DRUG DEVELOPMENT COMMUNICATIONS, 2(6), 465-494 (1976)

THE DISSOLUTION RATE AND THE ORAL ABSORPTION EFFICIENCY OF SELECTED SALICYLATES FROM LIPID-DRUG DELIVERY SYSTEMS.

By Satishchandra P. Patel and Charles I. Jarowski[+]

(Department of Allied Health and Industrial Sciences, St. John's University, College of Pharmacy and Allied Health Professions, Jamaica, New York, 11439)

Summary

β-Sitosterol, cholesterol and its acetate and n-decylate esters were used in 3, 4.5 and 6-fold excess with salicylic acid, salicylamide, aspirin and methyl salicylate with and without lactose. Dissolution studies were conducted in simulated gastro-intestinal fluids with and without sodium cholate. The *in vitro* dissolution rate of salicylic acid was markedly enhanced in the presence of the bile salt. Although the dissolution rates of the salicylates from the lipid systems were significantly reduced, the rate and extent of appearance of salicylate in the urine of two test subjects were similar to plain salicylic acid. The urine recovery of free salicylate seemed to be increased when the lipid vehicle was cholesteryl n-decylate.

Introduction

Penicillins G and V coated with cholesteryl acetate showed improved stability in simulated gastric fluid. Oral administration of such coated penicillins, as well as erythromycin, resulted in

[+] To whom inquiries should be sent.

greater urinary recovery of antibiotic activity. The urinary recovery of the penicillins was also significantly higher for the 4 - 8 hour pooled samples as compared with the plain antibiotics (1). The delayed passage of the lipid-coated antibiotic particles from the stomach into the duodenum most likely accounts for the latter observation (2). Beyond the stomach, removal of the lipid coating would be expected to be rapid. The absorption of lipids is efficient and rapid after exposure to bile and pancreatic duct secretions.

In this report the dissolution rate and oral absorption of selected lipid-coated salicylates are investigated. Salicylic acid, salicylamide, aspirin and methyl salicylate were chosen as the drugs to be investigated since their biopharmaceutic and pharmacokinetic properties are well documented (3 - 13). The gastric irritation encountered with salicylic acid and aspirin might be prevented by lipid coatings such as cholesterol, cholesteryl acetate or n-decanoate or β-sitosterol. These water-insoluble, neutral, non-irritating compounds would be expected not to exert a deleterious effect on drug stability. It was expected that oral absorption of the lipid-coated salicylates would be more predictable than those with enteric coatings. Recently the absorption efficiency of the latter have been questioned (14, 15).

It was further decided to compare the various lipid-salicylate combinations with identical combinations solvent-deposited on lactose. The increased surface afforded by the latter would expectedly result in more prompt dissolution *in vitro* and faster absorption after oral administration.

Experimental

Materials- The following were obtained from commercial sources: salicylic acid[1], salicylamide[2], aspirin, powder (U.S.P.)[3],

methyl salicylate[2], cholesterol[4], cholesteryl acetate, β-sitosterol[4], cholesteryl n-decanoate[4], lactose, powder (U.S.P.)[5], sodium cholate[4], chloroform (N.F.)[5], sodium hydroxide[1], sodium phosphate, monobasic, anhydrous (Laboratory Grade)[6], potassium phosphate, dibasic, anhydrous (Laboratory Grade)[6], and hydrochloric acid, concentrated (Reagent Grade)[1].

Equipment- The following pieces of equipment were used: Constant Temperature Shaker Bath, model W.d.B.[7], Beckman Zeromatic, pH meter, Gyrotory Incubator Shaker, model G-25[7], Immersion Filter (5/8 inch by 2 inches), medium porosity[9], Beckman Grating Spectrophotometer, model DB-GT with digital display[8], Swinny Adapter (13 mm)[10], Millipore Filter Disc (13 mm diameter, 0.45 micron)[10]

Analytical Procedure for the Determination of Salicylic Acid, Salicylamide, Aspirin and Methyl Salicylate- Salicylic acid was assayed spectrophotometrically in simulated gastric fluid without pepsin (U.S.P. XIX)(303 nm) and in simulated intestinal fluid without pancreatin (U.S.P XIX) (298 nm). A linear plot of absorbance versus known concentrations in mcg/ml indicated that the Beer's relationship was operative.

Salicylamide was assayed spectrophotometrically in simulated gastric fluid without pepsin (300 nm) and in simulated intestinal fluid without pancreatin (303 nm). An absorbance versus concentration plot showed that Beer's relationship was being followed.

Aspirin was assayed spectrophotometrically in simulated gastrointestinal fluids by a reported differential procedure (16). It had been shown that differences between the ultraviolet absorption of aspirin and its hydrolysis products were sufficiently great to enable the accurate determination of both aspirin and salicylic acid. By means of simultaneous equations one can express the results in terms of total aspirin (17).

A colorimetric assay procedure was used for methyl salicylate. To 4 ml of aliquot sample was added 10 ml of 0.066 molar sodium phosphate, dibasic, 4 drops of 2 percent 4-aminoantipyrine solution and 2 ml of one percent potassium ferricyanide. The volume was made up to 20 ml with distilled water. The absorbance of the final solution was read at 510 nm. A Beer's plot was constructed by plotting absorbance versus known concentrations of methylsalicylate.

Determination of Various Salicylate Solubilities in Gastrointestinal Fluids- Excess drug (1 to 2.5 gm) was placed in a 120 ml glass bottle. Fifty ml of either simulated gastric or intestinal fluid was added. The bottles were screw-capped and shaken for 24 to 48 hours at 37°C. Samples of the solution were passed through a millipore filter (0.45 micron) positioned in a Swinny adapter. The filtrates were diluted to appropriate strengths with simulated gastrointestinal fluid and absorbance values were determined. Triplicate runs were made for each sample. These results are summarized in Table I.

Preparation of Solvent-Deposited Drug-Lipid and Drug-Lipid-Lactose Mixtures- Accurately weighed samples of drug and lipid were placed in a 400 ml beaker (Drug-Lipid ratios: 1:3, 1:4.5 and 1:6). Sufficient (10 to 25 ml) organic solvent (acetone, chloroform or methylene chloride) was added to dissolve the drug and lipid. The resulting solution was stirred with a magnetic stirrer and the solvent was evaporated by a gentle stream of nitrogen. The residue was dried in an oven at 37°C. (at least 2 hours). The dried residue was pulverized in a mortar and sieve sized to the 80-mesh range. After tumble blending for 15 minutes three samples were taken for an assay of content uniformity. Only those samples showing a uniform drug content (100 ± 5%) were used in the dissolution studies.

