were taken at the near and far positions with the filter turning at 300 rpm. These photographs showed that the flow at the tablet surface was uniform and parallel to the filter face with an even color distribution when the disk was at the far position from the stirring source. The tailing streams of color away from the tablet revealed the tangential nature of the stirring patterns. This overall visualization is reasonably close to that assumed by the model and is in keeping with the data analysis from the dissolution experiments.

For the near position, the colored photographs showed that the flow pattern at the surface was less uniform and in the direction of the spinning filter rather than parallel to it. Furthermore, a concentration of color appeared on the filter side of the tablet. The visualization procedure combined with dissolution data confirms that the flow pattern is influenced by the distance from the rotating stirring source. Dissolution rates measured from disintegrating tablets would presumably be influenced in a similar way, making basket placement a critical factor.

SUMMARY

At the farthest distance from the stirring source, the average numerical exponents for stirring speed and tablet radius were 0.58 and 1.54, respectively, which compares favorably with the theoretical values of 0.50 and 1.50. When the dissolving salicylic acid surface was positioned closer to the stirring source, the numerical exponent for the tablet radius was lowered to 1.07, indicating a change in dissolution as a function of distance from the stirring source. These data indicate that dissolution rates are not necessarily proportional to surface area, as predicted by the Nernst equation, and that distance from the stirring source is a significant factor. Convective diffusion models combined with easily accomplished visualization techniques provide the methodology needed to characterize various dissolution devices.

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Linear Pharmacokinetics of Orally Administered Fenoprofen Calcium

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Abstract □ The bioavailability of fenoprofen from three different fenoprofen calcium capsule formulations containing the equivalent of 60, 165, and 300 mg of fenoprofen was determined in two studies. In the first study, 12 subjects received one capsule of each formulation according to a three-period crossover design. The second study required each of 13 subjects to receive 300 mg of fenoprofen equivalent of the 60- and 300-mg capsules and 330 mg of the 165-mg capsule. The initial study provided information on the linearity of fenoprofen pharmacokinetics, and the second study established that the three capsule formulations were bioequivalent. The bioavailability parameters C_{max}, t_{max}, and $AUC_{0-12\ hr}$ for the drug in plasma were consistent with a linear pharmacokinetic model, as were the amounts of fenoprofen and hydroxyfenoprofen excreted in the urine. These data show linearity of kinetics for fenoprofen in plasma throughout the 60–300-mg dosage range after a single dose. Physical measurements of each capsule formulation drug content, weight variation, and dissolution showed the products to be uniform and readily soluble.

Keyphrases □ Fenoprofen—pharmacokinetics, oral administration, calcium salt □ Pharmacokinetics—fenoprofen calcium, oral administration □ Anti-inflammatory agents—fenoprofen calcium, pharmacokinetics, oral administration

Fenoprofen calcium[1] was shown to be a useful anti-inflammatory agent in osteoarthritis (1–4) and rheumatoid arthritis (5–16) in adults. To extend the therapeutic range of the compound, drug formulations containing 60–300 mg of fenoprofen equivalent as fenoprofen calcium[2] were selected for juvenile rheumatoid arthritis studies. This paper reports the linearity of fenoprofen pharmacokinetics, fenoprofen bioavailability, and the uniformity of drug excretion after a single-dose oral administration of capsules containing 60, 165, or 300 mg of fenoprofen equivalent in an adult population.

EXPERIMENTAL

Clinical Study Protocol—Healthy adult male volunteers, 18–50 years old, participated in the two studies. Their weight was ±10% of the ideal weight (17). The subjects had no history of significant GI disorder; hepatic, renal, hematological, or cardiovascular disease; or chronic alcoholism. Each subject underwent a urinalysis, hematology, and blood analysis[3] as well as a physical examination to ensure inclusion of only subjects in good health.

