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Research Article

The Area Function Method for Assessing the Drug Absorption Rate in Linear Systems with Zero-Order Input

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A noncompartmental approach for determination of the apparent zero-order absorption rate constant (k_0) has been developed. The procedure evolves from the convolution integral and requires individual oral-dose plasma concentration values and calculation of area intervals under the plasma concentration–time curves after intravenous administration. The proposed method was evaluated and compared with the Wagner–Nelson, Loo–Riegelman, deconvolution, nonlinear regression, and moment methods using errorless and errant simulation data for one- or two-compartment models. The area function method is generally equal to the best of these techniques (nonlinear regression) and superior to the weaker methods (moment, deconvolution, Loo–Riegelman), especially for errant two-compartment data. Coupled with a companion procedure for constructing fraction absorbed versus time plots and assessing first-order absorption rate constants, the area function methods offer direct and accurate means of discerning drug absorption kinetics without the need for assignment of a disposition model for drugs with linear elimination kinetics.

KEY WORDS: apparent zero-order absorption rate constant; deconvolution; Wagner–Nelson method; Loo–Riegelman method; moment analysis; nonlinear regression.

INTRODUCTION

The development of controlled-release dosage formulations has been receiving increasing attention in the pharmaceutical industry. Zero-order release and absorption of drugs is a frequent goal (1). In the evaluation of these products, it is important to characterize drug absorption and calculate the absorption rate constant. Several methods for estimating either first- or zero-order absorption rate constants have been reported. These include the Wagner–Nelson method (2), the Loo–Riegelman method (3), deconvolution (4), nonlinear regression analysis using NONLIN (5), and moment analysis (6).

In 1966, Rescigno and Segre (7) introduced deconvolution to determine the transfer function between two compartments. Later, the application of deconvolution to the evaluation of drug absorption was reported by Benet and Chiang (4). They recommended the use of the point-area method of deconvolution, in particular, to estimate the antitransform of the transfer function [$G(t_n)$] describing the absorption process (4). The values of this function obtained by deconvolution at various times is an approximation of the true values for a first-order process. In contrast, for a zero-order absorption process, an exact solution for $G(t_n)$ is obtained according to (4)

$$G(t_1) = \frac{C_{po}(t_1)}{AUC_{iv}^{0\rightarrow t_1}} \tag{1}$$

$$G(t_2) = \frac{C_{po}(t_2) - G(t_1) \cdot AUC_{iv}^{t_1\rightarrow t_2}}{AUC_{iv}^{0\rightarrow t_1}} \tag{2}$$

$$G(t_n) = \frac{\left[C_{po}(t_n) - \sum_{i=2}^{n} AUC_{iv}^{t_{i-1}\rightarrow t_i} \cdot G(t_{n-i+1})\right]}{AUC_{iv}^{0\rightarrow t_1}} \tag{3}$$

and

$$G(t_1) = G(t_2) = \ldots = G(t_n) = \frac{k_0}{D} \tag{4}$$

where $C_{po}(t_n)$ is the concentration at time, t_n, after the oral administration of drug, $AUC_{iv}^{t_{i-1}\rightarrow t_i}$ is the area interval under the intravenous blood concentration–time curve between t_{i-1} and t_i, k_0 is the apparent zero-order absorption rate constant, and D is the dose. Although the basis of the point-area deconvolution method which utilizes Eqs. (1)–(3) has been mathematically verified (8), Eqs. (1)–(4) have not been derived for a zero-order absorption process.

Recently, an area function method was developed to calculate the apparent first-order absorption rate constant (9). A similar derivation technique may be applied to estimate the apparent zero-order absorption rate constant. The purposes of this paper are (a) to present a new method to estimate k_0 and the fraction of the amount absorbed [$F_a(t)$] based on the relationship between oral plasma concentra-

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tions and area intervals obtained from plasma concentration–time curves after intravenous administration of drug; (b) to evaluate and compare this proposed method and the Wagner–Nelson method, the Loo–Riegelman method, deconvolution, nonlinear regression analysis, and moment analysis using errorless and errant data sets; and (c) to derive Eq. (4) and to discuss the relationship between the proposed method and deconvolution.

