Salicylate Absorption from Rectal Suppositories

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Abstract ☐ The absorption in humans of aspirin and sodium salicylate incorporated in six suppository bases was studied by means of urinary salicylate elimination. It was found that the rectal dose of aspirin and sodium salicylate was equivalent to the oral dose. Rectal absorption was altered by pharmaceutical factors, which affected the release of the drug from the suppository. Aspirin was rapidly released from suppositories of polyethylene glycol and polyoxyethylene (4) sorbitan monostearate with glyceryl monostearate; aspirin was poorly released from a suppository of sorbitan monopalmitate. Sodium salicylate was rapidly released from a suppository of theobroma oil. Data for the release from theobroma oil suppositories containing cholesterol and glyceryl monostearate were inconclusive.

Keyphrases ☐ Salicylate absorption—rectal suppositories ☐ Aspirin, sodium salicylate absorption, suppositories—comparison ☐ Rectal suppositories—salicylate availability ☐ Suppository bases—rectal absorption

Suppositories are indicated for systemic action in patients who are in a coma or who cannot tolerate oral medication due to emesis or pathological conditions of the upper gastrointestinal tract. A rectal suppository is a convenient dosage form for the administration of medication to infants and mentally disturbed patients. Although the use of rectal suppositories is recognized for the administration of analgesics, antispasmodics, sedatives, and tranquilizers, there are conflicting opinions on the amount of drug that should be given rectally as compared to the oral dose. Generally, the suggested rectal dose ranges from one-half to twice the oral dose. By assuming that the physiological factors were constant, the proper rectal dose would be dependent on the physicochemical properties (e.g., partition coefficient, physical state, and solubility) of the drug and on the properties (e.g., melting point, solubility, and surface activity) of the suppository (1).

Atropine, chloral hydrate, methylene blue, morphine, and sodium salicylate were reported to be absorbed rectally more quickly than with oral administration (2). The dosage requirement of sulfanilamide is said to be the same for an oral tablet and a glycerinated gelatin suppository (3). Formulation may be the limiting factor in rectal absorption because the drug can be absorbed only after it is released from the suppository. On the basis of plasma levels in man 2 hr. after administration, it was reported that the absorption of aspirin from a polyethylene glycol suppository and from a glycerinated gelatin suppository was 93 and 53%, respectively, of the plasma level obtained from oral administration (4). Thus, pharmaceutical factors may influence the bioavailability and dose of a drug administered in a suppository.

This study was undertaken to compare, in terms of dose, the rectal and oral absorption of aspirin and sodium salicylate and to demonstrate the effect of several suppository bases on absorption. Since both drugs are analgesic, the clinical choice between aspirin and sodium salicylate might be based on their solubilities in the rectal fluid and the suppository base.

Table I—Yield Value and Dissolution Profile of Aspirin and Sodium Salicylate from Various Suppository Bases

Suppository Formula, g.	Yield Value, kg.	Minutes	Percent of Sodium Salicylate Dissolved 25°	37°	Percent of Aspirin Dissolved 25°	37°
PEG[a] 1540	0.51	2.2	15	66.9	88.3	38.3	90.2
PEG 6000	0.69		30	81.3	97.2	58.0	97.4
PEG 400	0.3		45	93.9	97.9	78.3	102.0
			60	100	100	92.0	103.5
Theobroma oil[b]	2.0	2.2	15	2.9	92.2	0.8	2.0
			30	4.3	98.2	2.6	5.6
			45	5.9	100	5.4	13.5
			60	6.8	100	11.7	16.9
Theobroma oil	1.27	1.9	15	6.3	94.0		
Glyceryl monostearate[c]	0.15		30	8.3	96.0		
Distilled water	0.08		45	9.4	100		
			60	10.7	100		
Theobroma oil	1.40	2.1	15	6.4	86.5	0.8	82.0
Cholesterol[d]	0.03		30	7.0	87.0	2.6	91.0
Distilled water	0.07		45	8.5	85.4	5.4	93.9
			60	8.8	85.4	11.7	98.3
SMP[e]	1.50	8.8	15	6.8	8.8	0.8	1.6
			30	8.8	10.7	1.0	2.9
			45	10.8	14.6	1.2	3.7
			60	13.6	20.5	1.8	4.2
PSMS[f]	1.35	0.4	15	5.9	49.2	1.1	3.4
Glyceryl monolaurate[g]	0.15		30	9.8	62.0	1.1	34.9
			45	13.6	63.0	1.1	48.8
			60	16.8	67.0	2.3	53.8

