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ANTACID TABLETS: SHOULD THEY BE CHEWED OR SWALLOWED INTACT?

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ABSTRACT

Three commercially available antacids, two of them labeled either to be taken intact or to be chewed, (Bisodol®, Maalox® No. 1) and one of them (Riopan®) available in two formulations, chew tablets and swallow tablets, were tested *in vitro* for disintegration time, pressure resistance, acid consumption capacity and acid neutralizing capacity and *in vivo* in man using

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the Heidelberg Capsule. The total areas under the *in vivo* pH *versus* time curves obtained with the intact and chewed tablets, respectively, corrected for the individual $NaHCO_3$ response test were determined. Also the time to reach pH 3 and the period of time for pH *versus* time curve above pH 3 were determined. The preparations were evaluated for extent of antacid capacity, efficacy and lag time. From the results obtained it becomes evident that by chewing rather than swallowing the antacid intact tablet, a quicker and more effective relief is obtained.

INTRODUCTION

In a previous study the Heidelberg Capsule was used for *in vivo* evaluation of thirteen commercially available antacids in man, and a method for determination of extent of antacid availability or extent of antacid capacity, EAC, was developed (1). In that study one volunteer mistakenly swallowed the antacid tablet intact. The resulting pH *versus* time curve was markedly different from those obtained with chewed tablets. Since at least two products on the market are specifically labeled that the tablet may

either be taken intact or be chewed, and that one preparation is on the market in the form of swallow and of chew tablets it was the purpose of this study to investigate the mode of administration, i.e. chewing or swallowing of the tablet on the EAC.

Furthermore, the new bioavailability and bioequivalence regulation (2) specifically states, that a measurable pharmacologic response suffices for bioavailability testing of antacids. However, the authors do not agree with the new regulation in this point, because the cited statement: "This approach shall also be considered as sufficiently accurate for determining the bioavailability of dosage forms intended to deliver the therapeutic moiety locally, e.g., topical preparations for the skin, eye, ear, mucous membranes; oral dosage forms not intended to be absorbed, e.g., an antacid or a radiopaque medium; and bronchodilators administered by inhalation if the onset and duration of pharmacological activity are defined" is contradictory to the definition of bioavailability since antacids are not absorbed and usually act locally (3). Furthermore, the regulation specifically lists antacids among those drug products which qualify for waiver of evidence of in vivo bioavailability (4).

EXPERIMENTAL

Drug Products Investigated

Product A: Bisodol® Tablets[1], 0305-25A

Product B: Maalox® No. 1 Tablets[2], L 657 I, Control No. 26584

Product C: Riopan® Swallow Tablets[3], NDC 00460790-60, Lot #7010TE

Product D: Riopan® Chew Tablets[3], NDC 00460791-81, Lot #6506 UB

The tablets were purchased from a retail pharmacy.

In Vitro Testing

Mechanical pressure resistance (hardness): Ten tablets each were subjected to mechanical pressure resistance (hardness) testing using the Heberlein hardness tester[4]. The Heberlein tester was used since it was found to give the most reproducible, consistant and precise data when compared to other hardness testers (5).

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[1]Whitehall Laboratories Inc., N.Y.

[2]William H. Rorer, Inc., Fort Washington, Pa.

[3]Ayerst Laboratories Inc., N.Y.

[4]Heberlein Hardness Tester, Model 2E, Vector Corp., Hiawatha, Iowa

Disintegration Time

Disintegration was tested by the USP method (6), and by using the Erweka tester[5]. In both tests distilled water was the test fluid.

Acid-Consuming Capacity

The acid-consuming test was carried out according to the USP (7).

Acid Neutralizing Capacity

The acid neutralizing capacity test was carried out according to the Code to Federal Register (8).

In Vivo Testing

Healthy, male, Caucasian volunteers participated in the cross-over study for each preparation taken once intact (swallowed) and once chewed. Food and beverages were withheld for at least 3 hours prior to the experiment. Two tablets each were administered with 50 ml of water of room temperature.

The temperature of the water for rinsing was kept constant at 220°C since temperature may influence gastric emptying time (9).

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[5]Erweka, Model Type VZ 4, Chemical & Pharmaceutical Industry Co., Inc., New York, N.Y.

The calibration and use of the Heidelberg Capsule[6] and the test procedure was described in a previous communication (1).

