(174) Tilak, B. D., Thesis, Oxford University, 1946.
(175) Ghaisas, V. V., and Tilak, B. D., *J. Sci. Ind. Res. India*, **14B**, 11(1955).
(176) Rao, D. S., and Tilak, B. D., *ibid.*, **17B**, 260(1958).
(177) Ghaisas, V. V., Rabindran, K., and Tilak, B. D., *Proc. Indian Acad. Sci.*, **37A**, 144(1953).
(178) Ranadive, K. J., and Waravdekar, S. S., private communications; through Tilak, B. D., *Tetrahedron*, **9**, 76(1960).
(179) Ambaye, R. Y., Panse, T. B., and Tilak, B. D., *Proc. Indian Acad. Sci.*, **53A**, 149(1961); through *Chem. Abstr.*, **55**, 22511(1961).
(180) Sahasrabudhe, M. B., Narurkar, M. K., Tilak, B. D., and Bhavsar, M. D., *Brit. J. Cancer*, **14**, 547(1960).
(181) Gol'dfarb, Y. L., and Kondakova, M. S., *J. Gen. Chem. USSR, Eng. Transl.*, **30**, 107(1960).
(182) Scholefield, P. G., *Can. J. Biochem. Physiol.*, **39**, 1717(1961); through *Chem. Abstr.*, **56**, 7883(1962).
(183) Spurlock, J. J., *J. Am. Chem. Soc.*, **75**, 1115(1953).
(184) (*a*) Goodman, L. S., Toman, J. E. P., and Swinyard, E. A., *Proc. Soc. Exptl. Biol. N. Y.*, **68**, 584(1948); (*b*) Ensor, C. R., and Chen, G., *Arch. Neurol. Psychiat. Chicago*, **62**, 857(1949); (*c*) Swinyard, E. A., This Journal, **38**, 201 (1949); (*d*) Swinyard, E. A., Brown, W. C., and Goodman, L. S., *J. Pharmacol.*, **106**, 319(1952); (*e*) Chen, G., Ensor, C. R., and Clarke, I. G., *Arch. Neurol. Psychiat. Chicago*, **66**, 329(1951).
(185) Peterman, M. G., *Sth. Med. J. Nashville*, **41**, 62 (1948).
(186) U. S. pat. 2,468,168; through *Chem. Abstr.*, **43**, 5805 (1949).
(187) Aurousseau, M., *Anesthesie Analgesie Reanimation*, **17**, 415(1960); through *Chem. Abstr.*, **55**, 13649(1961).
(188) Campbell, K. N., Ackerman, J. F., and Campbell, B. K., *J. Am. Chem. Soc.*, **71**, 2905(1949).
(189) Nickerson, M., and Gump, W. S., *J. Pharmacol.*, **97**, 25(1949).
(190) Chapman, N. B., and Tompsett, A. J., *J. Chem. Soc.*, **1961**, 1291.
(191) (*a*) Todorov, S., and Robev, S., *Z. Naturforsch.*, **14B**, 383(1959); through *Chem. Abstr.*, **53**, 22206(1959); (*b*) Robev, S., and Todorov, S., *Compt. Rend. Acad. Bulgare Sci.*, **12**, 459(1959); through *Chem. Abstr.*, **55**, 693(1961); (*c*) Baev, I., and Robev, S., *Compt. Rend. Acad. Bulgare Sci.*, **13**, 733(1960); through *Chem. Abstr.*, **55**, 23817(1961).
(192) Nickolov, I., Baev, I., and Robev, S., *Compt. Rend. Acad. Bulgare Sci.*, **14**, 551(1961).
(193) Gadekar, K. N., and Sahasrabudhe, M. B., *Brit. J. Cancer*, **15**, 489(1961).
(194) Buzas, A., Frossard, J., and Teste, J., *Ann. Pharm. Franc.*, **19**, 449(1961); through *Chem. Abstr.*, **56**, 6603(1962).
(195) Stall, W., and Dietrich, H., Ger. pat. 1,139,507 (Nov. 15, 1962); *Swiss Appl.*, May 24, 1957; through *Chem. Abstr.*, **58**, 10173(1963).
(196) *France*, M1614, Jan. 14, 1963; *Ger. Appl.*, Nov. 23, 1960; through *Chem. Abstr.*, **58**, 12574(1963).
(197) Gol'dfarb, Y. L., Fabrichny, B. P., and Shalavina, I. F., *Tetrahedron*, **18**, 21(1962).
(198) (*a*) Christomanos, A. A., *Biochem. Z.*, **229**, 248 (1930); (*b*) Backert, P., *Arch. Exptl. Pathol. Pharmacol.*, **193**, 79(1939); (*c*) Chilcote, M. E., *Univ. Microfilms*, Pub. No. 672; through *Chem. Abstr.*, **39**, 2116(1945).

