Table V—Comparison of Absorption Rate Constants (j) between Subcutaneous (sc) and Intramuscular (im) Routes [a]

Compound	j, hr^{-1}	
	sc[b]	im[c]
Sulfamethoxazole	0.78	1.10 ± 0.07
p-Aminoazobenzene	0.14	0.18 ± 0.01
p-Hydroxyazobenzene	0.090 (0.12 ± 0.02)[d]	0.17 ± 0.01
o-Aminoazotoluene	0.040	0.093 ± 0.005
1-Phenylazo-2-naphthylamine	0.0050	0.0093 ± 0.0006

[a] Controlled suspension. C_0, 5 mg/ml; V_0, 0.05 ml. [b] Estimated by extrapolation of data shown in Table IV using Eq. 5. [c] Experimental data (with standard error) cited from the previous report (4). [d] Experimental value (with standard error).

parison using five controlled suspensions. To compare at the same drug concentration (C_0) and injection volume (V_0), the values estimated by extrapolation of the data shown in Table IV using Eq. 5 were used for the absorption rate constants (j) in the subcutaneous route. This comparison shows that the absorption rate from the subcutaneous route is slower than that from the intramuscular route for all the test suspensions. A similar tendency was previously observed for injections of drug-oil solutions (5). The relationship between j and C_0 in the subcutaneous route differed slightly from that in the intramuscular route (Eqs. 9 and 10). Therefore, it should be noted that the difference in j shown in Table V may increase with increasing C_0.

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Dissolution and Bioavailability Studies of Whole and Halved Sustained-Release Theophylline Tablets

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Received July 24, 1980, from the **Faculty of Pharmacy, and* ‡ *Section of Allergy and Clinical Immunology, Department of Pediatrics, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada, R3T 2N2.* Accepted for publication August 5, 1981.

Abstract □ In dissolution studies of whole and halved 100-mg sustained-release theophylline tablets, drug release from halved tablets was significantly higher. These differences were not reflected in the bioavailability studies. The area under the curve (AUC) mean absorption time and fraction-of-dose recovered in urine at 24 hr were not significantly different following the ingestion of whole or halved 100-mg tablets. The elimination rate constant, half-life, volume of distribution, plasma, and renal clearance values were consistent with values reported previously. Discrepancies were found in the 24-hr metabolite distribution as compared to literature values and may be accounted for by the age and health of the subjects and the frequency of dosing.

Keyphrases □ Dissolution—whole and halved sustained-release theophylline tablets □ Sustained-release system—dissolution of whole and halved theophylline tablets □ Bioavailability—whole and halved sustained-release theophylline tablets □ Theophylline—bioavailability and dissolution study of whole and halved sustained-release tablets

Breaking sustained-release theophylline tablets in half is commonly practiced to achieve more accurate milligrams per kilogram dosing in children. The extent to which this affects dissolution and bioavailability is unknown.

In this investigation, 100-mg sustained-release theophylline tablets[1] were used to study the effect of halving tablets on dissolution and bioavailability. No published information about the dissolution of these tablets was available. After oral administration of the 100-mg tablet, however, 90% of the dose was absorbed within 14 hr and almost 100% was absorbed by 28 hr (1). When 300-mg tablets were dissolved, 50% of the dose entered solution by 2 hr and > 90% of the dose entered solution by 6 hr (1).

EXPERIMENTAL

Dissolution—The official USP dissolution apparatus was used (2). Simulated gastric and intestinal fluids were used as dissolution media (2).

Simulated gastric fluid, USP (2), was prepared by dissolving 2 g of sodium chloride and 3.2 g of pepsin in 7 ml of HCl and diluting the solution to 1000 ml with distilled water. This test solution had a pH of 1.2.

Simulated intestinal fluid, USP (2), was prepared by dissolving 6.8 g

[1] Theo-Dur, Astra Pharmaceuticals Canada Ltd., Mississauga, Canada L4X 1M4.

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Table I—Percentage of Theophylline Dissolved of Total from 100-mg Sustained-Release Tablets

Time, hr	Gastric, 100 mg (0.5 tablet)	Gastric, 100 mg	Intestinal, 100 mg (0.5 tablet)	Intestinal, 100 mg
1	33.0 ± 3.2	21.2 ± 3.2	36.3 ± 4.5	29.1 ± 2.3
2	42.1 ± 3.7	29.6 ± 0.9	45.8 ± 7.2	37.2 ± 3.8
3	49.5 ± 4.2	34.0 ± 1.2	52.7 ± 7.4	43.1 ± 4.7
4	54.9 ± 4.3	39.4 ± 1.7	58.5 ± 7.8	47.2 ± 4.9
5	60.4 ± 4.5	43.5 ± 1.5	63.3 ± 8.2	52.3 ± 5.5
6	65.8 ± 4.7	46.1 ± 2.5	66.7 ± 8.6	56.0 ± 6.4
7			70.1 ± 7.2	61.0 ± 6.6
8			73.8 ± 8.5	64.5 ± 6.9
9			76.8 ± 7.6	67.7 ± 7.5
10			78.6 ± 6.5	72.0 ± 7.2
11			82.3 ± 8.4	75.2 ± 8.6
12			84.4 ± 6.7	78.4 ± 7.9
25			91.2 ± 3.5	95.1 ± 7.6

of potassium phosphate (KH_2PO_4) in 250 ml of distilled water. To this solution was added 190 ml of 0.2 *N* sodium hydroxide and 400 ml of distilled water. Ten grams of pancreatin were then added and the resulting solution adjusted to pH 7.5 ± 0.1 with 0.2 *N* sodium hydroxide. This solution was diluted to 1000 ml with distilled water.

