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SELECTING KEY FORMULATION FACTORS IN ANTACID SUSPENSIONS

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ABSTRACT

The physical characteristics and "in vitro" neutralisation capacity were measured for eight antacid suspensions in the absence and presence of an equilibrated standard diet. The results obtained permit an assessment to be made of the potential therapeutic advantages and disadvantages of these formulations.

INTRODUCTION

The formulation of antacid products in suspension is a therapeutically acceptable and for some indications the preferred dosage form for such products (1). Depending on the active substances and the excipients used these formulations will have differing physicochemical properties. In this study eight different antacid suspensions were subjected to a

selected group of physicochemical test measuring parameters that could be related to the potential of these products to provide rapid and prolonged relief of symptoms in patients with hiperacidity.

MATERIALS

Reagents

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

A standard and equilibrated diet (Biomanan, Merck) was used in the modified Schaub's experiments.

Dosage form samples

Samples of relevant marketed antacid suspensions were obtained from several countries. The brands used in the present study are shown in the "Table of Brands".

Instruments

A pH-meter (Radiometer 85, Denmark) fitted with a glass-calomel (KCl) electrode system was used. Viscosity determinations were performed with a Brookfield viscometer, spindle nr. 3, 50 r.p.m.

METHODS

a) Sedimentation

Each antacid suspension was shaken by hand for 30 seconds, then a volume (50 ml) placed into a well-stopered graduated

Table of Brands

Brand	Recommended unit dose (1)	Active principles per unit dose (2)	
Product (A) Almax Forte (Lab.Almirall, Spain)	15 ml, monodose sachet	Almagate	1.5 g
Product (B) Algicon (Rorer, U.K.)	10 or 20 ml suspension	Magnesium alginate Anhydrous aluminium hydroxide/ magnesium carbonate co-gel Magnesium carbonate Potassium bicarbonate	1 g 0.56 g 0.7 g 0.2 g
Product (C) Bemolan (Boehringer, Spain)	$\frac{1}{2}$ or 1 sachet of 10 ml	Magaldrate	0.8 g
Product (D) Maalox F (Rorer, Spain)	10 or 20 ml suspension	Aluminium hydroxide Magnesium hydroxide	0.45 g 0.4 g
Product (E) Maalox TC (Rorer, U.S.A)	5 or 10 ml suspension	Aluminium hydroxide Magnesium hydroxide	1.2 g 0.6 g
Product (F) Maaloxan (Rorer, Germany)	1 or 2 sachet of 10 ml	Magnesium hydroxide Aluminium hydroxide gel (equivalent to 0.46 g Al_2O_3)	0.8 g 4.8 g
Product (G) Minoton (Madaus, Spain)	10 ml sachet	Magaldrate	0.8 g
Product (H) Riopan (Ayerst, U.S.A)	5 or 10 ml suspension	Magaldrate	1.08 g

(1) According to manufacturer.
(2) In the cases where two doses are recommended, the amount of active principles are given for the higher dose.

cylinder and left to stand at room temperature until no further sedimentation was seen. Observations were performed during 30 days, but in almost all cases no additional sedimentation was observed after the second week.

The results are expressed as the ratio of the height of the sediment column (mm) after 30 days to the initial suspension height (mm) in the cylinder. The resulting values are recorded as a physical stability factor (PSF).

b) Viscosity

Viscosity determinations were performed on samples of the antacid suspensions, previously shaken as in the previous method, and maintained at 25 ± 0.5°C. Ten replicates were obtained at 1 minute intervals and the mean value was calculated.

