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Pharmacokinetics of Ibuprofen in Man IV: Absorption and Disposition

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Fifteen normal male volunters received 400, 800, and 1200 mg doses of ibuprofen as 1, 2, or 3 tablets, respectively, in crossover fashion, then 420 mg in solution form during the fourth week. Plasma concentration of ibuprofen was measured by an HPLC method. Individual subject concentration-time (C,t) data following the solution were analyzed by two different methods, and results unequivocally indicated the open two compartment model with first order absorption. However, the computer fitting of both arithmetic and geometric mean concentrations led to a different model. A method was developed to obtain absorption data (fraction of drug absorbed, F_a, versus time) for a multicompartmental system from oral data alone, without intravenous data. The method assumes that V_p is constant intrasubject and that absorption is complete following administration of both the solution and tablets. The method was successfully applied to the ibuprofen tablet data. It was shown also that such a method is necessary to obtain ibuprofen absorption data since intrasubject variation of the microscopic rate constants k_{12}, k_{21}, and k_{el} (as reflected by the intrasubject variation of the hybrid rate parameters λ_1 and λ_2 or β and α) is of the same order of magnitude as intersubject variation. Absorption of ibuprofen from tablets was shown not to be simple first order as for the solution. The absorption profiles following one tablet were S-shaped, while those following 2 or 3 tablets had partial linear segments indicating zero order absorption.

KEY WORDS: ibuprofen; absorption; disposition; multicompartmental model; solution; tablets; absorption in multicompartment system without intravenous data.

INTRODUCTION

Ibuprofen, [2-(4-isobutylphenyl)]propionic acid, is an orally administered, nonsteroidal antiinflammatory agent which is used extensively

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in the treatment of arthritis. Its biological properties (1, 2), metabolism (3), and binding to albumin (4, 5) have been described. Two GLC assay methods (6, 7) and several HPLC assay methods (8–14) have been reported. We have described an HPLC assay for ibuprofen and its major metabolites in biological fluids (15). Whitlam et al. (16) described the transsynovial distribution of ibuprofen in arthritic patients. Steady et al. (17) reported on the bioavailability of the drug in man following administration as tablets. In the first article in this series (18), we described a 15 subject study in young adults in which the subjects received 400, 800, and 1200 mg doses of ibuprofen as 1, 2, and 3 tablets, respectively, in crossover fashion one week apart; then on the fourth week all subjects received a dose of 420 mg of the drug in the form of an aqueous solution. Two other articles in this series have been published (19, 20).

Kearns and Wilson (14) administered 400 mg of sodium ibuprofen intravenously over a 5 min period to a dog. They fitted the post infusion data to a biexponential equation and modeled disposition of the drug using an open two compartment model. Unfortunately, to date there is no intravenous dosage form of ibuprofen available for use in man. In this article we infer the disposition model of ibuprofen in man from total plasma concentrations following administration of a 420 mg dose in the form of the aqueous solution. In addition, a new absorption equation (21), applicable to the open two compartment model, was applied to total plasma concentrations following administration of the different doses in tablet form to the young adults to produce absorption plots for ibuprofen in man.

EXPERIMENTAL PROCEDURE

Studies in Man

Fifteen Caucasian male subjects with mean age 25 (range 22–35) years and mean body weight 78 (range 70–92.5) kg were selected from respondents to an advertisement based on subject availability, reliability, medical history, physical examination, and results of blood and urinary analyses. In crossover fashion they were dosed with 1, 2, or 3 commercial 400 mg ibuprofen tablets (Motrin; Upjohn) with treatments one week apart. In the fourth week, all subjects received a 420 mg dose in the form of an aqueous solution of ibuprofen. Following tablet treatments blood was collected at 0, 0.167, 0.333, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr, and following solution treatment, blood was collected at 0, 0.0833, 0.167, 0.25, 0.333, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hr. The sampling schemes for tablets and solution were different because the drug was absorbed appreciably faster following administration of the solution than following the tablets. Blood was converted to plasma

immediately after collection, frozen, and stored in the freezer at −10°C until just prior to assay. Plasma was assayed for total ibuprofen by the HPLC assay described formerly (15).

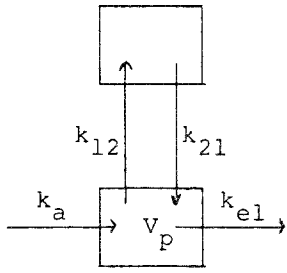
Data Analysis

Individual subject sets of concentration-time (C,t) data were fitted to a triexponential equation using the method of least squares in a program written by Dr. Jeffrey Fox and an Apple II microcomputer. Initial estimates were obtained with Dr. Fox's program, called RSTRIP, also using the microcomputer. Both arithmetic and geometric mean plasma concentrations of the 15 subjects following the solution were fitted by the same procedure using equal, $1/Y$ and $1/Y^2$ weights for different fits to provide six different triexponential equations.

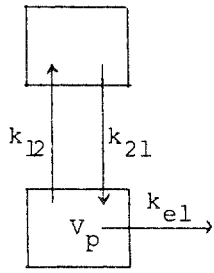
For those data sets which gave a triexponential equation such that the negative coefficient, $-(B_1+B_2)$, was associated with the largest exponent, k_a, the absorption rate constant, then the model of Scheme I was assumed, and the parameters k_{12}, k_{21}, k_{el}, and V_p were estimated from the three coefficients, three exponents, and the dose using the equations of Wagner (22). The new "Exact Loo–Riegelman" equation of Wagner (21) is given as Eq. (1) and applies if the disposition model is as shown in Scheme II. Here

$$\frac{A_T}{V_p} = C_T + k_{el}\int_0^T C\,dt + k_{12}\,e^{-k_{21}T}\int_0^T e^{+k_{21}t}\cdot C\cdot dt \qquad (1)$$

where A_T is the amount of drug absorbed to time T; V_p is the volume of the central compartment; C_T is the concentration of drug in the central compartment at time T; $\int_0^T C\,dt$ is the area under the C,t curve to time T; $\int_0^T e^{+k_{21}t}\cdot C\cdot dt$ is the area under the curve of $e^{+k_{21}t}C,t$; and the rate constants are those of Schemes I and II. In addition, the total amount of



Scheme I.