Research Articles

Gastrointestinal Factors in Aspirin Absorption

A Quantitative Study

By EDWARD B. TRUITT, Jr., and ANN M. MORGAN

Three gastrointestinal factors influencing aspirin absorption have been selectively adjusted for quantitative measurement of their effect on the rate of salicylate absorption in humans and dogs. These are (a) gastric emptying, (b) aspirin dissolution rate, and (c) intragastric pH. Other factors such as tablet disintegration time, aspirin particle size, and intersubject variability have been eliminated or reduced where possible. The major portion of the salicylate in the blood during the first 20 minutes comes from the stomach. Impedance of gastric emptying by the use of atropine and placing the subjects in a left lateral position did not eliminate the higher plasma salicylate levels produced by the inclusion of the buffer antacids in aspirin tablets. The major effect of these antacids appears to be an acceleration of aspirin dissolution. This has been confirmed in this study by an *in vivo* demonstration of more rapid absorption from solutions of aspirin than from tablets. Aspirin in solution has a lower pH alone than with the inclusion of buffering antacids. Selective adjustment of the degree of aspirin and sodium salicylate ionization through the use of various buffers provided a method of study of the influence of intragastric pH on the rate of aspirin absorption. Support was obtained from dog and human studies in favor of the pH partition hypothesis that salicylates are absorbed more rapidly at low pH values.

MANY INVESTIGATIONS of salicylate absorption have been made because of the ease with which salicylic acid can be measured in body fluids. Despite this, some factors regulating this membranous transfer have only recently been measured under physiologic conditions in man. One such factor is the direct transfer of salicylate from the stomach into the blood circulation (1, 2).

The claim of Paul, *et al.* (3), that certain antacids increased the gastrointestinal absorption rate of aspirin has received considerable examination. Despite a number of studies showing no significant differences (4–7), quite a few tests using adequate numbers and crossover design to reduce intersubject variability have shown clearly

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significant acceleration of aspirin tablet absorption rate (8–10). In addition, claims of accelerated gastric salicylate absorption have been reported for solutions of sodium acetylsalicylate (11), calcium aspirin (8), and for combinations of salicylates with magnesium aluminum hydroxide (12), mephenesin (13), methocarbamol (14), glucosamine (15), and an effervescent mixture (16).

Those factors which are theoretically involved in controlling the rate of absorption of oral aspirin tablets include: (*a*) tablet disintegration time, (*b*) aspirin particle size, (*c*) aggregation between aspirin particles and other tablet components such as disintegrators, binders, excipients, etc. (a function of tablet compression force), (*d*) aspirin dissolution time, (*e*) the gastric pH (by affecting the ratio of ionized to unionized drug), (*f*) the rate of gastric emptying, and (*g*) the presence of interfering factors such as gastric mucus, food, and other adsorbents and diluents Some of these factors can be experimentally controlled in human subjects to a degree that permits an evaluation of their quantitative function in the absorptive process. It is the purpose of this study to investigate the role of three factors—(*a*) gastric emptying, (*b*) aspirin dissolution rate, and (*c*) gastric pH—on the early absorption rate of aspirin. By testing these factors with and without the addition of the buffer antacids, magnesium carbonate, and dihydroxyaluminum aminoacetate, some evidence can be deduced concerning the mechanism by which they accelerate aspirin absorption.

METHODS AND MATERIALS

Twenty healthy subjects were tested following an overnight fast in a crossover comparison of a plain[1] and a buffered aspirin.[2] Each subject received 0.4 mg. of atropine sulfate orally 30 minutes before the salicylate drugs. After a control blood sample was withdrawn, each subject swallowed (without chewing) two tablets of one of the salicylate products, with 100 ml. of cool tap water. Each tablet contained 0.32 Gm. of acetylsalicylic acid. The subjects were then placed in the left lateral position. Blood samples were drawn at 5, 10, and 20 minutes with the subjects remaining in the recumbent position and were analyzed for total plasma salicylate by the Routh and Dryer modification of the Brodie method (17). After a 72-hour interval the experiment was completed.