THEORETICAL

The following equation has been derived previously (9) for a linear mammillary system:

$$G(s) = \frac{In_s^{po}}{In_s^{iv}} \tag{5}$$

where $G(s)$ is the transfer function between the absorption site and the central compartment and In_s is the Laplace transform of the input function (7).

For an intravenous bolus,

$$In_s^{iv} = D \tag{6}$$

For zero-order input from the GI tract,

$$In_s^{po} = k_o/s \tag{7}$$

Therefore, substituting both Eq. (6) and Eq. (7) into Eq. (5) yields

$$G(s) = \frac{C_{po}(s)}{C_{iv}(s)} = \frac{k_o/s}{D} = \frac{k_o}{D \cdot s} \tag{8}$$

Rearrangement of terms gives

$$D \cdot [C_{po}(s)] = \frac{k_o}{s} \cdot [C_{iv}(s)] \tag{9}$$

Taking the anti-Laplace transform of both sides of Eq. (9) yields

$$L^{-1}\{D \cdot [C_{po}(s)]\} = L^{-1}\left\{\frac{k_o}{s} \cdot [C_{iv}(s)]\right\} \tag{10}$$

or

$$D \cdot C_{po}(t) = k_o \cdot \int_o^t C_{iv}(t)dt \tag{11}$$

or

$$k_o = \frac{D \cdot C_{po}(t)}{\int_o^t C_{iv}(t)dt} = \frac{D \cdot C_{po}(t)}{AUC_{iv}^{o \to t}} \tag{12a, b}$$

or

$$k_o = \frac{D \cdot C_{po}(t)}{AUCF(t)} \tag{13}$$

where AUCF (t) denotes the area function,

$$AUCF(t) = AUC_{iv}^{o \to t} \tag{14}$$

Therefore, k_o can be obtained from the ratio given in Eq. (13) at any time in the absorption phase. This derivation provides the theoretical basis for the point/area method of deconvolution for zero-order input functions (see Appendix).

Assuming that the bolus dose and oral dose are the same and equal to D, the fraction of the amount absorbed at time t [$F_a(t)$] can be calculated according to the following equation:

$$F_a(t) = \frac{t}{\tau} = \frac{t \cdot k_o}{F \cdot D} \tag{15a, b}$$

where τ is the duration of the input process. The fraction (F) of the dose absorbed is generated from

$$F = AUC_{po}/AUC_{iv} \tag{16}$$

Substituting Eq. (13) into Eq. (15b) yields

$$F_a(t) = \frac{t \cdot C_{po}(t)}{F \cdot AUCF(t)} \tag{17}$$

Thus, Eq. (17) can be used to estimate the fraction of the amount absorbed at any time in the absorption phase.

Differentiating both sides of Eqs. (15a) and (15b) with respect to time t yields

$$\frac{dF_a(t)}{dt} = \frac{1}{\tau} = \frac{k_o}{F \cdot D} \tag{18a, b}$$

Substituting Eq. (13) into Eq. (18b) yields

$$\frac{dF_a(t)}{dt} = \frac{C_{po}(t)}{F \cdot AUCF(t)} \tag{19}$$

Substituting Eq. (A2) into Eq. (19) yields

$$\frac{dF_a(t)}{dt} = \frac{G(t)}{F} \tag{20}$$

or

$$G(t) = F \cdot \frac{dF_a(t)}{dt} \tag{21}$$

It can also be shown that Eq. (21) is valid for a first-order absorption process. Thus, antitransform of the transfer function describing the zero- or first-order absorption process equals the product of bioavailability and the fractional absorption rate.