The 100-mg sustained-release theophylline tablets, as whole or halved tablets, were tested up to six times in each dissolution medium. The tablet, or tablet halves, were placed in the gold-plated basket and immersed in 900 ml of dissolution medium at 37° in the dissolution apparatus. The basket was rotated at 100 ± 5 rpm. Samples were withdrawn at 1, 2, 3, 4, 5, and 6 hr in gastric fluid and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 25 hr in intestinal fluid under sink conditions.

Bioavailability—Relative bioavailability studies were carried out in seven normal adult volunteers, four female and three male, on 2 study days, 1 week apart, after informed consent was obtained. Their mean age was 30 ± 7 yr (range: 21–39 yr) and their mean weight was 72 ± 21 kg (range: 54–100 kg). As determined by a comprehensive medical history they were in excellent health, were nonsmokers, and were not taking any medication at the time of the study. All volunteers had normal complete blood counts and normal screening tests for renal and hepatic function.

All subjects refrained from the ingestion of tea, coffee, chocolate, and cola for 48 hr before and during the 2 separate study days. On each study day, after an overnight fast with ingestion of no more than 480 ml of water, a heparin lock was inserted, a control blood sample was withdrawn, and a control urine specimen collected. Each subject received a mean 5.20 ± 0.24 mg/kg (range: 4.9–4.6 mg/kg) dose of theophylline to the nearest whole 100-mg sustained-release tablet. Tablets were administered whole or halved along with 120 ml of water. Subjects were assigned by random choice into Study Group 1 or Study Group 2. Study Group 1 received whole tablets the first week and halved tablets the second week. Study Group 2 received the halved tablets the first week and whole tablets the second week.

Blood samples were withdrawn at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 18, and 24 hr. Serum was separated and frozen along with an aliquot of accurately measured pooled 24-hr urine until analysis for theophylline content could be performed. Subjects ate meals of uniform composition 4 and 8 hr after ingestion of the dose.

Assay Procedure—There are many methods for measuring theophylline concentrations and these have been adequately reviewed (3). Reversed-phase high-pressure liquid chromatography (HPLC) appears to be the method of choice and was used in this study[2]. Although direct injection methods are available for both theophylline (4–7) and its metabolites (8), the chromatograms obtained using these methods were not satisfactory. Since theophylline is bound to plasma proteins (9) some of these methods only measured unbound drug. The procedures developed and used were based on older methods (10) involving extraction.

Theophylline Extraction Procedure—To 50 μl of dissolution medium, urine, or serum in a 10 × 75-mm test tube was added 50 μl of aqueous solution of β-hydroxyethyltheophylline (15 μg/ml) as internal standard. A 25-μl aliquot of 20% trichloroacetic acid was added and the solution was vortexed and centrifuged. The supernate was transferred into a clean 13 × 100-mm test tube. After buffering with 300 μl of 2.5 *M* acetate buffer (pH 6.4) the solution was extracted with 2 ml of chloroform–isopropanol (20:1) by vortexing and centrifugation. The aqueous supernate was aspirated and the organic layer evaporated to dryness using low heat and a stream of dry nitrogen. The sample was redissolved in 50–100 μl of mobile phase and a 25 μl aliquot was injected directly onto the column. Theophylline concentration was calculated from a calibration curve of the peak height ratio of theophylline to the internal standard *versus* concentration.

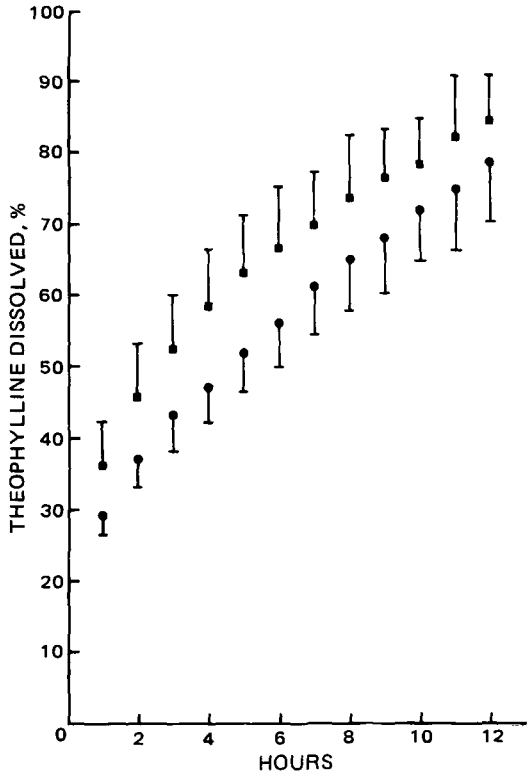

Figure 1—*Percent theophylline dissolved in simulated intestinal fluid* versus *time, from whole, (●) or halved (■) 100-mg sustained-release tablets.*

Theophylline Metabolite Extraction Procedure—To 200 μl of urine, test sample, or standards in solution in urine was added 50 μl of aqueous solution of theobromine (150 μg/ml). After buffering with 150 μl of 2.5 *M* acetate buffer (pH 6.4), the solution was extracted with 4 ml of chloroform–isopropanol (20:1) by vortexing and centrifugation.

The supernate was transferred to a clean test tube with a Pasteur pipet, and 50 μl was diluted with 200 μl filtered, distilled water to yield a final dilution of 1:10 of the urine sample. Exactly 25 μl of the diluted supernate was injected into the HPLC. The concentration of 1-methyluric acid was calculated from a calibration curve in which absolute peak heights *versus* concentration were plotted.

The organic layer from the sample was transferred to a clean, dry test tube and evaporated to dryness in a water bath at 60° with dry nitrogen. The sample was redissolved in 500 μl of mobile phase, and 25 μl was injected onto the chromatograph. The concentrations of 3-methylxanthine and 1,3-dimethyluric acid were calculated from calibration curves constructed by plotting the peak height ratios of the two metabolites to theobromine *versus* concentration of the metabolites.