Scheme II.

drug absorbed, A_∞, divided by V_p, is given by

$$\frac{A_\infty}{V_p} = k_{el} \int_0^\infty C\,dt \tag{2}$$

and the fraction of drug absorbed, F_a, is given by

$$F_a = \frac{A_T/V_p}{A_\infty/V_p} = \frac{A_T}{A_\infty} \tag{3}$$

Initially, in evaluating C,t data following tablets, Eqs. (1) and (2) were applied using the k_{12}, k_{21}, and k_{el} values derived from solution data via the triexponentail fitting. However, in almost all cases the A_T/V_p values increased with time then decreased, or the values kept increasing throughout most of the time sampling. It was found that these trends were indicative that the wrong rate constants were being employed in Eq. (1), and they were "wrong" as a result of intrasubject variation, particularly in k_{12} and k_{21}. Hence, a new procedure was evolved to derive the constants from terminal C,t data of the same data set to which Eq. (1) was applied to the initial C,t data.

The new procedure involved the assumption that V_p is constant intrasubject for solution and tablet treatments and that absorption following both solution and tablet treatments is complete. Bioavailability of ibuprofen from tablets relative to the solution was discussed in a previous article (18). The procedure is as follows. V_p is estimated from solution data using

$$V_p = \frac{D_s}{k_{el}^s (AUC\ 0\text{–}\infty)_s} \tag{4}$$

Here D_s is the dose of ibuprofen (420 mg) administered in solution form, k_{el}^s is the first order model elimination rate constant (Scheme I) estimated from the triexponential fit of the solution C,t data, and $(AUC\ 0\text{–}\infty)_s$ is the total area under the C,t curve following the solution.

Terminal C,t data from 3 to 12 hr following a tablet treatment were fitted to the biexponential equation (Eq. 5) by the same procedure as described above to obtain the triexponential fits of solution data for 0–8 hr (Eq. 6) where t_0 is the lag time:

$$C = B_1\, e^{-\lambda_1 t} + B_2\, e^{-\lambda_2 t} \tag{5}$$

$$C = B_1\, e^{-\lambda_1 (t-t_0)} + B_2\, e^{-\lambda_2 (t-t_0)} - (B_1 + B_2)\, e^{-k_a (t-t_0)} \tag{6}$$

It should be noted that pharmacokinetic theory indicates that the magnitudes of B_1 and B_2 in Eqs. (5) and (6) are different. However, λ_1 and λ_2 would be the same if there was no intrasubject variation, but of different magnitudes if there was intrasubject variation in the parameters k_{12}, k_{21}, and k_{el}. The

model rate constants were estimated from tablet data using Eqs. (7)–(9). In these equations,

$$k_{el}^{t} = \frac{D_t}{V_p^s (AUC\ 0\text{–}\infty)_t} \tag{7}$$

$$k_{21}^{t} = \frac{\lambda_1 \lambda_2}{k_{el}^{t}} \tag{8}$$

$$k_{12}^{t} = \lambda_1 + \lambda_2 - k_{el}^{t} - k_{21}^{t} \tag{9}$$

D_t is the dose if ibuprofen is administered as tablets, V_p is from Eq. (4), $(AUC\ 0\text{–}\infty)_t$ is the total area under the C,t curve following the tablet treatment and λ_1 and λ_2 are from Eq. (5). The values of k_{12}^{t}, k_{21}^{t}, k_{el}^{t} obtained from Eqs. (7)–(9) were then substituted into Eq. (1), and Eq. (1) was applied to the C,t data in the 0–3 hr time range of the same data set which gave Eq. (5) in the 3–12 hr range.

In some cases (see note *a* of Table III), terminal tablet C,t data were fitted very well with only a monoexponential rather than a biexponential equation. In these cases, the Wagner-Nelson method (24) was applied rather than the method described herein using Eqs. (1)–(5) and (7)–(9). In some cases Eqs. (5) and (7)-(9) led to negative values of k_{12}^{t}. Attempts were then made to calculate a different k_{el}^{t} value using Eq. 10 from Dittert et al. (23),

$$k_{el}^{t} = \frac{(k_{12}^{s} + k_{21}^{s})\lambda_1 - (\lambda_1)^2}{k_{21}^{s} - \lambda_1} \tag{10}$$

where λ_1 is from the mono- or biexponential fit of terminal tablet C,t data. When solution C,t data were computer-fitted with the triexponential Eq. (6), an estimate of k_a, the absorption rate constant, was obtained. Hence, the fraction absorbed, F_a, following administration of the solution, could be described by Eq. (11). Values of F_a obtained with

$$F_a = 1 - e^{-k_a(t - t_0)} \tag{11}$$

were compared with values of F_a obtained from applications of Eqs. (1)-(3).

In the computer fitting of C,t data, three measures of fit were employed. These were as follows. The coefficient of determination, r^2, was obtained from Eqs. (12)–(14), where

$$r^2 = 1 - \frac{\sum d^2}{S_c^2} \tag{12}$$

$$S_c^2 = \sum C^2 - \frac{(\sum C)^2}{N} \tag{13}$$

$$\sum d^2 = \sum (C - \hat{C})^2 \tag{14}$$

Table I. Estimated Parameters and Measures of Fit of Total Ibuprofen Plasma Concentrations by Nonlinear Least Squares Fitting to a Triexponential Equation Following Oral Administration of a Solution of Ibuprofen[a]

		Estimated parameters				Measures of fit			Derived parameters			
Subject	Weighting	λ_1 (hr^{-1})	λ_2 (hr^{-1})	k_a (hr^{-1})	t_0 (hr)	r^2	Corr.	S ($\mu g/ml$)	V_p (L)	k_{12}^s (hr^{-1})	k_{21}^s (hr^{-1})	k_{el}^s (hr^{-1})
1	$1/Y^2$	0.223	1.58	2.35	0.027	0.982	0.991	4.50	7.13[b] (7.39)[c]	0.850	0.935	0.369
2	Equal	0.203	1.11	1.62	0.039	0.982	0.991	2.11	5.62 (6.36)	0.359	0.432	0.520
4	Equal	0.359	0.793	2.57	0.014	0.968	0.984	3.12	7.04 (7.10)	0.0789	0.593	0.481
5	$1/Y^2$	0.341	1.08	1.30	0.008	0.983	0.992	2.84	10.91 (10.35)	0.0301	1.03	0.356
6	$1/Y^2$	0.367	4.51	7.54	0.043	0.998	0.999	2.06	6.07 (6.10)	2.55	2.33	0.711
7	Equal	0.309	1.27	1.66	0.01	0.980	0.980	2.05	6.31 (6.61)	0.302	0.765	0.513
8	$1/Y^2$	0.413	0.545	9.25	0.05	0.994	0.997	2.31	6.71 (5.08)	0.366	0.380	0.591
9	$1/Y^2$	0.425	7.13	18.7	0.056	0.998	0.999	2.34	4.76 (4.62)	3.42	4.14	0.733
10	$1/Y^2$	0.327	3.49	12.7	0.062	0.9996	0.9998	1.24	7.32 (7.21)	1.01	2.31	0.494
11	$1/Y^2$	0.405	14.4	14.4	0.0	0.989	0.995	4.86	6.75 (6.72)	0.768	13.6	0.428
12	Equal	0.418	2.55	10.52	0.063	0.992	0.996	2.37	6.36 (6.23)	0.318	2.15	0.495
13	Equal	0.333	0.848	7.34	0.044	0.987	0.994	3.37	5.33 (5.34)	0.116	0.566	0.498
14	$1/Y^2$	0.351	3.94	6.75	0.0	0.997	0.998	2.20	6.30 (6.16)	1.60	2.00	0.691
15[d]	$1/Y^2$	0.286	11.65	2.09	0.0674	0.995	0.998	0.905	2.24 (2.18)	7.95	2.79	1.20
Mean		0.340	3.92	7.06	0.035				6.35 (6.22)	1.41	2.43	0.577
C.V. (%)		20.1	109.9	78.3	70				29.0 (31.9)	151	140	37.1