Table I. Saturation Solubility of Selected Salicylates in Simulated Gastrointestinal Fluids (without enzymes) at 37°C. (Average of three determinations ± S.E.).

	Solubility (mg/ml)	
Drug	Simulated Gastric Fluid	Simulated Intestinal Fluid
Salicylic acid	1.983 ± 0.023	9.316 ± 0.189
Salicylamide	2.956 ± 0.053	3.333 ± 0.115
Aspirin+	5.661 ± 0.055	18.174 ± 0.026
Methyl salicylate	34.216 ± 0.032	34.686 ± 0.025

+ Hydrolysis of aspirin occurred during the solubility determination. The solubility figures shown represent aspirin plus salicylic acid.

Solvent deposition of drug and lipid on the surface of lactose (Drug-Lipid-Lactose ratios: 1:3:6, 1:4.5:6 and 1:6:6) was carried out by suspending the lactose in the solvent solution containing the drug and lipid. Evaporation, drying, pulverization, sieve-sizing and assay for drug content uniformity were conducted as previously described.

It was expected that the Lipid-Methyl Salicylate combinations would be difficult to handle since the latter is a liquid. However the 80-mesh particles, except for having the characteristic oil of wintergreen odor, were perfectly dry and free-flowing.

Determination of the In Vitro Dissolution Rate- Determination of the dissolution rate for the pure drug and drug mixtures was conducted in simulated gastric juice (without pepsin) or simulated intestinal juice (without pancreatin) with or without 0.04 molar sodium cholate. Two hundred ml of simulated gastrointestinal fluid in a 300 ml beaker was maintained at 37 ± 0.5°C. in a constant temperature bath. The U.S.P. XIX dissolution basket was centered in the dissolution medium 20 mm above the bottom of the beaker. The basket was rotated at 60 ± 5 r.p.m. Accurately weighed samples of the pure drug or the drug mixtures were spread over the surface of the dissolution medium. Aggregates were lightly broken up with the aid of a spatula within 50 seconds after adding the sample.

Five ml aliquots were withdrawn at various time intervals by means of a pipet attached with a piece of rubber tubing to a fritted glass immersion filter (coarse porosity). These aliquots were replaced with 5 ml of gastrointestinal fluid equilibrated at 37°C. The aliquots withdrawn for assay were filtered through a millipore pad (0.45 micron) held in a Swinny adapter (13 mm diameter). Two ml of the filtrate was diluted to an appropriate volume and assayed

spectrophotometrically by the procedures described above. The gastrointestinal fluid, diluted with water in a similar manner, was used as the blank.

Each data point represents the average of at least two determinations. There was no interference from lactose, lipid or sodium cholate on the assay for the four salicylates. Here again it was expected that the lipid-methyl salicylate 60-mesh granules might technical problems in the dissolution study, such as, liquid ester separation or turbidity. Neither problem was encountered.

Bioavailability of Salicylate from Drug-Lipid Delivery Systems- Two healthy male, human subjects, 23 and 56 years of age were used for the *in vivo* studies. A salicylic acid dose of 650 mg or drug-lipid mixtures containing the same dose was administered orally to the subjects who had fasted overnight. The drug-lipid combinations of 40/60 mesh particle size were administered as suspensions in 100 to 150 ml of water. Urine samples collected before drug administration were used as blanks. The subjects fasted for 3 hours after drug administration. Urine samples were collected: 0 - 1 hour, 1 - 2 hours, 2 - 4 hours, 4 - 8 hours, 8 - 12 hours, 12 - 24 hours, 24 - 36 hours, 36 - 48 hours, 48 - 72 hours and 72 - 96 hours. The total volume and pH of the urine collected during each interval was noted. The test subjects drank liberal quantities of water to insure a urine output of 50 - 100 ml per hour.

Quantitative determination of free salicylic acid in urine was conducted by the method of Smith *et al.* (18) as modified by Levy and Procknal (19). Total salicylate was determined by the modified method of Bedford *et al.* (20). All samples were kept frozen until assayed. Analyses were conducted within 3 days after collection of the samples. All samples were assayed in duplicate.

Results and Discussion

Caru (8) had reported that both gastric secretion and emptying are inhibited by fats and fatty acids. As a consequence a delayed passage of the lipid-coated drug particles from the stomach was expected. Selection of the quantity of drug to be used in the dissolution studies was given careful consideration. It was felt that drug concentrations approaching saturation in the dissolution medium would be more predictive of *in vivo* results obtained after oral administration. Drug delivery systems that remained in the stomach longer would be exposed to smaller volumes of gastrointestinal fluid until passage beyond the pylorus had taken place.

In Table I are shown the saturation solubilities of the four salicylates in simulated gastric and intestinal fluid at 37°C. A significant increase in solubility in the latter only occurred for those salicylates possessing the free carboxyl group. As shown in Table II and Figure 1, the rate of dissolution in simulated gastr fluid is directly related to the degree of saturation. Thus, as t sample weight decreased from 356.9 mg (90% saturation of 200 ml) to 113 mg (30% saturation) the rate of dissolution increased. A plot of log per cent remaining undissolved against time for selected data is shown in Figure 2. The points are experimental, while the lines are drawn from the predicted values obtained from the least squares method using a computer. The dissolution rates for salicylic acid at 90% saturation follows simple first order kinetics. On the other hand, the data for salicylic acid:cholesterol:lactose (ratio, 1:4.5:6) shows two apparent first order rates. The higher rate occurred during the first 60 minutes. Gibaldi (21) had described a similar observation in plotting dissolution data for drugs with limited aqueous solubility. He demonstrated that such apparent first order plots are obtained under sink conditions. The higher rate

Table II. Effect of the Degree of Saturation on the In Vitro Dissolution Rate of Salicylic Acid in Simulated Gastric Fluid at 37°C.

