Table VI—Correlation [a] of *In Vivo* Excretion and *In Vitro* Dissolution for Four Brands of Aspirin Using Regression Analysis and the *F* Test

	In Vitro Methods															
	USP				Levy				Regular Basket				Large Basket			
In Vivo Time, hr	10 min	20 min	30 min	40 min	10 min	20 min	30 min	40 min	10 min	20 min	30 min	40 min	10 min	20 min	30 min	40 min
1.0	—	—	S	S	S	S	S	S	—	S	S	S	S	S	—	—
1.5	—	—	—	S	S	—	S	S	—	—	—	S	—	—	S	S
2.0	—	—	—	S	—	—	—	—	—	—	—	S	—	S	—	S
3.0	—	—	—	—	S	S	S	S	—	—	—	—	—	—	—	—
4.0	—	—	—	S	—	—	—	—	—	—	—	S	—	S	S	S
6.0	—	—	—	S	—	—	—	—	—	—	—	S	—	S	S	S

[a] S indicates significant correlation at $\alpha = 0.95$.

in vitro times, and the regular magnetic basket showed significant correlations at three of the four times.

In summary, significant differences in the cumulative urinary excretion of the four aspirin products could only be determined at the 1-hr excretion time, although the ANOV indicated a difference at the 2-hr sample time. Statistically significant differences also were found between these four products and between the four dissolution methods at selected times in the dissolution profiles. Attempts to use a simple sequential order correlation showed a random array of significant correlations between *in vitro* data and a number of excretion times that exceeded the limits of dissolution rate-controlled absorption. The regression analysis, on the other hand, showed the best correlation with *in vivo* 1-hr excretion times. This result indicates a need to analyze both *in vitro* and *in vivo* data statistically before selecting the parameters for data correlation. Adoption of this approach shows that, for aspirin, the Levy beaker and regular magnetic basket provide the best correlation with urinary excretion.

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Sensitive Electron-Capture GLC Determination of Metoclopramide in Biological Fluids

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Received October 3, 1977, from the *Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada.* Accepted for publication November 18, 1977.

Abstract □ A highly sensitive and specific electron-capture GLC assay capable of detecting picogram quantities of metoclopramide, a procaine derivative, in biological fluids was developed. This assay consisted of extracting metoclopramide from an alkalinized aqueous layer into benzene. A portion of the organic phase was derivatized with heptafluorobutyric anhydride. Quantitative estimation of the derivative was accomplished by adding diazepam, the internal standard, in benzene (750 ng/ml). A calibration curve was prepared for the plasma extracts. Linearity was observed in the range studied (91–825 ng/ml). No interference from endogenous substances was observed. The minimum detectable amount was 1 pg/injection. The structure of the derivative was confirmed by electron-impact and chemical-ionization mass spectrometry. The applicability of this method was shown by a preliminary study of the elimination kinetics of metoclopramide in rats after a 10-mg/kg iv dose.

Keyphrases □ Metoclopramide—electron-capture GLC analysis in biological fluids □ GLC, electron capture—analysis, metoclopramide in biological fluids □ Antiemetics—metoclopramide, electron-capture GLC analysis in biological fluids

Metoclopramide, 4-amino-5-chloro-2-methoxy-*N*-(2-diethylaminoethyl)benzamide, an antiemetic procaine derivative (1), is currently used in GI diagnostics (2, 3) and in the treatment of various GI disorders (4, 5). Metoclopramide increases the tone and peristalsis of the stomach and the duodenum, distends the duodenal bulb, and im-

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Table I—Quantitative Estimation of Metoclopramide in Plasma

Amount Added, ng	n^a	Mean Area Ratio	SE
91.636	4	0.232	±0.003
229.090	5	0.544	±0.017
458.180	4	1.099	±0.020
641.450	5	1.596	±0.006
824.723	5	2.061	±0.038

[a] Each n is the average of three determinations.

proves the pyloric activity, thus promoting gastric motility and reducing gastric emptying time (6, 7). This effect of metoclopramide has led to the increased absorption of several drugs—*viz.*, acetaminophen (8), tetracycline (9), pivampicillin (9), and levodopa (10). Moreover, metoclopramide enhanced griseofulvin absorption from solution but depressed its absorption from a suspension (11). Similarly, digoxin absorption from a tablet was reduced, resulting in lowered steady-state blood digoxin levels (12) after concomitant administration of metoclopramide.

