# Drug Absorption from the Rectum III: Aspirin and Some Aspirin Derivatives

WERNER LOWENTHAL, JOSEPH F. BORZELLECA, and CHARLES D. CORDER, Jr.

**Abstract** ☐ The rectal absorption of aspirin, aluminum aspirin, and calcium carbaspirin was studied in dogs. Cocoa butter, polysorbate 61, polyethylene glycol mixture, and a mixture of natural saturated vegetable fatty acid glycerides were the bases used. The areas under the plasma concentration–time curves, peak salicylate levels, and the time the peak levels occurred were used as the criteria for comparison The absorption of aluminum aspirin from cocoa butter and the polyethylene glycol mixture was poor. Plasma salicylate levels from aspirin and calcium carbaspirin in the polysorbate 61 base were minimal. The highest peak and largest area under the curve were seen with calcium carbaspirin in vegetable fatty acid glycerides base The commercial aspirin product had the lowest peak and smallest area under the curve but the earliest peak. The two latest peaks in salicylate plasma levels were observed following the use of cocoa butter base suppositories. No conclusions can be reached concerning any differences in absorption of aspirin or calcium carbaspirin in the various bases or the commercial aspirin product.

**Keyphrases** ☐ Drug absorption—aspirin, derivatives, rectum, dog ☐ Aspirin, derivatives—drug absorption, rectum, dog ☐ Rectal absorption, dog—aspirin, derivatives ☐ Suppositories, absorption—aspirin, derivatives, dog

Suppositories resemble a type of sustained-release tablet where it is desired that the matrix rapidly disintegrates. The drug is incorporated into a wax-type matrix which can be either hydrophilic, such as polyethylene glycol waxes, or hydrophobic, such as cocoa butter. With this in mind, one would expect the ordinary suppository to release the drug more slowly than a rapidly disintegrating tablet. This should result in slower absorption and possibly a lower peak. In addition, there is relatively little fluid present in the rectum compared to the stomach and intestine. As a result, as the suppository matrix liquifies, the drug is diffused through a viscous medium to get to the absorbing membrane. This also decreases the rate of absorption and may explain the erratic and incomplete absorption that occurs in the rectum.

Aspirin suppositories became official in the USP XVII and are widely used. Coldwell and Boyd (1) reported that $LD_{50}$ of rectally administered suppositories to male albino rats was significantly less than the $LD_{50}$ of orally administered aspirin.

Only a few *in vivo* studies have been reported (2). Thomsen (3) indicated that polysorbate 60 at 20% concentration modified aspirin absorption from a mixture of natural saturated vegetable fatty acid glycerides base.[1] The surfactant caused an earlier peak level. Coldwell *et al.* (4) studied the effect of dosage form and route of administration on the absorption and excretion of aspirin in 10 human volunteers. Results indicated that oral absorption from tablets (640 mg.) proceeded uniformly with a peak in 2 hr. Absorption from suppositories (640 mg.) was more variable. Aspirin tablets given rectally had lower levels and gave erratic blood level patterns. The rate of disappearance of salicylate from plasma was slower for the rectal route than the oral route. No salicylate could be detected in the plasma following administration of an aspirin suspension rectally. Recovery of salicylate from urine was less for the tablets and the suspension given rectally than for tablets given orally or for aspirin rectal suppositories. Neuwald and Kunze (5) found that *in vitro* dissolution tests with suppositories were misleading and did not predict *in vivo* absorption.

Since there is a potential bioavailability problem with rectal suppositories and due to the potential toxic hazard, especially in children, it was decided to investigate the effects of various bases on the absorption of aspirin, aluminum aspirin,[2] and calcium carbaspirin (calcium aspirin carbamide).[3]