As soon as a constant baseline for gastric pH was registered, the alkali test was performed. The alkali test consisted of the peroral administration of 5 ml of saturated sodium bicarbonate solution together with 50 ml of water. Only subjects whose pH returned to the baseline level between 5 and 15 minutes were included in the experiment. When a constant baseline was obtained again, two antacid tablets of a given preparation were administered. On each subject the alkali test and the test for a given preparation with two tablets swallowed intact and two tablets masticated were performed. Ten minutes at baseline conditions was achieved between ingestion of the two sets of tablets. At the end of the experiment the thread was swallowed.

For Riopan®, Product C (the swallow tablets) was compared with Product D (the chew tablets). Thus the chew tablets were not given intact and the swallow tablets were not chewed.

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[6]Heidelberg Capsule, Electro-Medical Devices, Atlanta, Georgia

The individual pH *versus* time curves were evaluated with regard to area under the pH curves for pH above baseline from 0 to ∞ using the trapezoidal rule, the time needed to reach pH 3 and the time the pH remained above 3. Although opinions as to which pH range comprises optimal antacid effectiveness vary widely between investigators, a pH of above 3 was considered a good indication that the antacid effect has started since at a pH above 3, pepsin is practically inactivated. In order to obtain a relative measurement correlated for individual variation, the "extent of antacid capacity", EAC, for each type of administration of each given preparation was calculated according to equation 1:

$$\text{Extent of Antacid Capacity} = \frac{AUC^{0\to\infty}_{\text{Tablet}}}{AUC^{0\to\infty}_{\text{Alkali Test}}} \qquad \text{Eq. 1}$$

where $AUC^{0\to\infty}$ = total area under the pH *versus* time curve.

In addition to this, the "efficacy" and the "lag time" ratios were calculated according to equations 2 and 3, respectively:

$$\text{Efficacy} = \frac{(\text{Time pH above 3})_{\text{Tablet}}}{(\text{Time pH above 3})_{\text{Alkali Test}}} \qquad \text{Eq. 2}$$

$$\text{Lag time} = \frac{(\text{Time to reach pH 3})_{\text{Tablet}}}{(\text{Time to reach pH 3})_{\text{Alkali Test}}} \qquad \text{Eq. 3}$$

RESULTS AND DISCUSSION

The results for the tablet pressure resistance (hardness) and disintegration time are listed in Table 1. Plotting the disintegration time *versus* pressure resistance, as shown in Fig. 1, a linear relationship was demonstrated. The correlation coefficients for the regression lines of disintegration time by the USP and Erweka method, respectively, *versus* pressure resistance were r = 0.9981 and r = 0.9979, respectively.

All tablets were within specification limits of both acid-consuming capacity and acid neutralizing capacity as shown in Table 2.

A typical pH *versus* time profile obtained in the *in vivo* studies is shown in Fig. 2. The mean data ± S.D. for the alkali test expressed as $AUC^{0\to\infty}_{NaHCO_3}$, for the intact tablets $AUC^{0\to\infty}_{\text{Intact Tablet}}$, chewed tablets $AUC^{0\to\infty}_{\text{Chewed Tablet}}$, the EAC (according to eq. 1), the efficacy (according to equation 2) and the lag time (according to equation 3) are listed for the products A, B, C and D in tables 3, 4 and 5, respectively.

TABLE 1: Physical Testing of Antacid Tablets

Product	Pressure Resistance (Hardness) in kp ± S.D.	Disintegration Time in min. ± S.D. USP Method	Erweka Method
A	10.34 ± 1.35	11.47 ± 1.21	13.12 ± 1.72
B	7.35 ± 0.75	2.52 ± 0.38	2.99 ± 0.53
C	6.12 ± 1.51	0.43 ± 0.30	0.30 ± 0.04
D	14.65 ± 1.18	24.63 ± 1.78	24.19 ± 2.55

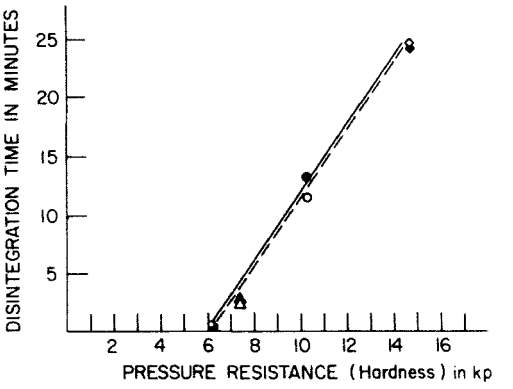

Fig. 1: Plot of disintegration time versus pressure resistance of antacid tablets tested. Open symbols disintegration time tested by USP-method, filled in symbols by ERWEKA-method.