[a] Subject 3 gave the triexponential equation $\hat{C} = 58.96e^{-0.368t} - 152.07e^{-2.06t} + 90.08e^{-2.82t}$, which indicates a different model.
[b] Nonbracketed value is from the triexponential fit.
[c] Bracketed value calculated as $V_p = D_s/k_{el}^s\,(AUC)_s$.
[d] This gave a triexponential equation of the form of Eq. (22), whereas the other subjects gave equations of the form of Eq. (6).

S_c^2 is the corrected sum of squares of the observed concentrations, C, and $\hat{C}$ is the model-predicted concentrations (from either Eq. 5 or 6). Corr. is the correlation coefficient for the linear regression of $\hat{C}$ on C. The standard deviation, S, was estimated with

$$S = \sqrt{\sum d^2/(N-P)} \tag{15}$$

where N is the number of data points fitted, and P is the number of parameters estimated, namely, 4 for Eq. (5) and 6 for Eq. (6). The weighting scheme which gave the smallest $\sum d^2$, and hence the smallest value of S (Eq. 15), and largest value of r^2 (Eq. 12) was chosen (Tables I and II).

RESULTS

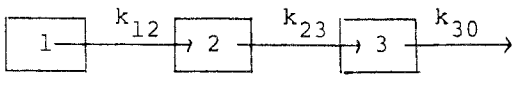
Table I lists results of fitting solution C,t data of 13 individual subjects to the triexponential Eq. (6). The type of weighting, namely equal, $1/Y$ and $1/Y^2$, which gave the best fit is indicated in the second column of Table I. The estimated parameters λ_1, λ_2, k_a, and t_0 (but not B_1 and B_2) are listed as well as the measures of fit obtained with Eqs. (12)–(15). In the last four columns are listed the derived parameters V_p, k_{12}^s, k_{21}^s, and k_{el}^s; note that $\lambda_1 < k_{21} < \lambda_2 < k_a$. These fittings indicate that the model of Scheme I is the appropriate model and the model of Scheme II is the disposition model. The solution data of subject # 3 gave a triexponential equation of the type of Eq. (16) where the negative coefficient, $-B_2$, is associated with the intermediate size rate constant, λ_2, which implies a different model:

$$C = B_1\, e^{-\lambda_1(t-t_0)} - B_2\, e^{-\lambda_2(t-t_0)} + B_3\, e^{-\lambda_3(t-t_0)} \tag{16}$$

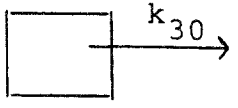
Both the arithmetic and geometric mean plasma concentrations of 15 subjects following the solution, each with equal, $1/Y$ or $1/Y^2$ weighting, gave equations like Eq. 16, as indicated in Table II. Such an equation is appropriate for the model shown in Scheme III, where $\lambda_1 = k_{30}$, $\lambda_2 = k_{12}$, $\lambda_3 = k_{23}$, and $k_{30} < k_{12} < k_{23}$. The corresponding disposition model would be the one compartment open model shown in Scheme IV. The solution data of subject # 15 gave a triexponential equation of the type

$$\hat{C} = B_1\, e^{-\lambda_1 t} - B_2\, e^{-\lambda_2 t} - B_3\, e^{-\lambda_3 t} \tag{17}$$

which indicates the model shown in Scheme I, but where $\lambda_1 < k_a < k_{21} < \lambda_2$. Thus, 14 out of 15 or 93% of the individual subject solution C,t data



Scheme III.



Scheme IV.

Table II. Estimated Parameters and Measure of Fit of Mean Total Ibuprofen Plasma Concentrations to a Triexponential Equation Following Oral Administration of an Aqueous Solution of Ibuprofen

Type of mean	Weighting	B_1 (μg/ml)	λ_1 (hr^{-1})	B_2 (μg/ml)	λ_2 (hr^{-1})	B_3 (μg/ml)	λ_3 (hr^{-1})	t_0 (hr)	r^2
Arithmetic	Equal	51.00	0.371	−12.61	1.86	−38.38	9.56	0.043	0.996
	$1/Y_i$	48.11	0.353	−24.89	4.13	−23.23	14.1	0.045	0.998
	$1/Y_i^2$	47.07	0.347	−26.21	4.58	−20.86	14.9	0.045	0.999
Geometric	Equal	47.00	0.352	−34.52	4.21	−12.48	10.1	0.036	0.996
	$1/Y_i$	47.11	0.355	−35.29	4.20	−11.82	10.5	0.036	0.998
	$1/Y_i^2$	46.58	0.352	−36.28	4.36	−10.30	10.8	0.037	0.999

indicated that the appropriate model is the open two compartment model of Schemes I and II, but the mean data did not reflect the same model (Table II).

Figure 1 shows a typical triexponential fit of solution C,t data (for subject # 2). The fitting of typical terminal tablet C,t data to a biexponential equation is also shown in the lower panel of Fig. 1. Figure 2 is a plot of F_a values for the solution estimated with Eq. (1)–(3) using the k_{12}^s, k_{21}^s, and k_{el}^s values listed in Table I vs. F_a values obtained with Eq. (11) using the k_a and t_0 values from the triexponential fittings listed in Table I. Figure 2 is based on the pooled data of the 13 subjects whose triexponential equation had the form of Eq. (6). This is evidence that Eqs. (1)–(3) provide accurate values of fraction of ibuprofen absorbed. The least squares line had a slope of 1.045, which did not differ significantly from unity, and an intercept of −0.0059, which did not differ significantly from zero, with $r = 0.980$. In Fig. 2, the line of identity with a slope equal to unity is drawn. Figure 3 is a plot of F_a versus time for the solution of ibuprofen showing data for subject # 9, who absorbed drug from the solution the most rapidly, and that for subject # 7, who absorbed the drug from solution the slowest. The points in the plots were obtained with Eqs. (1)–(3) while the solid lines drawn through the points were estimated with Eq. (16). Thus, this is additional evidence that Eqs. (1)–(3) provide accurate estimates of F_a.