Little information pertaining to the pharmacokinetics of this drug is available. Arita *et al.* (13) reported that conjugation is the major metabolic pathway and that deethylation is the major metabolic reaction in rabbits. Four additional metabolites were identified in rat liver slices using mass spectrometry (14). Interspecies variations in elimination kinetics were minimal after various intravenous doses (5–15 mg/kg) (15). However, major interspecies variations were seen after oral administration of a high dose (100 mg/kg).

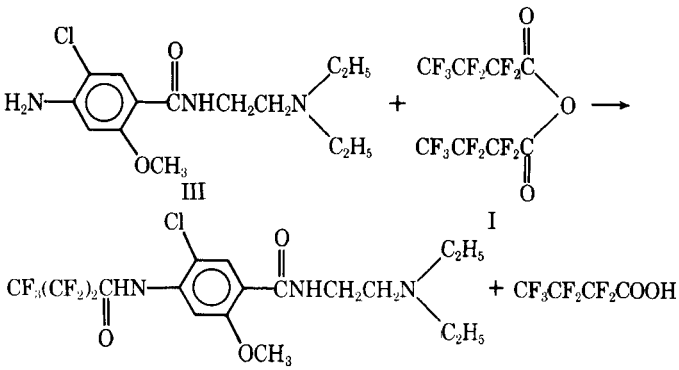
Tunon *et al.* (16) reported that, after giving rats an intravenous dose (10 mg/kg), the plasma data were best described by a two-compartment kinetic model with an elimination half-life of 13–20 min. Bakke and Segura (15) observed that metoclopramide followed apparent first-order elimination kinetics. The half-life of this drug varies from 13 to 60 min in the rat. This large variation in the reported half-life may be due to the lack of a sensitive assay capable of detecting trace quantities in biological fluids. The purpose of this study, therefore, was to develop a highly sensitive electron-capture GLC assay for metoclopramide capable of detecting trace quantities in small volumes of biological fluids.

EXPERIMENTAL

Materials—The following reagents were used: 1 *N* NaOH[1], benzene[2], 4% ammonium hydroxide[3], heptafluorobutyric anhydride[4] (I), metoclopramide monohydrochloride[5] (II) and diazepam[6].

GLC—A reporting gas–liquid chromatograph[7] equipped with a ^{63}Ni-electron-capture detector and a 1.8-m (6-ft) × 2-mm i.d. glass column, containing 3% OV-17 coated onto 80–100-mesh Chromosorb W, was used. The operating temperatures for routine analysis were: injection port, 250°; oven, 250°; and detector, 350°. The carrier gas (95% argon–5% methane) flow rate was 40 ml/min.

Differential Scanning Calorimetry—A differential scanning calorimeter[8] equipped for effluent gas analysis was employed. All samples were crimped. The rate of temperature increase was 10°/min for each run.



Scheme I

Preparation of Metoclopramide Free Base (III)—About 30 mg of II was dissolved in 1 ml of water and alkalinized by addition of 1 ml of 1 *N* NaOH. The formed free base was extracted repeatedly with 10 ml of benzene until the white precipitate in the aqueous layer disappeared. After the organic layer was removed into a 50-ml erlenmeyer flask, the content was dried under a gentle stream of nitrogen at 60°. The residue was recrystallized three times with benzene and dried at 125° for 2 hr under vacuum.

Extraction Procedure—To 0.1 ml of water, plasma, whole blood, or urine were added various amounts of II (Table I). To each sample, 1 ml of 1 *N* NaOH was added, and the total volume was made up to 2 ml with distilled water (pH 13). The aqueous phase was extracted with 6 ml of benzene. Five milliliters of the organic layer was pipetted into a 15-ml centrifuge tube. One milliliter of benzene containing the internal standard (diazepam, 750 ng/ml) was added, the mixture was dried under a gentle stream of nitrogen, and the residue was reconstituted with 1 ml of benzene.

Derivatization Procedure—Twenty microliters of I was added to the reconstituted solution (Scheme I). After thorough vortexing, the reaction mixture was incubated at 55° for 20 min. The sample was allowed to cool to room temperature, and then excess I was removed by hydrolysis with 0.5 ml of water and neutralization with 0.5 ml of 4% NH_4OH solution. Subsequent to centrifugation, the derivative was pipetted into a 2-ml vial for automatic injection into the gas chromatograph.