For all three parameters, namely, the EAC, efficacy and lag time, the ratios obtained for the intact tablets were compared with those for the chewed tablets by means of the Wilcoxon paired test (10) at a significant level of difference of $p = 0.05$. The results are given in Table 6.

From the results in Table 6 it is evident that there is a significant improvement in the EAC and lag time for product A and product B when these tablets were chewed before swallowing them. As far as

TABLE 2: Acid-Consuming and Acid-Neutralizing Capacity

Product	Acid-Consuming Capacity		Acid-Neutralizing Capacity		
	Weight of 3 Tablets in g ± S.D. (n = 3)	ml of 1 N H_2SO_4 ± S.D. per 3 Tablets consumed (n = 3)	Average Weight per tablet in g ± S.D. (n = 3)	ml of 0.5 N NaOH ± S.D. consumed (n = 3)	Calculated mEq (n = 3)
A	1.797 ±0.004	33.95 ± 0.15	0.598 ±0.003	38.42 ± 0.16	10.785
B	1.706 ±0.007	33.68 ± 0.19	0.605 ±0.014	34.70 ± 0.70	12.65
C	1.993 ±0.027	32.13 ± 0.70	0.659 ±0.001	37.78 ± 0.13	11.11
D	3.297 ±0.007	33.15 ± 0.59	1.035 ±0.006	38.87 ± 0.24	10.56

TABLE 3: Experimental Values and Calculated Parameters for Product A

EXTENT OF ANTACID CAPACITY

Volunteer	$AUC^{0\rightarrow\infty}$ $NaHCO_3$ (pH·min)	$AUC^{0\rightarrow\infty}$ Intact Tablet (pH·min)	$AUC^{0\infty}$ Chewed Tablet (pH·min)	EAC Intact Tablets	EAC Chewed Tablets
A	57.58	73.15	80.90	1.2704	1.4064
B	54.83	116.66	123.47	2.1277	2.2519
C	36.99	45.13	97.48	1.2201	2.6353
D	64.21	84.75	154.16	1.3199	2.4008
E	43.00	75.23	217.29	1.7495	5.0533
F	64.49	97.78	95.49	1.5162	1.4807
Average	53.52	82.12	128.15	1.5340	2.5381
± S.D.	±11.29	±24.25	±50.75	±0.3500	±1.3293

EFFICACY

Volunteer	Time that pH was above 3(min)			Efficacy	Efficacy
	$NaHCO_3$	Intact Tablet	Chewed Tablet	Intact Tablet	Chewed Tablet
A	16.17	33.34	16.62	2.06	1.03
B	9.95	23.33	25.00	2.34	2.51
C	8.28	0.00	19.95	0.0	2.41
D	7.80	23.33	24.75	2.99	3.17
E	9.95	3.40	32.28	0.34	3.24
F	14.95	28.33	18.33	1.89	1.23
Average	11.18	18.62	22.82	1.60	2.27
± S.D.	±3.52	±13.67	±5.74	±1.18	0.94

LAG TIME

Volunteer	Time to reach pH 3(min)			Lag time	Lag time
	$NaHCO_3$	Intact Tablet	Chewed Tablet	Intact Tablet	Chewed Tablet
A	0.50	8.33	0.05	16.66	0.10
B	0.05	1.67	1.67	33.40	33.40
C	0.05	>120.00	0.05	-	1
D	0.05	26.67	0.03	533.40	0.50
E	0.05	76.60	0.05	1532.00	1
F	0.05	41.67	1.67	833.0	33.40
Average	0.13	30.99	0.59	589.77	11.57
± S.D.	±0.18	±29.94	±0.84	±630.14	±16.91

