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EVALUATION OF CONTROLLED RELEASE FORMULATIONS: ESTIMATION OF THE DURATION OF THE ZERO-ORDER ABSORPTION AND ASCERTAINMENT OF ABSORPTION KINETICS

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ABSTRACT

A compartmental approach for estimating the duration of the zero-order absorption was developed. For drugs obeying one-compartment model disposition, the estimation is based on an explicit relationship while an iterative process is required for drugs represented by two-compartment kinetics. A method based on a double graphical plot for ascertaining absorption kinetics for drugs exhibiting one-compartment model disposition was also developed.

KEY WORDS Controlled release Zero-order absorption Estimation Absorption Kinetics

INTRODUCTION

A great number of controlled release (CR) formulations have been developed recently and used in clinical therapy. The most frequent theoretical goal associated with the design and development of CR formulations is a zero-order release combined with complete absorption of drug from the formulation.

An important parameter, inherently linked with the concept of the zero-order delivery, is the duration of the input process, τ. For most of the CR formulations, the absorption rate is limited by the release rate of drug from the formulation; therefore, the duration of the input process can be equated with the length of time taken to release the drug from the formulation. Analogously, the zero-order absorption rate constant, k_0, does, in fact, represent the zero-order release rate constant. During the formulation stages, attempts are made to achieve an ideal zero-order release rate constant and a physiologically relevant release period in order to provide satisfactory bioavailability. The three parameters of interest related to the rate, extent, and duration of absorption are linked by a simple relationship:

$$k_0 = \frac{FD}{\tau} \tag{1}$$

where F is the fraction of dose, D, absorbed.

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At the early stages of development of CR formulations, estimates for τ are derived from *in vitro* experiments by analysing the per cent release of drug vs time profiles in media of varying pH. However, the predictive value of the *in vitro* tests for the *in vivo* performance of CR formulations is frequently poor.

In fact, a reliable estimate for τ can be only derived after the completion of the *in vivo* studies with the *per os* administered CR formulation and an intravenously administered reference dose of the formulated drug. The estimation of τ is accomplished via equation (1) after the calculation of the values of k_0 and F. The parameter F is routinely estimated by comparing the areas to infinity under the concentration curves for an intravenous dose and the orally administered CR formulation. This comparison assumes no intrasubject variability in the kinetics of drug distribution and elimination between the intravenous and oral studies. However, human studies have shown variation in intrasubject plasma clearance from day to day.[1] As far as the estimation of the zero-order absorption rate constant, k_0, is concerned, several methods are available. These include the Wagner-Nelson method,[2] the Loo-Riegelman method,[3] deconvolution,[4] non-linear regression analysis using NONLIN,[5] moment analysis,[6] and the area function method.[7] It is worth noting that the most powerful of these methods, NONLIN, utilizes τ as an input value.

This study presents a method for the estimation of the duration of the zero-order input process without using data from an intravenous reference dose. The method does not require knowledge of either of the parameters k_0 and F but assumes knowledge of the appropriate disposition model, one or two compartment (Figure 1).

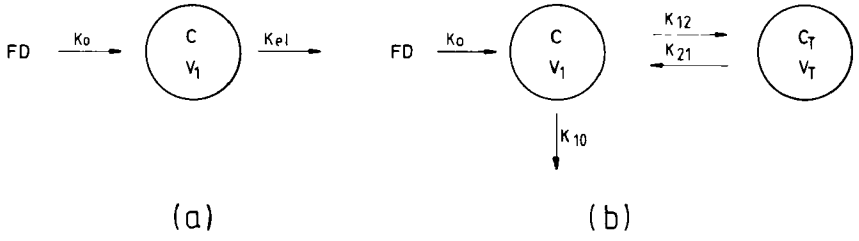

Figure 1. (a) One-compartment model for fraction (F) of dose (D) absorbed, drug concentration (C), volume of distribution (V_1), and rate constants for absorption (k_0) and elimination k_{el}. (b) Two-compartment model for fraction (F) of dose (D) absorbed, drug concentration (C) and (C_T) in the central and tissue compartment, respectively, volumes of distribution (V_1,V_T), the rate constant for absorption (k_0) and distribution and elimination constants (k_{12}, k_{21}, k_{10})

Another concern of the present study is the discernment of absorption kinetics. Thus a methodology utilizing the estimated value of τ and enabling the discernment of absorption kinetics for drugs subject to disposition according to a one-compartment model is also presented.