The determinations were exactly repeated at 37 ± 0.5°C on fresh samples of each antacid suspension.

c) Adherence

A previously described method (2) with some modifications was used. A clean and degreased glass microscope slide was weighed and then a sector of the slide (total surface 10 cm^2) was placed in the vertical position and slowly immersed into the antacid suspension maintained at 37 ± 0.5°C. After 10 seconds the slide was carefully removed. This operation was repeated five times and finally the slide with the suspension adhered layer was weighed again. Differences between this last and the former weight indicates the amount of antacid suspension adhered. It was recorded as $mg.cm^{-2}$.

d) Acid insulating power

The method proposed by Bossert et al. (2) was used. A combined glass calomel electrode was immersed into the antacid suspension as described above, and then immediately placed in an aqueous hydrochloric acid solution (0.1 N). The time (min) that the adhered antacid layer protected the electrode until it reach a value of pH=3 was determined.

e) "In-Vitro" antacid behaviour

The neutralization curves were obtained using Schaub's method (3) adapted with some minor modifications to our instrumentation.

A single dose of the antacid suspension was placed into a flask containing a volume (150 ml) of simulated gastric juice (fluid I, 0.15% pepsin in 0.05 N hydrochloric acid), and kept in a water bath at 37 ± 0,5°C with constant stirring. The pH was measured after 1, 3, 5, 10 and 20 minutes, and then every 10 minutes. After each reading, 20.0 ml of the reaction mixture were removed and replaced by 20.0 ml of fluid II (0.15% pepsin in 0.1 N hydrochloric acid). The experiment was finished when the pH value fell below 3.

The reaction time was evaluated as the period required by the antacid formulation to initially raise the bulk pH value to 3. The duration of antacid effect is the time that the pH value remains above 3.

A second series of "in-vitro" antacid trials were performed using the same conditions described for the Schaub's test, but with adition of 16.25 g of a standard light diet (Biomanan) to the simulated gastric juice before the antacid introduction and the start of the experiment.

In all of these studies a single dose of each antacid suspension, as recommended by the manufacturer in the package insert or label, was used. In those cases where two dose levels are mentioned, both levels were tested.

RESULTS AND DISCUSSION

The results obtained from the physical tests are shown in Table 1. Significant amounts of sedimentation were detected at the end of 30 days observations in almost all the preparations, with the exception of product A, which had high physical stability. The product H appeared to be particularly unstable in these tests.

A distinction should be made between the intrinsic viscosity of a suspension and its sensitivity to temperature variations. In this sense ideal behaviour was observed with product A, which at storage temperature was sufficiently viscous to ensure stability together with a correct dose delivery, whereas at 37°C (intragastric temperature) the viscosity decreased allowing adequate passage through the oesophagus and to coat the digestive mucosa.

The results in Table 1 show that the tendency of the suspensions to sediment is not directly related to their intrinsic viscosity values. This is particularly clear in the case of product B which, despite being the most viscous of the antacid suspensions studied, is also the second most prone to sedimentation. Other parameters, such as the solid content, its particle size, energy accumulated in the internal network of the suspension, etc., may account for the pseudoplastic behaviour of a formulation.

Product A clearly provides the greatest acid insulating power despite the fact that its adherence is lower than other

TABLE 1. Physical study of antacids in suspension

Product	PSF	Viscosity		Decrease (%)	Adherence ($mg.cm^{-2}$)	Acid-insulating power (min.)
		25ºC (mPa.s)	37ºC (mPa.s)			
A	1.00	243	167	31.2	8.1	71.0
B	0.72	463	329	28.9	17.3	63.0
C	0.97	360	360	0.0	24.9	11.1
D	0.91	130	120	7.7	8.3	< 1
E	0.86	150	147	2.0	12.0	< 1
F	0.86	110	110	0.0	8.8	< 1
G	0.96	290	310	-	20.9	15.3
H	0.56	53	50	5.6	11.3	2.0

suspensions. Probably this enhanced insulating power can be interpreted as an intrinsic property of the active ingredient (Almagate) and the general characteristics of this formulation as a monodose suspension. It forms a film on the electrode surface (even at this low adherence weight) that is difficult to penetrate by the acid present in the media. The product B is the second most potent in this test, but probably the result is due to the greater adherence related to its high viscosity at any temperature.

