Drug Absorption from the Rectum I

Suppository Bases: A Preliminary Report

By WERNER LOWENTHAL and JOSEPH F. BORZELLECA

Studies were begun to determine the process(es) by which drugs may be absorbed from the rectum, and the effect of suppository dosage form on these process(es). Using dogs, whose anatomy closely resembles that of humans, plasma salicylate levels from salicylic acid and sodium salicylate incorporated into four different suppository bases were studied. It was found that the drugs were released and absorbed equally well from cocoa butter, while from a base composed of a mixture of synthetic glycerides, a polyethylene glycol base, and from polyoxyethylene (4) sorbitan monostearate, salicylic acid gave higher plasma salicylate levels. A passive diffusion process is proposed. In the studies to follow, the effect of suppository base and physicochemical characteristics of the drugs on absorption from the rectum will be explored in detail.

A SUPPOSITORY is a semisolid dosage form, intended for insertion into body orifices, that may be used for local or systemic effects. For systemic effects, the use of suppositories offers many advantages over oral dosage forms. Among these advantages are: (*a*) the portal circulation is bypassed, thus preventing or retarding biotransformation by the liver (1, 2); (*b*) drugs irritating to the gastric mucosa may be given in this manner; (*c*) the influence of either pH or enzymatic activity of the gastrointestinal juices is circumvented; (*d*) they can be administered to subjects who cannot or will not swallow; (*e*) absorption from the rectum can be more rapid and more regular than from the stomach or intestine (3, 4); (*f*) duration of action may be prolonged (5). There are a few disadvantages: *e.g.*, (*a*) the lack of patient acceptability—not very esthetic; (*b*) the limited knowledge of the mechanism(s) of absorption from the rectum and some of the factors that will influence this absorption. Studies were therefore planned to determine the nature of the drug absorptive process(es) from the rectum (*e.g.*, active or passive, etc.), some of the factors that will modify this absorption (*e.g.*, depth of insertion, pH, ionization of the drugs, etc.), and the effect of suppository bases on these factors. Initial experiments are discussed in this report.

DISCUSSION

Most of the *in vivo* studies with suppositories are reported in the European literature and were done on rats, guinea pigs, or rabbits.

Charonnat *et al.* (6) reported that in guinea pigs methyl or benzyl nicotinate in a glycerinated gelatin base gave the most uniform temperature rise. In cocoa butter the drugs caused less rise in body temperature, while in a polyethylene glycol (PEG) base the temperature rise was erratic.

Trandafilov *et al.* (7) using a cocoa butter–hydrogenated vegetable oil–beeswax base, found potassium benzylpenicillin in the blood within 30 min., and the levels persisted for 3–4 hr. Backe-Hansen (8), using sodium benzylpenicillin in rabbits with renal ligation, obtained high blood levels within 15 min. with both cocoa butter and a base composed of a synthetic mixture of glycerides of fatty acids (Im.),[1] while the drug in PEG 1000 and glycerin–gelatin bases was absorbed more slowly. Sodium lauryl sulfate was first reported to increase the total absorption greatly, but this effect was later shown not to be so great (9). A mydriatic in cocoa butter was reported to be most rapidly and completely absorbed; polyoxyl 40 stearate[2] was next best, and polyoxyethylene 1000 monostearate[3] and PEG 1500 and 6000 bases were the poorest. Sorbitan monostearate and polysorbate 60 increased the quantity of the mydriatic absorbed (10). The hydrophile-lipophile balance of surfactants was reported to be related to the absorption rate of sulfonamides in rabbits, using PEG 4000, cocoa butter, and Im. E and H[4] as bases (11). Pennati and Steiger-Trippi (12) reported rectal absorption in rabbits to be directly dependent upon water solubility of sulfonamides; the highest level was obtained with a sodium salt in a base composed of lauric acid triglyceride and glyceryl monostearate (Ma).[5] Cocoa butter and a glycerin–gelatin–PEG 400–water base gave the most rapid absorption with either sulfisomidin or its sodium salt. A PEG base was poorest. Using the same drug, another study (13) showed the sodium salt to be more rapidly absorbed in humans than the acid form. The order of decreasing absorption from various bases for the sodium salt was: a PEG 1000 and 4000 base, a lyophilized base, Ma, and cocoa butter. Middendorf (14) reported that methylene blue appeared in the urine of humans more rapidly when incorporated into a PEG base than in cocoa butter. Blok and Dekker (15) reported similar results, and also showed that quinine HCl was absorbed more readily from a PEG base than from either cocoa butter or Ma base.

