DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(1), 169-185 (1985)

INFLUENCE OF HYDROXYPROPYL METHYLCELLULOSE AND OF MANUFACTURING TECHNIQUE ON IN VITRO PERFORMANCE OF SELECTED ANTACIDS

Parab, P.V., Nayak, M.P. and Ritschel, W.A.*

University of Cincinnati Medical Center,

College of Pharmacy, Mail Location #4,

Cincinnati, Ohio 45267, USA

ABSTRACT

Factors affecting the performance of antacids F-MA 11, dihydroxy aluminum aminoacetate, magaldrate and magnesium hydroxide were studied in vitro using Schaub's acid neutralization test, a modified Reheis reaction velocity test and the USP test. From the results obtained it was evident that type and combination of antacid, the adjuvants and formulation techniques used in preparation of antacids affect their performance. The USP preliminary antacid test and acid neutralization test are not optimal in vitro tests to evaluate in vitro onset and duration of action of antacids.

*To whom reprint requests should be addressed

0363-9045/85/1101-0169$3.50/0

INTRODUCTION

Recently Drake and Hollander[2] compared the acid neutralizing capacity of commercially available liquid and tablet antacid formulations with cost effectiveness. They suggested that the prescribing physician should take into account the neutralizing capacity per unit cost, sodium content, palatability and side effects of the antacid. They found higher neutralizing capacity of liquid formulations over tablet formulations having the same composition. The exception was Riopan Plus in which the tablet formulation had higher neutralizing capacity than the liquid formulation as shown in Table 1 which is an excerpt of the data of Drake and Hallander[2].

TABLE 1

Acid Neutralizing Capacity of Commercial Tablets and Liquid Dosage Forms. (Data compiled from Drake and Hollander[2])

Antacid	Dosage Form	meq/tablet or 5 ml liquid	Composition per tablet or 5 ml liquid
Mylanta II	tablet	11.0	Aluminum hydroxide 400 mg Magnesium hydroxide 400 mg Simethicone 30 mg
Gelusil II	tablet	8.2	Aluminum hydroxide 400 mg Magnesium hydroxide 400 mg Simethicone 30 mg
Mylanta II	liquid	18.0	Aluminum hydroxide 400 mg Magnesium hydroxide 400 mg Simethicone 30 mg
Gelusil II	liquid	15.0	Aluminum hydroxide 400 mg Magnesium hydroxide 400 mg Simethicone 30 mg
Riopan Plus	tablet	10.0	Magaldrate 480 mg Simethicone 20 mg
Riopan plus	liquid	9.0	Magaldrate 480 mg Simethicone 20 mg
Amphogel	tablet	2.0	Aluminum hydroxide 300 mg
Amphogel	liquid	7.0	Aluminum hydroxide 300 mg

If the quantity and combination of active ingredients in the formulations are the same in dosage forms manufactured by different companies, one may expect them to have identical acid neutralizing capacity. But this was not observed in the case of Mylanta II and Gelusil II tablet and liquid dosage forms. The Mylanta II tablet had higher neutralizing capacity than Gelusil II tablet. The Mylanta II liquid had higher neutralizing capacity than Gelusil II liquid. This difference among the tablets and liquids may be due to the difference in pharmaceutical processing and the adjuvants used by the manufacturer.

Several surveys of antacid products have been reported in the past decade[1-10], dealing with the evaluation of *in vivo* and *in vitro* parameters. Studies addressing the effect of adjuvants and manufacturing method on performance have been published in the sixties[11-12].

The purpose of this study was to evaluate *in vitro* the performance of four antacid compounds alone or in combination, the addition of an inert adjuvant (hydroxypropyl methylcellulose) and technological incorporation of the adjuvant into the formulation. Hydroxypropyl methylcellulose, HPMC, was the adjuvant of choice because it has been used widely as a suspending agent, binding agent and viscosity increasing agent in many of the pharmaceutical preparations.

MATERIAL AND METHODS

Material

Antacid compounds used were F-MA 11[a], dihydroxy aluminum aminoacetate (DAA)[b], magaldrate[c] and magnesium hydroxide[d]. The adjuvants [1a-1d] and reagents[2a-2c] used for the preparation of antacids were of pharmaceutical and reagent grade, respectively.

Preparation of Antacid Tablets

The composition of experimental tablet is shown in Table 2. There were three groups: APD 2 (DAA), APD 3 (magaldrate) and APD 4 (magaldrate + F-MA 11). In the APD 2 and APD 3 groups the distribution of HPMC was varied. For example APD 3-4 had 500 mg of magaldrate as active ingredient. HPMC was used in both the internal phase and the external phase and also used as granulating agent. APD 3-6 and APD 3-7 differ from APD 3-4, as the former one had HPMC in the external phase only and the latter one did not contain any HPMC.