Since small changes in the gastrointestinal pH profile can modifie dosage form performance, simulated fed conditions must be investigated when antacid formulations are under evaluation. Several combinations of solid/liquid meals have been propossed to this purpose (4-7), but for a full objetive trial a dietetic product should be choosed. In this sense the "in-vitro" behaviour of the suspensions was also studied in antacid tests designed to simulate pre- and postprandial conditions "in vivo".

The presence of the diet initially increased the bulk pH, and this was returned to the initial value due to the presence of excess acid. This modification mimics that which occurs on postprandial administration of an antacid when both food and free acid may coexist as consequence of an incomplete gastric emptying.

The most relevant results in the normal Schaub test, and the modified version, are summarized in Table 2 (complete profiles are recorded in Figures 1 to 4). The products B and F (all doses), and D and E (high doses) gave excessively high maximum pH values (above 6) in Schaub's test. Within pH 5 to 6 the pepsin activity is reduced by 90% (8), but this inactivation is reversible by modifying bulk acidity to lower pH values. At pH above 6 the stability of pepsin rapidly decrease, and she is irreversibly inactivated.

TABLE 2. Schaub's normal and modified test for antacids in suspension

Product	Assayed dose (ml)	Food absent			Food present		
		RT(1) (min.)	Max-pH	Time pH >3 (min.)	RT(1) (min.)	Max. pH	Time pH >3 (min.)
A	15	< 1	6.00	99.5	< 1	5.19	71.5
B	10	< 1	6.84	55.0	< 1	4.66	50.0
B	20	< 1	7.29	96.0	< 1	5.68	86.0
C	10	< 1	3.92	66.5	2.0	3.48	59.0
D	10	< 1	5.11	59.0	1.5	4.67	57.0
D	20	< 1	6.58	99.0	< 1	5.62	68.5
E	5	5.0	5.24	57.0	10.5	3.07	12.5
E	10	2.5	6.14	113.0	11.0	4.46	70.0
F	10	< 1	6.40	78.0	3.5	4.02	35.0
F	20	< 1	6.20	120.5	4.5	5.91	80.0
G	10	< 1	4.03	68.0	2.0	3.31	47.5
H	5	< 1	3.86	60.0	-	2.72	0.0
H	10	< 1	3.86	88.0	< 1	3.90	52.5