In the first bioavailability study, 12 subjects were placed into Groups I, II, and III. Each group consisted of four subjects, each of whom received a single capsule of 60, 165, or 300 mg of fenoprofen equivalent (Table I) on three consecutive occasions, with a 2-day washout period between each dose. Each subject was instructed to adhere to a standard protocol and

Table I—Fenoprofen Calcium Capsule Formulas [a]

Ingredient	Capsule[b], mg		
	60	165	300
Fenoprofen calcium	70.0	192.5	350.0
Silicone fluid 350 centistokes	3.0	8.2	15.0
Microcrystalline cellulose with carboxymethylcellulose sodium[c]	217.0	179.2	125.0

[a] Values in milligrams. [b] Fenoprofen equivalent. [c] Avicel RC-591 MCC, FMC Corp.

[1] Nalfon, Dista Products Co. (a Division of Eli Lilly and Co.).

[2] Drug weight is reported in this paper as fenoprofen equivalent of fenoprofen calcium.

[3] SMA 12/60.

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Table II—*In Vitro* Tests of Fenoprofen Calcium Capsules

Property	Number of Measurements	Capsule, mg[a] 60[b]	165[b]	300[c]
Fenoprofen[d]	$\bar{x}_{10}$	58.8	160.3	307.0
equivalent, mg	Range	(55.9–62.9)	(154–168)	(303–313)
Weight, mg	$\bar{x}_{10}$	291.8	374.2	491.9
	Range	(282.8–303.2)	(368.7–385.7)	(489.6–505.7)
Dissolution in	$\bar{x}_6$	59.4	40.6	38.1
10 min[e], %	Range	(56.9–62.6)	(36.4–43.6)	(34.3–42.1)
Dissolution in	$\bar{x}_6$	89.5	72.0	72.9
30 min[e], %	Range	(85.8–94.3)	(66.6–78.5)	(70.7–74.8)
Dissolution in	$\bar{x}_6$	97.4	84.0	87.6
60 min[e], %	Range	(91.4–104.4)	(77.4–89.5)	(85.7–89.7)

[a] Fenoprofen equivalent. [b] Nalfon Capsules, representative production size lots. [c] Nalfon Pulvules, lot OCF84, 300 mg of fenoprofen equivalent as fenoprofen calcium. [d] One hundred milligrams of fenoprofen is equivalent to 116.7 mg of fenoprofen calcium. [e] USP XIX dissolution apparatus: 1000 ml of 0.05 *M* phosphate buffer at 37°, pH 4.5, ionic strength 0.3, and stirring at 50 rpm.

Table III—Mean Fenoprofen Bioavailability Parameters from Single Capsules

Bioavailability Parameter	Capsule 60 mg[a]	60-mg Data Adjusted[b] to 300 mg	165 mg[a]	165-mg Data Adjusted[b] to 300 mg	300 mg[a]
0 hr	0.0 (0.0)		0.0 (0.0)		0.1 (0.3)
0.25 hr	1.6 (1.2)		2.9 (2.7)		4.4 (4.4)
0.5 hr	4.0 (2.0)		10.4 (5.6)		15.8 (10.0)
0.75 hr	4.7 (1.9)		13.8 (5.0)		21.1 (7.8)
1.0 hr	4.8 (1.7)		13.8 (5.0)		22.2 (8.0)
1.5 hr	4.3 (1.0)		13.6 (3.9)		21.9 (6.9)
2.0 hr	4.8 (1.4)		11.2 (3.2)		22.1 (7.4)
2.5 hr	3.9 (1.1)		9.7 (2.4)		18.1 (5.4)
3.0 hr	2.9 (1.0)		7.9 (2.7)		15.4 (4.6)
4.0 hr	2.2 (0.7)		5.7 (1.8)		10.8 (3.2)
6.0 hr	1.0 (0.5)		3.1 (1.2)		7.0 (2.9)
8.0 hr	0.5 (0.3)		1.5 (0.7)		3.7 (2.0)
12.0 hr	0.2 (0.2)		0.5 (0.4)		1.5 (1.4)
$AUC_{0\text{-}12\ hr}$, μg-hr/ml	20.2 (4.0)	100.9	55.3 (12.7)	100.6	105.2 (21.8)
C_{max}, μg/ml	6.2 (1.1)	31.0	17.2 (3.0)	31.2	28.3 (7.9)
t_{max}, hr	1.4 (0.6)	—	1.3 (0.7)	—	1.8 (1.4)
Urinary excretion, 0–24 hr, mg					
Fenoprofen	19.9 (10.5)	99.3	66.1 (27.8)	120.3	89.2 (42.0)
Hydroxyfenoprofen	20.9 (11.1)	104.7	71.5 (31.9)	130.1	99.2 (44.4)
Total drug	40.8 (20.8)	204.0	137.6 (57.3)	250.4	188.4 (82.7)