THEORETICAL

Estimation of τ *for the one-compartment model*

I Zero-Order absorption. After the zero-order delivery of drug from the formulation ceases, the concentration at time t, $C_{el}(t)$ is given[1] by

$$C_{el}(t) = C_\tau \cdot e^{-k_{el}(t-\tau)} \tag{2}$$

where $t \geqslant \tau$ and

$$C_\tau = \frac{F \cdot k_0}{V_1 \cdot k_{el}}(1 - e^{-k_{el}\tau}) \tag{3}$$

The concentration data of the absorption phase, $C_{ab}(t)$ are described[1] by the general form of equation (3)

$$C_{ab}(t) = \frac{F \cdot k_0}{V_1 \cdot k_{el}}(1 - e^{-k_{el}t}) \tag{4}$$

where $t \leqslant \tau$. As shown in the Appendix an estimate for τ can be derived from equation (5)

$$\tau = -\frac{\ln[1 + \exp[(\text{intercept})_{el} - \ln(\text{slope})_{ab}]]}{(\text{slope})_{el}} \tag{5}$$

Equation (5) indicates that for a given drug concentration vs time profile in plasma, with well-defined absorption and elimination phases, the value for τ can be evaluated by equation (5). In order to evaluate τ, a plot of $\ln(C_{el})$ vs t is constructed. The slope, $(\text{slope})_{el}$, and the intercept, $(\text{intercept})_{el}$, of the elimination phase are determined. Next, a plot of $C_{ab}(t)$ versus $1 - \exp(-k_{el}t)$, equation (4), is also constructed, from which the slope of the absorption phase, $(\text{slope})_{ab}$, is obtained. Finally, the value of τ is calculated by equation (5).

Based on the estimates for $(Fk_0/V_1k_{el}) = (\text{slope})_{ab}$ and k_{el}, fractional absorption and fractional elimination vs time (expressed in multiples of half-life) plots can be also constructed. The steady-state concentration, C_{ss}, which could be theoretically achieved after an unceasing zero-order delivery of drug is given[8] by equation (6):

$$C_{ss} = \frac{F \cdot k_0}{V_1 \cdot k_{el}} = (\text{slope})_{ab} \tag{6}$$

Therefore, the fractional absorption plot of the absorption phase data, $C_{ab}(t)$, relies on the equation:

$$\frac{C_{ab}(t)}{C_{ss}} = \frac{(F \cdot k_0/V_1 \cdot k_{el})(1 - e^{-k_{el}t})}{(F \cdot k_0/V_1 \cdot k_{el})} = 1 - e^{-0{\cdot}693t/t_{½}} = 1 - (0{\cdot}5)^n \tag{7}$$

where $n = t/t_{½}$

Similarly, the fractional elimination vs time plot is based on the 'initial-zero time' concentration, C_τ:

$$\frac{C_{el}(t)}{C_\tau} = \frac{C_\tau \cdot e^{-k_{el}(t-\tau)}}{C_\tau} = e^{-0.693(t-\tau)/t_{1/2}} = 1 - (0.5)^m \tag{8}$$

where $m = (t - \tau)/t_{1/2}$.

Subsequently, a double dimensionless graphical plot based on equations (7) and (8) can be used to evaluate the conformity of data to the theoretical curves, i.e. ascertain the absorption kinetics.

The assessment of τ and the discernment of absorption kinetics can be affected by the occurrence of lag time (t_{lag}). This can be detected as a significant negative y-intercept of the $C_{ab}(t)$ vs $1 - \exp(-k_{el}t)$ plot, equation (4). Under these circumstances, an estimate for t_{lag} can be obtained, and used in the calculations, from the early data points of the concentration vs time plot.