Similarly, for a first-order absorption process, $F_a(t)$ can be calculated according to the following equation:

$$F_a(t) = 1 - e^{-k_a \cdot t} \tag{22}$$

with k_a generated from the following equation (9):

$$k_a = \frac{C_{po}(t)}{F \cdot AUC_{iv}^{o \to t} - AUC_{po}^{o \to t}} \tag{23}$$

Differentiating both sides of Eq. (22) with respect to time t yields

$$\frac{dF_a(t)}{dt} = k_a \cdot e^{-k_a \cdot t} \tag{24}$$

METHODS

Drug concentration versus time data corresponding to intravenous and oral administration of a hypothetical drug [based on the properties of theophylline (Ref. 10)] following a one-compartment model (Fig. 1) were simulated by assigning $V_1 = 20$ liters, $k_{el} = 0.10\ hr^{-1}$, $\tau = 10.0$ hr, $F = 1$, and $D = 300$ mg to the following equations:

$$C_{iv}(t) = \frac{D}{V_1} \cdot e^{-k_{el} \cdot t} \tag{25}$$

and

$$C_{po}(t) = \frac{F \cdot D}{V_1 \cdot \tau \cdot k_{el}} (1 - e^{-k_{el} \cdot t}) \qquad \text{when } t \leq \tau \tag{26}$$

or

$$C_{po}(t) = \frac{F \cdot D}{V_1 \cdot \tau \cdot k_{el}} [e^{-k_{el}(t-\tau)} - e^{-k_{el} \cdot t}] \qquad \text{when } t > \tau \tag{27}$$

where τ is the period of time over which the zero-order absorption occurs and equals D/k_o. Sampling times of 0, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, and 32 hr were used for simulation. Ten additional data sets were generated by adding normally distributed random error with a relative standard deviation (RSD) of ±10% to each concentration value.

Similary, for a hypothetical drug [based on the properties of sulfisoxazole (11)] obeying a two-compartment model (Fig. 1), one set of errorless and 10 sets of errant data at times 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 12, 24, and 48 hr were generated by the following equations with $D = 2004$ mg, $F = 1$, $\tau = 3.0$ hr, $V_1 = 7.72$ liters, $k_{12} = 0.45\ hr^{-1}$, $k_{21} = 0.87\ hr^{-1}$, and $k_{10} = 0.20\ hr^{-1}$:

$$C_{iv}(t) = \frac{D(\lambda_1 - k_{21})}{V_1(\lambda_1 - \lambda_2)} \cdot e^{-\lambda_1 \cdot t} - \frac{D(\lambda_2 - k_{21})}{V_1(\lambda_1 - \lambda_2)} \cdot e^{-\lambda_2 \cdot t} \tag{28}$$

and

$$C_{po}(t) = \frac{F \cdot D \cdot (\lambda_1 - k_{21})}{V_1 \cdot \tau\,(\lambda_1 - \lambda_2) \cdot \lambda_1} \cdot [1 - e^{-\lambda_1 \cdot t}] - \frac{F \cdot D \cdot (\lambda_2 - k_{21})}{V_1 \cdot \tau \cdot (\lambda_1 - \lambda_2) \cdot \lambda_2} \cdot [1 - e^{-\lambda_2 \cdot t}] \qquad \text{when } t \leq \tau \tag{29}$$

or

$$C_{po}(t) = \frac{F \cdot D \cdot (\lambda_1 - k_{21})}{V_1 \cdot \tau\,(\lambda_1 - \lambda_2) \cdot \lambda_1} \cdot [e^{-\lambda_1 \cdot (t-\tau)} - e^{-\lambda_1 \cdot t}] - \frac{F \cdot D \cdot (\lambda_2 - k_{21})}{V_1 \cdot \tau \cdot (\lambda_1 - \lambda_2) \cdot \lambda_2} \cdot [e^{-\lambda_2 \cdot (t-\tau)} - e^{-\lambda_2 \cdot t}] \qquad \text{when } t > \tau \tag{30}$$

where k_{21} is the return rate constant from the peripheral compartment, and λ_1 and λ_2 are the macroconstants describing drug disposition slopes with $\lambda_1 > \lambda_2$. Values of k_o were then calculated from these data sets by using the proposed method, nonlinear regression analysis based on the simultaneous fit of intravenous data and oral data to appropriate equations using NONLIN84 (12), moment analysis, deconvolution, the Wagner–Nelson method, and the Loo–Riegelman method. In addition, values of $F_a(t)$ were also calculated by the proposed method, by the Wagner–Nelson method, and by the Loo–Riegelman method. It should be noted that in this work the Wagner–Nelson method was applied only to the data showing one-compartment model characteristics, while the Loo–Riegelman method was used only for the data generated from the two-compartment model.