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[1] Imhausen-mass. Now marketed as Witepsol by the Imhausen Co., G.m.b.H.
[2] Marketed as Myrj 52 by Atlas Chemical Industries, Inc., Wilmington, Del.
[3] Marketed as Cithrol 10 MS(Croda).
[4] Marketed as Witepsol E75 and H15.
[5] Marketed as Massupol by Crok and Loan.

The absorption of various radioactive chemicals from the rectum has been studied also. In guinea pigs, $Na_2H^{32}PO_4$ absorption was more rapid with cocoa butter and Im. H bases, than with bases composed of various polyethylene glycols (16, 17). Calcium gluconate (^{45}Ca) in cocoa butter was more rapidly absorbed from the rectum in mice than from a solution given orally (18). Peterson *et al.* (19) found that in rats a base composed of glyceryl–gelatin + 50% water gave the most rapid and cocoa butter the slowest release of $Na^{131}I$. Propylene glycol monostearate + 10% triethanolamine stearate, PEG 4000 + 10% water, and polyoxyethylene sorbitan monostearate (PSMS) + 10% glyceryl monolaurate, bases gave similar but erratic results.

Whitworth and LaRocca (20) found in their study that sodium pentobarbital absorption in rabbits was better from a base containing 35–40% of an emulsifier of the polysorbate or sorbitan fatty acid ester type with a partially hydrogenated cottonseed oil[6] or hydrogenated cottonseed oil,[7] than from cocoa butter. The proposed base had a melting point less than 48°. Lechat and Boissier (21) found that methyl nicotinate in cocoa butter or synthetic triglyceride bases[8] gave a similar temperature rise in guinea pigs. These bases also gave similar results in humans with *p*-aminobenzoic acid, NaI, and sodium dehydrochlorate. *N*-Acetyl-*p*-aminophenol was reported absorbed more rapidly from a glycerin–gelatin base than from a neutral fat base (22).

Schroff (23) found with suppositories composed of cocoa butter, lecithin, and cholesterol, that sodium salicylate appeared in the blood in 25–36 min. and NaI in 13–20 min. When human urine salicylate levels were compared, cocoa butter was reported to be a poorer base than ones composed of $C_6H_4[COO(CH_2)_{15}CH_3]_2$,[9] montan wax,[10] a PEG base, or a synthetic paraffin (24). Del Pozo and Cemeli (25), comparing peak salicylate levels following the administration of 1 Gm. of sodium salicylate, found some Im. bases better and others poorer than cocoa butter.

Cacchillo and Hassler (26) gave 10 gr. of aspirin orally to 11 male subjects and determined their blood levels after 2 hr. to be 3.51 mg. %. Aspirin in PEG base suppositories 2 hr. after insertion gave blood levels of 3.27 mg. %, in cocoa butter, 2.30 mg. %, and in glycerinated gelatin base, 2.30 mg. %. Using rabbits, Samelius and Åström (27) found that hexobarbital acid absorption from various suppository bases was not detectable within 1 hr. The sodium salt from the same bases showed marked effects. Cocoa butter suppositories containing sodium hexobarbital produced the most rapid and complete absorption. Absorption from Im. bases was less effective, while that from a PEG base or an Im. base with polysorbate 60 and 85 was poorest. In humans, these authors found that up to about 1 hr. plasma salicylate concentrations, resulting from the various bases tested, were about the same. After 1.5 hr., absorption from cocoa butter and a PEG base was at consistently lower levels than from Im. bases and Im.–polysorbate bases. At both 15 and 90 min. after rectal or oral drug administration, plasma salicylate levels were similar. Neuwald and Kunze (28) compared *in vitro* release and *in vivo* absorption of calcium aspirin, aspirin, and sodium salicylate in humans from cocoa butter and various mixtures of synthetic glycerides of fatty acids.[11] They found that the ester composition of the base was not a predictor of drug release or absorption. Water solubility of the drugs was directly related to *in vitro* release but not *in vivo* absorption. Melting of the base at body temperature was found important. Sodium salicylate was absorbed more rapidly, but peak levels for the three drugs were about the same.