---

[a]F-MA11, Reid-Provident Laboratories, Inc., N.W./Atlanta, GA 30308
[b]Dihydroxy aluminum aminoacetate, Lot No. 09164, A.M. Robins Company, Richmond, Virginia 23220
[c]Magaldrate, Lot No. B239BCE, Ayerst Laboratories, Inc., New York, NY 10017
[d]Magnesium hydroxide, Matheson Coleman and Bell, Norwood, OH 45212
[1a]Hydroxypropyl methylcellulose 4000, Fisher Scientific Company, Fair Lawn, NJ 07410
[1b]Talc, Matheson Coleman and Bell, Norwood, OH 45212
[1c]Potato starch, Matheson Coleman and Bell, Norwood, OH 45212
[1d]Mannitol, Matheson Coleman and Bell, Norwood, OH 45212
[2a]Pepsin, Fisher Scientific Company, Fair Lawn, New Jersey 07410
[2b]Hydrochloric acid, Matheson Coleman and Bell, Norwood, OH 45212
[2c]Sodium chloride, Matheson Coleman and Bell, Norwood, OH 45212

TABLE 2

Composition of Experimental Antacid Tablets

Code	Magaldrate [mg]	Dihydroxy Aluminum Aminoacetate [mg]	F-MA 11 [mg]	Magnesium hydroxide [mg]	Hydroxypropyl methylcellulose		
					Internal Phase [mg]	Granulating Agent [mg]	External Phase [mg]
APD 2-4	-	500	-	-	25	12.5	12.5
APD 2-6	-	500	-	-	-	-	50
APD 2-7	-	500	-	-	-	-	-
APD 2-8	-	500	-	150	-	-	-
APD 2-5	-	500	-	150	-	-	50
APD 3-4	500	-	-	-	25	12.5	12.5
APD 3-6	500	-	-	-	-	-	50
APD 3-7	500	-	-	-	-	-	-
APD 3-8	500	-	-	150	-	-	-
APD 3-5	500	-	-	150	-	-	50
APD 4	250	-	250	150	-	-	-

The experimental tablets APD 3-5 and APD 3-8 had 500 mg of active ingredient (magaldrate) and 150 mg of magnesium hydroxide. They differed from each other as APD 3-5 had HPMC in the external phase, whereas APD 3-8 was without HPMC. Similar type of distribution of HPMC was done in the antacid tablet of the APD 2 group having DAA as the active ingredient.

The experimental tablet APD 4 was a combination of magaldrate, F-MA 11 and magnesium hydroxide. This group (APD 4) did not contain HPMC.

All experimental tablets contained 200 mg of mannitol, 5.1 % potato starch (disintegrating agent) and 2 % talc as lubricant.

The generalized procedure for preparation of the experimental tablets was as follows:

Mannitol, active ingredient (DAA or magaldrate or magaldrate +F-MA 11) were mixed. A dough mass was made using water or disperion of HPMC in water. The dough mass was passed through an oscillating granulator[3] having sieve size of 1 mm. The granules were dried at 60°C for 30 minutes. The dry mass was then passed through a sieve of 1 mm lumen size. The fines were separated using sieve No. 200. Ten percent fines, HPMC, magnesium hydroxide, potato starch and talc were added by tumbling method to the granules. The granules were compressed on a single punch tableting machine[4] to a biconvex tablet having 6 kg hardness.

[3]Erweka-Apparatebau, Type FGS, Model No. 24995, Heusenstamn, West Germany

[4]Tableting machine, Model No. 8909-70, Emil Korsch Machinenfabrik, Berlin, West Germany

In Vitro Testing

Modified Reheis Reaction Velocity Test

In the Reheis reaction velocity test[11] the weight of sample containing the equivalent of 0.5 gram of Al_2O_3 was added to 100 ml of 0.1 N HCl at 37.5°C and was agitated manually and the time noted to reach pH 3.5.

According to Fuchs[13] the human stomach contains the equivalent of approximately 50 ml of 0.1 N HCl shortly after meals. Hence, in the modified Reheis reaction velocity test, 0.5 gram of active substance, either single ingredient or combination, was added to 50 ml of 0.1 N HCl maintained at 37 ∓ 1°C. The mixture was agitated at 100 rpm using a magnetic stirrer and the time was recorded to reach pH 3.5.

Acid Neutralization Test

Recently Brouwers and Tytgat[17] obtained a good correlation between in vitro and in vivo evaluation of antacids using a modified Schaub's test and in vivo testing by stomach pH electrode.