(1) Reaction time to raise pH = 3

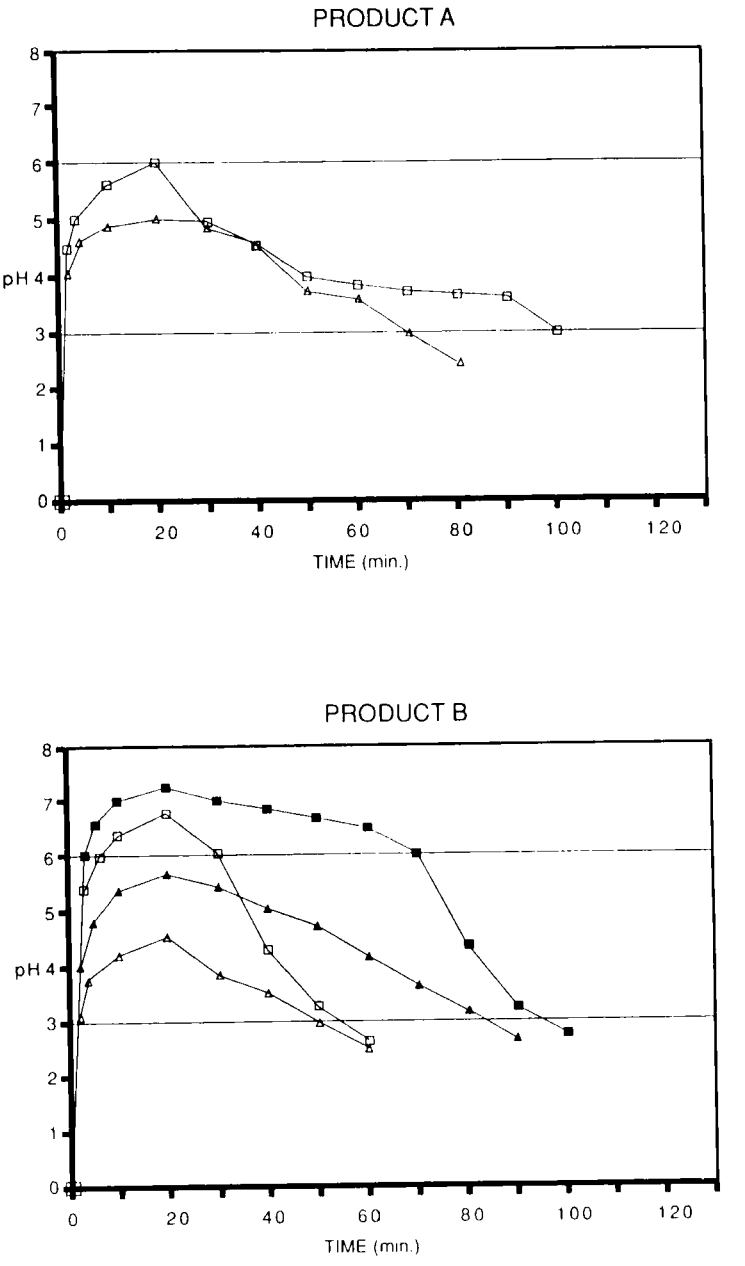

Fig. 1: Normal and modified Schaub's test.

□ Low dose, food absent ■ High dose, food absent

△ Low dose, food present ▲ High dose, food present

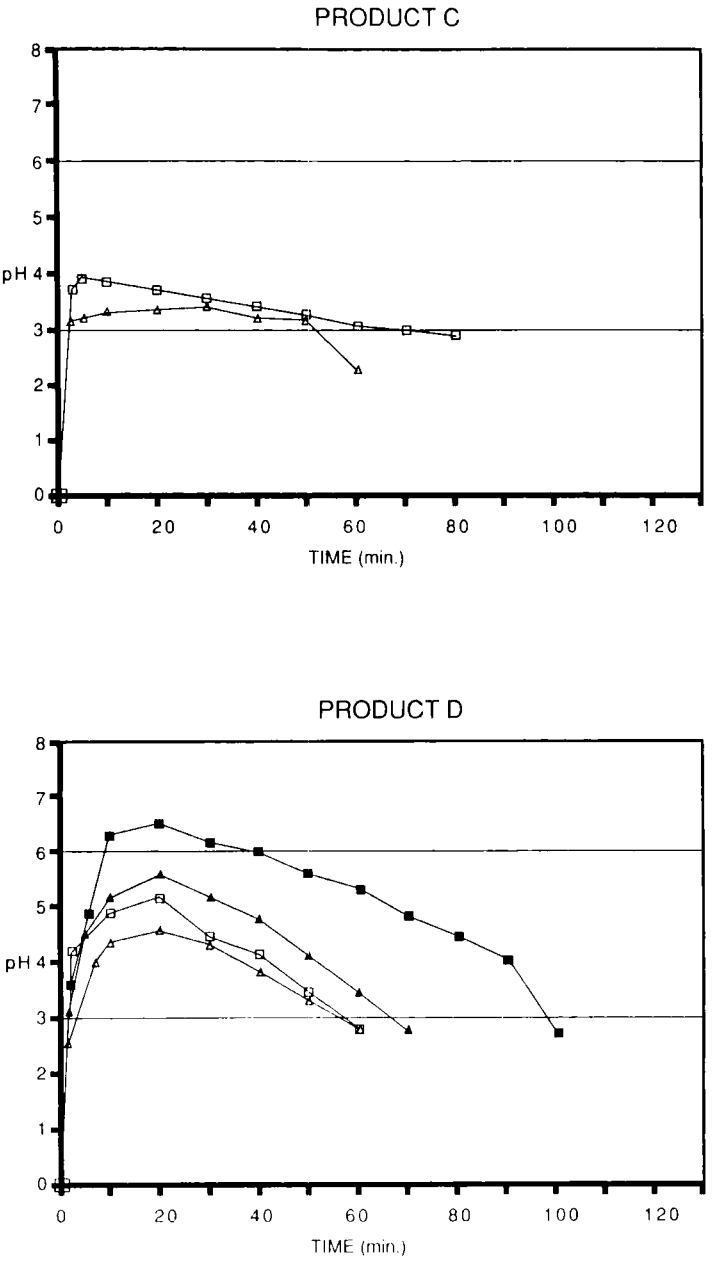

Fig. 2: Normal and modified Schaub's test.