[a] Mean plasma fenoprofen levels of 12 subjects in micrograms per milliliter (standard deviation). [b] Adjusted mean fenoprofen bioavailability parameters.

Table IV—Mean Fenoprofen Bioavailability Parameters from Multiple Capsules

Bioavailability Parameter	Capsule Five 60 mg	Two 165 mg	One 300 mg
0 hr	0.0[a] (0.0)	0.0 (0.0)	0.0 (0.0)
0.25 hr	9.5 (8.7)	4.7 (4.7)	5.2 (8.4)
0.5 hr	23.6 (8.6)	17.6 (11.5)	16.0 (12.5)
0.75 hr	26.7 (6.6)	24.3 (9.8)	19.0 (11.9)
1.0 hr	27.3 (6.4)	25.8 (9.0)	20.3 (9.3)
1.5 hr	24.8 (4.3)	23.3 (6.2)	21.6 (6.1)
2.0 hr	21.1 (2.7)	21.1 (6.1)	22.3 (4.1)
2.5 hr	17.2 (2.4)	19.9 (5.4)	19.3 (3.6)
3.0 hr	13.3 (2.0)	14.9 (3.8)	14.9 (2.9)
4.0 hr	9.2 (1.9)	10.3 (2.5)	10.1 (1.9)
6.0 hr	4.9 (1.2)	5.1 (1.6)	5.5 (1.6)
8.0 hr	2.5 (0.7)	2.7 (1.0)	2.8 (1.0)
12.0 hr	0.9 (0.4)	1.1 (0.5)	1.1 (0.6)
$AUC_{0\text{-}12\ hr}$, μg-hr/ml	99.6 (16.4)	100.6 (15.9)	97.2 (14.8)
C_{max}, μg/ml	31.2 (5.2)	31.0 (4.0)	28.4 (5.2)
t_{max}, hr	1.0 (0.5)	1.1 (0.6)	1.4 (0.8)
Urinary excretion, 0–24 hr, mg			
Fenoprofen	93.0 (35.7)	103.9 (36.9)	104.7 (25.4)
Hydroxyfenoprofen	117.6 (42.7)	146.3 (79.3)	130.0 (31.2)
Total drug	210.6 (55.7)	250.2 (87.5)	234.7 (40.2)

[a] Mean plasma fenoprofen levels of 13 subjects in micrograms per milliliter (standard deviation).

to abstain from taking any other medication 7 days preceding and 24 hr following the study drug administration. All subjects fasted for at least 8 hr prior to and 2 hr after medication. The subjects were given the capsules with 240 ml of water in the morning. After medication, they remained ambulatory or sitting for at least 2 hr.

Heparinized venous blood, 10 ml, was obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hr after medication. The blood samples were centrifuged within 1 hr, and the plasma was separated and frozen until assayed. Urine specimens were collected from 0 to 24 hr after medication. The collections were refrigerated as obtained. The specimens were mixed to ensure homogeneity, the volume was recorded, and a 50-ml aliquot was removed and frozen until assayed.