II First-order absorption. For a drug described by a one-compartment model and first-order absorption kinetics, the plasma concentration C as a function of time is given[8] by equation (9):

$$C = \frac{FDk_a}{V_1(k_a - k_{el})}(e^{-k_{el}t} - e^{-k_a t}) \tag{9}$$

where k_a is the absorption rate constant.

Estimation of τ for the two-compartment model

I Zero—order absorption. For a drug obeying two-compartment model kinetics, the data of the elimination phase, $C_{el}(t)$, after the termination of the absorption process are described[7] by equation (10):

$$C_{el}(t) = M[e^{-\lambda_1(t-\tau)} - e^{-\lambda_1 t}] - N[e^{-\lambda_2(t-\tau)} - e^{-\lambda_2 t}] \tag{10}$$

while the equation fitting the absorption phase data ($t \leqslant \tau$) is

$$C_{ab}(t) = M(1 - e^{-\lambda_1 t}) - N(1 - e^{-\lambda_2 t}) \tag{11}$$

where λ_1 and λ_2 are the macroconstants describing drug disposition slopes with $\lambda_1 > \lambda_2$ and

$$M = \frac{Fk_0(\lambda_1 - k_{21})}{V_1(\lambda_1 - \lambda_2)\lambda_1} \tag{12}$$

$$N = \frac{Fk_0(\lambda_2 - k_{21})}{V_1(\lambda_1 - \lambda_2)\lambda_2} \tag{13}$$

As shown in the Appendix an estimate for τ can be derived by fitting the absorption phase data to equation (14)

$$C_{ab(t)} = \frac{M_1(1 - e^{-\lambda_1 t})}{e^{\lambda_1 \tau} - 1} - \frac{N_1(1 - e^{-\lambda_2 t})}{1 - e^{\lambda_2 \tau}} \tag{14}$$

where M_1, N_1 are empirical constants derived from the analysis of elimination phase data. Thus, for the given experimental profile of $C_{el}(t)$ vs t, the values of M_1, N_1, λ_1, λ_2, are estimated by equation (A9) (quoted in the Appendix) using NONLIN. The results are substituted into equation (14), and the value of τ can be determined by the resulting equation using NONLIN provided that the profile of $C_{ab}(t)$ vs time is given.

II First-order absorption. For a drug described by a two-compartment model and first-order kinetics, the concentration in the central compartment at any given time t is:[1]

$$C = \frac{FDk_a}{V_1}\left[\frac{(k_{21} - \lambda_1).e^{-\lambda_1 t}}{(k_a - \lambda_1)(\lambda_2 - \lambda_1)} + \frac{(k_{21} - \lambda_2)e^{-\lambda_2 t}}{(k_a - \lambda_2)(\lambda_1 - \lambda_2)} + \frac{(k_{21} - k_a)e^{-k_a t}}{(\lambda_1 - k_a)(\lambda_2 - k_a)}\right] \tag{15}$$

METHODS

Drug concentration vs time data corresponding to oral administration for two hypothetical drugs with pharmacokinetic properties corresponding to theophylline[9] and sulfisoxazole[10] and following one- and two-compartment model kinetics, respectively, were simulated.

For the one-compartment model (Figure 1(a)), plasma concentrations expected at times 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, and 32 h were simulated for equation (2) and (4) with $V_1 = 20$ l, $k_{el} = 0{\cdot}10\,h^{-1}$, $F = 1$, $D = 300$ mg, $\tau = 10{\cdot}0$ h ($k_0 = FD/\tau = 30\,mg\,h^{-1}$), including rounding error. Additional datum sets of readings were also generated by adding normally distributed random error with a relative standard deviation (RSD) of either ± 10 per cent or ± 5 per cent into all of the data points. A total of forty errant sets of data were generated.

For the two-compartment model, Figure (1(b)), error free data expected at times 0·25, 0·50, 0·75, 1·0, 1·5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, and 48 h were simulated for equations (10) and (11). The values assigned to the parameters were as follows: $F = 1$, $D = 2004$ mg, $\tau = 3{\cdot}0$ h, ($k_0 = FD/\tau = 668\,mg\,h^{-1}$), $V_1 = 7{\cdot}72$ l, $k_{12} = 0{\cdot}45\,h^{-1}$, $k_{21} = 0{\cdot}87\,h^{-1}$, and $k_{10} = 0{\cdot}20\,h^{-1}$. Forty errant sets of data contaminated with an RSD of either ± 5 or ± 10 per cent were also simulated for equations (10) and (11).