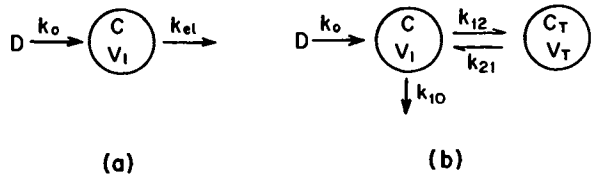

Fig. 1. (a) One-compartment model for drug concentration (C), volume of distribution (V_1), and rate constants for absorption (k_o) and elimination (k_{el}). (b) Two-compartment model depicting drug concentrations in the central (C) and tissue compartments (C_T), volumes of distribution (V_1, V_T), the rate constant for absorption (k_o), and distribution and elimination constants (k_{12}, k_{21}, k_{10}).

To illustrate the relationship between the proposed method and deconvolution, individual k_o values were obtained by deconvolution using Eqs. (1)–(4) at $t \leq t_{max}$ and the results were expressed as the mean ± the standard deviation (SD) of several individual k_o values.

The absorption rate profiles were compared as follows: one set of the errant data for the one-compartment model (Fig. 1) was used to calculate $\Delta F_a(t)/\Delta t$ values as a function of time. The theoretical values were also obtained. Similarly, the same procedure was applied to one errant data set exhibiting two-compartment model characteristics and first-order absorption kinetics (9) ($k_a = 0.4\ hr^{-1}$). In both cases, $\Delta F_a(t)/\Delta t$ versus time profiles were constructed.

RESULTS

The data obtained following zero-order input for two hypothetical drugs were used to estimate the zero-order absorption rate constants. As shown in Table I, when applied to both errorless and errant data, which showed one-compartment model characteristics, all five methods generally performed satisfactorily, with very little deviation from the theoretical value (0 to 1.3%). Application of both the proposed method and deconvolution to errorless data yielded the same, exact k_o values. However, when applied to errant data, a more accurate estimate of k_o was obtained by the area function method (Table I).

In addition, $F_a(t)$ values at various times were estimated from the same data sets by the proposed method and the Wagner–Nelson method. The results are listed in Table II. When applied to errorless as well as errant data, both methods gave estimates of $F_a(t)$ which were either identical or very close to the theoretical values. This is illustrated by the plot of $F_a(t)$ versus time shown in Fig. 2. According to Eq. (15b), a plot of $F_a(t)$ versus time yields a straight line with slope of $1/\tau$ and an intercept of zero. Indeed, this type of plot can be constructed to identify the kinetic nature of the absorption process.

Table I. Calculation of the Absorption Rate Constant for a One-Compartment Model by Five Methods for Errorless and Errant Data

Input value			Calculated k_o (mg/hr)				
k_{el} (hr^{-1})	k_o (mg/hr)	Data	This method	Nonlinear regression	Moment method	Deconvolution	Wagner–Nelson
0.1	30.0	Errorless	30.0 ± 0[a]	30.0	29.9	30.0 ± 0[b]	30.2
			(0)[c]	(0)	(0.3)	(0)	(0.7)
0.1	30.0	Errant	30.0 ± 1.1[d]	30.1 ± 1.0	30.1 ± 2.7	29.8 ± 3.5	29.6 ± 2.0
			(0)	(0.3)	(0.4)	(0.7)	(1.3)

[a] Mean ± SD; data points from time zero to t_{max} were used in Eq. (12) to calculate k_o.
[b] Mean ± SD; data points from time zero to t_{max} were used to calculate k_o.
[c] Number in parentheses is the percentage deviation from the theoretical value.
[d] Mean ± SD; $N = 10$.