Dissolved Aspirin Test.—A second panel of 20 fasted subjects (differing from the first group by six replacements) were tested using solutions of freshly dissolved aspirin with and without the buffer antacids. Each subject drank 250 ml. of water containing either (*a*) 648 mg. of aspirin (U.S.P. Monsanto brand) or (*b*) 648 mg. of aspirin

[1] Marketed as Bayer aspirin, lot No. L0228, by Winthrop Laboratories, New York, N. Y.
[2] Marketed as Bufferin, lot No. 1B08, by the Bristol-Myers Co., New York, N. Y.

TABLE I.—PLASMA SALICYLATE LEVELS (mg./100 ml.) IN 20 SUBJECTS WITH AND WITHOUT 0.4 mg. ATROPINE SULFATE AND L.L.P. 30 MINUTES BEFORE BUFFERED ASPIRIN ADMINISTRATION (0.648 Gm.)

Subject	$AtSO_4$ and L.L.P. Time, min. 5	10	20	No $AtSO_4$ Time, min. 10	20
1	0.10	0.30	0.80	0.80	1.95
2[a]	0.05	0.68	2.20	0.95	3.85
3	0.15	0.40	0.50	0.10	2.60
4	0.20	1.05	3.05	1.10	4.40
5	0	0.38	0.92	0.68	1.95
6	0	0.30	0.68	0.40	1.40
7	0	0.10	0.70	...	...
8	0.25	0.40	1.48	0.10	2.70
9[a]	0.10	0.40	1.25	0.89	5.69
10[a]	0.30	...	1.10	...	2.58
11[a]	0	0.60	2.65	0.65	2.15
12	0.32	1.00	2.90	0.95	4.00
13	0.10	1.70	3.90	0.45	3.51
14	0.30	0.70	1.76	0.85	3.40
15[a]	0.20	2.62	3.32	1.98	6.45
16	0	0.10	0.70	0.79	1.90
17[a]	0.15	1.40	3.30	1.85	4.30
18[a]	0.10	0.70	1.85	...	...
19	0.30	0.40	1.38	1.30	3.75
20	0	1.65	3.40	1.25	2.30
Mean	0.131	0.78	1.89	0.84	3.27

[a] Female.

TABLE II.—PLASMA SALICYLATE LEVELS (mg./100 ml.) IN 20 SUBJECTS WITH AND WITHOUT 0.4 mg. ATROPINE SULFATE AND L.L.P. 30 MINUTES BEFORE ASPIRIN ADMINISTRATION (0.648 Gm.)

Subject	$AtSO_4$ and L.L.P. Time, min. 5	10	20	No $AtSO_4$ Time, min. 10	20
1	0.05	0.55	2.00	0.35	0.60
2[a]	0.10	0.60	1.80	1.15	1.20
3	0.10	0.30	0.40	0.68	2.00
4	0.20	0.70	2.26	0.68	1.75
5	0	0.30	0.32	0	0.50
6	0	0.70	1.85	1.76	4.80
7	0	0.32	0.92	...	...
8	0	0.05	0.68	0	0.35
9[a]	0.32	0.70	3.05	0.75	1.95
10	0	0.30	0.92	1.85	5.60
11[a]	0	0.10	0.70	0.63	2.65
12	0	0.20	0.90	0.20	1.20
13	0.30	0.38	1.62	0.85	1.78
14	0	0.15	0.68	0.35	1.85
15[a]	0	0.30	1.00	0.60	0.95
16	0.30	0.35	1.40	0.70	1.80
17[a]	0.30	1.00	1.78	1.09	1.09
18[a]	0	0.10	1.05	...	
19	0.30	0.70	1.60	1.40	3.50
20	0.60	0.90	1.75	0.20	1.30
Mean	0.129	0.44	1.33	0.74	1.94

[a] Female.

TABLE III.—AVERAGE PLASMA SALICYLATE LEVELS IN 20 FASTING SUBJECTS WITH IMPEDED GASTRIC EMPTYING OWING TO ATROPINE AND A LEFT LATERAL POSITION (L.L.P.)

Treatment	Av. Plasma Salicylate, mg./100 ml. 5 min.	10 min.	20 min.
Buffered aspirin	0.131	0.78	1.89
Aspirin	0.128	0.44	1.33
Mean individual difference	0.003	0.34	0.54
S.E. difference	0.005	0.15	0.27
p	>0.90	<0.05	<0.10
		>0.02	>0.05

TABLE IV.—PLASMA SALICYLATE LEVELS IN 20 FASTING SUBJECTS AFTER DRINKING 250 ml. OF ASPIRIN SOLUTION (648 mg.) WITH AND WITHOUT BUFFER ANTACIDS (MAGNESIUM CARBONATE, 194 mg., AND DIHYDROXYALUMINUM AMINOACETATE, 97 mg.)