[a] Polyethylene glycol marketed as Carbowax, Union Carbide Chemicals. [b] Hershey's. [c] Purified, Fisher Scientific Co. [d] USP, Merck. [e] Sorbitan monopalmitate marketed as Span 40, Atlas Chemical Industries, Inc. [f] Polyoxyethylene (4) sorbitan monostearate marketed as Tween 61, Atlas Chemical Industries, Inc. [g] Marketed as Aldo MLD, Glyco Chemicals, Inc.
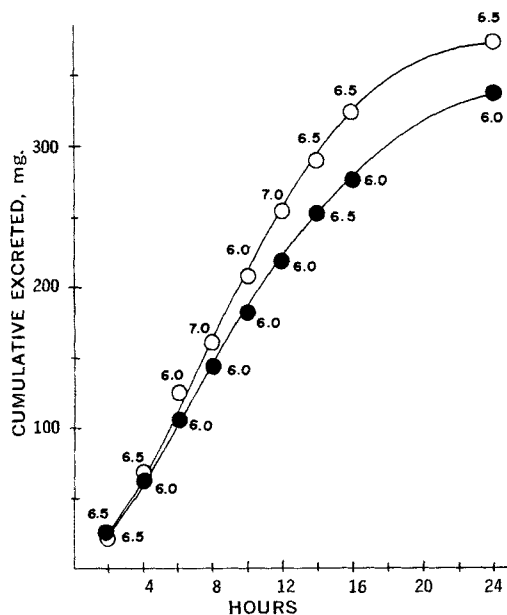
Figure 1—*Cumulative urinary salicylate excretion from Subject P. S. after the administration of 600 mg. of aspirin orally and rectally in a polyethylene glycol suppository. Values at each point are the urinary pH. Key: O, capsule; and ●, suppository.*

EXPERIMENTAL

Protocol—Ten healthy male and two healthy female human subjects, from 24 to 37 years of age and weighing from 52 to 84 kg., were used in this study. Six hundred milligrams of aspirin powder or 534 mg. of sodium salicylate powder in a gelatin capsule was administered orally upon arising. Subjects were ambulatory and permitted to ingest food and fluid as desired. Urine samples were collected at 2-hr. intervals. Volumes were measured, and aliquots were retained for analysis. The pH of the urine was determined at the time of collection of each sample. No attempt was made to control the urinary pH.

After 1 week, a suppository containing the same dose of drug was administered rectally, and urine samples were collected according to the protocol. Each subject served as his control in the comparison
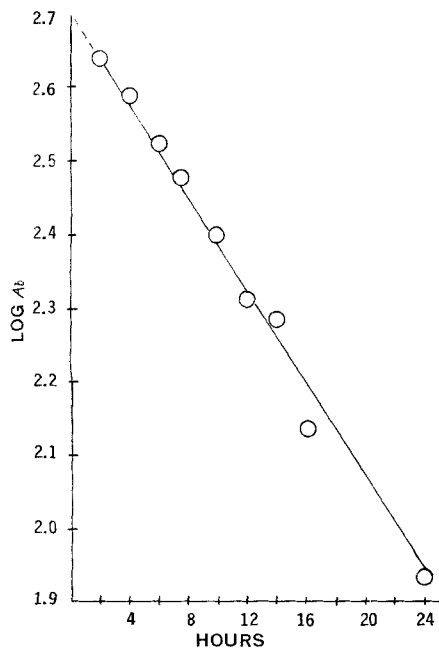
Table II—Quantity of Salicylate, Volume, and pH of Urine Excreted at 2-hr. Intervals following Oral and Rectal Administration of 600 mg. of Aspirin

Hour	pH	Urine, ml.	Salicylate Excreted, mg.	Cumulative Excreted, mg.	Milligrams in Body
Orally					
0	6.5	—	—	—	480
2	6.5	75	22.9	22.9	437.1
4	6.5	4)	48.0	70.9	389.1
6	6.0	85	55.2	126.1	333.9
8	7.0	85	35.1	161.2	298.8
10	6.0	95	46.8	208.0	252.0
12	7.0	90	46.2	254.2	205.8
14	6.5	73	36.5	290.7	169.3
16	6.5	87	33.9	324.6	135.4
24	6.5	280	49.0	373.6	86.4
Rectally					
0	—	—	—	—	
2	6.5	45.0	27.0	27.0	
4	6.0	55	37.1	64.1	
6	6.0	70	42.0	106.1	
8	6.0	60	39.0	145.1	
10	6.0	50	37.5	182.6	
12	6.0	45	36.6	219.2	
14	6.5	65	33.7	252.9	
16	6.0	55	25.9	278.8	
24	6.0	215	59.1	337.9	

of the urinary excretion of the drug from oral and rectal administration.