HPLC Conditions—A 30-cm × 3.9-mm i.d. stainless steel column[3] was used in all assay procedures.

The mobile phase for theophylline was 9% acetonitrile in 0.01 *M* acetate buffer (pH 4.0). At a flow rate of 2 ml/min and an operating pressure of 1500–2000 psi, theophylline and β-hydroxyethyltheophylline had retention times of 4.9 and 6.2 min, respectively.

The mobile phase for 1-methyluric acid was 5% methanol in 0.05 *M* phosphate buffer (pH 4.75). At a flow rate of 2.0 ml/min the 1-methyluric acid had a retention time of 4.0 min.

The mobile phase for the other two theophylline metabolites was 11% methanol in 0.05 *M* phosphate buffer (pH 4.75). At a flow rate of 2 ml/min, 3-methylxanthine, 1,3-dimethyluric acid, and theobromine had retention times of 2.9, 4.2, and 5.1 min, respectively.

[2] The HPLC system consisted of a Model U6K injector, a Model 6000A high-pressure pump, and a Model 440 absorbance detector, all from Waters Associates, Milford, Mass. A 10 mv Omniscribe recorder from Houston Instrument, Austin, Tex. completed the system.

[3] μ Bondapak C_{18}, Waters Associates, Milford, MA 01757

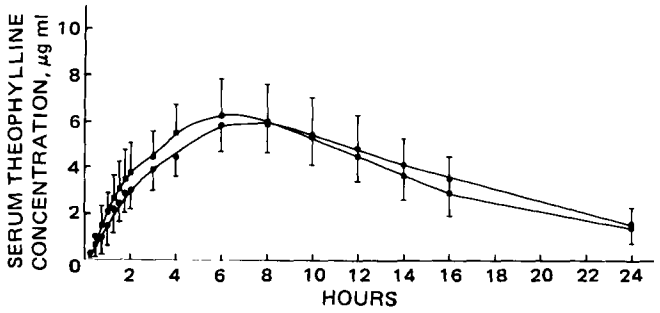

Figure 2—*Mean serum theophylline concentration* versus *time curves from seven normal volunteers who ingested a 5-mg/kg dose as whole (●) or halved (■) 100-mg sustained-release tablets.*

Data Analysis—The theophylline concentration *versus* time curve data from halved and whole 100-mg sustained-release tablets in simulated gastric and intestinal fluid were analyzed by plotting the cumulative percent dissolved *versus* time.

From each of the seven subjects who ingested a mean 5.2 mg/kg dose of theophylline as whole or halved 100-mg tablets, the log serum theophylline concentrations *versus* time curve was plotted. From the terminal linear portion of the curve, the first-order elimination rate constant (K_e) was calculated by:

$$\log Cp = \log Cp_0 - \frac{K_e}{2.303} t \qquad \text{(Eq. 1)}$$

where Cp is the serum theophylline concentration at any time t, and Cp_0 is the extrapolated serum theophylline concentration at zero time, *i.e.*, the y intercept. Elimination half-life values ($t_{1/2}$) were calculated by:

$$t_{1/2} = \frac{0.693}{K_e} \qquad \text{(Eq. 2)}$$

The fraction of the dose absorbed (f) at any time t was calculated by the formula:

$$f = \frac{(Xa)^t}{(Xa)^\infty} = \frac{Cp + K_e \int_0^t Cp\, dt}{K_e \int_0^\infty Cp\, dt} \qquad \text{(Eq. 3)}$$

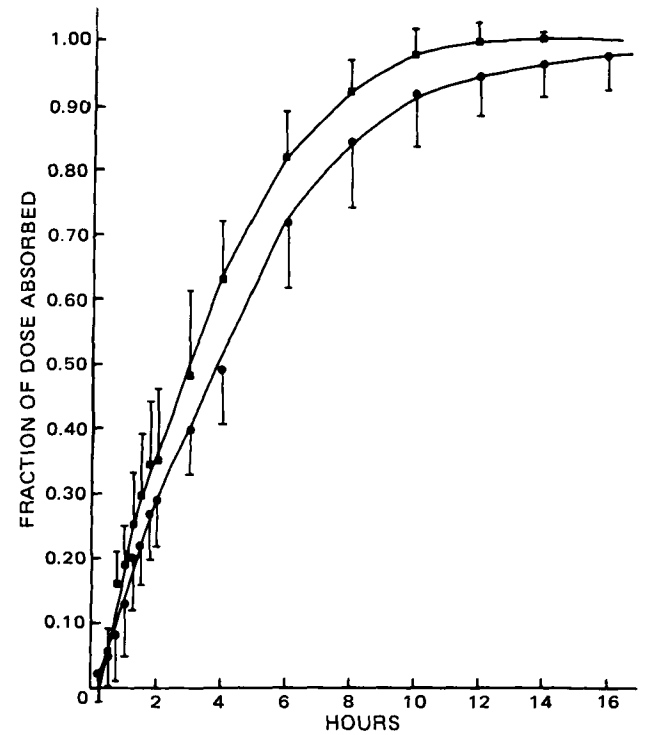

Figure 3—*Mean fractions of a 5-mg/kg dose of theophylline absorbed* versus *time in seven normal volunteers who ingested whole (●) or halved (■) 100-mg sustained-release tablets.*

Table II—Serum Theophylline Concentrations (μg/ml) at Each Sampling Time following the Ingestion of a 5-mg/kg Dose as Whole or Halved 100-mg Sustained-Release Tablets