GLC–Mass Spectrometry—A computerized gas chromatograph–electron-impact mass spectrometer[9] was used to study the fragmentation pattern of the heptafluorobutyryl derivative. The following conditions were used for the gas chromatograph: injection port temperature, 250°; oven temperature, 250°; and helium (carrier gas) flow rate, 40 ml/min. The 2-m × 2-mm i.d. glass column was packed with 3% OV-17 coated on 80–100-mesh Chromosorb W. For the mass spectrometer, the ionization beam energy was 70 ev, the electron multiplier voltage was 2 kv, the analyzer temperature was 50°, and the separator oven temperature was 200°.

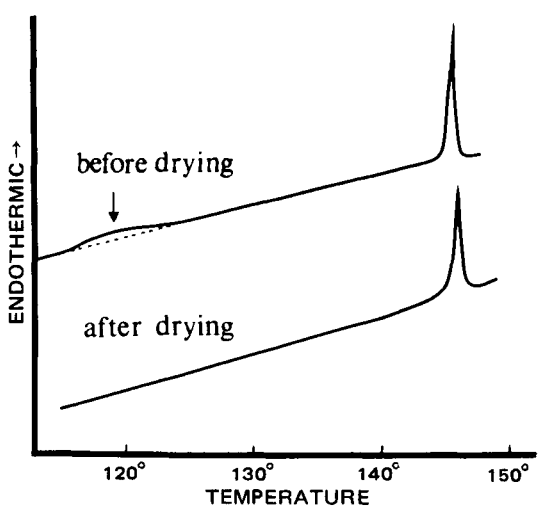


Figure 1—*Differential scanning calorimetry spectra of the free base before and after drying at 125° under vacuum.*

[1] Mallinckrodt Chemical Works, St. Louis, Mo.
[2] Distilled in glass, Caledon, Georgetown, Ontario, Canada.
[3] Reagent ACS code 1293, Allied Chemical Canada Ltd., Claire, Quebec, Canada.
[4] Pierce Chemical Co., Rockford, Ill.
[5] Catalog No. L-593, 856-01F06, Merck Sharp and Dohme Research Laboratories, West Point, Pa.
[6] Lot R-6685, Hoffmann-La Roche, Montreal, Canada.
[7] Hewlett-Packard model 5833A.
[8] Perkin-Elmer model DSC-1B.
[9] Model 3200, Finnigan Corp., Sunnyvale, Calif.