EXPERIMENTAL

Procedures and Materials.—*Animals.*—Adult male mongrel dogs, weighing between 9.5 and 17.3 Kg., were used. The dog was chosen because of the remarkable similarity between the large intestine (including rectum) of the dog and the human (29). Following an overnight fast, the dogs were anesthetized initially with sodium pentobarbital, 30 mg./Kg. body weight, administered intravenously. Supplemental sodium pentobarbital was administered when needed. When anesthetized, all animals were intubated with a Magill endotracheal tube. The rectal area was then examined, and, if found free of lesions, a glass tube 25 × 120 mm. lightly lubricated with petrolatum was inserted. Several minutes later this was removed, and the dogs usually defecated. Following removal of all fecal material, the suppositories were inserted to a depth of 120 mm. Expulsion of the suppositories was prevented by means of the glass restraining tube described above. Blood samples were removed periodically from the left or right saphenous vein. At the end of the determinations, the restraining tube was removed and in all cases no suppository mass was found. No dog was used more often than once every 7 days.

Analytical Procedures.—Salicylate determinations were made using the colorimetric method described by Trinder (30).

Suppository Formulation.—Salicylic acid (J. T. Baker Chemical Co., reagent grade) and sodium salicylate (Mallinckrodt Chemical Works, analytical reagent grade) are the two drugs discussed in this report. 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 calculated (31). Salicylic acid crystals were reduced in particle size by trituration. The drugs were mixed with the melted base, poured into the molds, and the molten mass was allowed to solidify overnight in a refrigerator. The two drugs were soluble in the polyoxyethylene (4) sorbitan monostearate[12] (PSMS) and PEG bases. The suppositories were removed from the molds and stored in a refrigerator in a well-closed container until used. The same molds were used throughout the study. The range of suppository weights containing 0.5 Gm. of the drug was 1.54–1.90 Gm. for cocoa butter, 1.63–1.70 Gm. for

[6] Marketed as Cotmar by Procter & Gamble Co.
[7] Marketed as Coto Flakes by Procter & Gamble Co.
[8] Marketed as Supane S36, S36EM, and S39 by Etablissement Nyco.
[9] Marketed as Lasupol by Deutsche Hydrierwerke, Rodleben.
[10] Marketed as Suppobasin.
[11] Witepsol bases.
[12] Marketed as Tween 61 by Atlas Chemical Industries, Inc., Wilmington, Del.

TABLE I.—PLASMA SALICYLATE LEVELS IN DOGS[a] AFTER ADMINISTRATION OF SODIUM SALICYLATE SUPPOSITORIES

Time, min.	Suppository Bases: Cocoa Butter mg. %	S.E.[b]	PSMS mg. %	S.E.	S-55 mg. %	S.E.	PEG mg. %	S.E.
15	0.24 ±	0.45	0.48 ±	0.15	1.32 ±	0.28	0.43 ±	0.18
30	3.43	0.59	0.60	0.17	2.12	0.44	0.80	0.25
60	4.55	0.87	1.18	0.22	3.50	0.59	1.17	0.15
120	5.13	1.20	1.82	0.31	4.53	0.66	1.10	0.21
240	6.24	1.11	2.58	0.67	4.13	0.82	1.20	0.29
360	6.55	1.07	1.33	0.067	4.37	0.72	1.03	0.19

[a] Average of four dogs. [b] Standard error.

TABLE II.—PLASMA SALICYLATE LEVELS IN DOGS[a] AFTER ADMINISTRATION OF SALICYLIC ACID SUPPOSITORIES

Time, min.	Suppository Bases: Cocoa Butter mg. %	S.E.[b]	PSMS mg. %	S.E.	S-55 mg. %	S.E.	PEG mg. %	S.E.
5	0.75 ±	0.19	1.18 ±	0.62	1.11 ±	0.14	0.44 ±	0.025
15	1.54	0.30	2.16	1.09	2.08	0.62	1.30	0.20
30	2.41	0.59	3.39	1.32	3.01	1.14	1.83	0.035
60	4.08	0.38	4.71	1.30	5.00	1.78	3.25	0.28
120	5.45	0.72	6.72	1.00	7.15	1.43	4.27	0.46
180	5.98	0.78	8.23	0.68	7.89	1.41	4.75	0.91
240	6.27	0.64	6.57	0.59	7.55	1.65	4.90	1.15
300	6.46	0.84	...	...	7.99	1.37	5.11	1.46
360	5.55	0.72	6.68	1.08	7.05	1.45	4.99	1.47

[a] Average of three dogs. [b] Standard error.