These methods, except for the Wagner–Nelson method, were also evaluated using data simulated for a hypothetical drug exhibiting two-compartment model characteristics. As indicated in Table III, all procedures were generally adequate, as values of k_o are within 11% of the true value. Both the area function method and nonlinear regression analysis were less sensitive to fluctuations in data than deconvolution and moment analysis. For errorless data, both the proposed method and deconvolution gave identical results. In contrast, they yielded different k_o values when applied to errant data, with 8.5% error in the deconvolution method versus 1.1% error in the area function method (Table III). When the Loo–Riegelman method was applied to the same sets of data, it gave the largest percentage error (10.8% with errant data) in estimating k_o.

Inaccurate estimation of the apparent first-order absorption rate constant (k_a) by the Loo–Riegelman method has been reported (13,14). Here we demonstrated that this method performed most poorly in estimating k_o. This is due mainly to inaccurate estimates of the k_{12}, k_{21}, and AUC values which are needed in the k_o calculation. It has been shown that estimates of k_a by this method could be improved by assessing concentrations more frequently in the absorption phase (14). However, estimates of k_o by *any* method can usually be improved by sampling more frequently during the absorption phase.

Values of $F_a(t)$ obtained by the area function and Loo–Riegelman methods using the same data sets are listed in Table IV. Again, the proposed method gave reasonably good results, whereas the Loo–Riegelman method performed more poorly. This is also illustrated in Fig. 3, showing the linear relationship between $F_a(t)$ and time with a slope of $1/\tau$ and an intercept of zero.

Since a zero-order absorption process ceases at t_{max}, the k_o and $F_a(t)$ values obtained after t_{max} are not meaningful. To apply this method successfully to estimate k_o and $F_a(t)$, we suggest using only those data obtained in the absorption phase ($t \leq t_{max}$). The same applies to deconvolution, the Wagner–Nelson method, and the Loo–Riegelman method. We also recommend that the results obtained by the proposed method be expressed as the mean ± SD of several individual k_o values.

As shown in Figs. 4 and 5, the theoretical absorption rate is constant for zero-order input but follows an exponential decay for first-order input. The absorption rate profiles obtained by the proposed method using errant data are displayed as a set of rectangular pulses. These pulses were generated assuming constant absorption in each sampling

Table II. Calculation of the Fraction of the Amount Absorbed for a One-Compartment Model by the Proposed Method and by the Wagner–Nelson Method

Time (hr)	Theoretical $F_a(t)$	Data	Calculated $F_a(t)$	
			This method	Wagner–Nelson
1	0.100	Errorless	0.100[a]	0.099
		Errant	0.103 ± 0.010[b]	0.103 ± 0.012
2	0.200	Errorless	0.200	0.199
		Errant	0.198 ± 0.017	0.197 ± 0.022
4	0.400	Errorless	0.400	0.398
		Errant	0.394 ± 0.032	0.394 ± 0.038
6	0.600	Errorless	0.600	0.596
		Errant	0.595 ± 0.059	0.597 ± 0.068
8	0.800	Errorless	0.800	0.795
		Errant	0.791 ± 0.048	0.791 ± 0.072
10	1.000	Errorless	1.000	0.994
		Errant	1.001 ± 0.083	0.993 ± 0.069

[a] Equation (17) was used to calculate $F_a(t)$.
[b] Mean ± SD; $N = 10$.

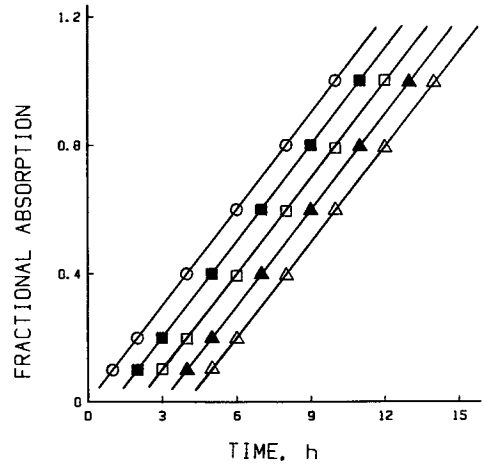

Fig. 2. Fractional absorption [$F_a(t)$] versus time plots based on the data in Table II. (○) Theoretical values; (■) this method (errorless data); (□) this method (errant data); (▲) the Wagner—Nelson method (errorless data); (△) the Wagner–Nelson method (errant data). The data for each method are displaced by 1 hr on the time axis from results of the preceding technique.

time interval. For a first-order absorption process, this assumption is valid only when the time intervals are short. Figures 4 and 5 also show that the generated rate profiles have some divergences from the theoretical values. This variability reflects the randomly assigned errors in the data as well as errors owing to large sampling time intervals employed for the first-order absorption process.