Terminal C,t data following the ibuprofen solution were also fitted to biexponential equations (Eq. 5), and Eqs. (7)–(9) were then applied to generate k_{12}^s, k_{21}^s, and k_{el}^s values (rather than the k_{12}^t, k_{21}^t, and k_{el}^t as in Eqs. 7–9). These were different values than those listed in Table I. The two sets of microscopic rate constants for the solution were then used, separately, in Eqs. (1)–(3) to generate two sets of F_aT values. In Fig. 4, F_a from the biexponential fit is plotted vs. F_a from the triexponential fit. The least squares line had a slope of 1.096, which was not significantly different from unity, and an intercept of −0.039, which was not significantly different from zero, with $r = 0.972$. The line drawn through the points is the line of identity with slope equal to unity. This figure provides support for the fitting of terminal C,t data to biexponential equations in order to estimate the λ_1 and λ_2 values from which k_{12} and k_{21} values could be estimated. Table III lists the estimated parameters and measures of fit of terminal tablet C,t data to monoexponential or biexponential equations. These were excellent fits.

The apparent elimination rate constants (λ_1) obtained in the monoexponential or biexponential fittings (for treatments with 1, 2, or 3 tablets) and triexponential fittings (solution data) are listed in Tables I and III. Typical absorption plots following tablet treatments A, B, and C are shown in Figs. 5, 6, and 7, respectively. Although absorption of ibuprofen from

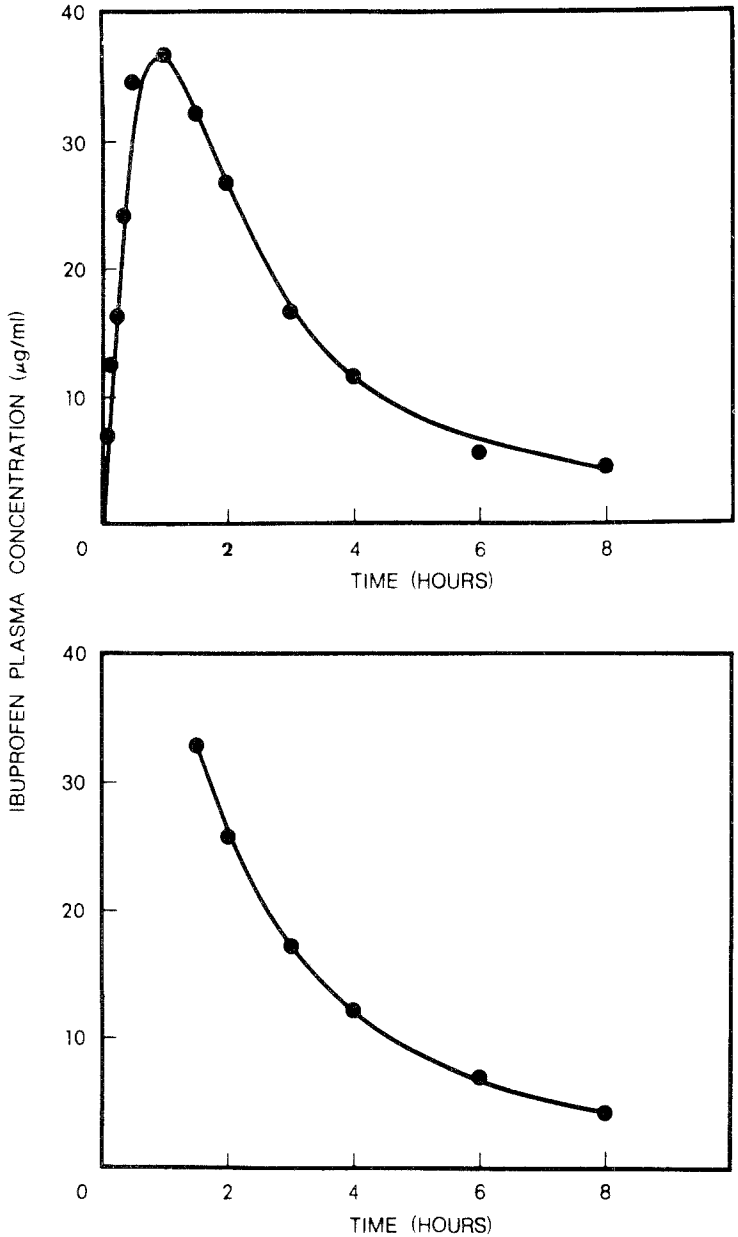


Fig. 1. Upper panel: typical triexponential fit (to Eq. 6) of solution C,t data of subject # 2 (see Table I for estimated parameters and measures of fit). Lower panel: typical biexponential fit of terminal C,t tablet data.

