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RESEARCH PAPER

Evaluation of the In Vitro Activity of Several Antacid Preparations

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ABSTRACT

The physicochemical properties of antacid preparations determine their activity in vivo. It is possible to determine in a laboratory several physicochemical parameters related to the activity of such preparations. In this work, in vitro activity is determined for the most common antacid suspensions in Spain.

INTRODUCTION

The aim of antacid preparations is to neutralize the acidity of the gastric medium and, hence, reduce at the same time the irritating chemical action on the damaged gastric mucosa and the pain. The action of antacids is mainly symptomatic. From the chemical point of view, antacid agents are combinations of rather strong bases (Na^+, Ca^{2+}, Mg^{2+}, Al^{3+}) with weaker acids (carbonates, silicates and sulfates) or hydroxides, which in HCl of gastric medium are displaced by Cl^--forming chlorides.

The physicochemical properties of an antacid preparation determine its in vivo activity. Therefore, it is possible to analyze in the laboratory some physicochemical parameters which could be related to the activity of such preparations, in order to obtain a quick and prolonged relief of symptoms in patients with hyperacidity.

Among antacid preparations, those administered by suspension are the most popular. In this work, in vitro activity is determined for the most used antacid suspensions in Spain.

The studies conducted are as follows:

- Acid-neutralizing capacity
- Neutralization curves according to the pH–Stat titration method
- pH profile test
- Antipepsin activity

MATERIALS AND METHODS

The study was carried out with marketed samples. Data of such samples are summarized in Table 1.

Table 1

Antacid Preparations Used in the Study

Preparation	Recommended Dose[a]	Active Drugs per Dose
Preparation A Bemolan 2000 Boehringer Mannheim, S.A.	12.5 ml (gel, 1 single-dose sachet)	Magaldrate 2000 mg
Preparation B Almax Forte Lab. Almirall, S.A.	15 ml (suspension, 1 single-dose sachet)	Almagate 1500 mg
Preparation C Bemolan Gel Boehringer Mannheim, S.A.	10 ml (gel, 1 single-dose sachet)	Magaldrate 800 mg
Preparation D Almax Lab. Almirall, S.A.	7.5 ml (suspension, bottle)	Almagate 1000 mg
Preparation E Maalox concentrado Rhône-Poulenc Rorer, S.A.	5 ml (suspension, bottle)	Aluminum hydroxide 600 mg Magnesium hydroxide 300 mg
Preparation F Maalox concentrado Rhône-Poulenc Rorer, S.A.	10 ml (suspension, bottle)	Aluminum hydroxide 1200 mg Magnesium hydroxide 600 mg
Preparation G Alubifar Rottapharm, S.A.	4.6 ml (granule, 1 single-dose sachet)	Almasilate 1300 mg
Preparation H Pyreses Berenguer Infalc	5 g (granule, 1 single-dose sachet)	Aloglutamol 1000 mg

[a]According to manufacturer.

Acid-Neutralizing Capacity

This has been determined by the USP 23 method (1).

Neutralizing Curves According to the pH–Stat Titration Method

The neutralization curves were obtained by the pH–Stat titration method proposed by Kerkhof et al. (2).

Materials

- Methrom 716 DMS TITRINO automatic titrator, provided with an electrode of combined pH
- 150-ml flask
- 1 N HCl
- Demineralized water

Method

Fix the automatic titrator conditions as follows:

- Titrator: 1 N HCl
- Temperature: 25°C
- Final pH: 3
- Maximum reagent addition speed: 10 ml/min
- Time of test: 60 min

Adjust to pH 3.0 an appropriate volume of demineralized water with 1 N HCl. In a 150-ml flask, pour one dose of antacid to be analyzed and enough aqueous solution pH 3 in order to obtain 22 ml.

Introduce the titrator electrode in the solution to evaluate. Switch the stirrer on and start the evaluation with 1 N HCl. Record the consumed milliequivalents of HCl versus time and plot the corresponding graph.

pH Profile Test

This test was carried out using the Schaub method (3).