Sets of errorless data expected at various time points exhibiting one-compartment model characteristics and first-order absorption kinetics were generated by equation (9) with $D = 300$ mg, $F = 1$, $V = 20$ l, $k_{el} = 0{\cdot}1\,h^{-1}$, and $k_a = 0{\cdot}12$, 0·20, 0·50, $0{\cdot}80\,h^{-1}$. The data with the first-order absorption were used for

comparative purposes in the methodology of the discernment of absorption kinetics.

RESULTS AND DISCUSSION

The errorless and errant data generated from equations (2), (4), (10), and (11) were used to estimate the duration of the input process, τ. For the one-compartment model, the data with $t \geqslant 12$ h were considered as the elimination phase data while those with $t \leqslant 8$ h were considered as representing the absorption phase data. For the two-compartment model, the elimination phase data were considered to be those with $t \geqslant 4$ h while the data of the absorption phase were characterized by $t \leqslant 2$ h.

The results obtained for the estimation of τ are presented in Table 1. In all cases, the method performed satisfactorily. More accurate estimates for τ were derived from the analysis of two-compartment model data than from the data adhering to the one-compartment model. This is certainly due to the superiority of nonlinear regression applied to the elimination phase data of the two-compartment model compared to the linear regression analysis utilized for the analysis of the elimination phase data of the one-compartment model. Moreover, the treatment of the absorption phase data for the estimation of τ in the one-compartment model relies again on simple linear regression (equation (4)) while τ is estimated by successive iteration (equation (14)) in the two-compartment model. It is also worthy noting that the standard deviations of the estimates for τ for the two-compartment model data, quoted in Table 1, are derived from the nonlinear fitting of data to equation (14) using NONLIN.

Table 1. Calculation of the duration of the zero-order input for errorless and errant data

Data*	Theoretical τ (h)	Calculated† τ (h)
One-compartment		
Errorless	10·00	9·99
Errant (±5%)	10·00	9·86 (0·38)
Errant (±10%)	10.00	9.51 (0·99)
Two-compartment		
Errorless	3·00	2·99
Errant (±5%)	3·00	2·99 (0·03)
Errant (±10%)	3·00	3·03 (0.05)

* Numbers in parentheses represent relative standard deviation of the normally distributed random error.
† SD of the parameter estimate in parentheses.