In the present study the acid neutralization test of Schaub was used[14-16]. The Schaub test simulates in vivo conditions of gastric secretion and gastric emptying. An antacid tablet is introduced into a beaker containing 150 ml of artificial gastric fluid "A" (pepsin 1.5 grams, 0.05 N HCl q.s. 1 Liter), kept at 37°C in a thermostatically controlled water bath. Using a magnetic

stirrer the content is agitated at 100 rpm. The pH is measured[5] after 1, 3, 5 and 10 minutes, and thereafter every 10 minutes. After every 10 minute pH reading, 20 ml of the gastric antacid mixture is withdrawn by means of a pipette and replaced by 20 ml of gastric fluid "B" (pepsin 1.5 grams, 0.1 N HCl q.s. 1 Liter). The procedure is continued until the pH drops below pH 3. The onset of action is the time needed to reach pH 3 and the duration of action is the time the pH remains above 3.

Preliminary Antacid Test

The preliminary antacid test was performed according to the USP[18].

Acid Neutralizing Capacity Test

The acid neutralizing capacity test was performed according to USP[18].

Disintegration Time

Disintegration was tested according to the USP[18] using the Erweka disintegration test apparatus[6].

RESULTS AND DISCUSSION

The rates of neutralization determined by the modified Reheis reaction velocity test are given in Table 3. Among the antacid

[5]Fisher Accumet® pH meter, Model 142, Fisher Scientific Company, Pittsburgh, PA 15219

[6]Disintegration test apparatus, Erweka, type 2T4, Heusenstamn, West Germany.

TABLE 3

Rate of Acid Neutralization for Various Antacids According to the Modified Reheis Reaction Velocity Test

Antacid	Time [seconds]
F-MA 11	60
F-MA 11 + Magnesium hydroxide (3:1.3)	23
Dihydroxy aluminum aminoacetate	163
Dihydroxy aluminum aminoacetate + Magnesium hydroxide (3:1.3)	34
Magaldrate	45
Magaldrate + Magnesium hydroxide (3:1.3)	20
Magnesium hydroxide	7

compounds, magnesium hydroxide had the fastest neutralization rate (7 seconds) followed by magaldrate (45 seconds), F-MA 11 (60 seconds) and DAA (163 seconds). When F-MA 11, DAA and magaldrate were combined with magnesium hydroxide in the ratio of (3:1.3), it was noted that in all the combinations the neutralization rate was accelerated compared to the individual neutralization rate. Especially the neutralization rate of DAA (163 seconds) was reduced to about one fifth when DAA and magnesium hydroxide combination was used (34 seconds). Hence for a compound of high neutralization capacity the onset can be greatly improved, if necessary, by combination with another antacid as demonstrated in Table 3.

It has been reported that the reaction velocity of aluminum hydroxide gel form was prolonged from 120 to 660 seconds after four

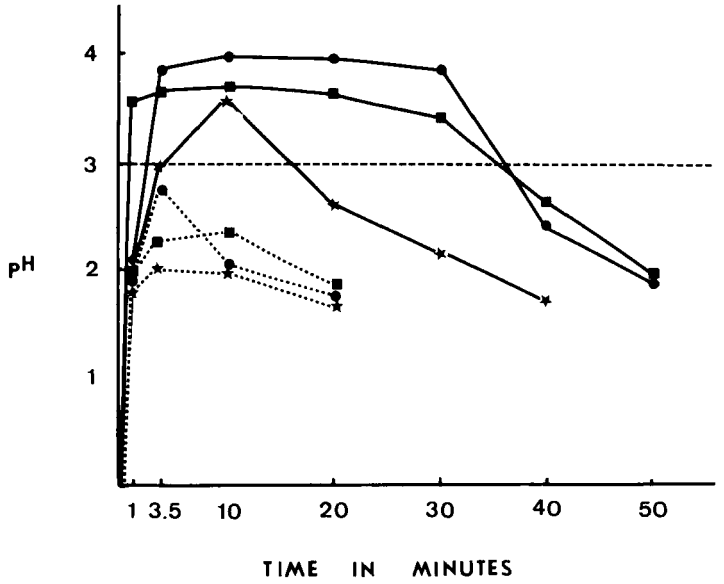

FIGURE 1

Acid neutralization of antacid determined by Schaub's method

F-MA 11	●	500mg	●	250mg
Magaldrate	■	500mg	■	250mg
DAA	★	500mg	★	250mg

years of storage[11]. Combination of antacids might be advantageous to prevent the change in reaction velocity which has to be further investigated.