Materials

- Thermostatic baths
- Heidolph RZR 1 stirrer
- Metrohm 704 pH meter
- 250-ml and 400-ml flasks
- Pipettes
- Test tubes
- Demineralized water
- Artificial gastric medium A
  Pepsin: 1.5 g
  0.05 N HCl sufficient to produce 1000 ml
- Artificial gastric medium B
  Pepsin 1.5 g
  0.1 N HCl sufficient to produce 1000 ml
- Light artificial diet: Biomanan Komplett®, Merck

Method

Pour 150 ml of artificial gastric medium A into a 400-ml flask. Introduce the flask in the thermostatic bath at 37° ± 0.5°C and stir the contents continuously. Introduce the pH meter electrode and record the pH. Add the antacid dose while stirring. When the antacid preparation is a suspension, add the dose directly. If it is granulated, dilute the dose previously by adding 100 ml of demineralized water. Determine the pH every minute during the first 10 min. After this time, remove 20 ml of the reaction suspension and pour it into a test tube placed in a bath at 13° ± 0.5°C. Add 20 ml of artificial gastric medium B to the starting reaction suspension in order to compensate the volume removed. Repeat the pH determination and the removal every 10 min until pH falls under 3. Plot the corresponding graphic of the pH values against time.

Repeat the whole test with the same conditions but adding 16.25 g of a light artificial diet to the artificial gastric medium A before the antacid dose.

Antipepsin Activity

The method proposed by Schaub (3) has been used on the samples which have been removed every 10 min in the previous test and stored in a thermostatic bath at 13° ± 0.5°C.

Materials

In addition to the materials used in the previous test, other materials are required:

- Schleicher & Schüll paper filters
- pH 4.9 acetate buffer:
  NaOH: 4.2 g
  Acetic acid: 9.2 ml
  Demineralized water sufficient to produce 100 ml
- Whole milk

Method

Into a test tube placed in a thermostatic bath at 13°C pour 2 ml of pH 4.9 acetate buffer solution, 1.5 ml of demineralized water, and 0.5 ml of sample (removed from the pH profile test) previously filtered. Add to this mixture 1 ml of a mixture of milk and pH 4.9 acetate buffer (1:1). Control the time required to reach coagulation of all the samples. Carry out a reference test considering that the artificial gastric medium A has an activity of 100%, and also a blank of 0.5 N HCl. Plot a graph with the percentage of activity versus time.

RESULTS AND DISCUSSION

According to Schaub (3), antacids can be classified in accordance with their in vitro activity, taking into account the following criteria:

1. An antacid should keep stomach pH between 3 and 5.
2. An antacid with quick action reaches pH 3 in less than 1 min.
3. A long-activity antacid keeps stomach pH between 3 and 5 for at least 1 hr.
4. An antacid should have a good antipepsin activity (i.e., under the antacid effect, proteolitic activity of stomach ferments should fall under 10% of the normal value).

The results obtained with the different antacid preparations are shown in Tables 2–4.

Preparation A appears to be the antacid with the highest acid-neutralizing capacity (60 mEq HCl/dose), followed by F (50 mEq HCl/dose) and B (40 mEq HCl/dose).

Table 2

Total Consumption Capacity of Antacid According to USP 23

Preparation	mEq HCl/Dose
A	60
B	40
C	23
D	28
E	25
F	50
G	25
H	9

Table 3

pH–Stat 3 Test: Kinetic Parameters and Total Consumption of HCl

Preparation	$t_{90\%}$ (min)	$t_{50\%}$ (min)	mEq HCl Consumed at 60 min
A	30	5.5	61.4
B	30	13	36.9
C	21	4	22.2
D	27	10.5	23.4
E	20	7.5	27.4
F	26	9	53.1
G	16	3.5	24.8
H	18	0.5	4.8