Analytical Method—The analysis of the urine samples was carried out by the method of Trinder (5). Analysis was carried out during the day following the collection of urine. For the measurement of dissolution from dosage forms containing aspirin, an aliquot of the dissolution medium was subjected to alkaline hydrolysis. This solution was then acidified, appropriately diluted with 0.1 N hydrochloric acid, and assayed spectrophotometrically in terms of salicylic acid (6).

Preparation of Dosage Forms—The six formulations for the suppositories are given in Table I. The suppositories were prepared by

Figure 2—*Plot for Subject P. S. of logarithm of unexcreted salicylate against time used to evaluate k. k = −2.303, slope = 0.073, hr.$^{-1}$.*
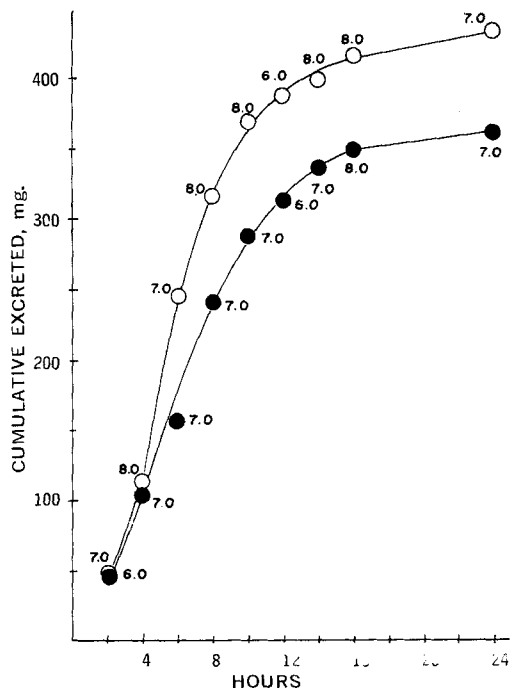

Figure 3—*Cumulative urinary salicylate excretion from Subject N. V. after the administration of 600 mg. of aspirin orally and rectally in a polyoxyethylene (4) sorbitan monostearate with glyceryl monolaurate suppository. Values at each point are the urinary pH. Key: O, capsule; and ●, suppository.*
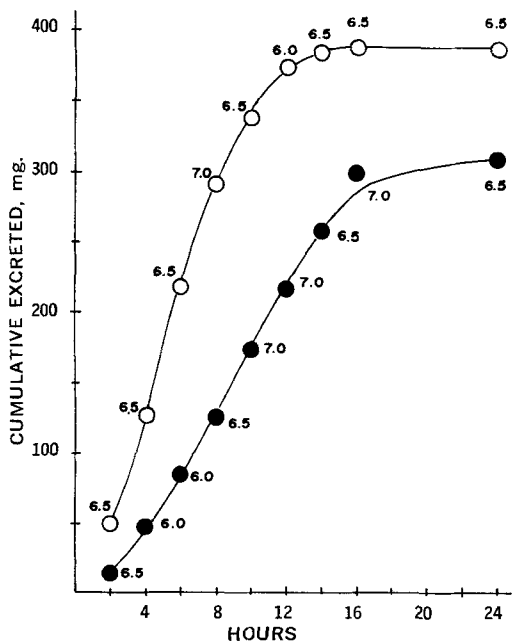
Figure 4—*Cumulative urinary salicylate excretion from Subject J. M. after the administration of 600 mg. of aspirin orally and rectally in a theobroma oil suppository. Values at each point are the urinary pH. Key: ○, capsule; and ●, suppository.*

the fusion method (7) and were utilized in 1 or 2 days after their preparation.

To determine the yield value, the suppository was first sliced in half, and the tapered end was discarded. The remaining uniform cylinder of the suppository was held in a vertical position by a small ring, and weights were added to a cardboard platform placed on the upper end. The yield value was considered to be the weight that caused deformation of the suppository at room temperature.