	Buffered Aspirin Solution				Plain Aspirin Solution			
	Time, min.				Time, min.			
Subject	5	10	20	30	5	10	20	30
1	0.50	1.95	4.05	6.50	0	0.70	3.50	3.90
2	0.70	1.58	3.00	5.30	0.30	2.70	5.35	6.90
3	0.35	1.30	4.30	7.50	0.75	1.48	4.80	7.60
4	...	3.05	3.85	4.30	0.38	1.55	3.88	5.60
5	0.70	2.60	5.30	7.25	0.95	2.90	5.95	6.90
6[a]	0	1.70	6.80	8.30	2.40	3.75	7.10	8.20
7	0.70	4.35	5.40	6.45	1.75	3.88	6.45	7.20
8[a]	1.40	5.60	7.50	7.50	...	...	6.15	7.95
9[a]	0.10	0.40	4.00	6.00	0.55	1.05	2.86	5.00
10[a]	0.80	2.70	7.60	8.40	1.65	3.78	7.50	7.50
11	0.35	2.30	5.30	5.90	1.50	4.80	6.55	6.45
12	0	0.80	4.00	5.40	1.50	3.90	5.50	6.60
13[a]	0	0.65	1.80	3.60	0.30	2.38	6.00	7.10
14[a]	0.70	2.95	5.85	6.35	1.10	4.35	7.10	7.60
15	0.40	1.95	4.70	6.15	0.35	2.75	5.85	6.15
16	0.65	2.38	5.20	6.00	1.75	3.30	5.35	6.35
17	0.25	1.70	4.35	4.80	1.05	3.10	5.50	6.45
18[a]	1.80	3.85	7.10	7.80	1.15	4.20	6.00	7.50
19	0.50	1.65	6.40	6.00	1.65	3.60	5.45	6.50
20	0.80	3.40	6.00	7.10	0.50	2.80	6.90	6.95
Mean	0.56	2.34	5.13	6.33	1.03	3.00	5.69	6.69

[a] Female.

TABLE V.—MEAN PLASMA SALICYLATE LEVELS IN 20 FASTING SUBJECTS AFTER DRINKING ASPIRIN SOLUTIONS—BUFFERED AND PLAIN

	Av. Plasma Salicylate, mg./100 ml.			
Treatment	5 min.	10 min.	20 min.	30 min.
Buffered aspirin solution	0.56	2.34	5.13	6.33
Aspirin solution	1.03	3.00	5.69	6.69
Mean individual difference	−0.55	−0.68	−0.56	−0.36
S.E. difference	0.189	0.30	0.295	0.275
p	<0.01	<0.05	<0.10	<0.3
		>0.02	>0.05	>0.2

with 194 mg. of magnesium carbonate and 97 mg. of dihydroxyaluminum aminoacetate. These solutions were prepared immediately before drinking with the aspirin fully dissolved; however, the buffers were incompletely dissolved in this limited amount of fluid. After 72 hours the subjects received the opposite portion of the crossover design.

Buffered Aspirin Solution Tests.—*Dog Study.*—Six dogs were tested for intragastric pH and plasma salicylate levels after receiving each of five citrate-phosphate buffer (0.15 *M*) solutions containing a 50 mg./Kg. dose of aspirin or sodium salicylate. The solutions were adjusted to pH's 3.2, 4.4, 5.2, 6.0, and 8.0, and the volume given was 200 ml. A control blood sample was removed; 0.025 mg./Kg. of atropine sulfate was injected intravenously. The dog was then intubated with a double lumen catheter having either a glass or antimony electrode at the tip (glass was necessary for low pH values). The indifferent electrode (calomel) was placed in contact with the skin using a salt paste for contact. The dog was trained to lie quietly on its left side and the stomach tube was adjusted to the fundic region of the stomach by markings on the tube which had been previously calibrated by X-ray photographs. The buffer was instilled through the catheter, washed in, and blood samples were taken at 5 and 10 minutes with the animal remaining in the left lateral position. Each dog received two tests with each aspirin buffer solution and one test for each sodium salicylate buffer solution, with no more than two tests per week.