The effect of type and amount of the antacids on onset and duration determined by Schaub's acid neutralization test is shown in Fig. 1. It was observed that magaldrate had the fastest onset followed by F-MA 11 and DAA. Magaldrate and F-MA 11 showed similar duration of action. F-MA 11 maintained a maximum pH in the range of 3.8 to 4 and magaldrate maintained a maximum pH in the range of 3.5 to 3.7. A different performance was observed in

TABLE 4

Acid Neutralization of Antacids by Schaub's Method

Antacid	Time to reach pH 3 [min.]	Time above pH 3 [min.]	Maximum pH
F-MA 11 (500 mg)	2.5	33.5	3.97
F-MA 11 (500 mg) + Magnesium hydroxide (150 mg)	< 1	49.0	4.14
Magaldrate (500 mg)	< 1	34.0	3.70
Magaldrate (500 mg) + Magnesium hydroxide (150 mg)	< 1	44.0	4.17
Dihydroxy aluminum aminoacetate (500 mg)	4.0	14.0	3.59
Dihydroxy aluminum aminoacetate (500 mg) + Magnesium hydroxide (150 mg)	2.0	32.0	4.0
Magaldrate (250 mg) + F-MA 11 (250 mg) + Magnesium hydroxide (150 mg)	< 1	56.0	4.11

DAA as it took 4 minutes to reach pH 3 and maintained this effect (pH > 3) only for 14 minutes. It was also observed that in all the three antacids, the 250 mg dose failed to raise the pH above 3.

The effect of combinations of antacid on the onset and duration determined by Schaub's method are given in Table 4. It was observed that in all the three antacids the inclusion of magnesium hydroxide reduced the time of onset and increased the duration of

the effect. A pronounced difference was observed for DAA. The inclusion of magnesium hydroxide resulted in onset of 2 minutes compared to 4 minutes and the duration of effect was increased from 14 minutes to 32 minutes.

The best results were observed in the combination of F-MA 11, magaldrate and magnesium hydroxide. The onset was immediate and the duration was 56 minutes. However, the chemical mechanism of decrease in onset and increase in duration of effect of these combinations needs further evaluation.

The results of acid neutralization test of the experimental tablets (Table 2) determined by Schaub's method are given in Table 5. The experimental tablet APD 2-7 which contained DAA, had an onset within 2.56 minutes and the duration of effect was 16.75 minutes. The inclusion of HPMC into the external phase (APD 2-6) increased the onset time to 6.93 minutes and the duration was reduced to 8 minutes. When the HPMC was distributed inside and outside the granules and as a granulating agent (APD 2-4) the tablets failed to raise the pH above 3. Incorporation of magnesium hydroxide into the external phase (APD 2-8) gave immediate onset, but when HPMC was incorporated along with magnesium hydroxide into the external phase (APD 2-5), the onset was delayed to 2.86 minutes. Similar observations were observed in the magaldrate group APD 3-4 to APD 3-8.

The experimental tablet APD 4 which is a combination of magaldrate, F-MA 11 and magnesium hydroxide, gave the best performance (Table 5) as the onset was within 2 minutes and gave a

TABLE 5

Acid Neutralization of Experimental Tablets by Schaub's Method (Mean ± S.D., n = 3)

Code	Composition	Time to attain pH 3 [min.]	Time above pH 3 [min]
APD 2-7	DAA	2.56 (0.90)	16.75 (1.10)
APD 2-6	DAA/HPMC	6.93 (1.00)	8.06 (3.76)
APD 2-4	DAA/HPMC	-	-
APD 2-8	DAA/$Mg(OH)_2$	0.66 (1.15)	29.57 (4.03)
APD 2-5	DAA/$Mg(OH)_2$ /HPMC	2.86 (1.20)	28.66 (2.3)
APD 3-7	Magaldrate	1.66 (0.57)	31.00 (3.00)
APD 3-6	Magaldrate/HPMC	2.33 (0.45)	22.66 (3.78)
APD 3-4	Magaldrate/HPMC	-	-
APD 3-8	Magaldrate/$Mg(OH)_2$	1.00 (0.43)	42.8 (0.28)
APD 3-5	Magaldrate/$Mg(OH)_2$ /HPMC	3.00 (1.5)	41.5 (2.5)
APD 4	Magaldrate/F-MA 11/ $Mg(OH)_2$	2.00 (0.00)	50.5 (2.67)

longer duration of effect (50 minutes) compared to other experimental tablets.

Hence, all these variations in onset and duration of actions illustrate the importance of the effect of adjuvants and the formulation technique on the performance of an antacid tablet.