The percent of drug dissolved from the suppository was determined by use of the USP disintegration apparatus. A suppository was placed in the apparatus and held within a single glass cylinder
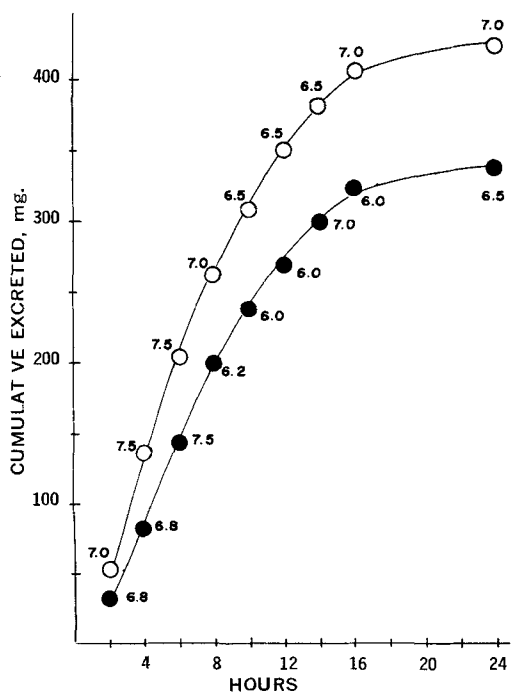

Figure 6—*Cumulative urinary salicylate excretion from Subject J. S. after the administration of 600 mg. of aspirin orally and rectally in a theobroma oil with glyceryl monostearate suppository. Values at each point are the urinary pH. Key: ○, capsule; and ●, suppository.*

by means of plastic tubing bent in the upper end of the cylinder so that it prevented the escape of the suppository. With the disintegration apparatus in operation in 1 l. of distilled water, samples were removed by a pipet fitted with a filter at 15, 30, 45, and 60 min. The samples were analyzed, and the percent dissolved at each time interval was calculated. Dissolution profiles were determined at 25 and 37°. The results are shown in Table I.

In preparing suppositories and capsules, a single batch of aspirin powder USP[1] and sodium salicylate powder USP[1] were used. Salicylate equivalents of each drug, *i.e.*, 600 mg. aspirin and 534 mg. sodium salicylate, were manually placed in a No. 0 hard gelatin capsule. The release of the drug from the capsule was determined in the USP disintegration apparatus, using distilled water and 0.1 N hydrochloric acid at 37°. The drugs were dissolved within 30 min.

RESULTS AND DISCUSSION

Typical experimental data for one subject are given in Table II. The pH of the urine did not fluctuate greatly, and this fluctuation

Figure 5—*Cumulative urinary salicylate excretion from Subject W. H. after the administration of 600 mg. of aspirin orally and rectally in a theobroma oil with cholesterol suppository. Values at each point are the urinary pH. Key: ○, capsule; and ●, suppository.*
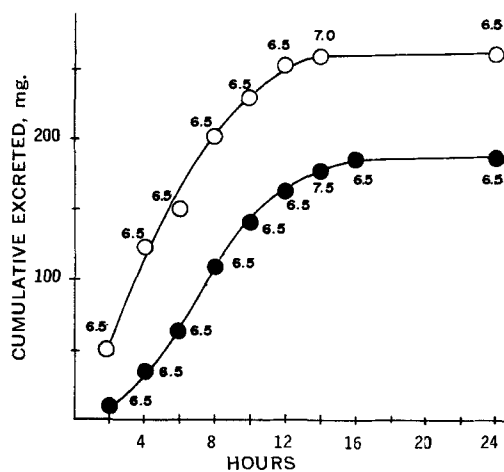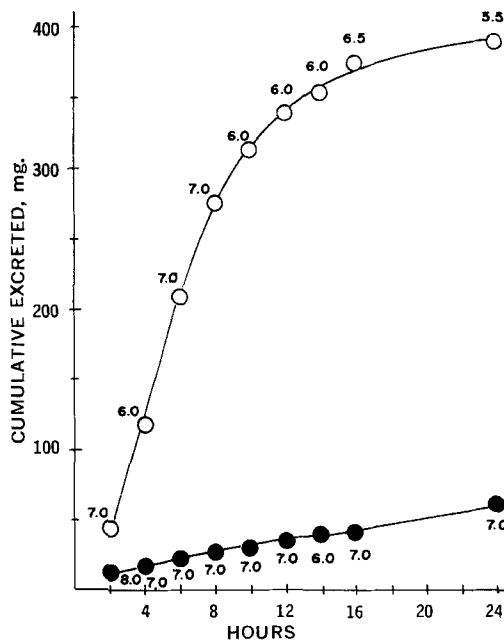

Figure 7—*Cumulative urinary salicylate excretion from Subject A. A. after the administration of 600 mg. of aspirin orally and rectally in a sorbitan monopalmitate suppository. Values at each point are the urinary pH. Key: ○, capsule; and ●, suppository.*

[1] Merck & Co., Inc.