DISCUSSION

A method has been derived and evaluated for estimating the apparent zero-order absorption rate constant and the fraction of the amount absorbed with time. The derivation technique employed in this method evolves from the convolution integral. It is interesting that the equation used by the proposed method to estimate k_o [Eq. (12)] is an analogous expression of the first equation employed in deconvolution [Eq. (1)]. As shown in the Appendix and the preceding analysis, the proposed method and deconvolution are theoretically identical, but simulations clearly indicate that the proposed method is more accurate and less sensitive to data variation. This is expected, since the equation [Eq. (13)] used for estimating individual k_o values is simpler and requires less data manipulation.

One of the important parameters for the evaluation and regulatory assessment of controlled-release dosage forms is the degree of fluctuation about the mean plasma concentration (C_{av}) (15). It is known that the larger the fraction remaining to be absorbed in the gut [$1 - F_a(t)$] during the next dosing interval, the greater the degree of fluctuation. Consequently, the fraction remained to be absorbed is a good indicator of the day-to-day variation in the fluctuation produced by multiple dosing of a controlled-release product. Since the fraction remaining to be absorbed can be determined from $F_a(t)$, this type of calculation was recommended as a condition of new drug approval for controlled-release drug products (15). When it is desirable to construct and evaluate the $F_a(t)$ versus time plots, techniques such as the Wagner–Nelson method and the Loo–Riegelman method are practicable. However, they are model dependent and apply specifically only to the one- and multiple-compartment models, respectively. The present method provides an alternative approach for estimates of $F_a(t)$. It performs as well as the Wagner–Nelson method and is superior to the Loo–Riegelman method under the simulation conditions. In addition, the proposed method is of value for several reasons. In theory, it does not assume any model for the drug disposition process; thus it is a "noncompartmental" approach. It does, however, require iv data and assumes no intrasubject variability in the kinetics of drug disposition between the intravenous and the oral studies. Thus, like the area function method reported previously (9), the proposed method is expected to be valid for any linear system regardless of where a drug is distributed or eliminated in the body. In addition, it yields estimates of k_o which, under the simulation conditions, are as accurate as those estimated by nonlinear regression analysis. Furthermore, the method is easy to execute and the calculations are straightforward.

A minor complication in the use of any method of assessing drug absorption is the occurrence of a lag time (t_{lag}). This is usually accommodated by the application of a time shift at some point in the calculations. For the area function method, Eq. (13) can be handled similarly by simply shifting the sampling time (t) of the oral data by the t_{lag} value (i.e., $t_2 = t - t_{lag}$).

An inherent limitation of the proposed method is that

Table III. Calculation of the Absorption Rate Constant for a Two-Compartment Model by Five Methods for Errorless and Errant Data

Input value				Calculated k_o (mg/hr)				
λ_1 (hr^{-1})	λ_2 (hr^{-1})	k_o (mg/hr)	Data	This method	Nonlinear regression	Moment method	Deconvolution	Loo–Riegelman
1.39	0.12	668.0	Errorless	656.8 ± 1.2[a] (1.7)[c]	668.0 (0)	715.7 (7.1)	656.8 ± 1.2[b] (1.7)	613.2 (8.2)
1.39	0.12	668.0	Errant	660.5 ± 35.9[d] (1.1)	669.2 ± 46.3 (0.2)	733.3 ± 230.4 (9.8)	611.4 ± 61.9 (8.5)	595.8 ± 49.5 (10.8)

[a] Mean ± SD; data points from time zero to t_{max} were used in Eq. (12) to calculate k_o.
[b] Mean ± SD; data points from time zero to t_{max} were used to calculate k_o.
[c] Number in parentheses is the percentage deviation from the theoretical value.
[d] Mean ± SD; $N = 10$.