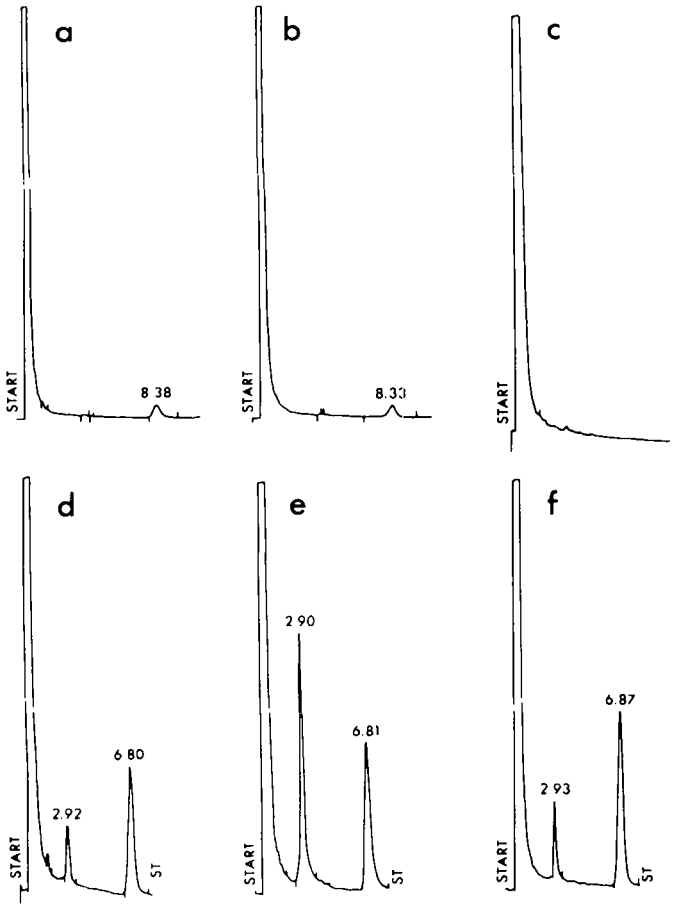


Figure 2—*Sample chromatograms from the extracts of biological specimens. Key:* a, *blank plasma extract;* b, *blank whole blood extract;* c, *blank urine extract;* d, *plasma extract (91.6 pg/injection);* e, *whole blood extract (229 pg/injection); and* f, *urine extract (91.6 pg/injection).*

Chemical-Ionization Mass Spectrometry—A chemical-ionization mass spectrometer[10] was employed to determine the molecular ion of the heptafluorobutyryl derivative. Samples were introduced by the direct probe method. The following conditions were used: probe temperature, 200°; source temperature, 150°; and ionization voltage, 70 v.

Quantitative Analysis—A 1-μl aliquot of the derivative solution was injected into the reporting gas chromatograph equipped with an automatic liquid sampler. Quantitative estimation of III in biological samples was accomplished by plotting the area ratios of the derivative and the internal standard against a series of known concentrations of III.

Animal Studies—An amount of II equivalent to 10 mg of III/kg in 0.9% NaCl was injected into a male Wistar rat (200–300 g) through a cannula inserted into the right jugular vein[11]. A 0.1–0.2-ml blood sample was taken at appropriate time intervals from the cannula, which was exteriorized

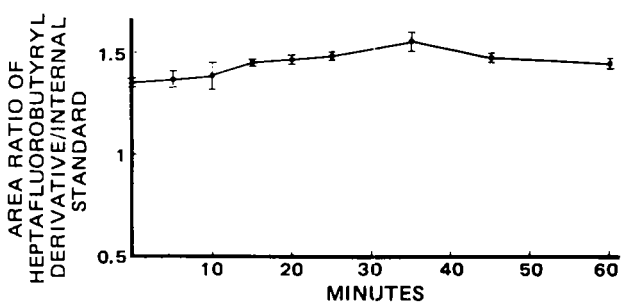


Figure 3—*Kinetics of the derivatizing reaction with respect to time.*

[10] DuPont model 21-490B.
[11] D. Soda, State University of New York at Buffalo, Amherst, NY, 1976.

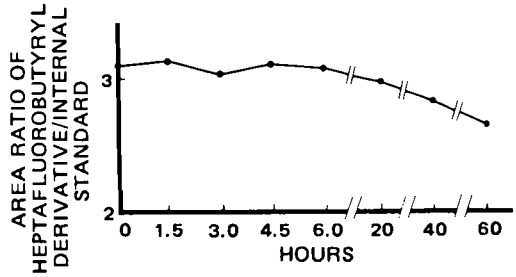


Figure 4—*Stability of the heptafluorobutyryl derivative with time.*

at the nape of the neck. The samples were immediately centrifuged and frozen until analysis. A plasma sample of 20–50 μl was extracted and analyzed as described.

RESULTS AND DISCUSSION

Purity Confirmation—The spectrum from the differential scanning calorimeter showed that II decomposed at 110°. No peaks were observed prior to decomposition, indicating that the purity of the hydrochloride salt was satisfactory.

After recrystallization of the free base from benzene, the differential scanning calorimetry spectra showed that an endothermic peak occurred at 120° before melting. When the samples were dried at 125° under vacuum for 2 hr, the peak disappeared (Fig. 1). It was postulated that benzene, the recrystallizing solvent, was either adsorbed onto or formed a solvate with the free base. The peak at 120° was confirmed to be a volatile substance by coupling the differential scanning calorimeter with effluent gas analysis. No further attempt was made to identify whether the solvent was adsorbed onto or incorporated into the crystal lattice of the free base.