Table III—Rate Constant for Salicylate Urinary Elimination and Comparison of f, the Fraction of 600-mg. Dose of Aspirin Recovered in Urine, at 4 and 24 hr. after Oral Ingestion of a Capsule and Rectal Administration in Various Suppository Bases

| Subject | k, hr.$^{-1}$ | For 24 hr. | | | For 4 hr. | Suppository Base[a] |
		f_{oral}	f_{rectal}	$\dfrac{f_{rectal}}{f_{oral}}$	$\dfrac{f_{rectal}}{f_{oral}}$	
P.S.	0.073	0.81	0.73	0.90	0.90	Polyethylene glycol
N.V.	0.160	0.94	0.79	0.84	0.92	Polyoxyethylene (4) sorbitan mono-stearate with glyceryl monolaurate
J.M.	0.150	0.84	0.67	0.80	0.38	Theobroma oil
W.H.	0.120	0.92	0.74	0.80	0.60	Theobroma oil with cholesterol
J.S.	0.067	0.56	0.41	0.73	0.30	Theobroma oil with glyceryl mono-stearate
A.A	0.110	0.84	0.14	0.17	0.12	Sorbitan monopalmitate
Average	0.11	0.82				
Range	0.067-0.15	0.56-0.94				

[a] See Table I for complete formula.

Table IV—Rate Constant for Salicylate Urinary Elimination and Comparison of f, the Fraction of 534-mg. Dose of Sodium Salicylate Recovered in the Urine, at 4 and 24 hr. after Oral Ingestion of a Capsule and Rectal Administration in Various Suppository Bases

| Subject | k, hr.$^{-1}$ | For 24 hr. | | | For 4 hr. | Suppository Base[a] |
		f_{oral}	f_{rectal}	$\dfrac{f_{rectal}}{f_{oral}}$	$\dfrac{f_{rectal}}{f_{oral}}$	
H.L.	0.110	0.81	0.74	0.91	0.64	Polyethylene glycol
I.H.	0.045	0.57	0.51	0.79	0.89	Theobroma oil
H.P.	0.093	0.81	0.71	0.87	0.50	Sorbitan monopalmitate
R.B.	0.095	0.79	0.63	0.80	0.68	Theobroma oil with glyceryl mono-stearate
C.R.	0.127	0.96	0.72	0.75	0.96	Theobroma oil with cholesterol
A.H.	0.064	0.68	0.31	0.45	0.62	Polyoxyethylene (4) sorbitan mono-stearate with glyceryl mono-laurate
Average	0.09	0.78				
Range	0.045-0.127	0.68-0.96				

[a] See Table I for complete formula.

would not appreciably affect salicylate elimination because the dose is small (8). The cumulative amount of salicylate eliminated in the urine is shown as a function of time in Table II and Fig. 1 for the oral and rectal administration of 600 mg. of aspirin. In view of the known rapid and complete gastrointestinal absorption of aspirin, the total excretable drug was assumed to be equal to the adminis-
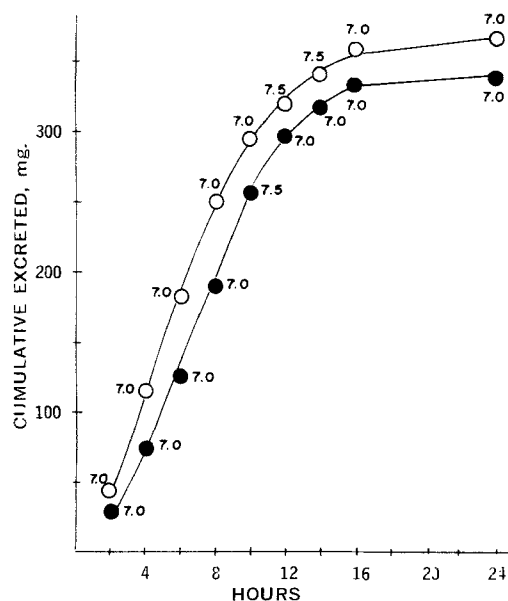
tered dose (9). The amounts (A_b) of salicylate remaining in the body after each urine collection time are then readily calculated. If the logarithm of the unexcreted drug is plotted against time, the rate constant (k) for urinary elimination may be determined (10–12). From the plot in Fig. 2 of the data in Table II, the k value for this subject was 0.073 hr.$^{-1}$.

