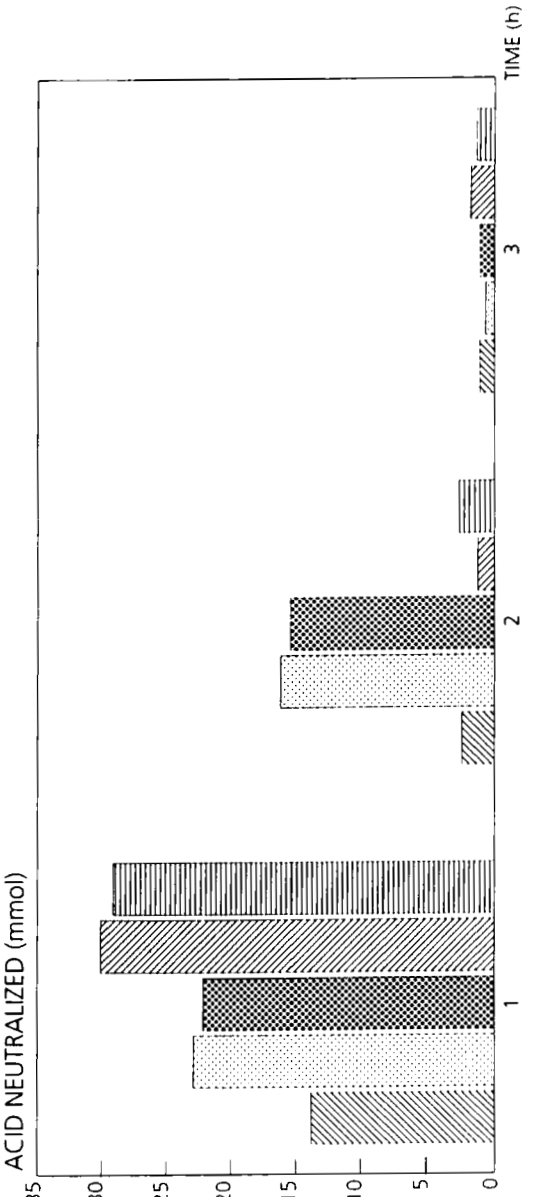

FIG. 1
PROLONGED BUFFERING PROFILE
PEPSIN PRESENT

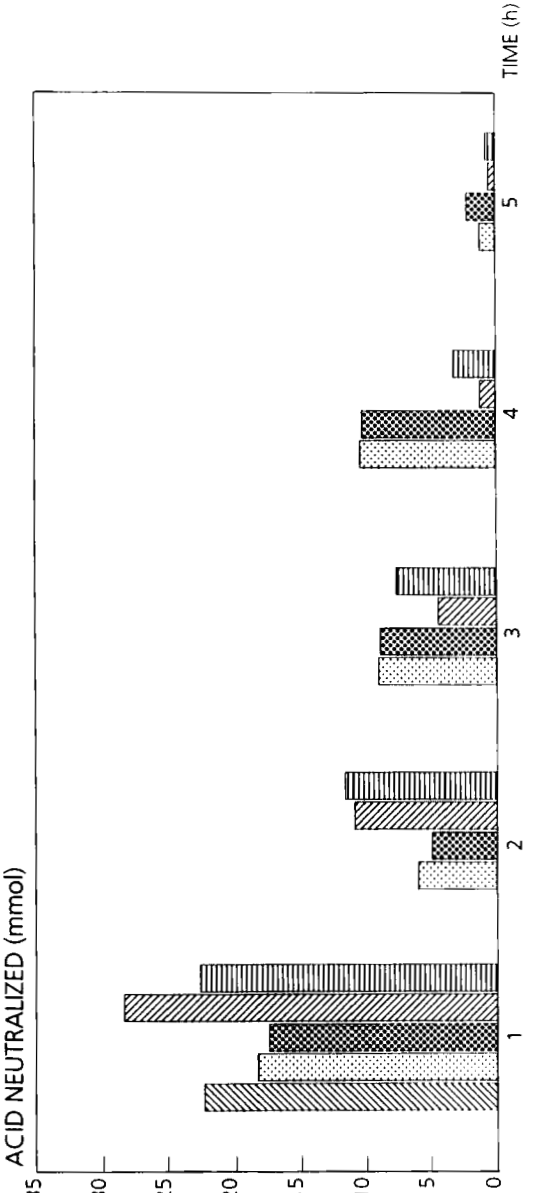

FIG. 2
PROLONGED BUFFERING PROFILE
PEPSIN ABSENT

for 20-25 minutes even though additional gastric juice was added periodically. The pH did not surpass 3,5 when product A was tested.

The test of Schaub was used to mimic the behaviour of the antacid products under a combined neutralization and forced emptying program. In this test suction withdrawal of a volume of reaction mixture was made at several time intervals, thereby forcing the outflow of some unreacted antacid. Under these conditions products B and C, controlled the pH value above 3 for an extended period (ca. 2.5 hours), with an acid consumption clearly superior to the other tested products.

The results obtained in the above tests allow the conclusion that the novel pharmaceutical formulation of products B and C (containing Almagate Flot-Coat®) does indeed confer a higher antacid potency together with a prolonged "in vitro" gastric residence time with a safe and extended delivery of antacid drug. In these respects it clearly differs from the standard antacid products in permiting a convenient dose of the active principle in a well equilibrated pharmaceutical formulation, with a unique antacid profile and lending support to its potential clinical usefulness.

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