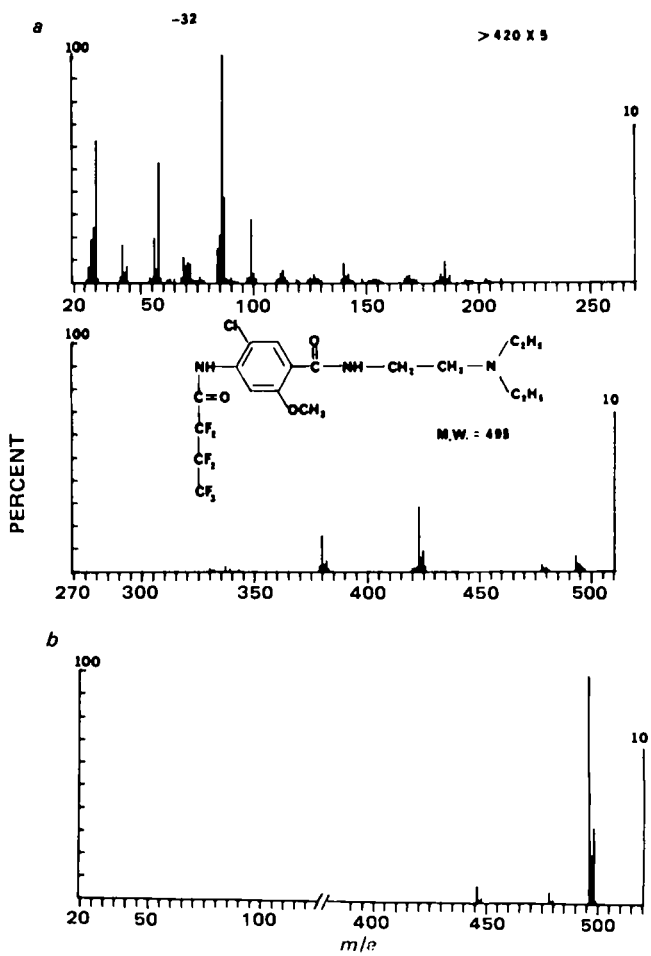


Figure 5—*Electron-impact* (a) *and chemical-ionization* (b) *mass spectra of the heptafluorobutyryl derivative of III extracted from plasma.*

Table II—Percent Recovery after Extraction from Biological Fluids

Metoclopramide Base Equivalent Added, ng	n^a	Plasma Extract		Whole Blood Extract		Urine Extract	
		% Recovered	% Deviation	% Recovered	% Deviation	% Recovered	% Deviation
229.09	5	92.84	±14.23	90.79	±0.84	94.16	±2.10
458.18	5	85.09	±6.35	82.83	±3.35	82.08	±6.55
641.45	5	85.56	±1.65	81.06	±5.54	84.42	±5.54
824.72	5	84.57	±7.75	79.33	±4.40	78.27	±1.04
Average		87.02	±4.49	83.50	±6.06	84.73	±8.00

[a] Each n is the average of three determinations.

GLC—Representative chromatograms from the extracts of the plasma, blood, and urine samples are shown in Fig. 2. A peak at 8.38 min was observed in the chromatograms of the blank plasma and the whole blood (Figs. 2*a* and 2*b*). The unidentified impurity did not interfere with either the derivative of III or the internal standard peak (Figs. 2*d* and 2*e*). No endogenous disturbances were found from the urine extract (Figs. 2*c* and 2*f*). Baseline resolution was achieved between the peaks when the 3% OV-17 column was used.

Chromatographic response was linear in the range studied (91.6–824.7 ng/ml). The calibration curve was obtained by analyzing blank plasma samples spiked with various amounts of the drug (Table I). From the linear regression analysis, the best fit through the data points was described by $y = 0.002508x - 0.019$, with $r^2 = 0.999$.

Reaction Time—The optimum derivatizing time was evaluated by incubating samples containing equivalent amounts of the base with I for various times at 55°. The yield of the derivative, as observed by the area ratio of the derivative to the internal standard, was monitored. No significant difference in response was found throughout the range of reaction time studied (0–60 min) (Fig. 3). To ensure complete derivatization, samples were incubated at 55° for 20 min during current analysis.

Stability of Derivative—As shown in Fig. 4, the area ratios of the derivative to the internal standard did not drop significantly after 20 hr of storage. The areas under the two peaks also did not change perceptibly during that time.