Similar experimental data were determined for the other subjects and are represented graphically in Figs. 3–7. The k value was determined graphically for each subject; the average k value was 0.11 hr.$^{-1}$, with a range from 0.067 to 0.15 hr.$^{-1}$ as shown in Table III. The fraction (f_{oral}) of the orally administered dose of aspirin re-
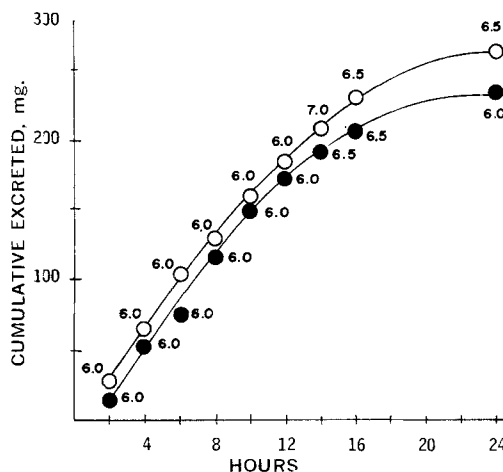

Figure 8—Cumulative urinary salicylate excretion from Subject H. L. after the administration of 534 mg. of sodium salicylate orally and rectally in a polyethylene glycol suppository. Values at each point are the urinary pH. Key: O, capsule; and ●, suppository.

Figure 9—Cumulative urinary salicylate excretion from Subject I. H. after the administration of 534 mg. of sodium salicylate orally and rectally in a theobroma oil suppository. Values at each point are the urinary pH. Key: O, capsule; and ●, suppository.
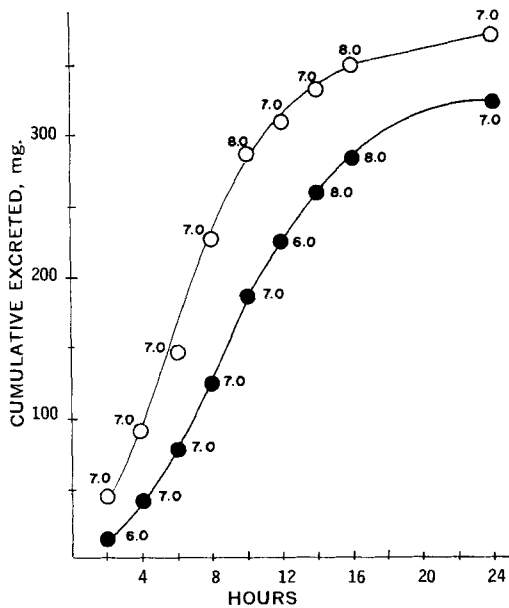
Figure 10—*Cumulative urinary salicylate excretion from Subject H. P. after the administration of 534 mg. of sodium salicylate orally and rectally in a sorbitan monopalmitate suppository. Values at each point are the urinary pH. Key: O, capsule; and ●, suppository.*

covered in the urine in 24 hr. was calculated for each subject; it ranged from 0.56 to 0.94 with an average of 0.82.

By using the same protocol for the administration of an equivalent dose of sodium salicylate, the cumulative amounts of salicylate eliminated in the urine were experimentally measured as a function of time for each subject, as shown in Figs. 8–13. The k and f_{oral} values were calculated as previously described. The average k value was 0.09 hr.$^{-1}$, with a range from 0.045 to 0.127 hr.$^{-1}$ as listed in Table IV. The fraction of the orally administered dose of sodium salicylate recovered in the urine in 24 hr. ranged from 0.68 to 0.96 with an average of 0.78.

Thus, the excretion and absorption of equivalent doses of aspirin and sodium salicylate are kinetically the same because the f_{oral} and k values for both drugs are the same.

The assumption that the mucosa of the entire gastrointestinal tract possesses the same absorption characteristics for the passively
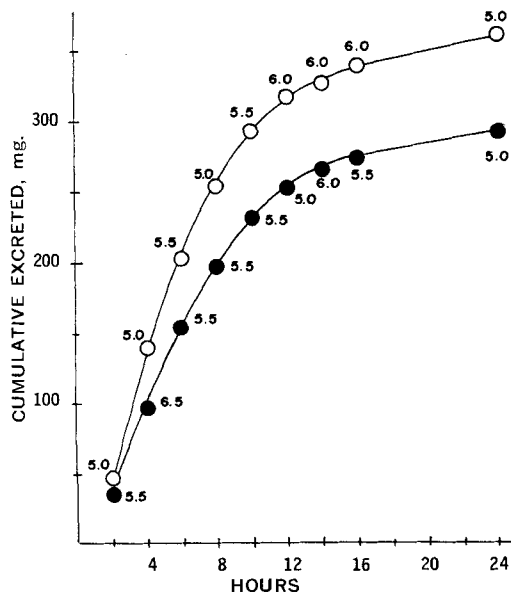