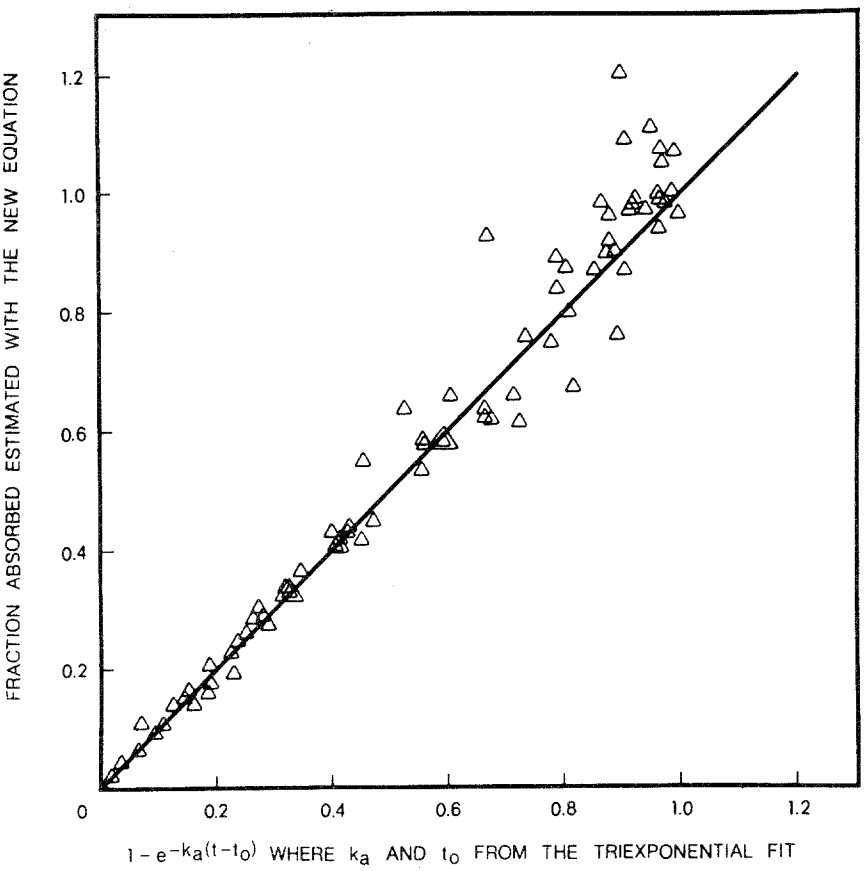


Fig. 2. A plot of F_a values obtained with Eqs. (1)–(3) using the k_{12}^s, k_{21}^s, and k_{el}^s values listed in Table I vs. the corresponding F_a values estimated with Eq. (16) using the k_a and t_0 values from the triexponential fittings of solution data (see Table I). This is excellent evidence to support the new absorption equation (Eq. 1). The least squares line for the data is $\hat{Y} = -1.045X - 0.0059$ with $r = 0.980$. Line is identity with slope equal to unity (see text).

solution obeys first order kinetics (Fig. 3), absorption of the drug following tablets is not simple first order. Following one 400 mg tablet, the absorption plots are S-shaped (Fig. 5) as Digenis (25) reported using scintography. Following the 800 mg two tablet dose, there begins to be evidence of some zero order absorption (Fig. 6). Following the 1200 mg three tablet dose, the evidence for zero order absorption becomes more pronounced (Fig. 7).

In the first article (18) it was reported that ibuprofen exhibits nonlinear plasma protein binding and that a plot of the area under the total (bound + free) plasma concentration-time curve was a nonlinear function of the mg/kg

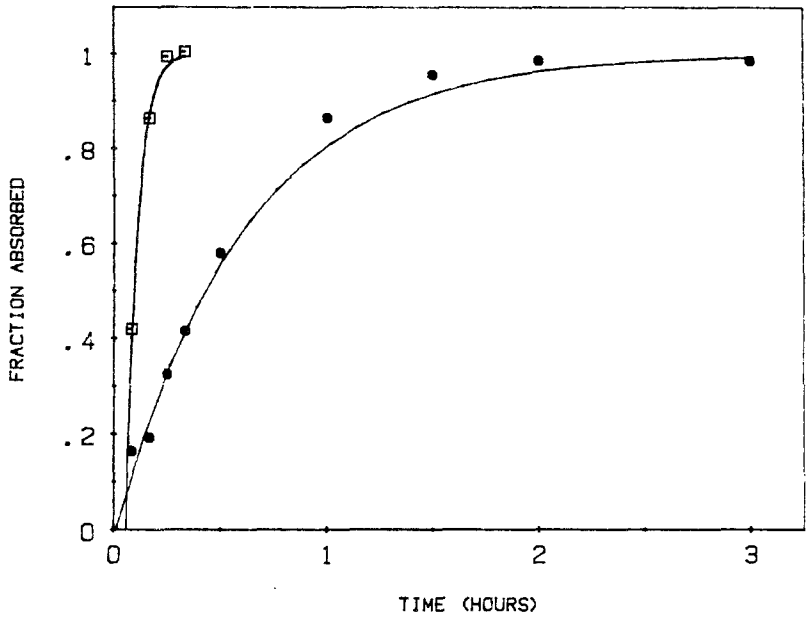


Fig. 3. Absorption plots for ibuprofen from solution showing the range of values. Open circles are for subject # 9, who absorbed the drug most rapidly. Closed circles are for subject # 7, who absorbed the drug the slowest of the panel. The points are derived from Eqs. (1)-(3). The lines are based on Eq. (16). This, again, provides excellent experimental evidence of validity of Eqs. (1)-(3).

dose of the drug; however, a plot of the area under the free (unbound) plasma concentration-time curve was essentially linear. Linearity of such plots implies constant plasma clearance. Although the average bound/free ratio of ibuprofen in the study under discussion (18) was 180, almost all the observed binding values were in the lower one-third of the overall binding curves. Hence, although the data were nonlinear, they were minimally so. Although we believe that input kinetics should be determined from total plasma concentrations of drug even in cases of such nonlinearity, one may ask what would happen if free concentrations were similarly analyzed. We have done so with the free ibuprofen plasma concentrations using the same methods as used for total concentrations. Free plasma concentrations following the solution of ibuprofen were computer-fitted to Eq. (6); rate constants, k_a, could be compared in 13 of the 15 subjects. The mean k_a^t from total concentrations, 6.76 hr^{-1}, did not differ significantly from the mean k_a^s from free concentrations, 6.07 hr^{-1} (paired $t = 1.89$, $0.10 > p > 0.05$); least squares linear regression of $Y = k_a^s$ from free vs.

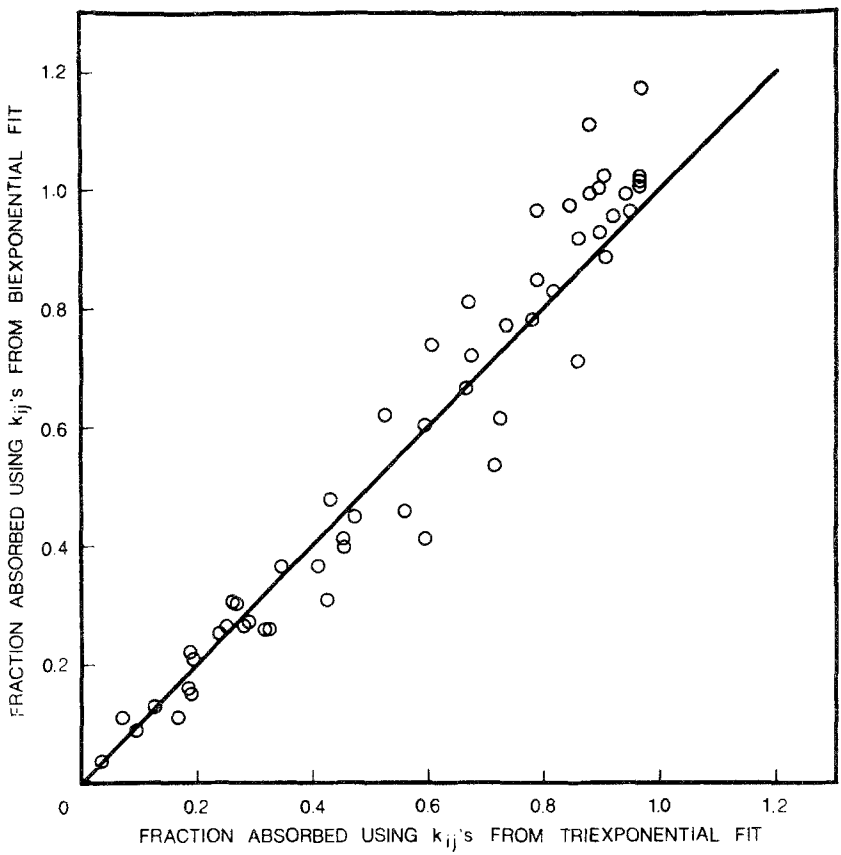


Fig. 4. A plot of F_a derived from terminal biexponential fits of solution data vs F_a derived from triexponential fittings of solution data. This provides justification for fitting terminal C,t data following tablets to a biexponential equation to estimate k^t_{12}, k^t_{21}, and k^t_{el}. The least squares line is $\hat{Y} = 1.096X - 0.039$ with $r = 0.970$. Line is identity with slope equal to unity (see text).