An obvious limitation of the present method is that one has to assume that

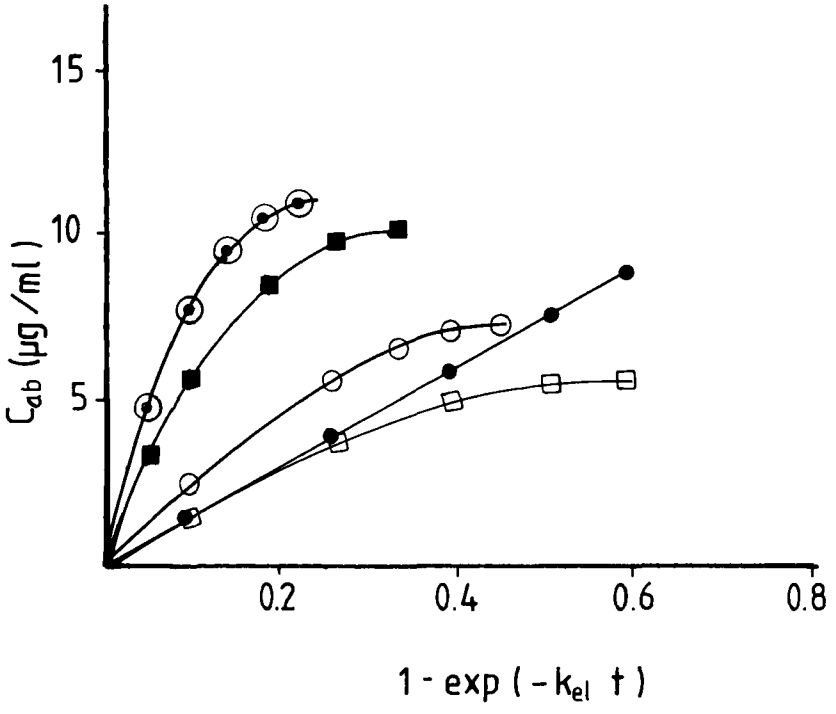

Figure 2. Concentration versus [1-exp($-k_{el}t$)] plots for errorless absorption phase data following first or zero order absorption kinetics. Estimates for k_{el} used for the plots were all derived from linear regression of logarithms of concentrations versus time using data at time points 24, 36, and 48 h. The estimates for k_{el} were: 0·079, 0·096, 0·100, 0·100 h^{-1} for the data following first order absorption and generated from equation (9) with k_a/k_{el}: (1·2, □), (2·0, ○), (5·0, ■), (8·0, ⊙), respectively. For the zero order data (●) the estimate for k_{el} was 0·100 h^{-1}; assigned values for the other parameters, $F = 1$, $D = 500$ mg, $\tau = 10{\cdot}0$ h, $V = 20$ l (equations (2) and (4), $k_0 = FD/\tau = 300/10 = 30$ mg h^{-1})

Table 2. Estimates of the duration of the absorption process for simulated errorless data plotted in Figure 2 and obeying first-order absorption and one-compartment kinetics

k_a/k_{el}	Time points (h) of absorption phase data used for regression	Theoretical t_{max} (h)	Estimated τ (h)
1·2	1·0, 3·0, 5·0, 7·0, 9·0	9·1	38·4
2·0	1·0, 3·0, 4·0, 5·0, 6·0	6·9	32·9
5·0	0·5, 1·0, 2·0, 3·0, 4·0	4·0	28·8
8·0	0·5, 1·0, 1·5, 2·0, 2·5	3·0	26·8

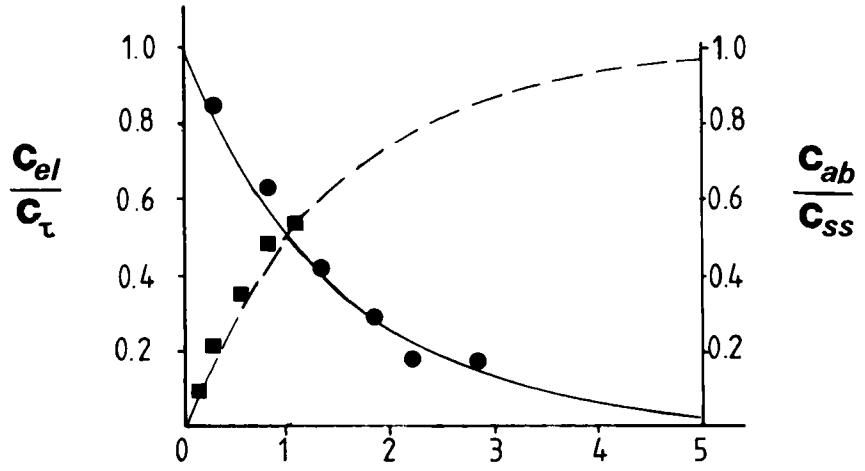

Figure 3. Theoretical profiles for the monoexponential drug absorption (– – –) and elimination (———) after zero-order absorption for a drug obeying one compartment kinetics. Ordinate left: blood concentration at the elimination phase as fraction of the concentration at time τ, C_τ. Ordinate right: blood concentration at the absorption phase as fraction of the hypothetical steady state concentration C_{ss} ($C_{ss} = (\text{slope})_{ab}$). Abscissa: time in multiples of half-life. The conformity to the theoretical lines of one set of errant data obeying zero-order absorption with a structure of error 10 per cent relative standard deviation is also presented for the absorption (■) and the elimination (●) phase