TABLE 4: Experimental Values and Calculated Parameters for Product B

EXTENT OF ANTACID CAPACITY

Volunteer	$AUC^{0\to\infty}$ $NaHCO_3$ (pH·min)	$AUC^{0\to\infty}$ Intact Tablet (pH·min)	$AUC^{0\to\infty}$ Chewed Tablet (pH·min)	EAC Intact Tablet	EAC Chewed Tablet
C	34.33	38.92	66.08	1.1337	1.9249
G	14.07	28.17	65.00	2.0021	4.6198
H	35.66	25.00	47.16	0.7010	1.3225
J	27.32	63.33	146.16	2.3181	5.3500
D	30.55	81.51	90.50	2.6690	2.9631
Average	28.39	47.39	82.98	1.7648	3.2361
± S.D.	±8.55	±24.30	±38.54	±0.8231	±1.7204

EFFICACY

Volunteer	Time that pH was above 3 (min)			Efficacy	Efficacy
	$NaHCO_3$	Intact Tablet	Chewed Tablet	Intact Tablet	Chewed Tablet
C	4.95	6.60	23.33	1.33	4.71
G	2.28	8.30	20.00	3.64	8.77
H	6.62	1.66	14.50	0.25	2.19
J	8.28	11.17	41.62	1.35	5.03
D	4.50	16.67	18.28	3.70	4.06
Average	5.33	8.88	23.55	2.05	4.95
± S.D.	±2.26	±5.56	±10.59	±2.05	±2.40

LAG TIME

Volunteer	Time to reach pH 3 (min)			Lag Time	Lag Time
	$NaHCO_3$	Intact Tablet	Chewed Tablet	Intact Tablet	Chewed Tablet
C	0.05	20.00	1.67	400.00	33.40
G	0.05	5.00	3.33	100.00	66.60
H	0.05	16.67	0.50	333.40	10.00
J	0.05	5.50	0.05	110.00	1.00
D	0.05	8.33	0.05	116.60	1.00
Average	0.05	11.10	1.12	222.00	22.40
± S.D.	±0.00	±6.83	±1.40	±136.56	±28.03

TABLE 5: Experimental Values and Calculated Parameters for Product C* and D**

EXTENT OF ANTACID CAPACITY

Volunteer	$AUC^{0\to\infty}$ $NaHCO_3$ (pH·min)	$AUC^{0\to\infty}$ Intact Tablet (pH·min)	$AUC^{0\to\infty}$ Chewed Tablet (pH·min)	EAC Intact Tablet*	EAC Chewed Tablet**
U	30.99	64.51	84.76	2.0816	2.7351
L	11.33	39.50	53.00	3.4863	4.6778
M	25.83	104.96	94.65	4.0635	3.6643
N	44.66	44.33	74.56	0.9926	1.6695
O	21.15	92.18	112.66	4.3584	5.3267
P	51.16	251.68	199.43	4.9099	3.8906
D	64.21	102.14	93.19	1.5907	1.4513
D	30.55	62.16	55.99	2.0349	1.8329
Average	35.00	95.18	96.03	2.9398	3.1560
± S.D.	±17.25	±67.94	±46.32	±1.4450	±1.4572

EFFICACY

Volunteer	Time that pH was above 3(min)			Efficacy	Efficacy
	$NaHCO_3$	Intact Tablet	Chewed Tablet	Intact Tablet*	Chewed Tablet**
U	11.58	41.67	33.28	3.60	2.87
L	1.62	0.000	6.66	0.00	4.11
M	11.62	24.97	0.00	2.15	0.0
N	9.95	0.00	10.00	0.00	1.01
O	6.62	23.33	23.33	3.52	3.52
P	9.95	48.33	43.33	4.86	4.35
D	8.28	11.02	6.17	1.34	0.75
D	4.5	10.00	13.28	2.22	2.95
Average	8.02	19.92	17.01	2.21	2.45
± S.D.	±3.55	±18.09	±15.00	±1.74	±2.45

LAG TIME

Volunteer	Time to reach pH 3(min)			Lag Time	Lag Time
	$NaHCO_3$	Intact Tablet	Chewed Tablet	Intact Tablet*	Chewed Tablet**
U	0.05	8.33	0.05	166.60	1.00
L	0.05	>120.00	1.67	-	33.40
M	0.05	8.33	>120.00	166.60	-
N	0.05	>120.00	8.33	-	166.60
O	0.05	1.67	1.67	33.40	33.40
P	0.05	1.67	6.67	33.40	133.40
D	0.05	0.50	0.50	10.00	10.00
D	0.05	3.33	0.05	66.60	1.00
Average	0.05	3.97	3.15	59.58	54.11
± S.D.	±0.00	±3.49	±3.47	±69.57	±67.56