Aspirin is soluble to the extent of 1 g. in 100 ml. water at 37° (6); aluminum aspirin NF is "insoluble"; and 1 g. calcium carbaspirin dissolves in 4.33 ml. of water at 20° (7). These were used to represent aspirin compounds with three different solubilities. The rate of absorption and the amount absorbed are dependent upon the rate of release of the drug from the dosage form matrix and the rate of solution of the drug in the rectum. To evaluate these factors, the three forms of aspirin were incorporated in four different suppository bases. The bases were: (*a*) cocoa butter USP;[4] (*b*) a mixture containing partial glycerides or triglycerides of natural saturated vegetable fatty acids of $C_{12-18}$ chain length with m.p. 33.5–35.5°, saponification value of 220–230, iodine value (Kaufman) of >7, and a hydroxyl value of 50–56[1] (S-55); (*c*) polysorbate 61 [polyoxyethylene (4) sorbitan monostearate];[5] and (*d*) a mixture of polyethylene glycols (PEG).

Cocoa butter and S-55 are hydrophobic bases melting below the normal body temperature of humans and dogs. Cocoa butter is widely used and may be considered a "standard" against which other bases are compared. S-55 represents the new synthetic bases which are being used as cocoa butter substitutes. Polysorbate 61 is a tan waxy solid, dispersible in water, with a pour-point of approximately 38° and a hydrophile–lipophile balance of 9.6, and represents the nonionic surfactant type of base. The polyethylene glycol mixture is a water-soluble base but does not melt at normal body temperature.

[1] Witepsol S-55, Chemische Werke Witten, G.m.b.H., Riches-Nelson, Inc.

[2] Abbott Laboratories, North Chicago, IL 60064
[3] Calurin, Dorsey Laboratories, a Division of the Wander Co.
[4] Charles Huisking & Co., Inc.
[5] Tween 61, Atlas Chemical Industries, Inc., Wilmington, DE 19899

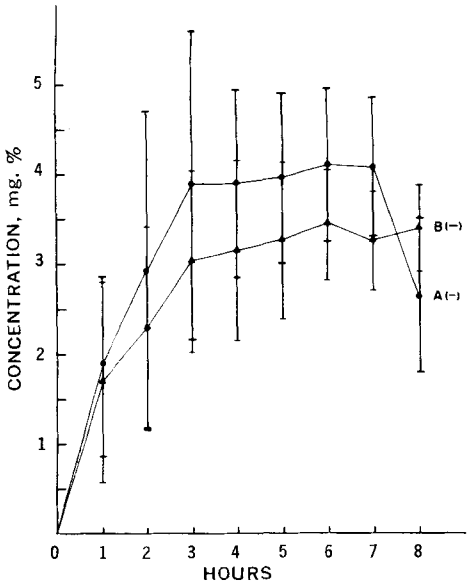


**Figure 1**—*Plasma salicylate levels for cocoa butter base suppositories. A, aspirin, standard deviation (—); B, calcium carbaspirin, standard deviation (—).*

As a result, three different drugs were to be studied in four different bases, resulting in 12 different products. A commercial aspirin product in a water-soluble base was included for comparative purposes.

## EXPERIMENTAL

**Procedures and Methods**—These were the same as those previously reported (2). The dogs used weighed between 11.3 and 14.5 kg. Dogs were used in this study because of their larger size and because the rectal physiology of the dog and the human are similar. Four or five dogs were used for each preparation.

**Analytical Procedure**—These were the same as those previously reported (2).

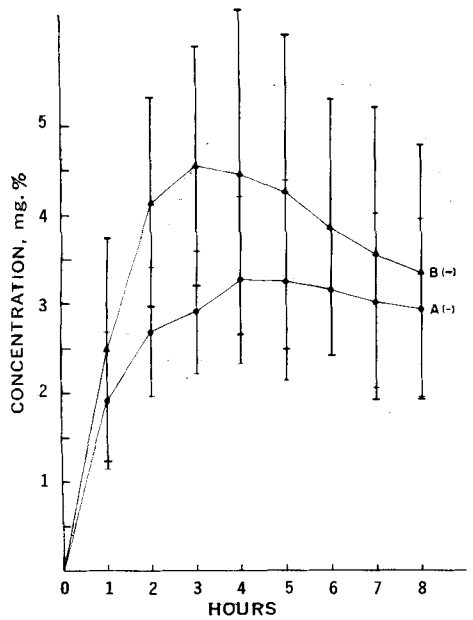


**Figure 2**—*Plasma salicylate levels for S-55 base suppositories. A, aspirin, standard deviation (—); and B, calcium carbaspirin, standard deviation (—).*