Same key as Fig. 1

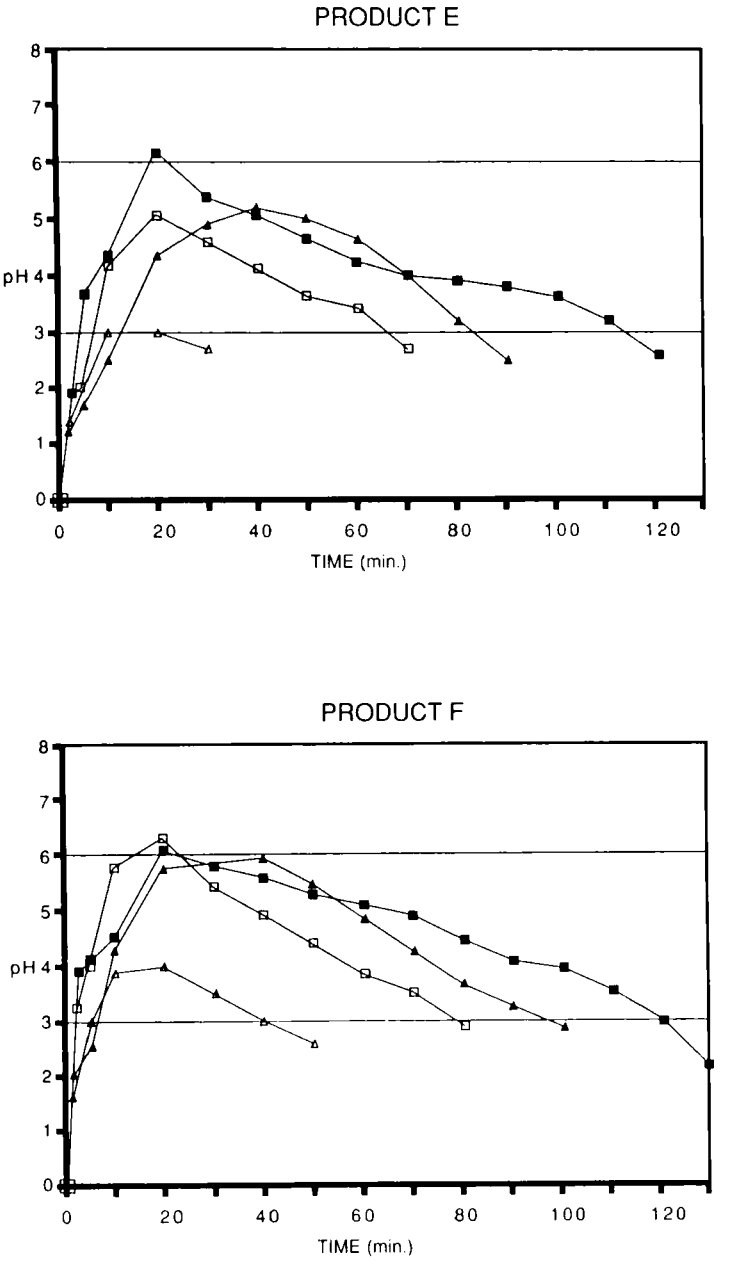

Fig. 3: Normal and modified Schaub's test.

Same key as Fig. 1.