HPMC has been used as a suspending and as a viscosity increasing agent in many formulations. The increased viscosity of antacid in the stomach may assist in delayed gastric emptying rate

TABLE 6

Acid Neutralizing Capacity, Preliminary Antacid Test and Disintegration Test of Experimental Tablets

Code	Acid neutralizing capacity, USP meq/dose	Preliminary antacid test, USP [pH]	Disintegration, USP [min]
APD 2-7	8.91	4.00	0.6 ± 0.13
APD 2-6	8.51	3.91	1.03 ± 0.05
APD 2-4	8.78	3.92	5.33 ± 1.44
APD 2-8	12.95	5.44	0.83 ± 0.14
APD 2-5	13.39	5.00	0.6 ± 0.13
APD 3-7	12.36	3.85	0.33 ± 0.14
APD 3-6	12.26	3.79	0.59 ± 0.16
APD 3-4	11.56	3.81	20.0 ± 1.2
APD 3-8	17.97	6.88	0.25 ± 0.0
APD 3-5	16.81	7.07	5.66 ± 0.28
APD 4	17.65	4.12	0.30 ± 0.1

and may prolong the antacid activity in the stomach. Hence, although the viscosity increasing agents are incorporated in many antacid preparations, they have to be evaluated for their performance by proper *in vitro* tests.

The results of the *in vitro* tests of the experimental tablets determined according to USP specifications[18] are given in Table 6. It was observed that the APD 2-4 group which failed to raise the pH to 3 in Schaub's neutralization test passed all USP tests[18].

Although the experimental tablets formulated by different techniques showed differences in their performances when tested by the neutralization test of Schaub, these differences were not predominant when the experimental tablets were tested according to USP[18]. For example APD 2-7 and APD 2-6 showed differences in their onset and duration when tested by Schaub's method (Table 5). However these differences are neither indicated by acid neutralization capacity test, preliminary antacid test nor disintegration test specified by the USP[18] (Table 6).

The preliminary antacid test USP[18] is a good screening test for antacid products and assures minimal neutralizing capacity. The acid neutralization capacity test USP[18], which gives a number of meq of acid neutralized by one dose of antacid in 15 minutes appears to be an indirect assay. These two official *in vitro* tests are not indicative regarding onset and duration of antacid preparation.

CONCLUSION

The following conclusions were drawn from the study:

1. The overall effect of an antacid depends on type of antacid.
2. For the compound of high neutralization capacity the onset if necessary can be greatly improved by combination with another antacid having high reaction velocity.
3. The inclusion of adjuvants and the formulation technique may affect the antacid performance.

4. The USP preliminary antacid test and acid neutralization capacity test seem not to discriminate enough to distinguish between "in vitro" onset and duration of antacid preparations.

REFERENCES

1) D. Drake and D. Hollander, Ann. Intern. Med., 94, 215 (1981)

2) T.D. Duffy, S.Z. Fawzy, D.S. Ireland and M.H. Rubinstein, J. Clin. Hosp. Pharm., 7, 53 (1982)

3) S.L. Hem, J.L. White, J.S. Beuhler, J.R. Luber, W.M. Grim and E.A. Lipka, Am. J. Hosp. Pharm., 39, 1925 (1982)

4) M.P. Dutro and A.B. Amerison, N. Engl. J. Med., 302, 967 (1980)

5) W.A. Ritschel and W. Erni, Drug Dev. Ind. Pharm., 4, 305 (1978)

6) R.E. Barry and J. Ford, Br. Med. J., 1, 413 (1978)

7) B. Jones, M. Rhodes and J. Rhodes, Practitioner, 219, 559 (1977)

8) D. Sklar and M.H. Liang, N. Engl. J. Med., 296, 1007 (1977)

9) J.S. Fordtran, S.G. Morawski and C.T. Richardson, N. Engl. J., 288, 923 (1973)

10) W.A. Ritschel and M. Banarer, Contemp. Pharm. Pract. 5, 246 (1982)

11) S. Beekman, J. Am. Pharm. Ass., 49, 191 (1960)

12) M. Gibaldi, J.L. Kanig and L. Amsel, J. Pharm. Sci. 53, 1375 (1964)

13) C. Fuchs, Drug Cosm. Ind., 64, 692 (1949)

14) V.K. Schaub, Pharm. Acta Helv., 37, 669 (1962)

15) V.K. Schaub, Pharm. Acta Helv., 37, 733 (1962)

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

17) J.R.B.J. Brouwers and G.N.J. Tytgat, J. Pharm. Sci., 30, 148 (1978)

18) United States Pharmacopeia XX, United States Pharmacopeial Convention, Inc., Rockville, MD, 1980, p. 992