Weight of Salicylic Acid Used (mg)	Degree of Saturation (%)	Per Cent Salicylic Acid Dissolved Time (minutes) 15	30	45	60	90	120	150	T_d^+ (min)	Log a++	b+++
356.9	90	12.0	24.50	35.0	45.47	60.16	72.75	81.14	95.4	2.1373	1.11
238.0	60	19.37	44.22	67.83	80.68	90.02	95.48	98.30	46.0	2.0794	1.25
178.5	45	18.75	43.91	73.73	91.91	99.80	100.0	100.0	36.85	2.9606	1.89
119.0	30	49.68	100.0	100.0	100.0	100.0	100.0	100.0	< 18.5	---	> 1.89

+ The time required to dissolve 63.2% of the drug. This is derived from the Weibull Cumulative Distribution Equation (21). (Figure 2)

++ The y-intercept of the line obtained by the least squares method with the use of a computer. (Figure 2)

+++ The slope of the line obtained by the least squares method with the use of a computer. (Figure 2)

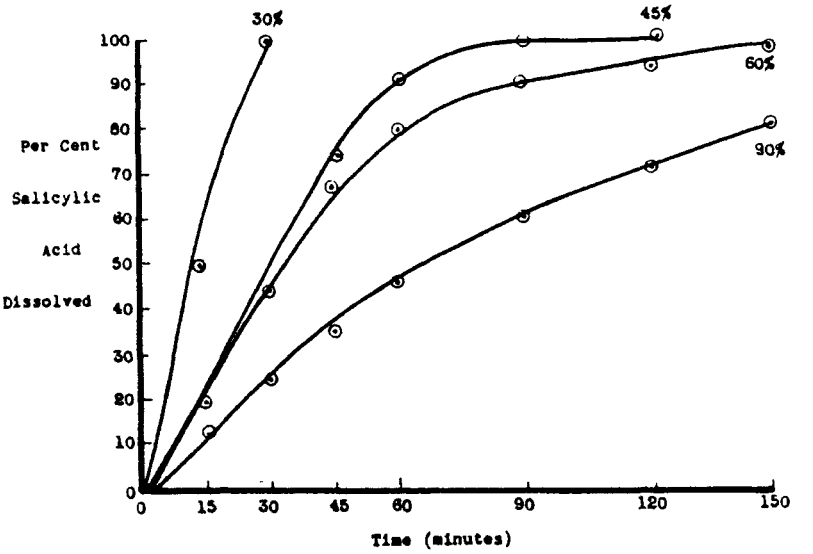

Figure 1. Effect of the Degree of Saturation on the In Vitro Dissolution Rate of Salicylic Acid in Simulated Gastric Fluid at 37°C.

constant represents the dissolution of fine particles, the other rate constant represents the dissolution of the remaining drug particles.

To avoid this, the Weibull distribution equation was used for plotting all the dissolution data:

$$\text{Log}\ (-\ln(1-m)) = b\ \text{Log}\ (t - T_1) - \text{Log}\ a$$

Langenbucher (22) reported that linearization of all common types of dissolution curves results from a Log-Log plot of $-\ln(1-m)$ versus $(t - T_1)$. The term m expresses the accumulated fraction of the drug in solution at time t; b represents the slope of the line; Log a is the y-intercept; T_1 represents the time lag before the actual onset of the dissolution process (in this instance, $T_1 = 0$). The

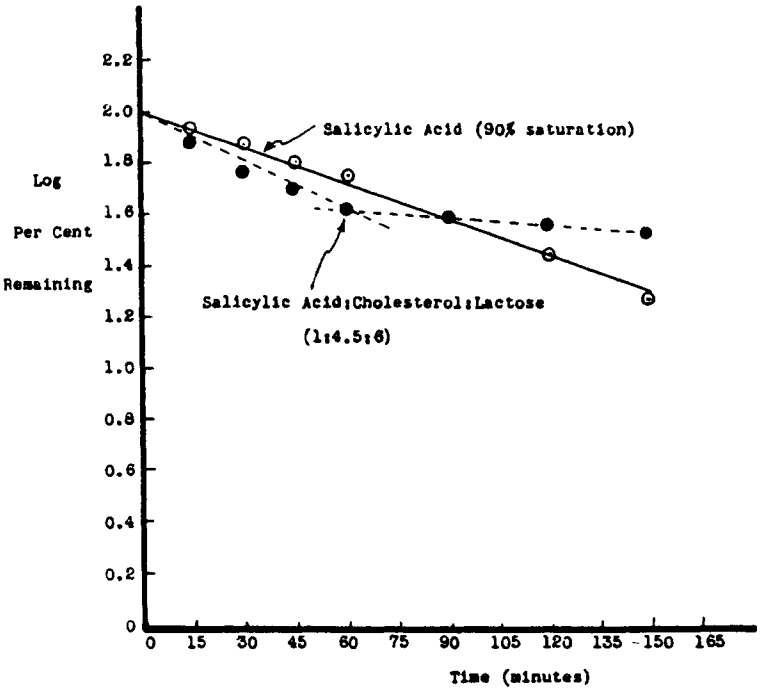

Figure 2. First Order Plot of Dissolution Rate Data for Salicylic Acid (90% saturation) and Salicylic Acid:Cholesterol: Lactose (1:4.5:6) in Simulated Gastric Juice at 37°C.

term T_d used in the Tables represents the time required to dissolve 63.2% of the drug (this is derived from the relationship $a = (T_d)^b$.

The T_d values derived from Figure 3 are summarized in Table II. When the dissolution rate was determined at 90% saturation, T_d was 95.4 minutes. At 30% saturation, this value was less than 18.5 minutes.

On the basis of these initial dissolution studies it was decided to conduct the experiments, at least for salicylic acid