the absorption process is zero order. However, whenever the absorption kinetics is not known, the plot of the percentage of unabsorbed drug vs time[2,3] can be used for the discernment of the kinetics of the absorption process. Moreover, the area function method[7] can be employed to elucidate the drug absorption kinetics provided that intravenous data are available. For drugs obeying one-compartment model kinetics, the construction of the plot of concentration of the absorption phase data vs $[1 - \exp(-k_{el}t)]$ (equation (4)) can also be useful. In theory, a linear plot should result only when zero-order absorption is operating (Figure 2). The data of Figure 2 following first-order absorption were generated from equation (9); time-points used for the simulation are given in Table 2 and in the legend of Figure 2. For comparative purposes a common value for k_{el}, $0{\cdot}100\,h^{-1}$, was utilized for all sets of data. However, in order to mimic experimental conditions, estimates for k_{el}, obtained as explained in the legend for Figure 2, were utilized for the plots. When a first-order input is encountered, such a plot is not linear (Figure 2). Caution should be exercised though, since the nonlinear character of the plot for first-order input becomes patent only when the magnitude of the first-order absorption and elimination rate constants differ considerably and absorption phase data close to C_{max} have been collected (Figure 2). Consequently, it is more than certain that the linear or the nonlinear character of the plot could be hardly identified under the conditions of experimental error. Nevertheless, the possibility that the data

Table 3. Analysis of theophylline data reported by Simons *et al.*[11]

Whole tablets					Halved tablets				
t_{lag}(h)	$(intercept)_{el}$	$(slope)_{el}$	$(slope)_{ab}$	τ(h)	t_{lag}(h)	$(intercept)_{el}$	$(slope)_{el}$	$(slope)_{ab}$	τ(h)
–	2·556	−0·083	–	–	–	2·601	−0·093	–	–
0·15	2·544	−0·083	21·299*	5·6	0·29	2·574	−0·093	22·955*	4·9
0·15	2·544	−0·083	14·509†	9·2	0·29	2·574	−0·093	13·646†	7.2

* Calculated from equation (4) utilizing the absorption phase data with $t \leqslant 2$ h.
† Calculated from equation (4) utilizing the absorption phase data with $t \leqslant 6$ h.

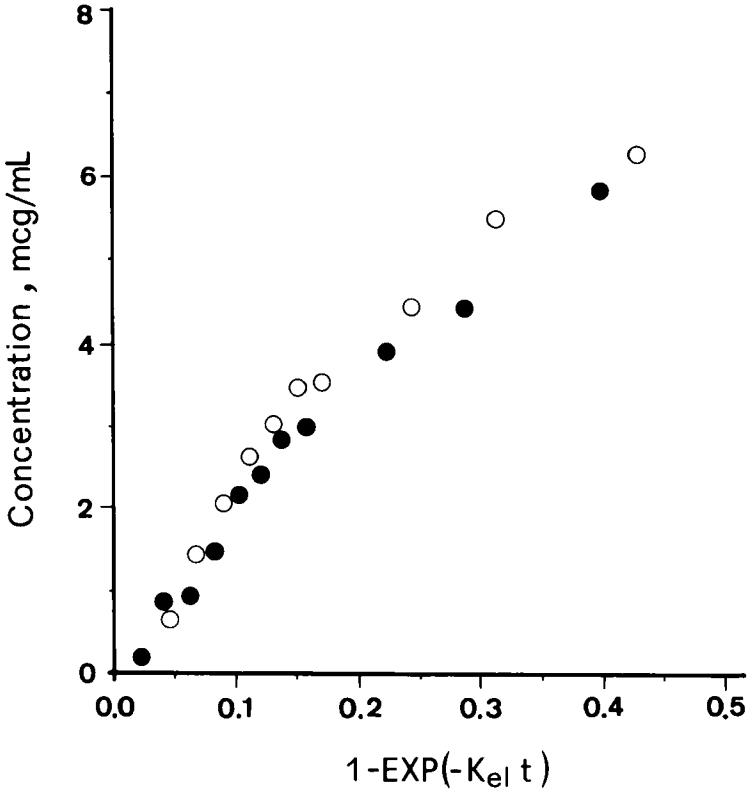

Figure 4. Theophylline concentration versus 1-exp($-k_{el}t$) plots for the whole (●) and halved (○) tablets study of Simons *et al.*[11]

used in Figure 2, which were generated from equation (9), follow zero-order absorption kinetics can be completely ruled out since the theoretical t_{max} values and the estimated values for τ are unrelated to each other (Table 2).