Removal of Excess I—Walle and Ehrsson (17) reported that the presence of trace amounts of a I residue produced chromatographic problems such as spurious peaks and a broad solvent front. Furthermore, excess I caused a huge solvent front, which masked the heptafluorobutyryl derivative peak. Therefore, a method that could remove the excess reagent without diminishing the response of the derivative was necessary.

Walle and Ehrsson (17) suggested two methods: after incubation, dry the reaction mixture by a gentle stream of nitrogen; and hydrolyze excess I with water and neutralize it with aqueous ammonia. The former method decreased the response of the derivative by at least two-thirds when compared to the latter. Both methods were capable of removing excess I. The decrease in response when the former method was applied was probably due to the volatility of the derivative (17), whereas the loss of the derivative from evaporation was minimal with the latter method.

Recovery—A standard curve was prepared by derivatizing a serial dilution of the free base in benzene. After extraction of known quantities of II from biological fluids, the amount of free base recovered in the organic phase was determined by using the free base calibration curve. The average percentages of III recovered from plasma, whole blood, and urine were 87.02, 83.5, and 84.73, respectively (Table II). The respective percentage standard deviations were 4.49, 6.06, and 8.00.

Structural Confirmation of Derivative—The fragmentation patterns of the derivatized free base and plasma extracted from metoclopramide-dosed animals were found to be identical by GLC–mass spectrometry, indicating that III was being analyzed from the plasma samples. Like III (18) and its procaine analogs (19), cleavage occurred at the amine bond (*m/e* 423), as well as the carbonyl–amide bond (*m/e* 99 and 380). The base peak, *m/e* 86, was a result of the cleavage at the carbon–carbon bond beta to the amine nitrogen (Scheme II).

Although a monosubstitution reaction was postulated, the molecular ion was not readily discernible (Fig. 5*a*) from the electron-impact mass spectrum, perhaps because of the high ionization energy of the source. Further investigation is underway to clarify the causative mechanism. Since electron-impact mass spectrometry was not conclusive, chemical-ionization mass spectrometry was employed to reveal the molecular ion. From the chemical-ionization mass spectrum (Fig. 5*b*), a very intense *m/e* 496 peak, which corresponded to the $(MH)^+$ peak, was observed. The other two peaks, *m/e* 478 and 446, were postulated to be $(MH - water)^+$ and $(MH - water - methyl\ alcohol)^+$, respectively.

Animal Data—The applicability of this method was demonstrated by studying the elimination kinetics of III in rats after a 10-mg/kg iv dose. Because of the extremely high sensitivity of this method, only small volumes of plasma (20–50 μl) were required. This method permits serial blood sampling from the same rat over a sufficient period to allow adequate characterization of the pharmacokinetics of III.

Distribution was extremely rapid within the first few minutes after injection. An apparent distribution equilibrium was established at around 16 min. From the semilog plot of the plasma profile (Fig. 6), a linear elimination phase was seen. The half-life calculated was 49.75 ± 8 min.

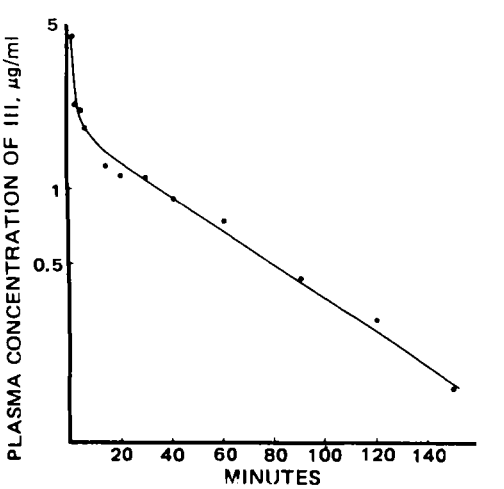
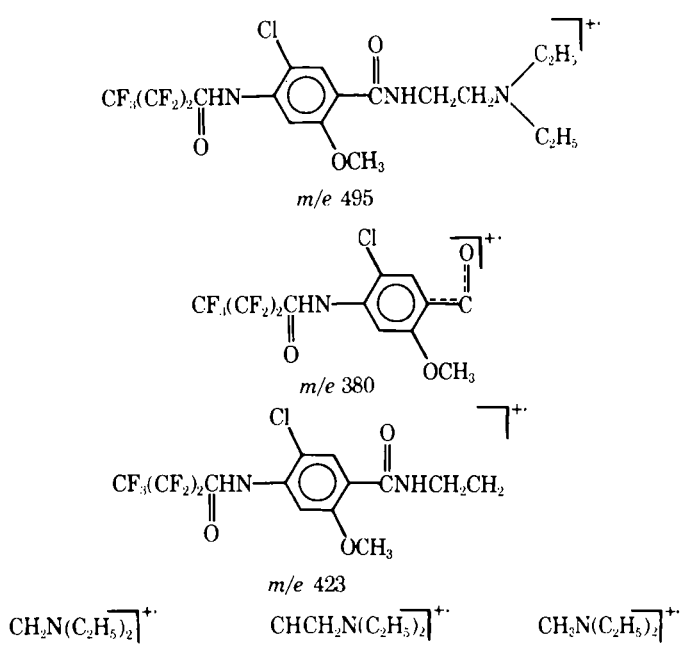