$X = k^t_a$ from total gave a slope of 0.934 with $r = 0.966$ ($p < 0.001$); the orthogonal least squares line had a slope of 0.965. For the highest dose (1200 mg as 3 tablets), fraction absorbed values derived from total concentrations, F^t_a, were compared with fraction absorbed values derived from free concentrations, F^f_a. A comparison was possible using the pooled data of 6 subjects with 31 pairs of F_a values. The mean F^t_a value of 0.513 did not differ significantly from the mean F^f_a value of 0.533 (paired $t = 1.62$, $p > 0.10$). The correlation of $Y = F^f_a$ vs. $X = F^t_a$ gave a slope of 1.03, which was not significantly different from unity, and an intercept of 0.02, which

Table III. Estimated Parameters and Measures of Fit of Terminal Total Ibuprofen Plasma Concentrations Following Ibuprofen Tablets to Mono- or Biexponential Equations

Subject and treatment	Time period (hr)	Weighting	Estimated parameters				Measures of fit		
			B_1 (μg/ml)	λ_1 (hr^{-1})	B_2 (μg/ml)	λ_2 (hr^{-1})	r^2	Corr.	S^a (μg/ml)
1A	3–12	Equal	43.87	0.286					
1B	3–12	Equal	22.91	0.176	112.83	0.597	0.998	0.999	0.749
1C	3–12	Equal	64.72	0.297	199.58	1.007	0.9999	0.9999	0.192
2A	2–12	Equal	35.95	0.232	10.07	0.489	0.997	0.999	0.603
2B	2–10	Equal	20.71	0.202	127.02	0.698	0.997	0.999	1.31
2C	3–12	Equal	117.05	0.363	557.58	1.428	0.9995	0.9998	0.608
4A	3–12	Equal	18.08	0.276	97.79	1.128	0.997	0.999	0.336
4B	1.5–10	$1/Y^2$	129.36	0.489			0.967	0.984	0.837
4C	2–10	$1/Y^2$	12.36	0.227	112.61	0.437	0.984	0.992	1.31
5A	3–12	$1/Y$	53.75	0.329			0.997	0.999	0.316
5B	2–12	$1/Y$	35.03	0.229	222.23	0.978	0.985	0.992	1.77
5C	3–12	$1/Y$	36.53	0.260	210.61	0.469	0.998	0.999	0.996
6A	3–12	$1/Y$	49.53	0.302			0.9996	0.999	0.237
6B	3–12	$1/Y^2$	40.21	0.231	101.71	0.694	0.9995	0.999	0.420
6C	3–12	$1/Y$	94.97	0.309			0.999	0.996	0.746
7A	3–12	Equal	49.97	0.288	413.82	1.800	0.999	0.999	0.473
7B	3–12	$1/Y$	91.87	0.287			0.997	0.993	1.21
7C	3–12	$1/Y^2$	57.60	0.245	67.37	0.529	0.999	0.992	0.983
8A	3–12	Equal	58.65	0.314	4822.6	2.084	0.992	0.996	1.63
8B	3–12	$1/Y^2$	40.29	0.270	154.8	0.507	0.9996	0.993	0.601
8C	3–12	$1/Y^2$	249.19	0.353			0.9996	0.999	1.15
9A	3–12	$1/Y^2$	5.78	0.160	158.9	0.656	0.9996	0.991	0.290
9B	3–12	$1/Y^2$	9.77	0.268	93.19	0.494	0.992	0.995	0.513
9C	3–12	$1/Y$	165.10	0.346			0.995	0.987	2.57
10A	4–12	$1/Y$	77.90	0.287			0.9998	0.9999	0.104
10B	3–12	Equal	88.06	0.315	256.71	1.020	0.999	0.9997	0.727
10C	3–12	Equal	190.63	0.384			0.9997	0.9998	0.460

11A	3–12	$1/Y$	25.38	0.324	24.64	0.697	0.9998	0.9999	0.0734
11B	3–12	$1/Y$	37.79	0.306	221.71	0.897	0.9999	0.9999	0.169
11C	3–12	$1/Y^2$	31.48	0.273	114.38	0.650	0.9995	0.997	0.416
12A	3–12	$1/Y^2$	8.07	0.158	68.74	0.566	0.998	0.999	0.484
12B	3–12	$1/Y^2$	75.36	0.321			0.949	0.976	0.902
12C	3–12	$1/Y^2$	17.38	0.269	192.19	0.465	0.991	0.996	0.593
13A	3–12	$1/Y^2$	23.76	0.249	81.21	0.584	0.999	0.991	0.456
13B	3–12	$1/Y^2$	98.63	0.336	3098.6	1.678	0.997	0.999	0.344
13C	3–12	$1/Y^2$	47.76	0.271	135.7	0.423	0.999	0.9996	0.288
14A	3–12	Equal	39.74	0.381			0.972	0.987	0.347
14B	3–12	Equal	89.14	0.386	30.41	0.572	0.998	0.999	0.835
14C	3–12	Equal	94.17	0.393	36.52	0.594	0.994	0.997	1.69
15A	3–12	$1/Y$	49.75	0.324			0.992	0.996	0.467
15B	3-12	$1/Y$	93.27	0.316			0.998	0.999	0.492
15C	3–12	$1/Y$	145.67	0.327			0.999	0.999	0.503
Mean				0.294		0.841			
C.V. (%)				22.2		60.7			