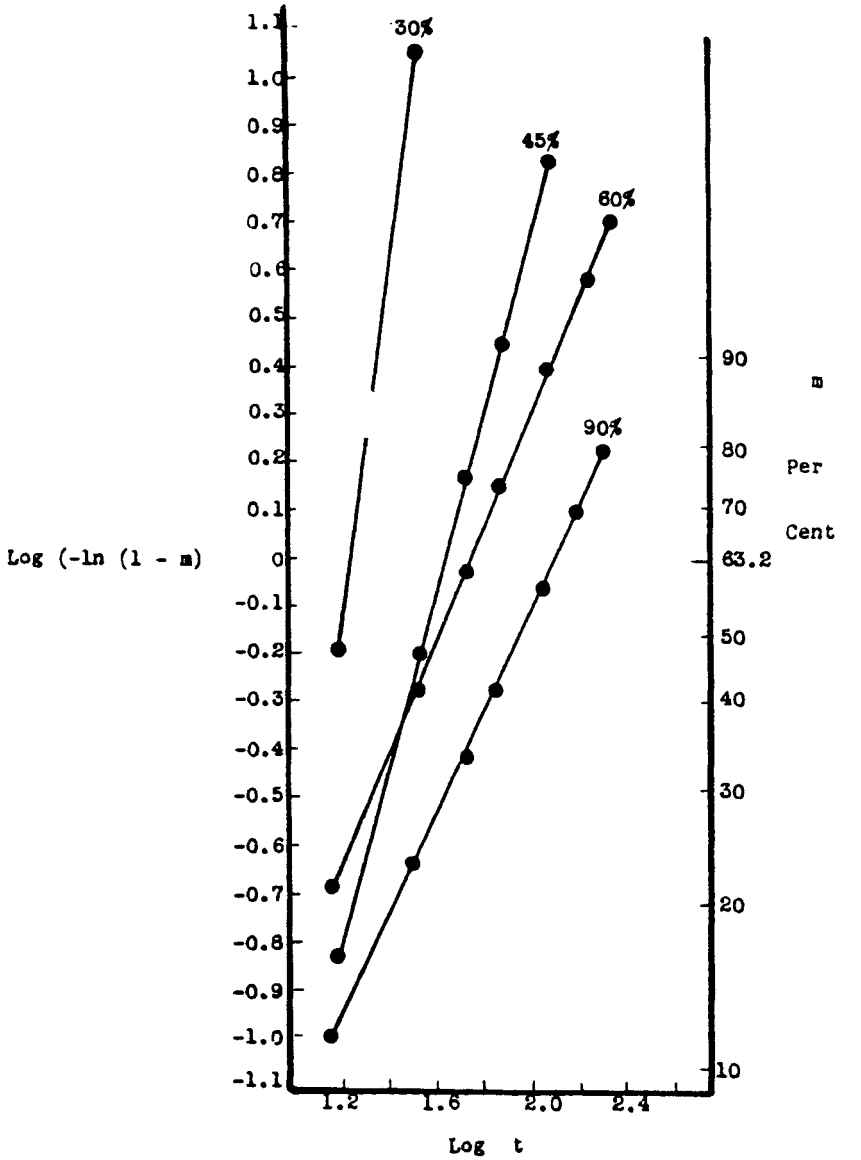

Figure 3. Effect of the Degree of Saturation on the In Vitro Dissolution Rate of Salicylic Acid in Simulated Gastric Fluid at 37°C., Plotted as Weibull Distribution.

and salicylamide, at 90% saturation. Because of the greater solubility of aspirin and methyl salicylate, the resulting bulk volume of drug:lipid:lactose solids required for 90% saturation was too great for the 200 ml of dissolution medium, consequently, lower weights were used (Table III).

The data in Table IV for the Drug:Lipid combinations shows no exception to the generalization that as lipid concentration is increased, T_d in simulated gastric fluid is increased. Deposition of the drug:lipid combination on lactose results in a reduction in T_d values. The only exception is aspirin:β-sitosterol:lactose (1:4.5:6); the T_d value for the drug:lipid combination (1:4.5) is 204.8 minutes, whereas that for the same combination with lactose is 205.2 minutes.

In Table V only the dissolution data of salicylic acid and aspirin in simulated intestinal fluid is shown. Single determinations

Table III. Weights of the Various Salicylates Used in the In Vitro Dissolution Rate Studies.

Drug	Weight (mg)	Degree of Saturation in 200 ml of Simulated Gastric Juice (%)
Salicylic Acid	356.9	90
Salicylamide	514.1	90
Aspirin	509.5	45+
Methyl Salicylate	273.7	4+

+ Lower degrees of saturation were necessitated because the more soluble salicylates would require an impractical volume of solids to be used in the dissolution study.

Table IV. Dissolution Rates in Simulated Gastric Fluid of the Various Salicylates and Their Combinations with Lipids with and without Lactose. (Abbreviations; Salicylic Acid = SA, Salicylamide= Sam, Aspirin = Asp, Methyl Salicylate = MS, Cholesterol = CH, Cholesterol Acetate = CH.Ac, β-Sitosterol = BS, Lactose = L)

Per Cent Salicylate Dissolved

		Time (minutes)							T_d		
Sample	Ratios	15	30	45	60	90	120	150	(min)	Log a^+	b^+
SA	---	8.2	14.8	28.7	45.8	61.1	73.1	81.9	97.6	2.7104	1.3623
SA:CH	1:3	10.5	18.5	23.2	27.7	31.3	34.7	38.1	444.7	1.6241	0.6133
	1:4.5	9.4	15.5	21.2	25.2	27.5	31.1	34.2	556.3	1.6818	0.6126
	1:6	8.2	14.9	19.9	22.2	25.6	28.6	31.0	657.0	1.7252	0.6123
SA:CH.Ac	1:3	7.0	7.2	7.9	10.5	12.5	13.9	16.1	1207.4	1.6952	0.4153
	1:4.5	4.1	7.1	8.5	10.4	11.9	13.3	15.4	3278.9	2.0103	0.5718
	1:6	3.8	6.5	8.5	9.8	11.3	12.9	14.4	3371.0	2.0521	0.5817
SA:BS	1:3	8.2	11.9	17.5	23.5	28.5	37.1	40.6	327.3	2.0583	0.9194
	1:4.5	3.5	7.1	10.8	16.9	19.7	23.7	25.4	470.3	2.5105	0.9394
	1:6	1.1	2.3	3.6	6.0	8.5	9.3	10.1	1095.5	3.1372	1.0321
SA:L	1:6	25.9	49.6	67.0	80.5	91.5	95.6	97.8	42.0	1.8080	1.1136