Human Study.—Ten fasted subjects (all except two from the first two panels) were tested for intragastric pH and plasma salicylate levels after receiving each of three citrate-phosphate buffer solutions containing an aspirin dose equivalent to two tablets. Intragastric pH was recorded using an antimony electrode in the catheter tip and was compared to a calomel reference electrode which made contact with the subject's hand through some salt-containing gelatin paste. The subjects were placed in the left lateral position and remained so throughout the test. After the positioning of the electrode, the catheter was taped to the subject's face to eliminate movement of the electrode into the intestine, etc. Three 0.15 *M* citrate-phosphate buffers of McIlvaine's series with pH values of 2.5, 4.5, and 6.5 were used to prepare solutions of aspirin containing 648 mg. in 250 ml. of buffer.

After the initial pH was measured and a control blood sample removed, the aspirin in buffer solution was injected through the catheter. With a buffer of pH 2.5 at 15°, it was not possible to dissolve more than about 80–90% of the aspirin and the rest was instilled as a mixture. Intragastric pH was recorded continuously and blood samples were taken at 10 and 20 minutes with the subject reclining. Total plasma salicylate concentration was measured as before.

RESULTS

Impeded Gastric Emptying Test.—The plasma salicylate levels were generally lower for both aspirin and buffered aspirin when emptying of the stomach was impeded than those values usually found with the subject in the upright position. These differences are shown in Tables I and II. The summarized values which were measured in this test are shown in Table III. Paired statistical analysis of individual differences showed that atropine combined with the left lateral position reduced salicylate levels significantly for aspirin at 10 minutes and buffered aspirin at 20 minutes.

It may be seen that the buffered aspirin tablets produce significantly higher plasma levels at 10 minutes and the difference is close to this level of significance at 20 minutes, but not at 5 minutes.

Dissolved Aspirin Test.—The plasma salicylate levels measured after administration of solutions of aspirin were the highest ever measured in this laboratory for this dose and absorption time. Tables IV and V show the levels of salicylic acid following each solution.

It is apparent from the data summarized in Table V that aspirin alone becomes the more rapidly absorbed product when the dissolution step (in the absorptive process) is accomplished before ingestion of the drug. The addition of the buffer antacids significantly slows absorption during the first 10 minutes, but not at later periods.

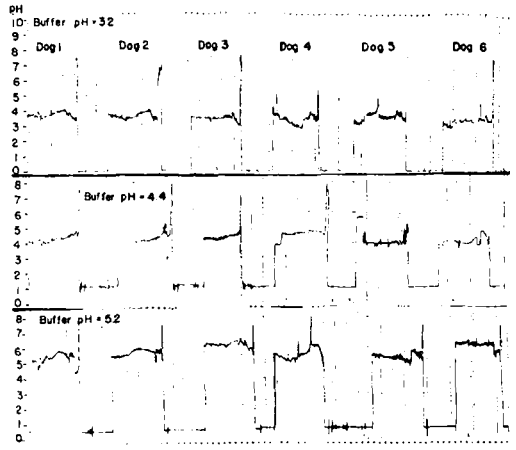

Fig. 1.—Dog intragastric pH after oral acetylsalicylic acid administration (50 mg./Kg.) in citrate-phosphate buffers.

Buffered Aspirin Solution Test.—*Dog Study.*—Figures 1 and 2 show the resulting 10-minute intragastric pH recordings for the six dogs at each of the five buffer pH values. It may be seen that the *in vivo* pH was stable and ranged about ±0.5 pH units of the value for the instilled buffer. Figures 3 and 4 show the plasma salicylate values for the test of sodium salicylate buffer solutions at the various recorded pH values and after 10 minutes of absorption. Although a large degree of individual variation in response occurred, there is a pronounced trend from high plasma levels at lower pH values to much lower levels at the high buffer pH values (*i.e.*, a suggestion that salicylate absorption is inversely correlated to intragastric pH). A similar relationship was found between intragastric pH and absorption rate for aspirin with these same buffers. The large interdog variation of these plasma salicylate levels prompted the larger study of this relationship in humans using a wider interval between buffer pH.

Human Study.—Generally the intragastric pH found after buffered aspirin instillation was close to the initial pH of the buffer *in vitro*. The magnitude of these differences are shown in Table VI.

These data suggest that the resultant intragastric pH following instillation of these buffers was within a reasonable range from the initial *in vitro* values. As expected, the two higher pH buffers were depressed, likely by gastric secretions. The lower value was raised, although the average initial pH measured in the stomach before administration of the buffer was 2.58 and quite uniform with a S.E. of ±0.13 pH units.

The rate of salicylate absorption may be expressed either in relation to the initial pH of the buffer *in vitro* or in terms of the resulting pH in the stomach. Table VII presents this relationship in correlation with the original pH of the instilled buffer.