A second similar bioavailability study was conducted in which five capsules of 60 mg, two capsules of 165 mg, and one capsule of 300 mg of

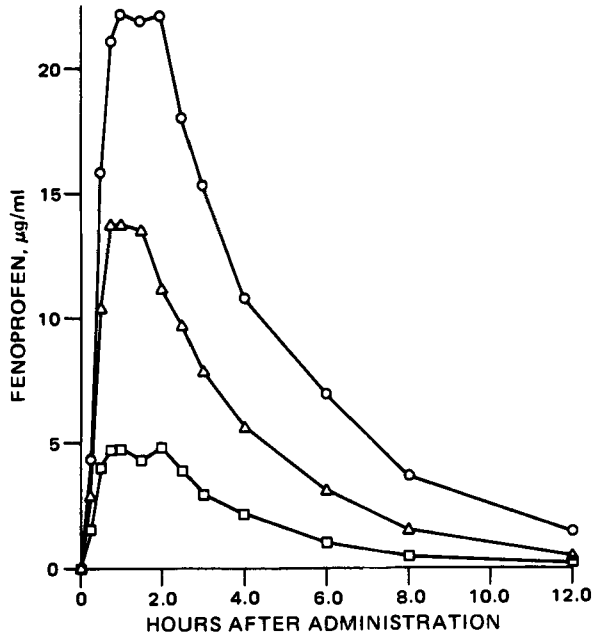

Figure 1—*Mean plasma fenoprofen levels of 12 subjects after administration of 60- (□), 165- (△), and 300- (○) mg capsules of fenoprofen equivalent as fenoprofen calcium.*

fenoprofen equivalent were administered to each of 13 subjects.

Assay of Plasma and Urine Samples—In the initial study, plasma samples were assayed for fenoprofen by GLC (18). In the second study, plasma samples were assayed by HPLC[4]. The total fenoprofen and 4-hydroxyfenoprofen (the free compounds and conjugates) in urine were determined by the following GLC procedure. A 100-μl urine sample was diluted with 200 μl of purified water and 50 μl of concentrated sulfuric acid. When thoroughly mixed, the sample was heated on a boiling water bath for 30 min. After cooling, 30 μg of *dl*-2-(4-phenoxyphenyl)valeric acid was added as an internal standard. The fenoprofen, hydroxyfenoprofen, and internal standard were extracted into 4 ml of ethylene dichloride. The ethylene dichloride was evaporated, and 50 μl of a 1:10 mixture of *N*-trimethylsilylimidazole–carbon disulfide was added to the residue. The silylated compounds were chromatographed under the same conditions as the plasma samples.

***In Vitro* Tests**—The USP XIX (19) capsule weight variation, the product assay, and the dissolution test results are reported in Table II.

RESULTS AND DISCUSSION

Plasma and Urine Drug Levels in Study 1—Table III summarizes the mean plasma fenoprofen level at each sampling time, along with the means of $AUC_{0\text{–}12\ hr}$, C_{max}, t_{max}, and 0–24-hr urinary recovery of fenoprofen and hydroxyfenoprofen. Figure 1 presents the mean plasma fenoprofen profiles graphically. Figure 2 shows the near linearity of the plots of dose *versus* $AUC_{0\text{–}12\ hr}$, C_{max}, and 0–24-hr urinary excretion. Linear regression analysis suggests that an increase of 1 mg of fenoprofen in a dose increases its $AUC_{0\text{–}12\ hr}$ by 0.35 μg-hr/ml, the C_{max} by 0.10 μg/ml, and the 0–24-hr urinary recovery by 0.68 mg.

Table III also contains $AUC_{0\text{–}12\ hr}$, C_{max}, and urinary recovery data adjusted so as to correspond to a single dose of 300 mg of fenoprofen equivalent under the hypothesis of pharmacokinetic linearity. An analysis of variance of these adjusted data indicated that there were no significant differences ($p > 0.05$) among the three capsule formulations with respect to adjusted *AUC*, adjusted C_{max}, and adjusted urinary drug recovery. An analysis of variance on unadjusted t_{max} estimates also failed to demonstrate any differences among the three capsule formulations.

Plasma and Urine Drug Levels in Study 2—Mean plasma fenoprofen levels, $AUC_{0\text{–}12\ hr}$, C_{max}, t_{max}, and 0–24-hr urinary recovery measurements from approximately equal doses of the 60-, 165-, and 300-mg capsules are reported in Table IV. The mean plasma fenoprofen profiles are presented in Fig. 3. Analyses of variance on these data indicated that there were no differences among the three capsule formulations

[4] To be published.