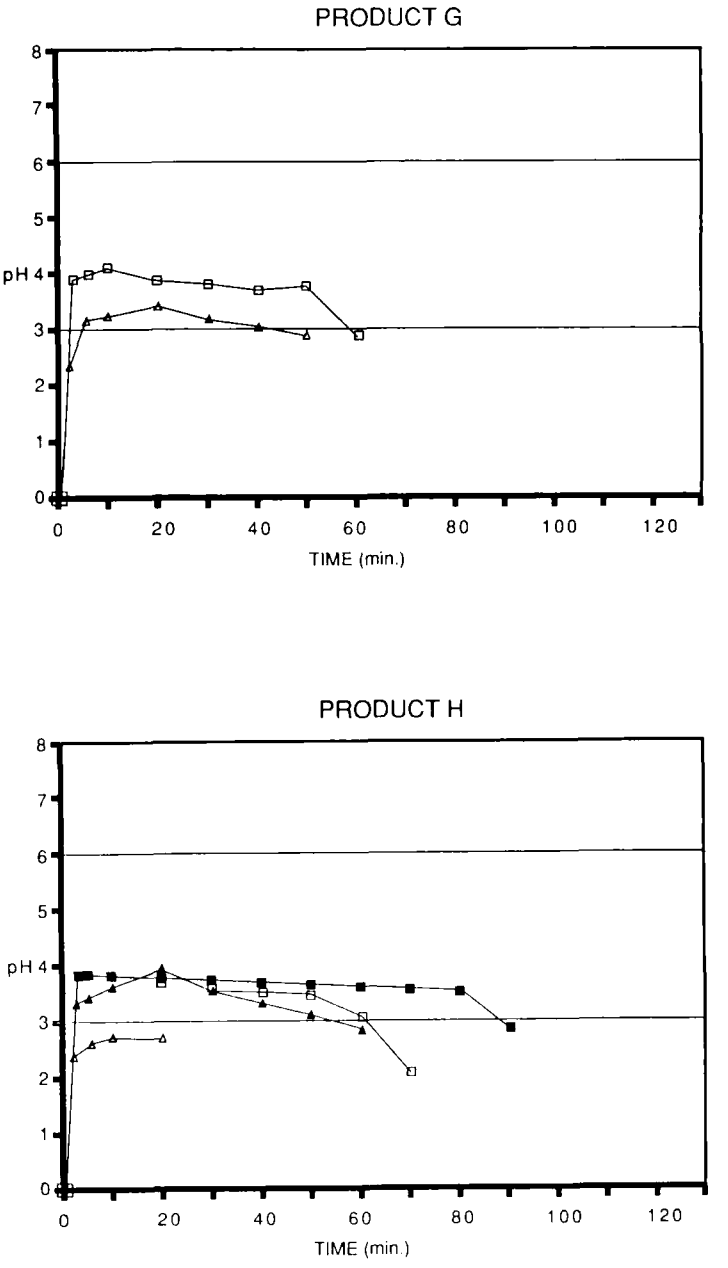

Fig. 4: Normal and modified Schaub's test.

Same key as Fig. 1.

Product E (low dose) in postprandial conditions needs more than 10 minutes to raise pH=3, and after this the efficacy period was the shortest observed. In the preceding conditions, product H (low dose) did not behave as an antacid formulation since the pH=3 value was not reached. Even in the largest recommended dose its neutralizing action is reduced to approximately 50 minutes. The product C and G have an identical concentration of the same active ingredient, thus the significant differences in the time above pH=3 must be related to their respective pharmaceutical formulations.

The observed variations between the two versions of the antacid test gave the expected results since the buffering effect of food is well known (9), and in some cases could be the cause for overevaluating the potency of an antacid material (10).

Within the antacid suspensions studied, product A may be advantageous due to its satisfactory physical stability, capacity to adhere to surfaces, and rapid reaction with acid. Furthermore, although the presence of food modified the neutralization profile, it still clearly maintained potential clinical usefulness under simulated "postprandial" conditions.

The preceding results demonstrate how appropriately chosen "in vitro" test permit an estimation of the probable "in vivo" behaviour of the antacid suspensions studied, showing that the proposed parameters given in Tables 1 and 2 can facilitate the choice of the most therapeutically suitable antacid suspension.

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