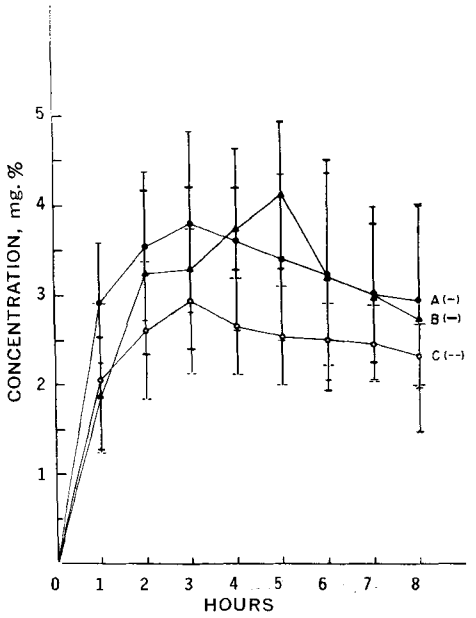


**Figure 3**—*Plasma salicylate levels for PEG mixture suppository base and the commercial aspirin product. A, aspirin, standard deviation (—); B, calcium carbaspirin, standard deviation (—); and C, commercial aspirin product, standard deviation (— —).*

**Suppository Formulation**—Aspirin[6] USP comminuted through an 80-mesh screen, aluminum aspirin[2] NF, and calcium carbaspirin[3] were used. The suppositories were made by the hot-melt method using metal molds. Drug displacement in the four bases was first determined, and the amount of base required was calculated (8). The drugs were mixed with the melted base and poured into molds; the molten mass was allowed to solidify in a refrigerator. The suppositories were removed from the molds and stored in a refrigerator in a well-closed container until used. The same molds were always used. The PEG base was made from 6 parts polyethylene glycol 1540[7] and 4 parts polyethylene glycol 6000[7]

A 330-mg. dose of aspirin base or equivalent amounts of aluminum aspirin and calcium carbaspirin were used. This dose was lower than the one used in the previous study. This was deemed necessary to reduce the interference by the biotransformation systems (9).

## RESULTS AND DISCUSSION

Aluminum aspirin was poorly absorbed from cocoa butter and PEG bases, and in two dogs no salicylate could be detected. When salicylate was detected in the plasma, its appearance was later then either the aspirin or calcium carbaspirin. Due to the insignificance of the low levels obtained, the data were not tabulated. The peak was about 1.21 mg.% in 4–7 hr. in cocoa butter and about 0.81 mg.% in 3–7 hr. in PEG base.

Calcium carbaspirin in polysorbate 61 base caused defecation and expulsion of the suppositories in 3 out of 4 dogs. Although there was no visual evidence of damage to the mucosa nor was any bleeding evident, irritation may have occurred and could have caused expulsion. Aspirin in polysorbate 61 base did not cause defecation, but the suppository or parts of it was removed in 3 out of 4 dogs. Again there was no visual evidence of mucosal damage or blood. The salicylate levels for these two products were very low and were not tabulated because they would be of doubtful value. The peak level for calcium carbaspirin was 1.84 mg.% in 8 hr., for aspirin it was 1.74 mg.% in 4–8 hr.

Individual dogs were fairly consistent in the salicylate levels they exhibited after administration of the various products; *e.g.*, dogs that showed high salicylate levels generally did so for all products.