Figure 11—*Cumulative urinary salicylate excretion from Subject R. B. after the administration of 534 mg. of sodium salicylate orally and rectally in a theobroma oil with glyceryl monostearate suppository. Values at each point are the urinary pH. Key: O, capsule; and ●, suppository.*
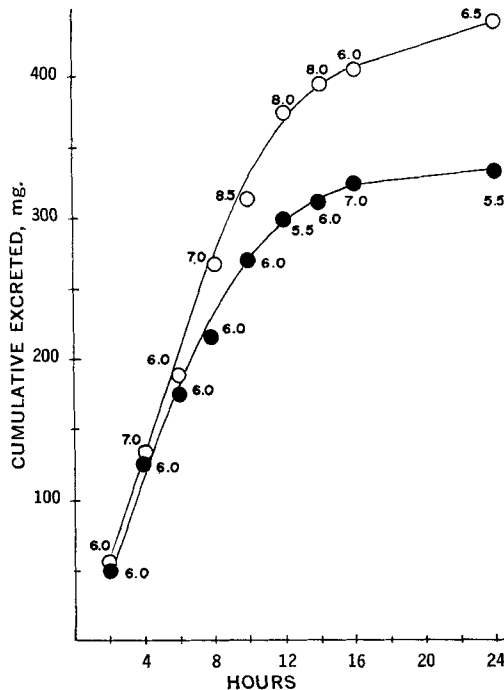

Figure 12—*Cumulative urinary salicylate excretion from Subject C. R. after the administration of 534 mg. of sodium salicylate orally and rectally in a theobroma oil with cholesterol suppository. Values at each point are the urinary pH. Key: O, capsule; and ●, suppository.*

absorbed aspirin and sodium salicylate seems valid, since the f_{rectal}/f_{oral} for aspirin was approximately 0.9 from suppository bases of polyethylene glycol and polyoxyethylene (4) sorbitan monostearate with glyceryl monolaurate at 4- and 24-hr. intervals, as shown in Figs. 1 and 3, and the f_{rectal}/f_{oral} for sodium salicylate was approximately 0.9 for suppository base of theobroma oil, as shown in Fig. 9. This assumption is also supported by the report that the plasma levels of aspirin administered in a rectal suppository were comparable to the plasma levels of aspirin administered orally (4).

Effect of Suppository Bases—The formulation of a suppository may affect absorption by controlling the release of the drug. Sorbitan monopalmitate is insoluble in water and melts at approximately 45°. As shown in Table II, only 4% of the aspirin was dissolved in 30 min., during which pieces of the sorbitan monopalmitate suppository were cast off gradually. Knowing these *in vitro*
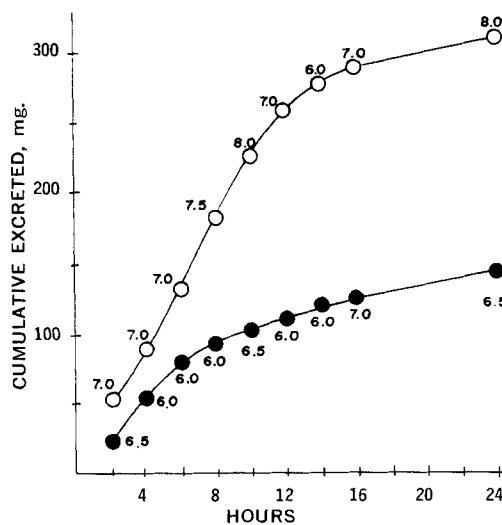

Figure 13—*Cumulative urinary salicylate excretion from Subject A. H. after the administration of 534 mg. of sodium salicylate orally and rectally in a polyoxyethylene (4) sorbitan monostearate with glyceryl monolaurate suppository. Values at each point are the urinary pH. Key: O, capsule; and ●, suppository.*

characteristics, one would anticipate a poor release of the drug. *In vivo*, the suppository remained intact for 30 min. and was difficult to retain. As shown in Fig. 7, the release of aspirin from a suppository of sorbitan monopalmitate was very poor at both the 4- and 24-hr. intervals.