Table IV. Calculation of the Fraction of the Amount Absorbed for a Two-Compartment Model by the Proposed Method and by the Loo–Riegelman Method

Time (hr)	Theoretical $F_a(t)$	Data	Calculated $F_a(t)$	
			This method	Loo–Riegelman
0.25	0.083	Errorless	0.082[a]	0.076
		Errant	0.083 ± 0.009[b]	0.076 ± 0.005
0.50	0.167	Errorless	0.164	0.153
		Errant	0.171 ± 0.016	0.156 ± 0.015
0.75	0.250	Errorless	0.246	0.229
		Errant	0.243 ± 0.032	0.226 ± 0.027
1.0	0.333	Errorless	0.328	0.306
		Errant	0.344 ± 0.025	0.316 ± 0.020
1.5	0.500	Errorless	0.492	0.459
		Errant	0.478 ± 0.054	0.451 ± 0.038
2.0	0.667	Errorless	0.656	0.612
		Errant	0.667 ± 0.070	0.626 ± 0.052
3.0	1.000	Errorless	0.984	0.917
		Errant	0.926 ± 0.104	0.882 ± 0.078

[a] Equation (17) was used to calculate $F_a(t)$.
[b] Mean ± SD; $N = 10$.

one must know or predetermine that the absorption process is zero order and then select this procedure [versus the k_a method (9)] to use. When predetermination of the absorption process is desirable, approaches such as construction of percentage unabsorbed versus time plots (2) and absorption rate profiles are feasible. Application of percentage unabsorbed versus time plots in the determination of the absorption process has been addressed previously (2,16). As shown in Fig. 4, a plot of absorption rate versus time yields rectangular pulses which fluctuate about a constant absorption rate ($1/\tau$). This indicates apparent zero-order absorption. In contrast, as illustrated in Fig. 5, an absorption rate profile with a decay curve is a characteristic of apparent first-order absorption. In this situation, the area function method for k_a [Eq. (23)] should be employed (9).

If first-order absorption occurs and Eq. (13) is used to calculate the absorption rate constant, depending on the size of the dose, the rate constant would be either underestimated or overestimated. In addition, the values calculated would not be constant. In the same situation, if Eq. (17) is used to estimate $F_a(t)$ values, the values would progressively increase, reach a maximum value at t_{max}, then progressively decrease to zero. Consequently, a plot of $F_a(t)$ versus time would not be linear. In contrast, as shown previously (Figs. 2 and 3), for a zero-order absorption process, this kind of plot would be linear.

Finally, although the simulations currently performed clearly indicate that the proposed method is at least as adequate as either nonlinear regression analysis or the Wagner–Nelson method and is superior to the Loo–Riegelman method, the performance of these methods under other sim-

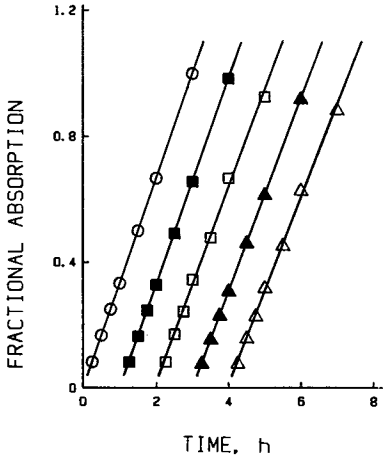

Fig. 3. Fractional absorption [$F_a(t)$] versus time plots based on the data in Table IV. (○) Theoretical values; (■) this method (errorless data); (□) this method (errant data); (▲) the Loo–Riegelman method (errorless data); (△) the Loo–Riegelman method (errant data). The data from each method are displaced by 1.0 hr from results of the preceding technique.