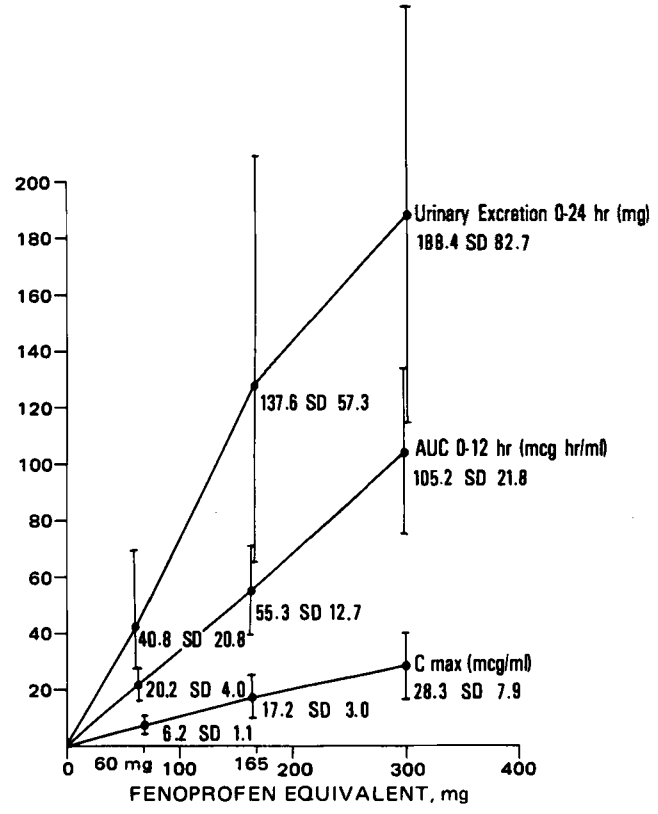

Figure 2—*Near linear plots of fenoprofen administered (60, 165, and 300 mg)* versus *means of* $AUC_{0\text{–}12\ hr}$, C_{max}, *and 0–24-hr urinary excretion.*

with respect to plasma levels at most sampling times, *AUC*, C_{max}, t_{max}, and urinary recovery.

Mean plasma levels from the one 300-mg capsule were significantly lower than those following five 60-mg capsules at 0.75 and 1 hr and significantly lower than those following two 165-mg capsules at 0.75 hr. The former differences may have been due to the apparently lower dissolution of the 300-mg capsules, as compared to the 60-mg capsules, while the

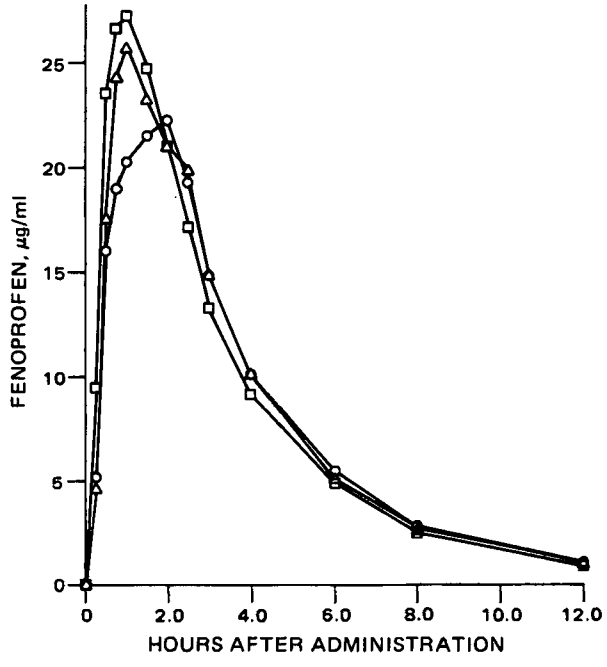

Figure 3—*Mean plasma fenoprofen levels of 13 subjects after administration of five 60- (□), two 165- (△), and one 300- (○) mg capsules of fenoprofen equivalent as fenoprofen calcium.*

latter may have been a result of the slightly larger dose of the 165-mg capsule. The equivalence of the capsule formulations with respect to all other variables suggests that any differences in the bioavailabilities of the three formulations are inconsequential.