Figure 6—*Representative semilog plot of the plasma profile of III in a rat after a 10-mg/kg iv dose.*



Scheme II

When these results were compared to the pharmacokinetic data obtained by Tunon *et al.* (16), it was found that the "elimination phase" previously reported was actually part of the distribution phase. Therefore, the half-life (13–20 min) calculated was erroneous. This error was due to the use of a relatively insensitive assay that was unable to detect any III after 16 min. The method reported here offers significant superiority over the Bakke and Segura (15) TLC–photodensitometry method. A smaller volume of plasma is required for analysis, thereby obviating the need for the sacrifice of individual rats to obtain data.

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Interaction of Sulindac and Metabolite with Human Serum Albumin

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Received April 28, 1977, from the *Department of Pharmaceutics, School of Pharmacy, University of Georgia, Athens, GA 30602.* Accepted for publication November 29, 1977.

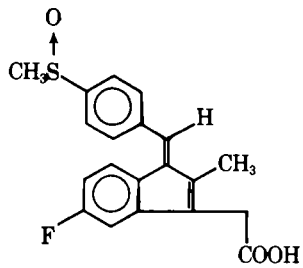
Abstract □ The binding of the newly developed nonsteroidal anti-inflammatory agent sulindac and its principal active metabolite, sulindac sulfide, to human serum albumin was investigated. With the methods of dialysis, fluorescence quenching, and difference spectrophotometry, it was found that both agents were extensively bound to albumin. The binding affinity of the metabolite was considerably higher than that of sulindac and this effect may be related to its prolonged plasma half-life *versus* the parent drug. Sulindac binding was albumin concentration dependent, which gave rise to an unfamiliar Scatchard analysis of the dialysis data.

Keyphrases □ Sulindac—and metabolite, binding to human serum albumin □ Binding, protein—sulindac and metabolite to human serum albumin □ Anti-inflammatory agents—sulindac and metabolite, binding to human serum albumin

Drug synthesis and testing for the treatment of arthritis are ongoing areas of research. Many nonsteroidal anti-inflammatory agents have been synthesized (1). Recently, sulindac[1], *cis*-5-fluoro-2-methyl-1-[*p*-(methylsulfinyl)-benzylidene]indene-3-acetic acid (I), was developed as a nonsteroidal anti-inflammatory agent (2). The drug is well absorbed after oral administration in all tested species.

Most anti-inflammatory drugs induce some GI side effects. However, sulindac does not induce significant irritative or erosive effects on the GI tracts of healthy subjects (3–8). In humans, the only significant enterohepatic biotransformations undergone by sulindac are irreversible oxidation of its sulfoxide function to sulfone and reversible reduction to sulfide (II) (9–12).

The potency of sulindac is approximately half that of indomethacin, while the safety ratio between the dose causing intestinal perforation or gastric hemorrhage and the anti-inflammatory dose is several times higher for sulindac than for indomethacin. Comparisons of activity were made among the sulfoxide, the sulfide, and the sulfone. The sulfone was not active at high doses in several assays, but the sulfide derivative was generally twice as active as the parent compound and was as active as in-



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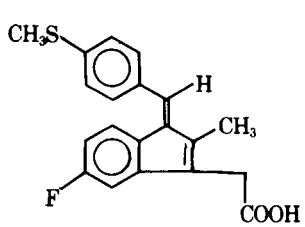

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