SA:CH:L	1:3:6	37.6	52.6	60.9	65.9	67.7	70.8	72.9	66.1	0.7724	0.4242
	1:4.5:6	26.4	41.9	50.9	57.4	60.0	63.8	66.9	104.4	1.0790	0.5344
	1:6:6	15.3	32.1	42.2	49.1	55.4	61.0	64.2	120.5	1.5862	0.7622
SA:CH.Ac:Ll	1:3:6	22.3	24.6	33.1	41.3	48.7	54.5	59.6	183.8	1.3625	0.6017
	1:4.5:6	11.7	15.5	21.2	26.4	29.9	34.2	37.9	501.2	1.6211	0.6004
	1:6:6	4.7	8.9	12.3	15.9	19.6	22.0	26.4	665.2	2.1926	0.7767
SA:BS:L	1:3:6	9.4	24.3	38.3	48.7	60.5	71.3	77.6	95.5	2.2966	1.1598
	1:4.5:6	7.0	15.4	27.5	34.3	46.7	54.9	66.4	135.6	2.4705	1.1585
	1:6:6	4.7	11.4	19.4	27.0	36.6	44.4	58.0	169.7	2.7190	1.2195
Sam	---	18.0	25.2	41.1	58.2	84.6	98.1	100.2	55.5	2.7676	1.5863
Sam:CH	1:3	5.7	10.9	22.8	24.6	28.8	32.6	37.6	302.1	2.2056	0.8893
	1:4.5	4.9	8.4	12.9	17.6	21.6	24.9	28.2	510.5	2.2631	0.8257
	1:6	3.3	6.7	9.5	12.3	17.1	18.4	20.7	740.3	2.4201	0.8434
Sam:CH.Ac	1:3	6.5	13.4	25.8	34.3	43.2	51.6	58.4	152.0	2.4618	1.1283
	1:4.5	4.9	11.7	24.1	31.7	38.7	46.0	53.6	166.1	2.6110	1.1759
	1:6	4.1	10.9	19.8	28.2	36.0	41.4	48.9	184.5	2.6993	1.1912
Sam:BS	1:3	4.1	6.7	10.7	12.5	15.3	19.3	22.6	843.9	2.2864	0.7813
	1:4.5	3.3	5.9	7.7	10.6	12.6	14.7	17.9	1282.0	2.3364	0.7517
	1:6	3.3	5.0	6.9	8.8	10.8	12.9	15.1	2042.6	2.2933	0.6928

Table IV. (continued)

Sample	Ratios	Time (minutes) 15	30	45	60	90	120	150	T_d (min)	Log a*	b*
Sam:L	1:6	38.5	69.6	85.9	92.4	97.2	99.2	100.5	25.7	1.7113	1.1734
Sam:CH:L	1:3:6	6.5	21.8	31.0	35.2	48.4	59.4	64.8	92.3	1.8514	1.4581
	1:4.5:6	5.7	15.1	25.8	33.4	39.6	46.0	56.5	162.7	1.4347	1.0987
	1:6:6	4.9	12.6	21.5	27.3	32.4	37.7	45.2	219.7	1.4207	1.0376
Sam:CH.Ac:L	1:3:6	7.4	31.0	50.3	65.9	81.0	94.8	99.3	60.3	3.0715	1.7029
	1:4.5:6	6.5	[illegible]	38.7	52.8	65.7	75.5	84.7	85.7	1.8767	1.3646
	1:6:6	6.5	15.9	24.4	38.7	46.8	55.2	61.2	134.1	1.4080	1.1318
Sam:BS:L	1:3:6	5.7	10.9	23.2	35.2	52.2	65.4	79.8	111.0	3.0116	1.4695
	1:4.5:6	4.1	8.4	17.2	26.4	37.3	46.0	54.6	167.4	2.9305	1.2178
	1:6:6	2.5	6.7	12.9	19.4	26.1	32.2	37.6	768.4	1.1756	0.4074
Asp	---	18.6	36.9	61.4	78.4	90.2	94.0	97.3	52.9	2.4417	1.4167
Asp:CH	1:3	20.6	29.5	38.8	51.1	61.4	73.9	81.7	89.5	1.7262	0.8842
	1:4.5	20.0	25.2	32.9	45.2	57.3	68.2	76.3	164.3	1.5271	0.6852
	1:6	11.8	18.4	31.6	41.9	55.7	65.3	72.2	113.5	2.1870	1.0641

Asp:CH.Ac	1:3	4.2	8.7	16.9	25.2	32.9	37.3	43.5	215.4	2.6891	1.1525
	1:4.5	3.9	8.6	15.5	24.3	29.9	35.3	40.9	232.8	2.6951	1.1386
	1:6	3.6	8.2	14.5	23.6	29.5	33.9	39.2	239.1	2.7433	1.1533
Asp:BS	1:3	3.2	9.7	15.3	19.7	30.2	39.5	51.2	194.8	2.9489	1.2879
	1:4.5	2.9	8.7	14.3	18.7	29.3	38.2	46.7	204.8	3.0039	1.2996
	1:6	2.9	8.7	14.1	18.1	27.5	36.2	43.9	220.6	2.9477	1.2577
Asp:L	1:6	29.45	63.8	71.4	79.8	89.9	91.7	93.9	38.2	1.3661	0.8632
Asp:CH:L	1:3:6	22.0	33.2	41.5	55.7	67.2	74.9	83.7	80.6	1.6610	0.8713
	1:4.5:6	20.7	31.3	38.9	50.2	62.7	73.0	78.9	91.1	1.6677	0.8510
	1:6:6	18.3	19.1	33.2	44.3	57.3	67.2	75.0	111.5	1.8864	0.9217
Asp:CH.Ac:L	1:3:6	4.7	9.3	17.5	26.7	36.2	39.7	43.5	195.9	2.6736	1.1664
	1:4.5:6	4.6	9.2	16.3	25.2	31.7	36.9	43.2	227.1	2.6008	1.1038
	1:6:6	3.9	9.1	15.2	23.4	31.2	35.7	41.2	230.2	2.6946	1.1407
Asp:BS:L	1:3:6	7.9	19.2	39.2	41.3	50.3	53.2	57.7	137.7	2.1365	0.9936
	1:4.5:6	5.9	16.2	20.7	24.7	31.7	46.2	51.0	205.2	2.2992	0.9943
	1:6:6	4.7	17.1	23.2	26.3	29.7	41.6	49.0	207.6	2.3810	1.0275
MS	---	11.1	22.4	34.0	57.1	69.5	75.7	84.2	85.0	2.3750	1.2310

Table IV. (continued)

Sample	Ratios	Time (minutes) 15	30	45	60	90	120	150	T_d (min)	Log e^+	b^+
MS:CH	1:3	6.7	17.7	29.3	41.3	51.0	54.6	60.2	133.4	2.3792	1.1125
	1:4.5	6.6	15.7	22.7	32.2	39.3	47.5	55.1	172.8	2.3408	1.0461
	1:6	4.4	9.0	18.0	27.5	33.3	41.6	50.0	189.5	2.7408	1.2023
MS:CH.Ac	1:3	8.9	18.2	22.7	32.2	39.5	47.3	52.6	194.8	2.0541	0.8971
	1:4.5	6.7	13.7	18.1	29.7	34.8	40.2	50.0	214.7	2.2933	0.9834
	1:6	4.4	11.3	15.7	24.9	32.4	37.5	42.9	226.1	2.5685	1.0909
MS:ES	1:3	8.9	18.0	36.0	41.5	46.8	54.6	58.0	143.2	2.0967	0.9725
	1:4.5	6.7	15.7	27.3	32.2	39.5	45.1	50.7	184.0	2.2310	0.9850
	1:6	4.4	11.1	20.2	25.3	32.7	40.2	49.7	197.0	2.6298	1.1452
MS:L	1:6	24.4	38.4	48.2	64.7	75.3	90.6	97.1	56.5	1.8963	1.0824
MS:CH:L	1:3:6	13.3	22.4	36.4	46.2	54.0	61.6	74.4	112.8	1.9704	0.9600
	1:4.5:6	11.1	20.2	29.7	38.8	49.1	57.1	65.0	138.1	2.0405	0.9534
	1:6:6	11.1	20.4	29.7	37.1	44.4	54.7	62.4	152.5	1.9753	0.9048
MS:CH.Ac:L	1:3:6	11.0	20.4	27.4	34.7	46.8	54.4	62.3	153.1	2.0083	0.9191
	1:4.5:6	6.7	15.7	24.9	32.2	36.0	47.3	57.1	173.8	2.3150	1.0334
	1:6:6	8.9	15.7	20.4	30.0	39.3	47.0	52.0	199.9	2.1277	0.9247