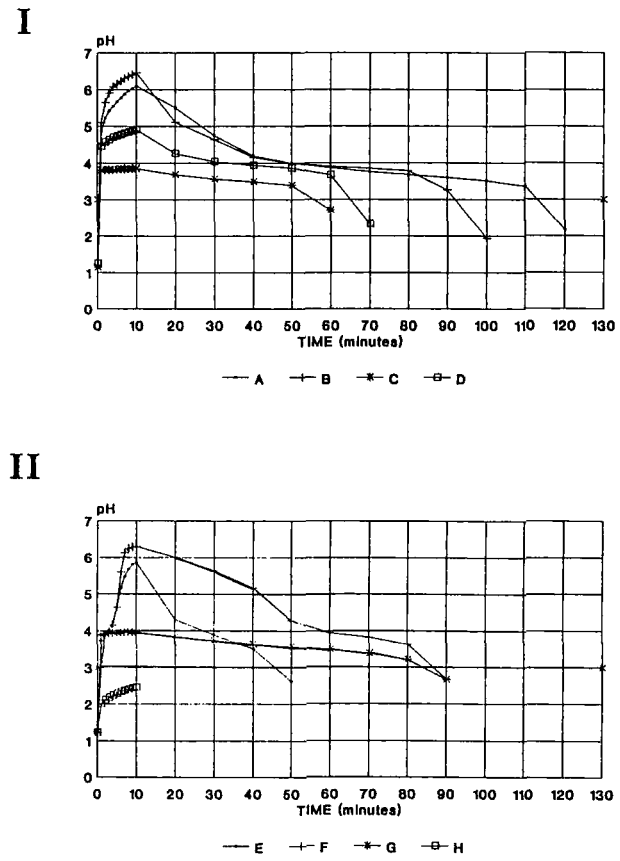


Figure 1. pH 3 curves for preparations A, B, C, and D (I) and preparations E, F, G, and H (II).

Table 3 shows the results obtained in the pH–Stat test. The milliequivalents of HCl consumed per dose at the end of the test are shown (60 min), and also the times in which 90% ($t_{90\%}$) and 50% ($t_{50\%}$) are consumed.

The values of hydrochloric acid consumed at the end of the test are similar to those obtained in the neutralizing activity test, except for preparation H. In this case, miliequivalents of HCl consumed after 60 min are about

Table 4

Antacid Behavior in an Artificial Gastric Medium

Preparation	Time to Reach pH 3 (min)	Time pH > 3 (min)	Maximum pH Reached	Time pH > 6 (min)
A	<1	>110	6.11	3
B	<1	>90	6.46	11
C	<1	>50	3.85	0
D	<1	>60	5.06	0
E	<1	>40	5.88	0
F	<1	>80	6.30	15
G	<1	>80	3.94	0
H	Not reached	0	2.96	0

Table 5

Antacid Behavior in an Artificial Gastric Medium with Food

Preparation	Time to Reach pH 3 (min)	Time pH > 3 (min)	Maximum pH Reached
A	<1	>120	5.93
B	<1	>110	5.97
C	<1	>80	5.21
D	<1	>80	5.85
E	<1	>70	5.60
F	<1	>90	5.79
G	<1	>90	5.54
H	<1	>40	4.78

53% of the total consumption revealed in the USP 23 test.

The neutralizing curves according to pH–Stat are shown in Fig. 1. The results of this test confirm those obtained in the previous one. On the other hand, preparation A shows the quickest action, followed by F and B. The significantly slow action of preparation H must be emphasized.

Table 4 shows the results obtained in the pH profile test for all preparations. Also shown in the table are time required to reach a pH over 3, time maintained over pH 3, maximum pH reached, and time maintained over 6. Figure 2 shows the pH profile curves.

The results show that preparation H does not reach pH 3 after the 10 min that the test lasts; the other preparations reach it before 1 min. Preparation A keeps the pH above 3 longer than any other. Preparations A, B, and F reach pH values over 6, although A keeps the pH over this value for a shorter time than the others.

Table 5 shows the results obtained in the pH profile test with food. The pH profile curves are shown in Fig. 3. For all cases the starting pH is over 3 and stays at that level longer than in the test with no food. Prepa-

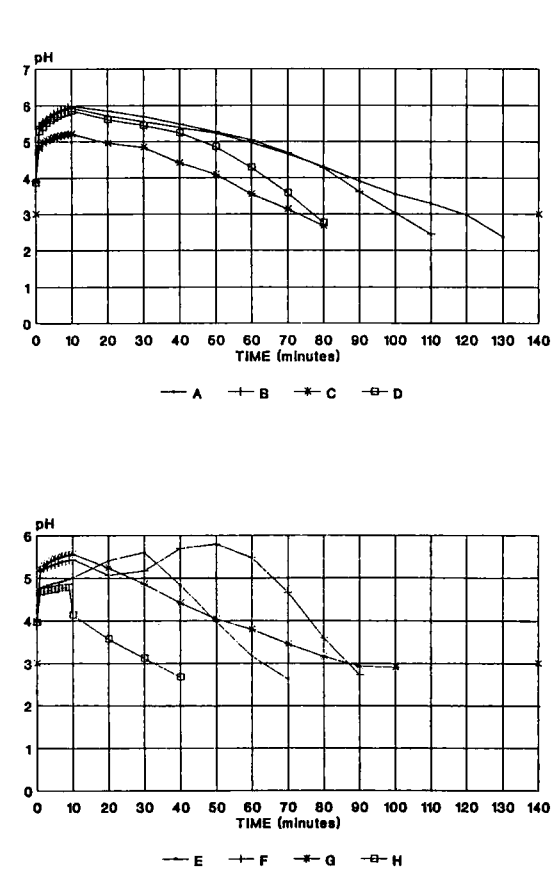


Figure 2. pH profile test for preparations A, B, C, and D (I) and preparations E, F, G, and H (II).