Subjects	Time, hr 0	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2	3	4	6	8	10	12	14	16	24
Whole Tablets																		
A	—	1.20	1.82	2.21	2.90	3.76	3.66	4.07	4.11	5.26	5.35	7.28	7.17	5.88	5.04	4.09	3.45	1.22
B	—	*tr*[a]	0.42	0.84	1.22	1.85	2.46	3.48	3.72	4.34	5.31	5.21	4.62	3.95	3.27	2.43	1.41	0.36
C	—	—	*tr*	0.90	1.21	1.73	1.87	2.33	2.39	2.81	3.25	4.61	4.03	3.40	2.49	1.76	1.16	*tr*
D	—	0.32	1.34	0.54	0.93	1.61	2.01	2.24	2.53	3.89	4.92	7.48	7.83	7.37	6.34	5.35	4.81	2.37
E	—	*tr*	*tr*	0.04	0.69	1.30	1.76	1.82	1.96	3.13	3.60	5.42	6.59	6.39	5.49	4.61	3.96	1.57
F	—	0.15	1.22	1.77	2.61	3.16	3.19	3.33	3.41	4.35	4.52	5.62	5.79	5.57	5.36	5.00	4.75	3.31
G	—	—	0.02	0.39	0.86	1.57	1.82	2.69	2.88	3.39	4.12	5.14	5.66	6.16	5.94	5.09	4.72	1.71
Mean ± *SD*		0.24 ± 0.12	0.86 ± 0.73	0.96 ± 0.77	1.49 ± 0.89	2.14 ± 0.93	2.40 ± 0.75	2.85 ± 0.80	3.00 ± 0.78	3.88 ± 0.85	4.44 ± 0.82	5.82 ± 1.11	5.96 ± 1.35	5.53 ± 1.40	4.85 ± 1.42	4.05 ± 1.41	3.47 ± 1.57	1.76 ± 1.01
Halved Tablets																		
A	—	*tr*	0.79	2.39	3.06	3.49	4.18	4.86	5.12	6.26	6.88	7.76	7.10	6.13	4.69	3.87	2.94	0.94
B	—	*tr*	0.67	2.02	2.25	2.53	2.91	3.78	3.46	4.49	4.90	5.43	4.52	3.54	2.73	1.70	1.08	0.05
C	—	*tr*	0.92	1.33	1.89	1.80	2.19	2.41	2.54	3.20	3.66	3.74	3.23	2.51	1.32	0.88	0.36	*tr*
D	*tr*	*tr*	0.27	0.79	1.53	2.84	3.49	3.62	3.85	5.41	6.47	8.21	7.85	7.18	5.92	4.75	3.87	1.93
E	—	*tr*	0.54	1.10	1.63	2.30	2.12	2.83	3.15	3.84	5.60	5.92	5.81	5.76	5.10	4.35	3.87	2.10
F	*tr*	*tr*	0.75	2.31	3.17	4.33	4.94	5.12	5.10	5.94	6.67	6.82	6.66	6.15	5.91	4.83	4.31	2.02
G	—	—	*tr*	0.20	0.86	1.21	1.36	1.76	1.40	1.80	4.31	5.85	6.16	6.18	5.46	5.05	4.03	1.65
Mean ± *SD*			0.66 ± 0.23	1.45 ± 0.82	2.06 ± 0.84	2.64 ± 1.04	3.03 ± 1.26	3.48 ± 1.24	3.52 ± 1.34	4.42 ± 1.60	5.50 ± 1.25	6.25 ± 1.51	5.90 ± 1.58	5.35 ± 1.67	4.45 ± 1.76	3.63 ± 1.66	2.92 ± 1.58	1.45 ± 0.80

[a] *tr* = Trace: indicates that theophylline was detected but the concentrations were too low to quantitate.

Table III—Fraction (f) of a 5-mg/kg Dose of Theophylline Absorbed at Each Sampling Time following Ingestion of Whole or Halved 100-mg Sustained-Release Tablets

Subject	Time, hr													
	0.25	0.5	0.75	1.0	1.25	1.5	1.75	2	3	4	6	8	10	12	14	16	24
								Whole Tablets									
A	0.10	0.15	0.19	0.25	0.33	0.33	0.37	0.38	0.51	0.57	0.84	0.95	0.97	1.00	1.00	1.02	1.00
B	0.0	0.04	0.07	0.11	0.17	0.23	0.32	0.36	0.47	0.62	0.77	0.87	0.94	0.99	1.01	0.98	1.00
C	0.0	0.0	0.10	0.14	0.21	0.23	0.29	0.31	0.40	0.50	0.79	0.88	0.94	0.94	0.94	0.92	0.94
D	0.03	0.12	0.05	0.08	0.14	0.18	0.20	0.23	0.37	0.49	0.79	0.92	0.99	0.99	0.99	1.01	1.00
E	0.0	0.0	0.0	0.06	0.12	0.17	0.18	0.19	0.32	0.40	0.64	0.86	0.96	0.99	1.00	1.02	1.00
F	0.01	0.10	0.15	0.22	0.28	0.28	0.30	0.31	0.42	0.46	0.62	0.71	0.77	0.82	0.86	0.91	1.00
G	0.0	0.0	0.03	0.07	0.13	0.15	0.23	0.25	0.31	0.40	0.57	0.70	0.84	0.93	0.96	1.01	1.00
Mean ± *SD*	0.02 ± 0.04	0.06 ± 0.06	0.08 ± 0.07	0.13 ± 0.08	0.20 ± 0.08	0.22 ± 0.06	0.27 ± 0.07	0.29 ± 0.07	0.40 ± 0.07	0.49 ± 0.08	0.72 ± 0.10	0.84 ± 0.10	0.92 ± 0.08	0.95 ± 0.06	0.97 ± 0.05	0.98 ± 0.05	
								Halved Tablets									
A	0.0	0.06	0.17	0.23	0.26	0.32	0.38	0.41	0.54	0.65	0.84	0.93	0.98	0.98	1.00	1.00	1.00
B	0.0	0.06	0.18	0.21	0.24	0.28	0.37	0.36	0.51	0.63	0.85	0.94	0.99	1.03	1.02	1.01	1.03
C	0.0	0.11	0.16	0.23	0.23	0.29	0.33	0.36	0.50	0.64	0.83	0.95	1.02	0.99	0.99	0.97	0.98
D	0.0	0.02	0.07	0.13	0.24	0.30	0.31	0.34	0.50	0.63	0.88	0.96	1.02	1.01	1.00	0.99	1.00
E	0.0	0.06	0.12	0.19	0.26	0.25	0.33	0.37	0.48	0.71	0.84	0.92	1.00	1.01	1.00	1.01	1.00
F	0.0	0.07	0.21	0.29	0.40	0.47	0.49	0.50	0.61	0.72	0.83	0.91	0.96	1.03	1.01	1.02	1.00
G	0.0	0.0	0.20	0.08	0.11	0.13	0.17	0.14	0.19	0.44	0.67	0.81	0.92	0.96	1.02	1.01	1.00
Mean ± *SD*	0.0	0.05 ± 0.04	0.16 ± 0.05	0.19 ± 0.07	0.25 ± 0.08	0.29 ± 0.10	0.34 ± 0.10	0.35 ± 0.11	0.48 ± 0.13	0.63 ± 0.09	0.82 ± 0.07	0.92 ± 0.05	0.98 ± 0.04	1.00 ± 0.03	1.01 ± 0.01		