MS:ES:L	1:3:6	11.1	20.2	38.2	46.0	53.7	64.0	71.1	112.2	2.1095	1.0289
	1:4.5:6	6.6	20.2	25.1	30.0	41.3	49.5	59.5	161.8	2.2931	1.0380
	1:6:6	6.7	15.7	20.4	30.1	37.3	44.7	54.7	182.3	2.3180	1.0208

+ Correlation coefficients of linear regression analyses ranged from 0.913 to 0.999.

Table V. Dissolution Rates in Simulated Intestinal Fluid of Salicylic Acid and Aspirin and Their Combinations with Lipids with and without Lactose.

		Per Cent Salicylate Dissolved									
		Time (minutes)							T_a		
Sample	Ratios	15	30	45	60	90	120	150	(min)	log a*	b*
SA	---	15.2	30.8	46.7	64.3	80.0	95.9	104.5	58.8	2.4980	1.3492
SA:CH	1:3	16.7	22.7	31.4	40.4	49.5	62.6	70.9	121.2	1.7182	0.5117
	1:4.5	14.0	20.8	28.4	31.9	42.1	56.2	64.3	165.0	1.8412	0.5303
	1:6	12.3	18.0	25.9	30.2	39.4	50.3	59.7	169.9	1.8858	0.5176
SA:CH.Ac	1:3	5.9	9.5	9.7	11.1	13.2	15.2	16.7	662.9	1.7208	0.4503
	1:4.5	4.7	7.1	9.0	10.4	11.8	14.5	16.4	3941.0	1.9223	0.5374
	1:6	3.5	5.9	8.4	9.7	11.2	13.8	14.1	8501.0	2.1541	0.6029
SA:BS	1:3	9.4	14.3	20.0	25.6	32.7	41.7	50.2	426.9	1.9093	0.7153
	1:4.5	9.4	13.1	15.7	20.2	26.0	33.6	40.3	447.3	1.9105	0.7262
	1:6	10.5	11.9	13.4	18.4	21.8	27.6	33.5	901.4	1.7174	0.5512
SA:L	1:6	60.9	74.7	86.5	100.2	104.3	104.3	104.3	18.8	1.6185	1.2667
SA:CH:L	1:3:6	56.2	59.9	62.5	72.2	79.2	85.1	91.7	32.0	0.7209	0.4795
	1:4.5:6	33.9	51.2	58.3	67.3	72.9	78.2	83.5	56.6	1.0775	0.6148
	1:6:6	19.8	41.4	51.8	62.4	66.3	70.2	75.3	81.1	1.4477	0.7582

SA:CH.Ac:L	1:3:6	11.7	47.1	69.3	82.7	91.7	96.2	98.5	48.2	2.4448	1.4526
	1:4.5:6	5.9	24.7	35.9	47.9	53.7	61.9	68.1	110.0	2.4279	1.1892
	1:6:6	4.1	12.9	20.3	24.9	28.4	32.0	36.3	278.9	2.3636	0.9865
SA:BS:L	1:3:6	27.5	67.4	85.4	92.2	96.7	99.9	100.0	29.8	2.4014	1.6282
	1:4.5:6	19.9	51.9	70.8	77.2	81.4	86.8	92.3	49.7	1.6522	0.9740
	1:6:6	15.2	44.3	59.9	69.0	75.4	82.4	84.9	63.5	1.8054	1.0014
Asp	---	17.0	39.2	69.7	79.5	92.2	98.3	99.2	44.5	2.5895	1.5709
Asp:CH	1:3	23.5	32.7	41.8	56.5	66.5	74.9	85.2	79.4	1.6321	0.9559
	1:4.5	21.3	29.7	36.9	47.2	59.7	72.5	79.3	96.4	1.6681	0.9407
	1:6	16.3	29.5	36.3	41.9	59.7	69.3	74.9	104.7	1.8042	0.8932
Asp:CH.Ac	1:3	6.2	10.9	19.3	26.5	39.2	44.5	53.2	185.0	2.5153	1.1094
	1:4.5	6.2	9.7	18.9	26.5	37.2	44.1	51.3	192.1	2.5296	1.1077
	1:6	6.5	9.1	17.3	24.2	36.7	41.9	49.2	208.8	2.4987	1.0771
Asp:BS	1:3	4.7	10.9	19.2	22.7	36.3	41.5	53.2	187.8	2.6712	1.1748
	1:4.5	3.9	10.3	19.3	21.5	33.9	44.2	50.7	184.8	2.8028	1.2364
	1:6	3.7	9.7	18.2	19.7	35.2	38.9	49.2	195.8	2.8206	1.2307
Asp:L	1:6	30.0	65.3	79.3	89.4	97.3	99.7	100.0	10.0	0.1360	0.0003
Asp:CH:L	1:3:6	29.3	39.7	49.3	59.2	69.7	79.1	89.7	65.8	1.4461	0.7953
	1:4.5:6	27.3	33.2	39.7	59.2	67.9	76.2	81.9	79.4	1.4945	0.7966
	1:6:6	20.9	21.9	36.3	49.2	59.7	69.3	76.5	102.9	1.7521	0.8705

Table V. (continued)