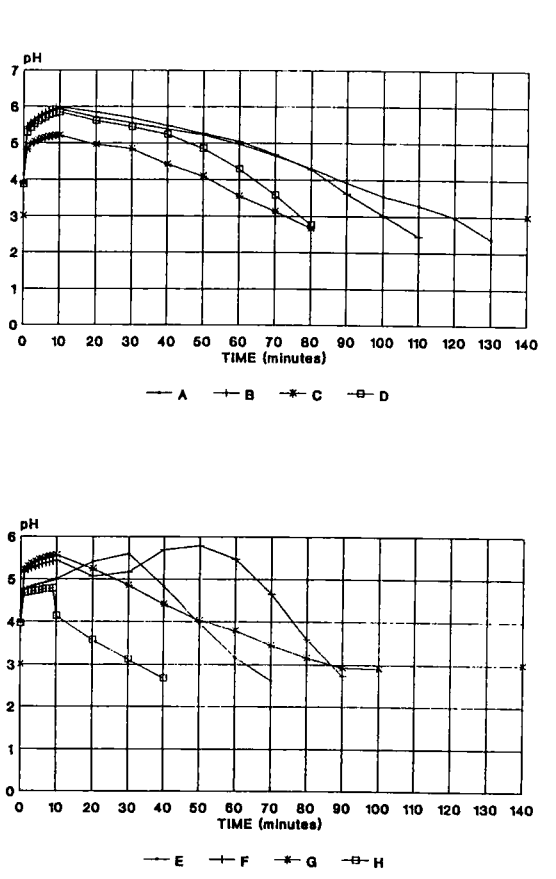
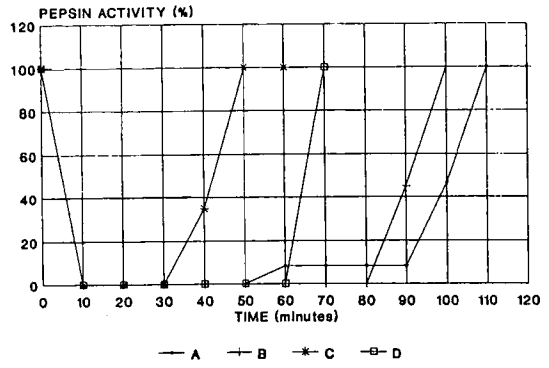


Figure 3. pH curves in food for preparations A, B, C, and D (I) and preparations E, F, G, and H (II).

I



II

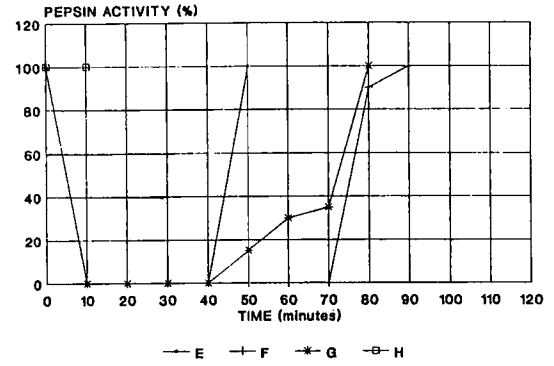


Figure 4. Antipepsin activity for preparations A, B, C, and D (I) and preparations E, F, G, and H (II).

ration A again is the one that maintains the pH over 3 for the longest time.

The action on pepsin of the antacids studied is shown in Fig. 4. Preparation A appears to keep the pepsin activity under 10% the longest, and preparation H does not inhibit it at all.

If we observe the results as a whole, we can conclude that preparation A has a more advantageous antacid activity, followed by preparations F and B. Preparations C, D, E, and G have similar actions. Preparations C and G stand out for not raising the gastric medium pH over 4. Preparation H would have a very low antacid activity in accordance with the criteria applied.

REFERENCES

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3. K. Schaub, Pharm. Acta Helv., 38, 15 (1963).