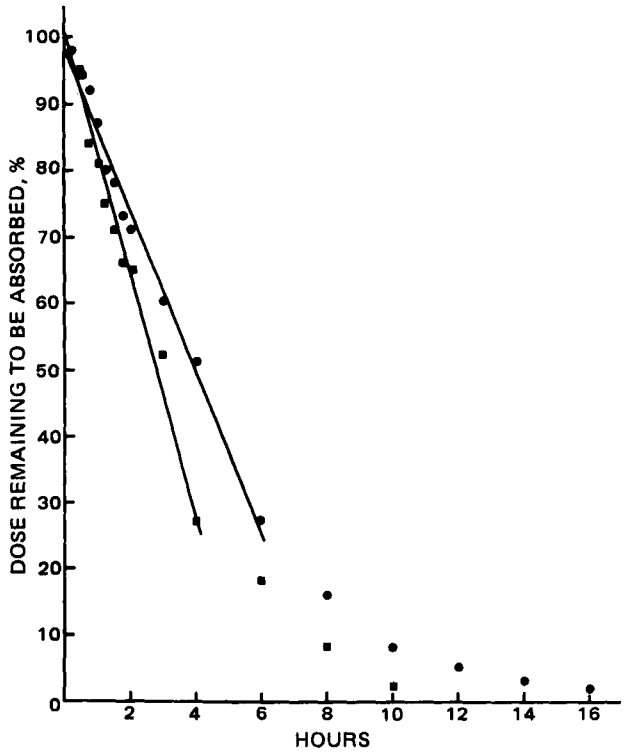

Figure 4—*Mean percentages of a 5-mg/kg dose of theophylline remaining to be absorbed* versus *time in seven normal volunteers who ingested whole (●) or halved (■) 100-mg sustained-release tablets.*

where $\int_0^t Cp\,dt$ and $\int_0^\infty Cp\,dt$ are the areas under the serum concentration *versus* time curves for time 0 to any time t and time 0 to infinity (*i.e.*, total amount absorbed), respectively. The areas $\int_0^t Cp\,dt$ and $\int_0^{t_n} Cp\,dt$ were calculated using the trapezoid method to time t_n. The area $t_n \int^\infty Cp\,dt$ was calculated using Eq. 4 and added to the area $\int_0^{t_n} Cp\,dt$ (11).

$$\int_{t_n}^{\infty} Cp\,dt = \frac{Cp_n}{K_e} \qquad \text{(Eq. 4)}$$

The mean absorption time (MAT) was calculated by (12):

$$\text{MAT} = \frac{\int_0^\infty Cpt\,dt}{\int_0^\infty Cp\,dt} - \frac{1}{K_e} \qquad \text{(Eq. 5)}$$

Plasma clearance (Cl) of theophylline was given by:

$$Cl = \frac{\text{dose}}{\int_0^\infty Cp\,dt} \qquad \text{(Eq. 6)}$$

where $\int_0^\infty Cp\,dt$ is the area under the serum concentration *versus* time curve for time zero to infinity as calculated in Eq. 3.

The apparent volume of distribution for theophylline (V_d) was calculated from:

$$V_d = \frac{Cl}{K_e} \qquad \text{(Eq. 7)}$$

The renal clearance of theophylline (Cl_R) was calculated by the formula:

$$Cl_R = f_e Cl \qquad \text{(Eq. 8)}$$

where f_e is the fraction of the total amount of the dose in 24 hr urine excreted as theophylline (11).

RESULTS

The mean cumulative percentage of theophylline dissolved from the whole and halved 100-mg sustained-release tablets at each sample time in simulated gastric and intestinal fluids is tabulated in Table I. The mean cumulative percent of theophylline dissolved from the whole and halved 100-mg tablets in intestinal fluid *versus* time is shown in Fig. 1.