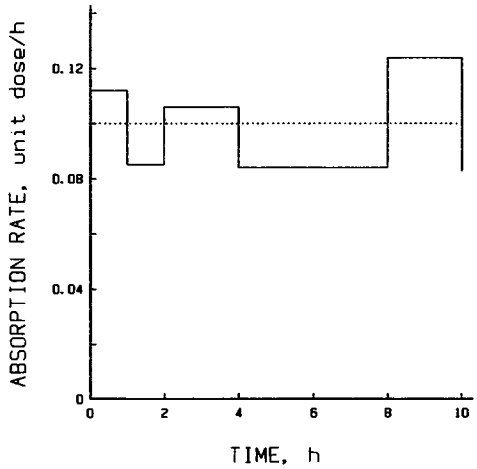

Fig. 4. The profiles of the absorption rate for a drug that enters the body by an apparent zero-order absorption process. (···) Theoretical absorption rate; (——) absorption rate estimated from an errant data set.

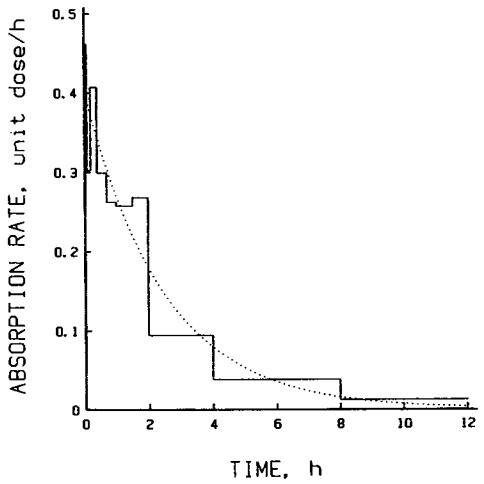

Fig. 5. The profiles of the absorption rate for a drug that enters the body by an apparent first-order absorption process (k_a = 0.4 hr^{-1}). (···) Theoretical absorption rate; (——) absorption rate estimated from an errant data set.

ulation conditions reflecting variable absorption and disposition rates merits further investigation.

APPENDIX

Derivation of Eq. (4)

Since

$$G(s) = \frac{k_o}{D \cdot s} \tag{8}$$

taking the anti-Laplace transform of Eq. (8) yields

$$G(t) = \frac{k_o}{D} \tag{A1}$$

or

$$G(t_1) = G(t_2) = \ldots = G(t_n) = \frac{k_o}{D} \tag{4}$$

Derivation of Eq. (4) from Eqs. (1), (2), and (3)

Substituting Eq. (12) into Eq. (A1) yields

$$G(t) = \frac{C_{po}(t)}{AUC_{iv}^{o\to t}} \tag{A2}$$

when $t = t_1$ or t_2:

$$G(t_1) = \frac{C_{po}(t_1)}{AUC_{iv}^{o\to t_1}} = \frac{C_{po}(t_2)}{AUC_{iv}^{o\to t_2}} = G(t_2) \tag{A3a, b, c}$$

Since, in general, $r = (a - c)/(b - d)$, if $r = a/b = c/d$, it follows that

$$G(t_1) = \frac{C_{po}(t_2) - C_{po}(t_1)}{AUC_{iv}^{o\to t_2} - AUC_{iv}^{o\to t_1}} = \frac{C_{po}(t_2) - C_{po}(t_1)}{AUC_{iv}^{t_1\to t_2}} \tag{A4a, b}$$

or

$$G(t_1) \cdot AUC_{iv}^{t_1\to t_2} = C_{po}(t_2) - C_{po}(t_1) \tag{A5}$$

Substituting Eq. (A5) into Eq. (2) yields

$$G(t_2) = \frac{C_{po}(t_2) - [C_{po}(t_2) - C_{po}(t_1)]}{AUC_{iv}^{o\to t_1}} = \frac{C_{po}(t_1)}{AUC_{iv}^{o\to t_1}} \tag{A6a, b}$$

Substituting Eq. (1) into Eq. (A6b) yields

$$G(t_2) = G(t_1) \tag{A7}$$

Similarly, we can show that

$$G(t_3) = G(t_1) \tag{A8}$$

$$\vdots$$

$$G(t_n) = G(t_1) \tag{A9}$$

Thus, combining Eqs. (A1), (A7), (A8), and A9 yields Eq. (4).

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