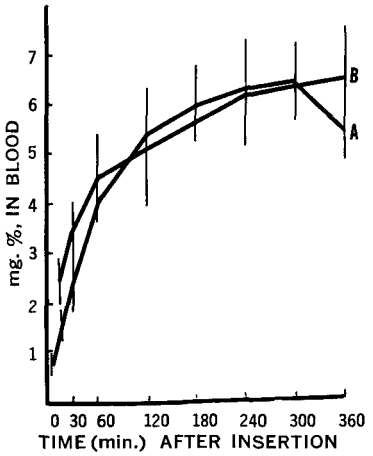

Fig. 1.—Plasma salicylate levels in dogs using cocoa butter as base. Key: A, salicylic acid; B, sodium salicylate.

PSMS, 1.45–1.55 Gm. for S-55, and 1.69–1.74 Gm. for PEG. The four bases used were cocoa butter U.S.P. (Chas. L. Huisking and Co., Inc.), PSMS, S-55 which is a mixture containing partial glycerides of triglycerides of natural saturated fatty acids of C_{12}-C_{18} chain length,[13] and a mixture of 6 parts PEG 1540 and 4 parts PEG 6000.[14] Cocoa butter was included because of its extensive use and the amount of information available. PSMS was used as an example of a water-insoluble nonionic surfactant, melting at about 38°, which has been recommended as a suppository base. S-55 has been extensively tested in Europe and represents a synthetic product resembling cocoa butter, but without the problems associated with the melting of cocoa butter. This base melts at 33.5–35.5°. The PEG mixture represents a water-soluble base melting at about 55°. The ratio of PEG 1540 and 6000 was chosen to give an acceptable product with the two drugs.

Results and Discussion.—Tables I and II present the data for the absorption of sodium salicylate and salicylic acid in dogs from the four suppository bases. Figures 1–4 compare the absorption of the drugs from the four bases. It can be seen that with

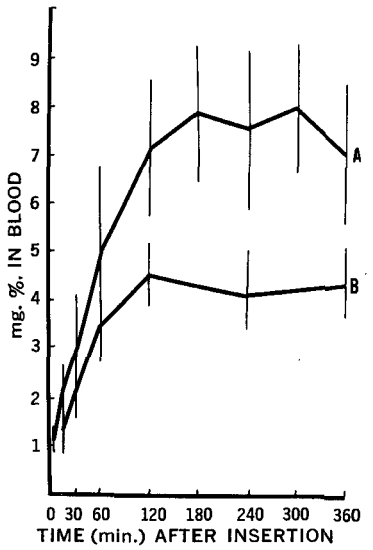

Fig. 2.—Plasma salicylate levels in dogs, using S-55 as base. Key: A, salicylic acid; B, sodium salicylate.

[13] Marketed as Witepsol S-55 by Chemische Werke Witten G.m.b.H.
[14] Marketed as Carbowax 1540 and 6000 by Union Carbide Chemicals Co.

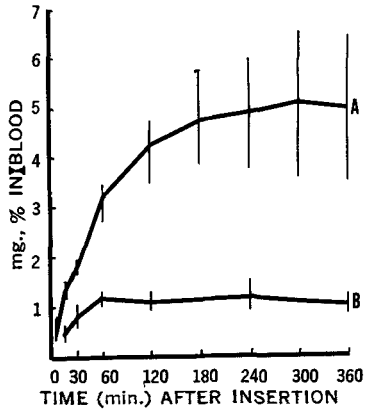

Fig. 3.—Plasma salicylate levels in dogs using PEG base. Key: A, salicylic acid; B, sodium salicylate.

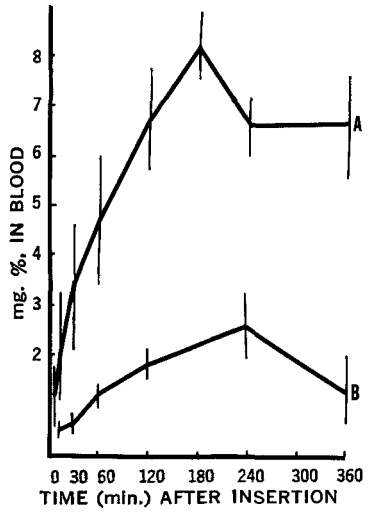

Fig. 4.—Plasma salicylate levels in dogs using PSMS base. Key: A, salicylic acid; B, sodium salicylate.

cocoa butter no differences can be detected between the absorption of salicylic acid and its sodium salt. There is no apparent difference between the two drugs in the initial rate of appearance of salicylate in the plasma from S-55. A difference does occur between 60 and 120 min., when salicylic acid produces a higher equilibrium level. PSMS and PEG bases were least consistent, giving very poor levels with sodium salicylate and good levels with the acid form. The results observed with PSMS and PEG bases may be due to varying degrees of complex formation between the salicylate and the ethylene oxide chains in these bases (32–34). The plasma levels were higher from suppositories containing salicylic acid, because it is present in the unionized form, the form in which it is primarily absorbed. Cocoa butter appears to promote or allow the two drugs to be readily absorbed. Although the precise mechanism is presently unknown, cocoa butter could minimize ionization or aid the transport of the drugs across the membrane barrier.