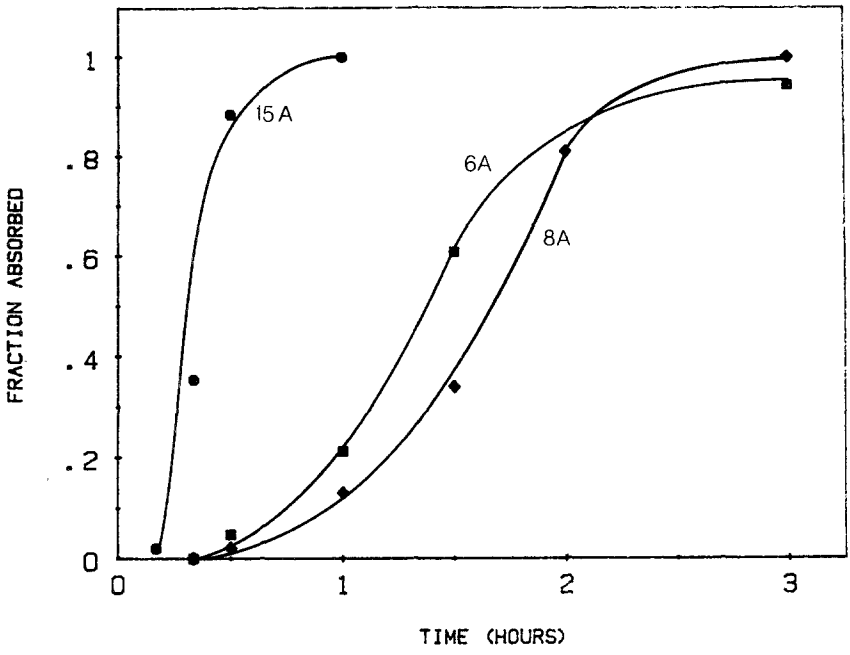


Fig. 5. Typical plots of F_a vs time following treatment A (one tablet). Numbers refer to subjects.

was not significantly different from zero, with $r = 0.973$ ($p < 0.001$). Thus, results obtained by analyzing free concentrations were essentially the same as those obtained by analyzing total concentrations. In addition, intrasubject variation of pharmacokinetic parameters derived from free concentrations were of the same magnitude as those derived from total concentrations.

DISCUSSION

Although first order absorption is often assumed in pharmacokinetics, there are few examples in the literature where there is convincing evidence of this. We have shown that ibuprofen administered orally in the form of an aqueous solution was absorbed according to first order kinetics in 14 of 15 subjects. This was shown in two different ways: (a) by computer fitting C,t data following the solution to a triexponential equation, which was based upon first order absorption; and (b) by applying a new absorption equation (21) using the microscopic rate constants k_{12}^s, k_{21}^s, and k_{el}^s, which were derived from the triexponential fit.

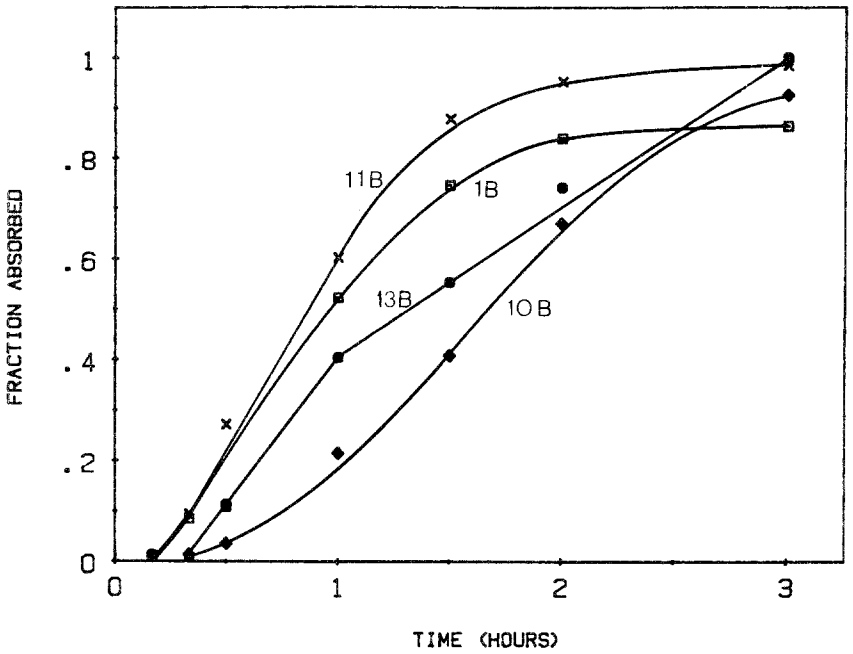


Fig. 6. Typical plots of F_a vs time following treatment B (two tablets). Numbers refer to subjects.

A new method has been described to obtain absorption plots for a multicompartmental system without intravenous data. The method is based on estimating V_p following administration of the drug in solution form, fitting terminal C,t data following tablet(s) to a biexponential equation (Eq. 5), then estimating the microscopic rate constants, k_{12}^t, k_{21}^t, and k_{el}^t (using Eqs. 7–9), followed by application of a new absorption equation (Eq. 1). The method is valid if the absorption following solution and tablet forms to the same subject is complete in both cases. The method was successfully applied to ibuprofen C,t tablet data. The new method was developed since the usual assumption of the constancy of the distribution rate constants, k_{12} and k_{21}, of the open two compartment model was found to be invalid in the case of ibuprofen. Although such constancy has hitherto been assumed in the case of application of the Loo-Reigelman method (26), the assumption has never been well tested.

A most interesting result of the analyses of the ibuprofen data is that the pharmacokinetic model which one would elaborate from mean C,t ibuprofen solution data (see Scheme III) is not the same as the open two compartment model (see Scheme I) which is indicated by the analysis of

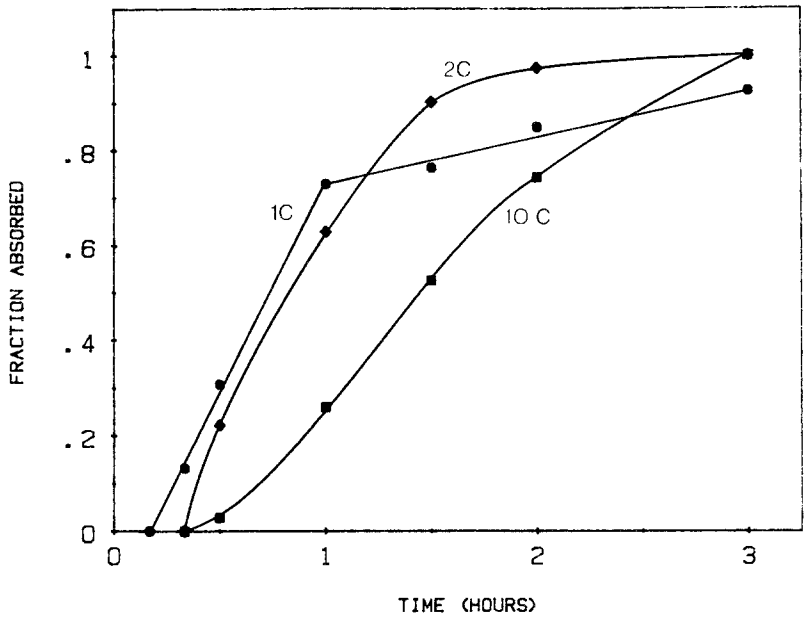


Fig. 7. Typical plots of F_a vs time following treatment C (three tablets). Numbers refer to subjects. Note the zero order absorption particularly of subject 1.