Sample	Ratios	Time (minutes) 15	30	45	60	90	120	150	T_d (min)	Log a^+	b^+
Asp:CH.Ac:L	1:3:6	6.5	10.3	18.5	29.7	39.2	44.5	51.3	187.4	2.4871	1.0942
	1:4.5:6	6.5	11.3	17.9	29.3	36.2	41.9	49.2	205.4	2.4014	1.0384
	1:6:6	5.3	10.9	16.8	27.5	33.9	29.9	43.6	221.1	2.4769	1.0564
Asp:BS:L	1:3:6	8.5	26.3	41.9	49.3	53.9	57.2	65.3	120.8	2.0159	0.9681
	1:4.5:6	5.6	19.7	24.3	32..	39.7	49.3	59.2	156.9	2.4086	1.0970
	1:6:6	5.7	19.2	23.9	26.9	39.0	44.5	52.9	188.7	2.3103	1.0151

+ Correlation coefficients of linear regression analyses ranged from 0.899 to 0.994 with the exception of Asp:CH:L, which had a correlation coefficient of 0.446.

of the dissolution rate of salicylamide and methyl salicylate and several of their lipid combinations were conducted. There was no significant difference from the data collected in simulated gastric fluid. This observation was not unexpected since these compounds showed insignificant increases in solubility in simulated intestinal fluid (Table I). On the other hand, the greater solubility of salicylic acid and aspirin in simulated intestinal fluid should have an effect on the dissolution rate. Comparison of the data in Tables IV and V bears out this expectation. Except for the two combinations, salicylic acid:cholesteryl acetate (1:4.5) and salicylic acid:β-sitosterol (1:3), the T_d values are consistently lower when the dissolution medium was simulated intestinal fluid.

The presence of the surface active bile salt, sodium cholate, in the simulated intestinal fluid was expected to accelerate the dissolution rate of salicylic acid from the various lipid matrices. Bates et al (23) reported that bile salts enhanced the dissolution rate of hexoestrol and griseofulvin. In addition, several reports have appeared in the literature (24, 25) on the importance of bile salts in the intestinal absorption of cholesterol. Consequently, it was not surprising to learn after comparing the results in Tables V and VI, that marked reductions in T_d values occur when bile salt is present. Interestingly, the greater the lipid content, the smaller the T_d value in the case of cholesterol and cholesteryl acetate. Thus, the T_d values are 43.5, 38.5 and 13.5 minutes, respectively, for the 1:3, 1:4.5 and 1:6 ratios of salicylic acid: cholesterol. In the case of salicylic acid:cholesteryl acetate, ratios of 1:3, 1:4.5 and 1:6 exhibit T_d values of 33.0, 24.6 and 6.4 minutes respectively. It is also of interest to point out that there is essentially no difference in T_d values for all three of the β-sitosterol combinations.

Table VI. Dissolution Rates in Simulated Intestinal Fluid Containing 0.04 M Sodium Cholate of Salicylic Acid and its Combinations with Lipids.

		Per Cent Salicylic Acid Dissolved Time (minutes)							T_d		
Sample	Ratios	15	30	45	60	90	120	150	(min)	Log a^+	b^+
SA	---	79.1	91.8	99.9	102.7	103.0	103.0	103.0	11.5	1.3581	1.2787
SA:CH	1:3	13.9	58.9	71.9	82.9	92.2	96.7	99.6	43.5	2.3103	1.4092
	1:4.5	30.2	55.4	70.5	79.2	90.8	100.0	100.0	38.5	1.6613	1.0474
	1:6	68.1	82.7	93.1	97.1	100.1	103.1	103.0	13.5	0.9214	0.8155
SA:CH.Ac	1:3	35.8	68.2	75.5	81.3	87.6	91.5	94.6	33.0	1.1468	0.7548
	1:4.5	45.1	72.1	83.2	90.0	96.5	100.0	100.0	24.6	1.3139	0.9471
	1:6	79.4	86.3	91.3	94.4	97.7	100.0	100.0	6.4	0.3892	0.4808
SA:BS	1:3	74.1	84.2	95.5	97.0	101.6	102.0	102.0	11.9	0.9406	0.8734
	1:4.5	72.5	82.1	93.5	98.9	100.0	100.0	100.0	12.7	0.9583	0.8663
	1:6	74.6	81.7	91.2	94.9	98.1	99.7	100.0	11.5	0.7325	0.6899

+ Correlation coefficients of linear regression analyses ranged from 0.903 to 0.999.

The *in vitro* dissolution data in the three simulated gastrointestinal media indicated that the oral absorption efficiency of salicylic acid from the lipid delivery systems should be satisfactory. The urinary excretion data summarized in Table VII confirms this expectation. The rapid appearance of salicylate in the urine after oral administration of the lipid combinations was unexpected since it was assumed that the lipids would cause lengthier residence of the drug delivery system in the stomach where dissolution was slowest. Since only two subjects were used in the urine recovery studies no significance can be attached to the differences in total salicylate recovered after 24 hours for the various samples tested. The evaluation of salicylic acid:cholesteryl n-decylate (1:6) was undertaken because of the observation by Kim (26) that the dissolution rate of hydrocortisone was most effectively depressed by the n-decylate ester from a series of cholesteryl esters. It would appear that the free salicylate recovered in the urine after oral administration of salicylic acid:cholesteryl n-decylate (1:6) was double that obtained with salicylic acid for both subjects. Here again, the significance of this observation must await a more extensive oral absorption study. Kapp and Coburn (27) reported that adolescents and adults excrete about 80% of ingested sodium salicylate. The total salicylate recovered consists of: salicylate (20%), salicylurate (55%), glucuronides (25%) and gentisic acid and related compounds (4 - 8%). On the basis of their report, the 24 hour cumulative excretion of salicylate should have been 13.7% for CIJ (20% of 68.6) and 12.6% for SP. These interesting results deserve further confirmation to establish whether the salicylate:lipid delivery systems can reduce the metabolic transformation of orally administered drugs.

Table VII. Cumulative 24 hour Urinary Recovery of Total Salicylate and Free Salicylic Acid after Oral Administration of 650 mg of Salicylic Acid in Lipid Matrices.