Table IV—Theophylline Pharmacokinetics Parameters in Normal Volunteers following the Ingestion of a 5-mg/kg Dose as Whole or Halved 100-mg Sustained-Release Tablets

Subject	AUC, μg/ml/hr	MAT, hr	Elimination Values from Log Plot		Volume of Distribution, (V_d), l/kg	Plasma Clearance (Cl), ml/min/kg	Renal Clearance (Cl_R), ml/min/kg
			K_e, hr^{-1}	$t_{1/2}$, hr			
			Whole Tablets				
A	112.75	3.60	0.11	6.30	0.40	0.74	0.09
B	66.65	4.21	0.18	3.85	0.46	1.36	0.17
C	56.82	4.08	0.16	4.33	0.55	1.47	0.12
D	147.00	4.01	0.08	8.66	0.47	0.63	0.20
E	109.94	5.05	0.10	6.93	0.47	0.79	0.20
F	150.16	5.91	0.03	23.10	1.17	0.58	0.14
G	115.18	6.14	0.11	6.30	0.39	0.71	0.08
Mean ± *SD*	108.36 ± 35.35	4.71 ± 1.00	0.11 ± 0.05	8.50 ± 6.64	0.56 ± 0.27	0.90 ± 0.36	0.14 ± 0.05
			Halved Tablets				
A	109.26	3.37	0.13	5.33	0.35	0.76	0.07
B	59.23	3.86	0.20	3.47	0.46	1.54	0.12
C	39.64	3.35	0.23	3.01	0.55	2.10	0.21
D	136.99	3.29	0.09	7.70	0.45	0.68	0.21
E	128.47	3.44	0.07	9.90	0.58	0.67	0.22
F	139.91	2.64	0.09	7.70	0.42	0.63	0.12
G	111.14	5.28	0.10	6.93	0.44	0.74	0.12
Mean ± *SD*	103.52 ± 39.16	3.60 ± 0.82	0.13 ± 0.06	6.29 ± 2.48	0.46 ± 0.08	1.02 ± 0.57	0.15 ± 0.06

Serum theophylline concentrations from the seven subjects following the administration of a mean theophylline dose of 5.2 mg/kg theophylline as whole or halved 100-mg tablets are listed in Table II. The mean serum theophylline concentration *versus* time plots for the two doses are shown in Fig. 2.

The fractions of the dose of theophylline absorbed (f) at each time interval for each subject following the dose as whole and halved tablets are shown in Table III. The mean values following each dose *versus* time is shown in Fig. 3. The pharmacokinetic parameters, AUC, MAT, K_e, $t_{1/2}$, V_d, Cl_1, and Cl_R for each subject, following both doses, are listed in Table IV. The mean percentage of the dose to be absorbed following the ingestion of whole or halved 100-mg tablets *versus* time is given in Fig. 4. The amounts of the dose recovered in 24 hr in the urine as unchanged theophylline and the various metabolites are shown in Table V. In Table VI the metabolites and theophylline recovery is reported as percentages of theophylline equivalents of the 24-hr urine recovery.

DISCUSSION

The only reference to dissolution data in the literature was from the manufacturer as reported by one group of investigators (1). From the 300-mg sustained-release tablets, 50% of the dose was reported to be in solution by 2 hr and > 90% was in solution by 6 hr. No specifications were reported. In the present study, in gastric fluid, 46.1 ± 2.5 and 65.8 ± 4.7% of the dose was in solution at 6 hr from whole and halved 100-mg tablets, respectively (Table I). The stomach mean emptying time for enteric-coated tablets has been reported to be 3.61 ± 1.47 hr (13); therefore, dissolution studies in gastric fluid were stopped at 6 hr.

In intestinal fluid, 52.7 ± 7.8% of the dose was released in 3 hr by halved 100-mg tablets, and 52.3 ± 5.5% was released in 5 hr by whole 100-mg tablets. After 12 hr, 84.4 ± 6.7% of the dose was in solution from halved tablets and 78.4 ± 7.9% of the dose in 10 hr from whole tablets (Table I). With the paucity of information available in the literature (1), it was not possible to compare previously reported results with the results from the present study.

These sustained-release theophylline tablets are reported to release theophylline by a zero-order rate, *i.e.*, equivalent to an infusion; therefore, plots of percentage released *versus* time should be linear. It was possible to fit a straight line by linear regression ($r = 0.99$) to the terminal portion of the percentage released *versus* time curve. However, the lines did not pass through the origin (Fig. 1). From these data it would appear that the first portion of any dose is probably released by first-order diffusion.

Table V—Fraction of a 5-mg/kg Dose of Theophylline Excreted as Unchanged Drug or Metabolites in 24 hr following the Ingestion of Whole or Halved 100-mg Sustained-Release Tablets by Normal Volunteers

Subject	Theophylline and Metabolites, mg/24 hr				Total Xanthines [a]	Dose	Dose Recovered, %
	1-Methyluric Acid	3-Methylxanthine	1,3-Dimethyluric Acid	Theophylline			
				Whole Tablets			
A	71.28	41.33	193.08	38.34	330.94	500	66.19
B	61.85	36.08	102.72	27.89	228.20	300	76.07
C	64.32	39.46	131.15	19.34	246.44	300	82.15
D	30.56	21.39	52.11	47.36	148.84	300	49.33
E	36.32	23.09	67.26	40.66	163.58	400	40.90
F	50.13	31.72	115.12	64.27	254.13	300	84.71
G	56.08	34.52	204.25	36.76	317.04	500	63.41
							66.11 ± 16.47
				Halved Tablets			
A	70.45	39.20	233.53	32.29	358.75	500	71.75
B	51.89	36.39	187.72	22.30	285.36	300	95.12
C	62.36	37.28	102.38	21.53	218.02	300	72.67
D	43.05	22.75	46.67	48.36	158.78	300	52.93
E	30.05	15.56	44.81	43.87	131.77	400	32.94
F	56.30	33.28	114.16	47.82	244.65	300	81.55
G	44.22	25.33	158.68	41.00	269.23	500	51.55
							65.50 ± 20.97

[a] Calculated as theophylline equivalents on a molar basis.