[6] Aspirin, Merck & Co., Inc., Rahway, NJ 07065
[7] Carbowax 1540 and Carbowax 6000, Union Carbide Chemicals Co., New York, NY 10017

Table I—Data from Graphical Concentration of Salicylate in Plasma–Time Plots

| Preparation | Area under Curve, mg./hr. | Peak Level | |
|---|---|---|---|
| | | Height,[a] mg. % | Time,[a] hr. |
| Aspirin–cocoa butter | 26.1 | 4.10 (2.85–6.27) | 6(3–7) |
| Calcium carbaspirin–cocoa butter | 21.9 | 3.46 (2.85–4.40) | 6(4–6) |
| Aspirin–commercial product | 18.9 | 2.94 (1.86–3.70) | 3(2–4) |
| Aspirin–PEG | 24.9 | 3.80 (2.77–4.95) | 3(3–4) |
| Calcium carbaspirin–PEG | 23.8 | 4.12 (3.28–4.91) | 5(4–6) |
| Aspirin–S-55 | 21.7 | 3.27 (2.48–4.30) | 4(2–5) |
| Calcium carbaspirin–S-55 | 29.0 | 4.56 (2.95–6.39) | 3(3–4) |

[a] Obtained by averaging data for individual dogs. Numbers in parenthesis are the ranges.

The average salicylate levels at the various sampling intervals and the standard deviations are shown in Figs. 1–3. As can be seen, there are no trends or consistencies among the drugs or bases.

Areas under the curves were determined with a planimeter.[8] These findings, together with the height of the peaks and time the peak levels occurred, are given in Table I. Using this information the products were ranked in the following ways: (*a*) order of decreasing area under the curves; (*b*) order of decreasing peak height; and (*c*) order of increasing length of time for peak blood level to occur.

*Decreasing Area under the Curve:*

1. Calcium carbaspirin—S-55
2. Aspirin—cocoa butter
3. Aspirin—PEG
4. Calcium carbaspirin—PEG
5. Calcium carbaspirin—cocoa butter
6. Aspirin—S-55
7. Commercial aspirin product

*Decreasing Height of Peak:*

1. Calcium carbaspirin—S-55
2. Calcium carbaspirin—PEG
3. Aspirin—cocoa butter
4. Aspirin—PEG
5. Calcium carbaspirin—cocoa butter
6. Aspirin—S-55
7. Commercial aspirin product

*Time Peak Occurs:*

1. Commercial aspirin product
2. Calcium carbaspirin—S-55
3. Aspirin—PEG
4. Aspirin—S-55
5. Calcium carbaspirin—PEG
6. Calcium carbaspirin—cocoa butter
7. Aspirin—cocoa butter

From these rankings the following conclusions can be made:

1. Calcium carbaspirin in S-55 base has the highest peak and the largest area under the curve but only the second earliest peak.
2. The commercial aspirin suppositories in a water-soluble base had the smallest area under the curve and the lowest peak height, but the peak occurred earliest.
3. Calcium carbaspirin in cocoa butter base ranked fifth in area under the curve and peak height and sixth in time of occurrence of the peak.
4. Aspirin in S-55 base ranked sixth in area under the curve and height of peak level but was fourth in time that the peak level occurred.
5. The two latest peaks in salicylate blood levels were observed following the use of cocoa butter base suppositories.

No conclusions can be made concerning any difference in absorption of aspirin or calcium carbaspirin in cocoa butter, PEG, or the synthetic fatty base. Aluminum aspirin appears to be only poorly absorbed from the rectum in 8 hr. The reasons may be the insolubility of the salt and the lack of fluid to dissolve it. Also the reason postulated by Levy and Procknal (10) that a protective gel forms around the drug to reduce its bioavailability may also occur in the rectum. Polysorbate 61 appears to cause irritations resulting in expulsion of the suppositories, although absorption from this base does occur. There was no visual evidence of tissue damage or bleeding due to polysorbate 61. The results here do confirm those of Neuwald and Kunze (5) who reported that aspirin and calcium salicylate absorption was identical. The peak blood levels were of similar height. Cummings *et al.* (11) reported that a polymeric condensation product of $Al_2O_3$ and aspirin from the interaction of aluminum isopropoxide and aspirin was absorbed equally well as was aspirin after oral administration. Absorption of the aluminum aspirin was delayed about 0.5 to 1 hr, but the total salicylate excreted in the urine was the same for the two products. This aluminum aspirin compound should also be tested for rectal absorption.

[8] K and E Compensating Polar Planimeter, model 4236M.

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