An adequate test of the relationship between buffer pH and absorption rate was not completely possible, especially at the earlier time period, since the total amount of aspirin could not be fully dissolved in a pH 2.5 buffer. Thus, at 10 minutes the absorption of salicylate was greater for the pH 4.5 and 6.5 buffers, as expected. However, at 20 minutes the highest plasma levels occurred with the pH 4.5 buffer.

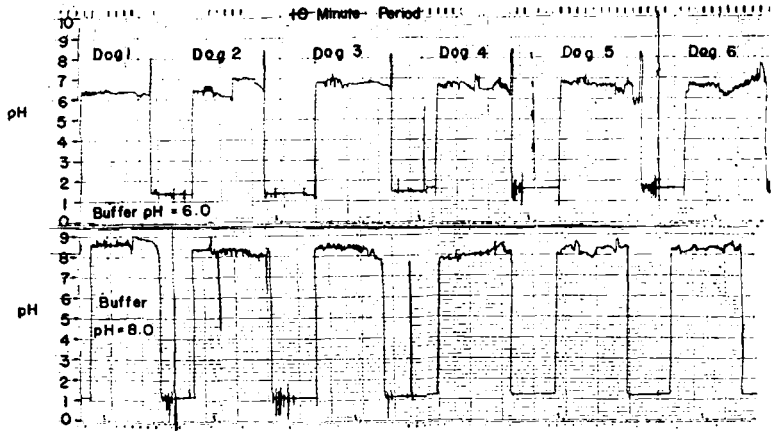

Fig. 2.—Dog intragastric pH after oral acetylsalicylic acid administration (50 mg./Kg.) in citrate-phosphate buffers.

If the plasma salicylate levels are compared instead to the actual pH measured from the intragastric electrode, a somewhat different pattern emerges. This is shown in Table VIII.

On this basis, an increased salicylate absorption is evident in two separate ranges, pH 3.0 to 3.9 and above pH 5.0. The peaks are better defined at the later time period, probably for the same reason of incomplete solubility for the lower pH buffer suggested before.

DISCUSSION

The well known accelerating action of antacids upon gastric emptying prompted the evaluation of this factor as the first possible explanation of the more rapid absorption of buffered aspirin. It was expected that if faster absorption by the buffered drug disappeared with the use of atropine and the left side position, it could be taken as evidence of a role for gastric emptying in its absorption. Roentgenographic evidence for the effectiveness of this procedure in delaying gastric emptying has been previously illustrated (2).

Impedance of gastric emptying produces a significant reduction in the total salicylate levels as shown in Table IV but did not eliminate the faster absorption of buffered aspirin as shown in Table V. This indicates that although a portion of the early absorption of each drug is dependent upon gastric emptying, the restriction of this factor does not eliminate the faster rise in blood salicylate with the buffered aspirin.

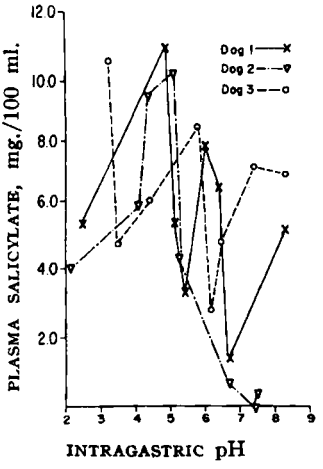

Fig. 3.—Salicylate absorption 10 minutes after 50 mg./Kg. sodium salicylate in citrate-phosphate buffers.

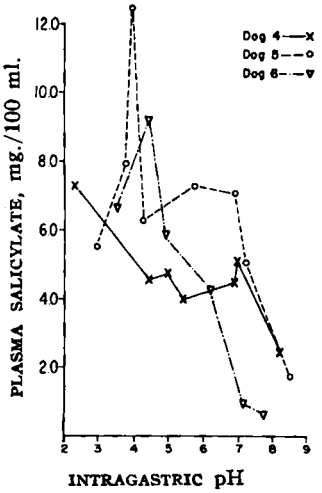

Fig. 4.—Salicylate absorption 10 minutes after 50 mg./Kg. sodium salicylate in citrate-phosphate buffers.