Table VI—Fraction of the 24-hr Urine Content of a 5-mg/kg Dose of Theophylline Excreted as Unchanged Drug or Metabolites following the Ingestion of Whole or Halved 100-mg Sustained-Release Tablets by Normal Volunteers

Subject	Distribution of Theophylline Metabolites in 24 hr, %			
	1-Methyl-uric Acid	3-Methyl-xanthine	1,3-Dimethyl-uric Acid	Theo-phylline
	Whole Tablets			
A	21.42	13.71	53.29	11.59
B	26.95	15.81	45.01	12.22
C	25.95	17.57	48.62	7.84
D	20.42	15.78	31.99	31.82
E	22.08	15.49	37.57	24.86
F	19.62	13.70	41.39	25.29
G	17.59	11.95	58.86	11.60
Mean ± *SD*	22.00 ± 3.37	14.86 ± 1.85	45.25 ± 9.23	17.89 ± 9.22
	Halved Tablets			
A	19.53	11.99	59.48	9.00
B	18.08	14.00	60.11	7.82
C	28.44	18.77	42.91	9.88
D	26.96	15.66	26.86	30.46
E	22.68	12.96	31.07	33.29
F	22.89	14.93	42.64	19.55
G	17.06	10.79	56.25	15.91
Mean ± *SD*	22.23 ± 4.34	14.16 ± 2.63	45.62 ± 13.51	17.99 ± 10.38

A fraction of each dose in these tablets is contained in uncoated granules. As the tablets do not readily disintegrate, the availability of this portion of the dose by pore diffusion would account for the nonlinear 2–3 hr first-order release of drug. The remaining fraction of the dose is contained in coated pellets. As the tablet begins to disintegrate and the portion of the dose in these pellets is released, the rate of drug availability begins to approximate a zero-order infusion release. This ultimately causes the terminal portion of the curve to approach linearity as shown in Fig. 1. Fractions of the dose released from halved tablets were significantly higher than from whole tablets at all times ($p < 0.05$). This is probably due to the increased surface area exposed by breaking the tablets.

In this bioavailability study in normal subjects of whole and halved 100-mg sustained-release theophylline tablets, relative bioavailability was assessed by comparing the areas (time zero to infinity) under the serum concentration *versus* time curves (*AUC*) (Fig. 2). For halved 100-mg tablets, the *AUC* was 103.52 ± 39.16 μg/ml/hr and for whole tablets 108.36 ± 35.83 μg/ml/hr (Table IV). These were not significantly different ($p = 0.05$). In addition, although the mean serum theophylline concentrations following the ingestion of the halved tablets were numerically higher than the values obtained for the whole tablets up to 8 hr, none of the values were significantly different ($p = 0.05$) (Table II).

The fraction of the dose absorbed at any time (f) was calculated using Eq. 3. All subjects absorbed 50% of the dose from either whole or halved 100-mg sustained-release tablets in the 3–4 hr period (Table III, Fig. 3). Except for subject F, following the ingestion of the whole tablets, all other subjects absorbed 90–100% of the dose in the 8–12 hr period. This is consistent with previous reports (1).

The mean percentage of the dose remaining to be absorbed *versus* time is shown in Fig. 4. The initial portion of the graph is linear. These results can be used to confirm the results of dissolution data that there is apparent zero-order release of theophylline from these tablets. The terminal nonlinear portion of the curve is probably due to the fact that the fraction absorbed calculated using Eq. 3 is approaching the asymptote. Theophylline absorption is rapid and complete once the drug is in solution (14).

The mean absorption times (MAT) calculated from Eq. 5 are shown in Table IV. The average MAT of 3.60 ± 0.82 hr following ingestion of the halved tablet was not significantly different ($p = 0.05$) from the value of 4.71 ± 1.00 hr obtained from the whole tablets. In addition, these values are not significantly different ($p = 0.05$) from previously reported values (15) of 5.67 ± 1.40 and 4.20 ± 1.48 hr following the ingestion of whole and halved 300-mg sustained-release tablets, respectively.

The mean theophylline elimination half-life values in these seven subjects following ingestion of these 100-mg sustained-release tablets were 8.50 ± 6.64 hr for whole tablets and 6.29 ± 2.48 hr for halved tablets. These values are not significantly different ($p = 0.05$) and are comparable to literature values of 3.6–12.8 hr in normal, healthy adults (16). Subject F had an extremely long half-life of 23 hr (Table IV) following ingestion of the whole tablets.This is probably not the true half-life, but a value distorted by continued absorption from the sustained-release dosage form. The half-life in this subject following the halved tablet was 7.70 hr.

The apparent volume of distribution for theophylline following ingestion of whole 100-mg tablets was 0.56 ± 0.27 liter/kg. This was not significantly different ($p = 0.05$) from 0.46 ± 0.08 liter/kg obtained from the halved 100-mg tablets. Both values were comparable to those reported in the literature (16).

Total body clearance of theophylline was found to be 0.90 ± 0.36 and 1.02 ± 0.57 ml/min/kg following ingestion of whole and halved 100-mg sustained-release theophylline tablets, respectively. These clearances were not significantly different ($p = 0.05$) from each other or from values reported in the literature (16). Renal clearance of theophylline has been shown to be dependent upon the urine flow rate (17). However, the values found in this study of 0.14 ± 0.05 and 0.15 ± 0.06 ml/min/kg following the ingestion of whole and halved 100-mg tablets, respectively, were not significantly different ($p = 0.05$) from each other or from values previously reported in the literature (17, 18).