14 out of 15 sets of individual subject data. Both the arithmetic and geometric mean data were fitted by a triexponential equation in which the coefficient with a negative sign was associated with the intermediate-sized rate constant. However, in 14 out of 15 sets of individual subject C,t ibuprofen solution data, the coefficient with a negative sign was associated with the largest rate constant. The methods discussed in this article have been applied successfully to results obtained in a similar study with flurbiprofen, and those results will be the subject of a future publication.

REFERENCES

1. S. S. Adams, E. E. Cliffe, B. Lessel, and J. S. Nicholson. Some biological properties of 2-(4-isobutylphenyl)propionic acid. *J. Pharm. Sci.* **56:**1686 (1967).
2. E. F. Davies and G. S. Avery. Ibuprofen: a review of its pharmacological properties and therapeutic efficacy in rheumatoid disorders. *Drugs* **2:**416–446 (1981).
3. R. F. N. Mills, S. S. Adams, E. E. Cliffe, W. Dickinson, and J. S. Nicholson. The metabolism of ibuprofen. *Xenobiotica* **3:**589–598 (1973).
4. J. B. Whitlam, M. J. Crooks, K. F. Brown, and P. Veng Pedersen. Binding of nonsteroidal antiinflammatory agents to proteins I. Ibuprofen-serum albumin interation. *Biochem. Pharmacol.* **28:**675–678 (1979).

5. A. Kober and I. Sjöholm. The binding sites on human serum albumin for some nonsteroidal antiinflammatory drugs. *Mol. Pharmacol.* **18:**421–426 (1980).
6. D. G. Kaiser and G. J. Vangiessen. GLC determination of ibuprofen [(±)-2-(p-isobutylphenyl)propionic acid] in plasma. *J. Pharm. Sci.* **63:**219–222 (1974).
7. D. G. Kaiser and R. S. Martin. Electron-capture determination of ibuprofen in serum. *J. Pharm. Sci.* **67:**627–630 (1978).
8. D. Pitre and M. Grandi. Rapid determination of ibuprofen in plasma by high-performance liquid chromatography. *J. Chromatogr.* **170:**278–281 (1979).
9. L. J. Dusci and L. P. Hackett. Determination of some anti-inflammatory drugs in serum by high-performance liquid chromatography. *J. Chromatogr.* **172:**516–519 (1979).
10. R. A. Upton, J. N. Buskin, T. W. Guentert, R. L. Williams, and S. Riegelman. Convenient and sensitive hgih-performance liquid chromatography assay for ketoprofen, naproxen and other allied drugs in plasma or urine. *J. Chromatogr.* **190:**119–128 (1980).
11. J. K. Baker and E. Kim Fifer. High-pressure liquid chromatographic identification of drugs used in the management of arthritis. *J. Pharm. Sci.* **69:**590–592 (1980).
12. A. Ali, S. Kazmi, and F. M. Plakogiannis. High-pressure liquid chromatographic determination of ibuprofen in plasma. *J. Pharm. Sci.* **70:**944–945 (1981).
13. B. G. Snider, L. J. Beaubien, D. J. Sears, and P. D. Rahn. Determination of flurbiprofen and ibuprofen in dog serum with automated sample preparation. *J. Pharm. Sci.* **70:**1347–1349 (1981).
14. G. L. Kearns and J. T. Wilson. Determination of ibuprofen in serum by high-performance liquid chromatography and application to ibuprofen disposition. *J. Chromatogr.* **226:**183–190 (1981).
15. G. F. Lockwood and J. G. Wagner. High-performance liquid chromatographic determination of ibuprofen and its major metabolites in biological fluids. *J. Chromatogr.* **232:**335–343 (1982).
16. J. B. Whitlam, K. F. Brown, M. J. Crooks, and G. F. W. Room. Transsynovial distribution of ibuprofen in arthritic patients. *Clin. Pharmacol. Ther.* **29:**487–492 (1981).
17. J. A. Steady, M. Freeman, E. G. John, G. T. Ward, and B. Whiting. Ibuprofen tablets: dissolution and bioavailability. *Int. J. Pharm.* **14:**59–72 (1983).
18. G. F. Lockwood, K. S. Albert, W. R. Gillespie, G. G. Bole, T. M. Harkcom, G. J. Szpunar, and J. G. Wagner. Pharmacokinetics of ibuprofen in man I. Free and total area-dose relationships. *Clin. Pharmacol. Ther.* **34:**97–103 (1983).
19. K. S. Albert, W. R. Gillespie, J. G. Wagner, A. Pau, and G. F. Lockwood. Pharmacokinetics of ibuprofen in man II. Effect of age. *Am. J. Med.*, **77:**47–50 (1984).
20. G. F. Lockwood, K. S. Albert, G. J. Szpunar, and J. G. Wagner. Pharmacokinetics of ibuprofen in man. III. Plasma protein binding. *J. Pharmacokin. Biopharm.* **11:**469–482 (1983).
21. J. G. Wagner. Pharmacokinetic absorption plots from oral data alone or oral/intravenous data and an exact Loo-Riegelman equation. *J. Pharm. Sci.* **72:**838–842 (1983).
22. J. G. Wagner. In *Fundamentals of Clinical Pharmacokinetics.* Drug Intelligence Publications, Hamilton, Ill. 1975, pp. 102–103.
23. L. W. Dittert, W. A. Cressman, S. A. Kaplan, S. Riegelman, and J. G. Wagner. *Guidelines for Biopharmaceutical Studies in Man.* American Pharmaceutical Association, Academy of Pharmaceutical Sciences, Washington, D.C., 1972, p. 14.
24. J. G. Wagner and E. Nelson. Percent absorbed time plots derived from blood level and/or urinary excretion data. *J. Pharm. Sci.* **52:**610–611 (1963).
25. G. A. Digenis. The utilization of short-lived radionuclides in the assessment of formulation and in vivo disposition of drugs. In C. G. Wilson, J. G. Hardy, with S. S. Davis and M. Frier (eds.), *Radionuclide Imaging in Drug Research.* Crown Helm, London, 1982, pp. 103–143.
26. J. C. K. Loo and S. Riegelman. New method for calculating the intrinsic absorption rate of drugs. *J. Pharm. Sci.* **57:**918–928 (1968).