TABLE VI.—DEVIATIONS OF INTRAGASTRIC pH VALUES FROM INITIAL BUFFER pH *In Vitro* IN TEN FASTING SUBJECTS AFTER 250 ml. OF ASPIRIN-BUFFER SOLUTION

Initial Buffer, pH	Av. Deviations of Intragastric pH from Buffer pH 10 min.	S.E.	20 min.	S.E.
2.5	+0.35	0.24	+0.47	0.25
4.5	−0.50	0.19	−0.66	0.21
6.5	−0.54	0.26	−0.96	0.29

TABLE VII.—CORRELATION IN TEN SUBJECTS OF PLASMA SALICYLATE LEVEL WITH INITIAL pH *In Vitro* OF CITRATE-PHOSPHATE BUFFERS CONTAINING 648 mg. ASPIRIN

Initial Buffer, pH	Plasma Salicylate, mg./100 ml. 10 min. Av.	S.E.	20 min. Av.	S.E.
2.5[a]	0.68	0.10	2.32	0.28
4.5	0.95	0.09	2.73	0.21
6.5	1.02	0.15	2.56	0.42

[a] Aspirin not completely soluble at this pH and amount.

TABLE VIII.—CORRELATION OF PLASMA SALICYLATE LEVEL WITH INTRAGASTRIC pH AFTER INSTILLATION OF BUFFERS CONTAINING 648 mg. OF ASPIRIN

Intragastric pH Range	Plasma Salicylate Level, mg./100 ml. 10 min. No.	Av.	S.E.	20 min. No.	Av.	S.E.
2.0 to 2.9	9	0.68	0.12	8	2.26	0.19
3.0 to 3.9	3	1.01	0.19	7	3.07	0.33
4.0 to 4.9	8	0.76	0.17	7	2.27	0.21
over 5.0	9	1.01	0.17	8	2.56	0.39

Although it is frequently confused with tablet disintegration time, the rate of aspirin dissolution is probably the rate-limiting step in the absorptive process (18). Disintegration of the tablet may be rate limiting if prolonged, but was not significant here because it was less than 1 minute for each product. Dissolution time is a slow and quite variable process with different aspirin preparations (19). It is dependent upon aspirin particle size, aggregation between particles, pH, temperature, agitation, and other factors. Two of the products tested by Levy and Hayes (19) having the slowest disintegration times (calcium aspirin and buffered aspirin) showed the most rapid dissolution rates.

The rate limiting effect of dissolution time, suggested by Edwards (18), was confirmed *in vivo* by Nelson and Schaldemose (20), and by Levy and Hayes (19), but in both cases the evidence was accumulated using urinary excretion rates of salicylic acid rather than blood determinations as in this study. While both methods for estimating gastric absorption rates are indirect, blood levels are considered as more closely reflecting effective tissue levels of the drug than are urinary concentrations for the early absorption period as studied here. Although Leonards (11) showed that a solution of sodium acetylsalicylate was absorbed faster than an aspirin suspension, using a blood measurement, this comparison involved a difference in pH between a neutralized form of the drug in solution and an undissolved suspension of acetylsalicylic acid.

A comparison of the data in this study for aspirin solutions to previous data for aspirin tablets (10) showed that plasma SAL levels are 6.5 times higher at 10 minutes, 4.3 times at 20 minutes, and 3.3 times at 30 minutes. The ratios are much less for buffered aspirin solutions—2.7 at 10 minutes, 1.9 at 20 minutes, and 1.6 at 30 minutes. The essential difference between these two solutions is one of acidity. Aspirin in solution at this concentration gives a pH of about 3.0; whereas, when combined with magnesium carbonate and dihydroxyaluminum glycinate, the pH is 4.6. It was this difference in absorption of two aspirin solutions differing mainly in pH that prompted the last portion of the investigation with buffer adjustment of intragastric acidity.

The pKa of salicylic acid is 3.0 and that of acetylsalicylic acid is 3.5. According to a pH partition hypothesis for drug absorption (21), the rate of salicylate absorption from the solute state into the systemic circulation is dependent upon the concentration of unionized, lipid soluble molecules which increase at lower pH values. Schanker (22) showed that absorption of salicylates was more rapid from 0.1 *N* HCl than from bicarbonate solution in the rat, using ligation to assure gastric absorption. The tests of this hypothesis in dogs and in humans in this study generally agree with the idea that absorption is greater at lower pH values. However, in the human study and in some of the dog patterns, a second peak of absorption appears near neutrality. The optimum pH for absorption in this experiment was about pH 3.5 to 5.0 for dogs and 3.0 to 4.0 for humans. Owing to difficulties of dissolving aspirin at low pH values it cannot be said that the lower pH values represent the true lower limit of maximal absorption rates. Rubin, *et al.* (23), claimed that the amounts of antacid buffers included in buffered aspirin tablets were unable to alter gastric pH significantly. These results suggest that the environmental pH conferred upon aspirin particles by the presence in the same tablet of magnesium carbonate and dihydroxyaluminum glycinate with a buffer action at about pH 4.5 (3) do not markedly decrease aspirin absorption as shown in the dissolved aspirin test and by buffer adjustment of intragastric pH. Indeed, this pH of 4.5 may represent an optimum between high pH values which increase the rate of dissolution and low pH values which increase the rate of gastric absorption.