*Swallow Tablet
**Chew Tablet

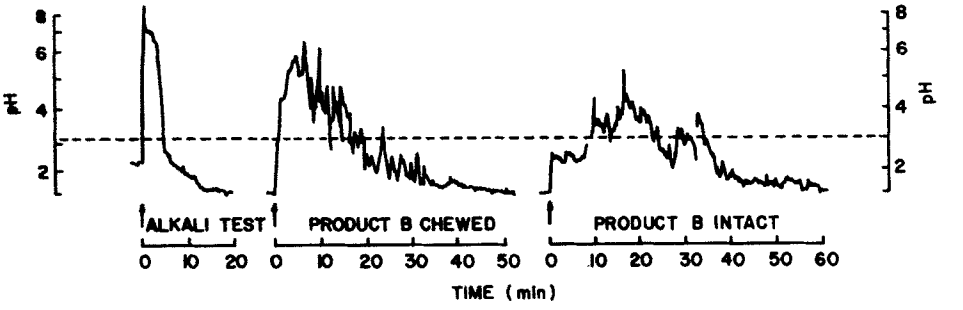

Fig. 2: Typical recording of pH as function of time with the Heidelberg Telemetric Capsule.

efficacy is concerned (time that pH was raised above pH 3) the difference between chewed and intact tablets for product B was significant but not for product A. For products C and D tablet differences between chewed and intact tablets could not be proven in any of the parameters.

If the disintegration times and hardness of the various tablets are also considered, it is evident that the effectiveness of product C could in fact not be influenced much by these physical properties since the disintegration times are relatively very short. In product D, the disintegration time and hardness of the tablets were the highest of all the tablets tested, yet between the chew and the swallow tablets no significant differences in the three parameters were found. Product B tablets had a relatively fast disintegration time (2.52 min) and a tablet hardness

TABLE 6: Parameters to Evaluate the Effectiveness of Intact and Chewed Antacid Tablets

Antacid Tablets	INTACT			CHEWED		
	EAC	EFFICACY	LAG TIME	EAC	EFFICACY	LAG TIME
Product A	82.12[x]	1.60	589.77*	128.15[x]	2.27	11.57[x]
Product B	47.39[x]	2.05[x]	222.0[x]	82.98[x]	4.95[x]	22.40[x]
Product C,D	95.18	2.21	42.86	96.03	2.45	54.10

[x]Significant differences between the parameters for INTACT and CHEWED TABLETS as determined with a paired Wilcoxon test with p = 0.05.

roughly half that of product D, with a significant difference between intact and chewed tablets for all three parameters. For product A significant differences existed between the "EAC" and lag time for the intact and chewed tablets with a disintegration time of 11.47 min. and a tablet hardness 10.34 kp.

From the results obtained it becomes apparent that by chewing rather than swallowing the antacid tablet intact, a quicker and more effective relief is obtained as shown in the bar diagram of Figure 3.

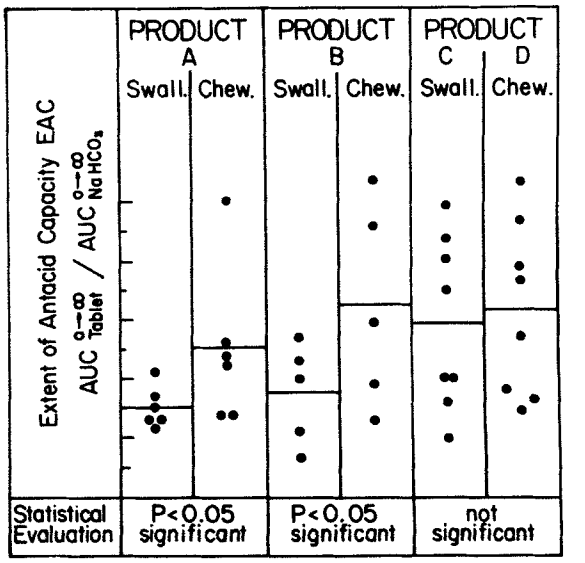

Fig. 3: Bar diagram of extent of antacid capacity for products tested when either tablets are swallowed intact or are chewed and masticated.

Although various in vitro techniques simulating in vivo tests have been tried, none have as yet been successful. When such an in vitro method can be established, various physical factors of the tablets that might influence the effectiveness of antacid tablets could be investigated more easily.

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