		Cumulative Per Cent Urinary Recovery Time (hours)													
		1		2		4		6		8		12		24++	
Sample	Ratios	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free
CIJ, 56 year old male															
SA	---	3.2	1.2	9.4	4.1	21.5	5.6	33.6	6.9	46.1	7.5	64.2	8.6	80.0	10.6
SA:CH	1:3	1.2	0.6	6.4	2.0	17.1	2.5	27.1	4.4	44.8	7.2	64.8	9.0	86.1	11.5
SA:CH	1:6	2.5	0.5	7.5	2.0	21.1	5.2	36.0	8.5	43.9	10.1	72.8	13.2	81.1	14.3
SA:CH.Ac	1:3	1.1	0.9	5.4	2.8	14.6	3.6	23.1	6.3	39.6	10.2	56.6	12.7	74.8	16.2
SA:CH.Ac	1:6	2.1	0.7	6.4	2.5	18.0	6.4	30.7	10.5	37.4	12.5	62.0	16.3	69.0	17.1
SA:BS	1:3	1.2	0.5	6.3	1.9	16.9	2.4	26.7	4.2	45.9	6.9	65.6	8.6	81.1	11.0
SA:BS	1:6	2.4	0.5	7.4	1.8	20.8	4.8	35.6	7.9	43.3	9.3	71.9	12.4	80.1	13.7
SA:CHnD+	1:6	2.1	0.8	6.3	3.2	17.9	8.3	30.5	13.7	31.2	16.3	61.6	21.3	68.6	23.5
SP, 29 year old male															
SA	---	2.1	1.0	8.5	3.5	19.4	4.8	30.5	6.1	41.7	6.5	58.1	9.1	72.4	9.1
SA:CH	1:3	1.1	0.6	5.9	1.8	15.9	2.3	25.2	4.0	43.4	6.5	62.0	8.1	81.7	10.2
SA:CH	1:6	2.2	0.5	8.9	1.5	19.2	4.0	32.8	6.7	40.0	7.9	66.3	10.4	73.8	11.5

SA:CH.Ac	1:3	1.0	0.8	5.1	2.2	13.7	2.9	21.7	5.0	32.2	8.1	52.2	10.1	70.4	12.8
SA:CH.Ac	1:6	2.0	0.5	6.0	1.9	16.9	4.8	28.9	8.0	35.2	9.5	58.4	12.4	65.0	13.8
SA:BS	1:3	1.1	0.6	5.8	1.8	15.4	2.3	24.4	4.0	41.9	6.5	60.0	8.1	79.2	10.3
SA:BS	1:6	2.2	0.4	6.7	1.6	18.8	4.2	32.1	6.9	39.1	8.2	64.9	10.8	72.3	12.0
SA:CHnD	1:6	1.8	0.7	5.8	2.6	16.3	6.8	27.9	11.1	34.1	13.2	56.4	17.2	62.8	19.1

+ CHnD is the abbreviation being used for Cholesteryl n-decylate.

++ Samples collected beyond 24 hours showed insignificant quantities of salicylate.

The use of lipids in preparing specialized drug delivery systems warrants further study. An earlier study (1) had shown that acid labile antibiotics were protected by the lipid system and thus they were more completely absorbed after oral administration. The present study has shown that rapid absorption of salicylate takes place from such lipid:drug delivery systems. Thus, gastric irritation induced by salicylates should be mitigated by such lipid coatings without impairment of salicylate bioavailability. The interesting observation that unchanged salicylate was recovered in seemingly higher concentration in the urine of the two subjects when cholesteryl n-decylate was used, warrants further exploration.

FOOTNOTES

1. J.T. Baker Chemical Co., Phillipsburg, N.J.
2. Eastman Kodak Company, Rochester, New York.
3. Merck and Co., Inc., Chemical Division, Rahway, N.J.
4. K and K Laboratories, Inc., Plainview, N.Y.
5. Matheson, Coleman and Bell, Norwood, Ohio.
6. Fischer Scientific Co., Fair Lawn, N.J.
7. New Brunswick Scientific Co., New Brunswick, N.J.
8. Beckman Instrument Co., Fullerton, California.
9. Arthur H. Thomas Co., Chicago, Illinois.
10. Millipore Corporation, Bedford, Mass.

References

(1) S.P. Patel and C.I. Jarowski, J. Pharm. Sci., 64, 869 (1975).

(2) W.I. Cara, Amer. J. Digest. Dis., 8, 47 (1941).

(3) W.J. McKeehan and L.C. Lappas, J. Pharm. Sci., 53, 695 (1964).

(4) L.C. Lappas and R.F. Dempski, ibid., 54, 931 (1965).

(5) R.E. Dempski and G.P. Polli, ibid., 55, 645 (1966).

(6) G.P. Polli and L.J. Ravin, ibid., 56, 781 (1967).

(7) L.J. Ravin and P.D. Bernardo, ibid., 57, 1075 (1968).

(8) P.D. Bernardo and E.J. Russo, ibid., 58, 777 (1969).

(9) E.J. Russo and T.L. Benny, ibid., 59, 883 (1970).

(10) T.L. Benny and W.E. Hamlin, ibid., 60, 959 (1971).

(11) S.J.A. Kazmi and A.G. Mitchell, ibid., 60, 1422 (1971).

(12) W.E. Hamlin and A.C. Shah, ibid., 61, 989 (1972).

(13) A.C. Shah and A.K. Herd, ibid., 62, 1033 (1973).

(14) A.B. Morrison and J.A. Campbell, J. Amer. Pharm. Assn. Sci. Ed., 49, 473 (1960).

(15) J.G. Wagner, G.W. Rayan, E. Kubiak and S. Long, ibid., 49, 133 (1960).

(16) L.J. Edwards, Trans. Faraday Soc., 47, 1191 (1951).

(17) H.H. Willard, L.L. Merritt Jr. and J.A. Dean, "Instrumental Methods of Analysis" 3rd Edition, Princeton, J.J. Van Nostrand, (1958), page 120.

(18) P.K. Smith, H.L. Gleason, C.G. Stoll and S. Ogorzaled, J. Pharmacol. Exp. Ther., 87, 237 (1946).

(19) G. Levy and J.A. Procknal, J. Pharm. Sci., 57, 1650 (1968).

(20) C. Bedford, A.J. Cummings and B.K. Martin, Brit. J. Pharmacol., 24, 413 (1965).

(21) M. Gibaldi and S. Feldman, J. Pharm. Sci., 56, 1238 (1967).

(22) F. Langenbucher, J. Pharm. Pharmacol., 24, 979 (1972).

(23) T.R. Bates, M. Gibaldi and J.L. Kanig, Nature, 210, 1331 (1966).

(24) T.R. Bates, M. Gibaldi and J.L. Kanig, J. Pharm. Sci., 55, 901 (1966).

(25) M.D. Siperstein, I. L. Chaikoff and W.O. Reinhardt, J. Biol. Chem., 193, 111 (1952).

(26) K.H. Kim, St. John's University Thesis.

(27) E.M. Kapp and A.F. Coburn, J. Biol. Chem., 145, 549 (1942).