REFERENCES

(1) Hogben, C. A. M., Schanker, L. S., Tocco, D. J., and Brodie, B. B., *J. Pharmacol. Exptl. Therap.*, **120**, 540 (1957).
(2) Truitt, E. B., Jr., and Morgan, A. M., *Toxicol. Appl. Pharmacol.*, **2**, 237(1960).
(3) Paul, W. D., Dryer, R. L., and Routh, J. I., THIS JOURNAL, **39**, 21(1950).
(4) Batterman, R. C., *New Engl. J. Med.*, **258**, 213(1958).
(5) Cronk, G. A., *ibid.*, **258**, 219(1958).
(6) Harrisson, J. W. E., Packman, E. W., and Abbott, D. D., THIS JOURNAL, **48**, 50(1959).
(7) Lampe, K. F., *Ind. Med. Surg.*, **30**, 296(1961).
(8) Sleight, P., *Lancet*, **1**, 305(1960).
(9) Levy, G., THIS JOURNAL, **50**, 388(1961).
(10) Truitt, E. B., Jr., and Morgan, A. M., *Arch. Intern. Pharmacodyn.*, **135**, 105(1962).
(11) Leonards, J. R., *Proc. Soc. Exptl. Biol. Med.*, **110**, 304(1962).
(12) Feinblatt, T. M., Feinblatt, H. M., Ferguson, E. H., Price, A. H., Healy, J. E., and Allison, W., *N. Y. State J. Med.*, **58**, 897(1958).
(13) Carr, J. J., Mouratoff, G. J., and Batterman, R. C., *J. Pharmacol. Exptl. Therap.*, **124**, 312(1958).
(14) Truitt, E. B., Jr., Morgan, A. M., and Nachman, H. M., *Southern Med. J.*, **54**, 318(1961).
(15) U. S. pat. 3,008,874; abstracted from *Drug Cosmetic Ind.*, **90**, 80(1962).
(16) Carlo, P. E., Cambosos, N. M., Feeney, G. C., and Smith, P. K., THIS JOURNAL, **44**, 396(1955).
(17) Routh, J. I., and Dryer, R. L., in "Standard Methods of Clinical Chemistry," Academic Press, New York, N. Y., Vol. 3, 1961, 194.
(18) Edwards, L. J., *Trans. Faraday Soc.*, **47**, 1191(1951).
(19) Levy, G., and Hayes, B. A., *New Engl. J. Med.*, **262**, 1053(1960).
(20) Nelson, E., and Schaldemose, I., THIS JOURNAL, **48**, 489(1959).
(21) Shore, P. A., Brodie, B. B., and Hogben, C. A. M., *J. Pharmacol. Exptl. Therap.*, **119**, 361(1957).
(22) Schanker, L. S., Shore, P. A., Brodie, B. B., and Hogben, C. A. M., *J. Pharmacol. Exptl. Therap.*, **120**, 528 (1957).
(23) Rubin, R., Pelikan, E. W., and Kensler, C. J., *New Engl. J. Med.*, **261**, 1208(1959).

Pharmacology of Alkylamino Ethanol Esters of *p*-Ethoxybenzoic Acid

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A series of eight alkylaminoethanol esters of *p*-ethoxybenzoic acid were examined for local anesthetic activity on the rabbit cornea and frog sciatic nerve, for acute toxicity in mice, for irritancy on the rabbit cornea and by the trypan blue test in rabbits, and for their spasmolytic activity on the isolated rabbit ileum. In general, sciatic nerve block was hastened, irritancy was increased, acute toxicity increased, and duration of topical anesthesia decreased as the alkylamino portion of the molecule was enlarged.

THE SYNTHESIS and pharmacology of methylbenzyl monoethanolamine paraethoxybenzoate hydrochloride was previously reported by Millikan and Feurt (1). Although this compound appeared to have adequate spasmolytic and local anesthetic activities, its irritant properties were too pronounced for its acceptance as an injectable drug. The present work constitutes a study of

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