The quantities of theophylline and its metabolites, 1-methyluric acid, 3-methylxanthine, and 1,3-dimethyluric acid, recovered in 24-hr urine following ingestion of ~5-mg/kg dose as whole or halved 100-mg tablets are shown in Table V. The metabolite recovery values were converted to theophylline equivalents and reported along with theophylline as total xanthines. This permitted the calculation of the percentage of the dose recovered in the urine as unchanged drug and metabolites during the 24 hr period. Mean recoveries of 66.11 ± 16.47 and 65.50 ± 20.97% following ingestion of whole and halved tablets, respectively, were not significantly different ($p = 0.05$).

The distribution of the various metabolites following the whole or halved tablet doses (Table VI) were not significantly different ($p = 0.05$). This is not surprising since the other parameters such as *AUC*, MAT, K_e, $t_{1/2}$, V_d, Cl and Cl_R were not significantly affected by halving the tablets. However, when compared to other values in the literature, some differences were observed. In a study where 15 older patients were given sustained-release tablets (19), theophylline recovery was 7.7 ± 6.1%, whereas in the present study 17.89 ± 9.27% was found. The recovery of 3-methylxanthine (19) was 36.2 ± 7.3%, while only 14.86 ± 1.85% was recovered in this study. The recoveries of 16.5 ± 3.3% and 39.6 ± 4.5% for 1-methyluric acid and 1,3-dimethyluric acid, respectively (19), were not significantly different ($p = 0.05$) from the present study.

In the previously reported study (19), middle-aged to elderly patients were used, whereas the present study used healthy, young subjects. The older patients were at steady state and 116 ± 36% of the 24-hr dose was recovered in the urine. The younger subjects only received a single dose and only 66.11 ± 47% of the dose was recovered in the 24-hr urine. These differences may account for the discrepancies.

In summary the theophylline elimination parameters such as half-life ($t_{1/2}$), elimination rate constant (K_e), apparent volume of distribution (V_d), clearance (Cl), and renal clearance (Cl_R) were not significantly different from literature values obtained in similar subjects. The metabolite excretion pattern differed from that previously reported but the differences in subject age and in the dosage regimen may have accounted for these discrepancies. In conclusion, halving the sustained-release 100-mg theophylline tablets to achieve more accurate mg/kg doses should not affect drug therapy in patients.

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Determination of Related Compounds in Aspirin by Liquid Chromatography

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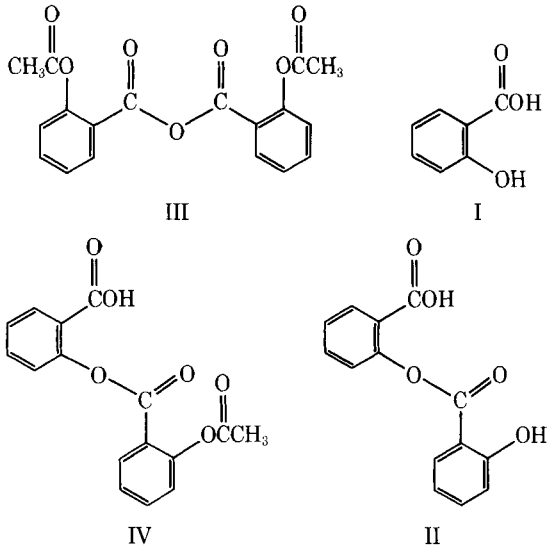
Abstract □ A rapid liquid chromatographic procedure has been validated for the determination of salicylic acid, salsalate, acetylsalicylsalicylic acid, and acetylsalicylic anhydride in aspirin. Samples are dissolved in methylene chloride and analyzed directly by adsorption chromatography in a 7-min separation using an isocratic mobile phase. Recoveries averaged 99% over a 200–10,000 ppm concentration range with standard deviations of <4% for the four compounds of interest. Detection limits ranged from 5 to 36 ppm. Compared to a recently published reversed-phase liquid chromatographic procedure for analyzing aspirin, this method is twice as fast, more sensitive, and avoids the use of hydroxylic solvents which lead to degradation of aspirin and acetylsalicylic anhydride.

Keyphrases □ Aspirin—determination of salicylic acid and related compounds by liquid chromatography □ Liquid chromatography—determination of salicylic acid and related compounds in aspirin □ Salicylic acid—determination in aspirin by liquid chromatography, related compounds

Several recent papers (1–5) have discussed the possible immunological response to the presence of low levels of related compounds in aspirin. Methods, too numerous to discuss, employing gas chromatography, spectrophotometry, liquid chromatography, *etc.*, have been published describing the determination of salicylic acid (I), salsalate (II), acetylsalicylic anhydride (III), and acetylsalicylsalicylic acid (IV) in aspirin. Liquid chromatography (LC) appears to be the most useful approach with respect to specificity, speed, and sensitivity. Various LC methods have appeared in the literature employing adsorption, polar bonded phase, as well as reversed-phase column packings.

After considering the various LC methods, it appeared that the methods employing adsorption chromatography are most appropriate for the determination of related compounds in aspirin on a routine basis. Reversed-phase methods are not desirable because III and aspirin are not stable in the mixed aqueous–organic eluents used in that



form of LC (5). In addition, the selectivity of the reversed-phase system is such that I elutes from the column immediately following aspirin and a poor detection limit is found for I because the larger aspirin peak tails into the peak for I. This difficulty can be avoided by using fluorescence detection (6) to selectively detect I, but this requires the use of dual detectors which increases the cost and complexity of the LC system.

Several normal-phase LC systems have been published for these analyses. A silica gel support containing perchloric acid as a stationary phase for the determination of I, III, and IV in aspirin has been used (7). In another study (8) a polar bonded phase[1] column has been used for the separation of II, III, IV, and other compounds. However,

[1] CYANO.

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