As demonstrated in Table I, the *in vitro* testing of suppositories should be done at body temperature. Obviously, temperature is most important with bases such as theobroma oil and polyoxyethylene (4) sorbitan monostearate, which melt at body temperature. This is strikingly demonstrated with sodium salicylate in theobroma oil from which only 7% was released in 1 hr. at 25° but from which 98% was released in 15 min. at 37°. As suggested by this *in vitro* release, the *in vivo* release was rapid because at 4 hr. the f_{rectal}/f_{oral} for sodium salicylate in theobroma oil was 0.79 as shown in Fig. 9.

For suppository bases containing theobroma oil, the f_{rectal}/f_{oral} for aspirin was approximately 0.8 at 24 hr.; however, at a 4-hr. interval the ratio was greatly reduced, as seen in Table III. Thus, to obtain the desired effect within 4 hr., the rectal dose of aspirin in theobroma oil should be 3–4 times as great as the oral dose. The addition of glyceryl monostearate and cholesterol to theobroma oil suppositories did not appear to have any significant effect, as shown in Figs. 5, 6, 11, and 12; however, the results were inconclusive.

For sodium salicylate in suppository bases of polyethylene glycol, sorbitan monopalmitate, and theobroma oil at 24 hr., the f_{rectal}/f_{oral} was approximately 0.9. At 4 hr., a larger f_{rectal}/f_{oral} value was obtained with sodium salicylate in theobroma oil than in polyethylene glycol and sorbitan monopalmitate suppositories. Since the diffusion of the drug is slow in the solid sorbitan monopalmitate suppository and time is required for the rectal fluid to dissolve the polyethylene glycol suppository, the effect is due to the rapid melting and increased contact between the melted theobroma oil and the aqueous rectal fluid, which rapidly partitions the water-soluble sodium salicylate from the oleaginous layer.

Effect of Drug—In addition to selecting a suitable suppository base for the administration of a particular drug, occasionally the pharmacist may be in a position to select the form of the drug best suited for rapid absorption. As a general practice, rapid and more complete rectal absorption is obtained by the choice of a water-soluble form of the parent drug (13).

Since rapid release is generally desired with systemic treatment, the comparison of f_{rectal}/f_{oral} at 4 hr. is more meaningful than the 24-hr. interval. According to the data in Tables III and IV, the f_{rectal}/f_{oral} at 4 hr. for sodium salicylate and aspirin in theobroma oil was 0.89 and 0.38, respectively. This absorption is presumably a consequence of the partition coefficient, which favors the partitioning of the water-soluble sodium salicylate from the liquid oleaginous phase but does not favor the release of the water-insoluble aspirin. Thus, if rapid release from an oleaginous suppository, which melts at body temperature, is desired, the water-soluble form of the drug should be used (13).

Similarly, at 4 hr. the f_{rectal}/f_{oral} for sodium salicylate and aspirin in sorbitan monopalmitate was 0.5 and 0.12, respectively. Although sorbitan monopalmitate does not melt and the diffusion of drugs would be anticipated to be slower than in the liquefied theobroma oil, the more water-soluble sodium salicylate was partitioned from the sorbitan monopalmitate more readily than the less water-soluble aspirin.

The absorption of aspirin and sodium salicylate was approximately the same from the polyethylene glycol suppository. Apparently, the limiting step in the absorption of both drugs was the dissolution of the polyethylene glycol suppository in the rectal fluid.

Since the rate of dissolution of the polyethylene glycol suppository is the same, the release of aspirin and sodium salicylate was the same, as shown in Figs. 1 and 8.

In the suppository composed of polyoxyethylene (4) sorbitan monostearate and glyceryl monolaurate, absorption of aspirin was greater than sodium salicylate, as shown in Figs. 3 and 13. This is comparable to the report of Lowenthal and Borzelleca (14) in which salicylic acid was absorbed better than sodium salicylate from polyoxyethylene (4) sorbitan monostearate suppositories administered to dogs. The surface activity of the polyoxyethylene (4) sorbitan monostearate may peptize the mucus and make additional absorption surface available for the unionized aspirin (15).

SUMMARY

1. The rectal dose of aspirin and sodium salicylate is equivalent to the oral dose.

2. Rectal absorption may be altered by pharmaceutical factors which affect the release of the drug from the suppository base.

3. Polyethylene glycol and polyoxyethylene (4) sorbitan monostearate with glyceryl monolaurate are good suppository bases for the rapid release of aspirin.

4. Theobroma oil is a good suppository base for the rapid release of sodium salicylate.

5. In general, the water-soluble sodium salicylate is more readily released from a suppository base than the water-insoluble aspirin.

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