According to previous reports (20, 21), fenoprofen pharmacokinetics after an oral or intravenous dose of 250 mg can be adequately represented by a two-compartment open model. Under such a model, plasma levels are a linear function of the dose administered (22).

The results of Study 1 are sufficient to corroborate linearity of orally administered fenoprofen pharmacokinetics in the 60–300-mg dose range only if nonlinearities are not obscured by bioinequivalencies of the three capsule formulations. Since Study 2 established that the three formulations are essentially bioequivalent, the differences among the formulations in Study 1 probably were due solely to differing doses. Since the Study 1 bioavailability parameters are proportional to the dose, as established by the analysis of variance of the adjusted variables, these experiments provide additional evidence that orally administered fenoprofen pharmacokinetics are linear over the 60–300-mg dose range.

A previous study (23) reported nonlinearity of plasma levels to high doses of another α-methylarylacetic acid, naproxen. The nonlinearity occurred at doses of >500 mg while lower doses two times a day yielded a linear dose–response curve. This fenoprofen study included single doses of 60–300 mg. Higher fenoprofen doses were not investigated.

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Cholesterol Solubility in Organic Solvents

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Received August 9, 1977, from the **College of Pharmacy, University of Michigan, Ann Arbor, MI 48109,* and the ‡*School of Medicine, University of California, San Diego, CA 92103.* Accepted for publication March 1, 1979.

Abstract □ The 37° cholesterol solubilities in over 50 solvents, including the homologous *n*-alkanols through dodecanol and homologous ethyl carboxylates through the undecanoate, and the 37° β-sitosterol solubilities in the *n*-alkanols through decanol are reported. Additionally, solubility data for cholesterol at 7, 17, and 27° in the alcohol series were obtained. These measurements allowed the calculation of heats of solution for cholesterol in the alkanols, which range from 7.5 kcal for methanol to 4.3 kcal for decanol and which tend to decrease, although irregularly, with increasing alkanol chain length. A solubility maximum in all of these series for both solutes was observed between a chain length of six and seven. A surprisingly irregular, odd–even alternating solubility pattern was noted for cholesterol in the alkanols at all four temperatures. Experimental evidence indicated that this pattern was due to solvent-induced crystalline changes, presumably solvate formation, in each alkanol solvent through C_{10}. Overall, the solubility studies screened solvents for their utility in dissolving cholesterol and, thus, cholesterol gallstones. To these ends, some limited dissolution experiments were performed, which indicated that the solution rate is directly related to the measured solubility in organic solvents. The dissolution behavior is thus different from micellar bile salt solutions, in which a significant interfacial barrier controls kinetics.

Keyphrases □ Cholesterol—solubility in organic solvents, *n*-alkanols, ethyl carboxylates, structure–activity relationships □ β-Sitosterol—solubility in organic solvents, *n*-alkanols, structure–activity relationships □ Gallstones—cholesterol, solubility in organic solvents, treatment of stones retained in common bile duct □ Organic solvents—cholesterol dissolution, treatment of gallstones retained in common bile duct, structure–activity relationships

Cholesterol is an important biological membrane constituent and is the principal component of many gallstones. It also has been indicted as a causative agent in arteriosclerosis. The physicochemical properties of cholesterol are important to its necessary membrane functions, to its role as an initiator and component of gallstones, and to its presumed involvement in vascular diseases. Indeed, the understanding of cholesterol's natural and pathophysiological roles is dependent on a thorough knowledge of cholesterol's biochemistry and physical chemistry. Particularly important is cholesterol solubilization in the major aqueous biological fluids, blood and bile (1–3). Elucidation of cholesterol's biological solubility and deposition would be aided by an understanding of its solubility behavior *in vitro*.

BACKGROUND

A promising direct application of cholesterol solubility data is the dissolution of small cholesterol stones in the common bile duct of patients

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