The study of drug absorption from suppository bases is more complex than absorption from aqueous solutions or perfusion fluids. In order to be absorbed, a drug must first dissolve, and it has been shown that the dissolution process is influenced to varying degrees by the dosage form. The release of the drug from the suppository base may be the rate-determining step. The pH and amount of fluid in the rectum differs considerably from that in the stomach and intestine. It may be that the melting of the suppository base could contribute considerably to the fluid content of the rectum. As a result of this melting, the solvent system in the rectum may be essentially organic and nonpolar in nature and thus affect the degree of ionization of any drug present.

The drugs are absorbed initially as rapidly as they are released from the suppository surface since measurable salicylate plasma levels were found within 5 min. in 16 out of 17 animals tested. The smaller standard errors found at the early levels may be the result of very little softened or melted base in the rectal lumen to interfere with the absorptive process(es). As the bases soften or melt, they possibly inhibit further drug absorption. In addition, individual variation in rates of tissue distribution, biotransformation, and elimination very likely contribute to the larger standard errors seen at the later times.

Drugs may be absorbed by three processes: (*a*) active transport, (*b*) passive transport, and (*c*) specialized transport. Specialized transport involves pinocytosis or phagocytosis, and at present only some fats are known to be absorbed by this process. Active transport, involving energy expenditure, may be involved in the absorption of 5-fluorouracil and 5-bromouracil. Passive transport or diffusion, involving little energy expenditure has been shown to be the process by which most drugs, including salicylates, are absorbed (35). It may be hypothesized that the two drugs used in this study are absorbed by passive diffusion from the rectum, but this hypothesis must be substantiated by further evidence.

The authors' results are not consistent with some of those reported in the literature. This may be due to a number of reasons, not the least of which is that dogs whose diet, rectal anatomy, and physiology closely resemble that of humans were used in this study. Since the reported diameter of the rectum of the dog and human is almost the same, a dog may be given a suppository of the same size without rectal distention. Suppository placement and prevention of leakage of the melted base which has not been considered in other studies has been taken into account here. Meaningful comparisons of literature reports of blood levels, urine levels, or physiological effects cannot be made because these observations result from different body processes. Blood levels show rate of appearance of a substance in the circulation after absorption. Urine levels show a rate of elimination from the blood after biotransformation and tissue distribution. A physiological effect is only shown after a sufficiently high concentration of the drug has been reached in specific target tissues. In addition to the possible rate-limiting step of drug release from the base, the base may be absorbed at varying rates and carry the drug along with it,

either through the pores or through the lipoprotein membrane, or the base may coat the mucous membrane to delay or minimize absorption.

In the studies to follow, the effect of suppository base and physicochemical characteristics of the drug on absorption from the rectum will be explored.

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Technical Articles

Count Loss with the Coulter Counter

By JOSEPH C. SAMYN and J. PATRICK McGEE

Count loss was shown to occur in samples meeting the suggested size specifications of the Coulter counter. This count loss was related to the size and frequency of the larger particles in the sample. The voltages generated in the process were considered. Amplifier blocking of the smaller voltage pulses due to the increased fall time of the larger voltages appeared to be the explanation for the count loss. Accurate frequency counts for the smaller particles necessitate the removal of the larger particles from the sample. It was calculated that the 100-μ aperture can accurately measure down to 2 μ, the suggested lower limit, only in the absence of particles larger than 10 μ. The two Coulter counters used in this study differed in their count loss behavior. This difference suggests that the performance of each counter is apt to change with age, use, etc. The appearance of the oscilloscope pattern was also noted in these studies. In many instances count loss occurred when the oscilloscope pattern was judged to be satisfactory. The importance of the count loss was considered for an oil/water emulsion. The possible error is largest when the frequency data are used directly, as in a dissolution study.

THE COULTER counter[1] is widely used for particle counting. Its basic operation and many of its specific uses have been described. This paper discusses count loss which can occur in the use of the Coulter counter due to the larger particles in the sample.

The particles to be measured are supposed to be between 2 and 40% of the aperture diameter

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[1] Distributed by Counter Electronics Industrial Division, Chicago, Ill.