Another approach, which can be more discriminatory in elucidating the kinetics of the absorption process, is to develop the fractional absorption and fractional elimination vs time (expressed in multiples of half-life) plots described by equations (7) and (8), respectively, and plotted in Figure 3. This type of plot has a universal applicability since any dependence on a specific value of k_{el}, which governs kinetically both phases, has been replaced by relative time, a dimensionless quantity given by multiples of the half-life. Therefore, conformity of the data to the monoexponential, fractional absorption, and fractional elimination is clear proof of the zero-order absorption for drugs following one-compartment disposition. Figure 3 shows that both the absorption and elimination phase data, of an errant set of data obeying zero-order absorption, are in accord with the monoexponential profiles of fractional absorption and elimination.

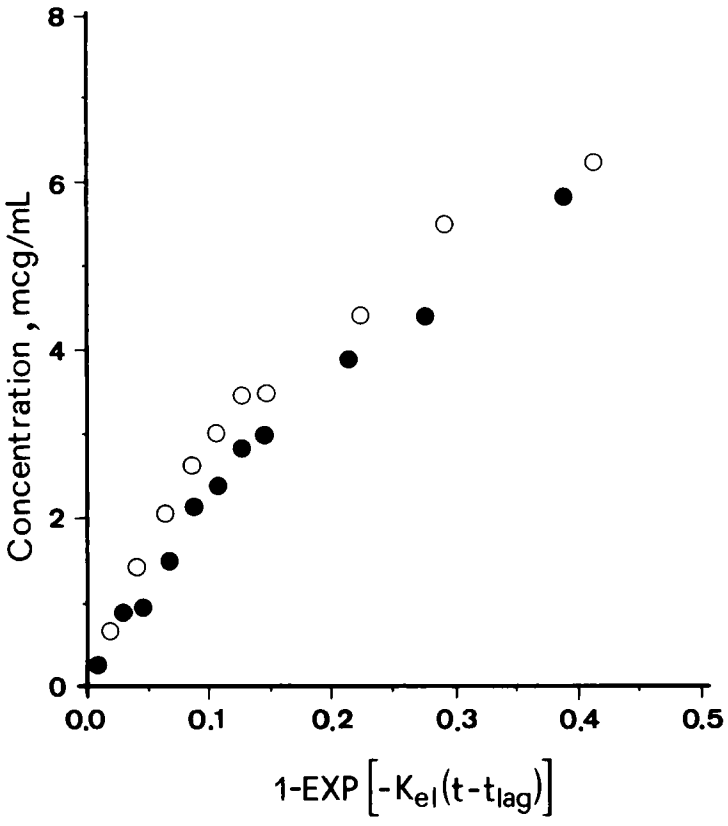

Figure 5. Theophylline concentration versus 1-exp[$-k_{el}(t - t_{lag})$] plots for the whole (●) and halved (○) tablets study of Simons *et al.*[11]

Analysis of real plasma data

The methods developed were applied to two sets of theophylline data reported by Simons *et al.*[11] Both studies (whole and halved tablets), utilizing the mean concentration values reported, were considered. The elimination phase data with $t \geqslant 10$ h were analysed according to equation (A1) and the estimates for the $(\text{intercept})_{el}$ and the $(\text{slope})_{el}$ are quoted in Table 3. The estimates for k_{el}, i.e. $-(\text{slope})_{el}$, were employed to construct the plots shown in Figure 4 for the absorption phase data with $t \leqslant 6$ h. For both sets, a first-order input profile is demonstrated (contrast Figures 2 and 4). In addition, a significant y-negative intercept, corresponding to the extrapolated initial steep rise of theophylline concentration, is observed. Accordingly, corrections in the sampling times were made by calculating the t_{lag} values (Table 3) assuming linearity for the first two mean concentration–time data points reported.[11] The elimination phase data were re-analysed (Table 3) and the absorption phase data were replotted

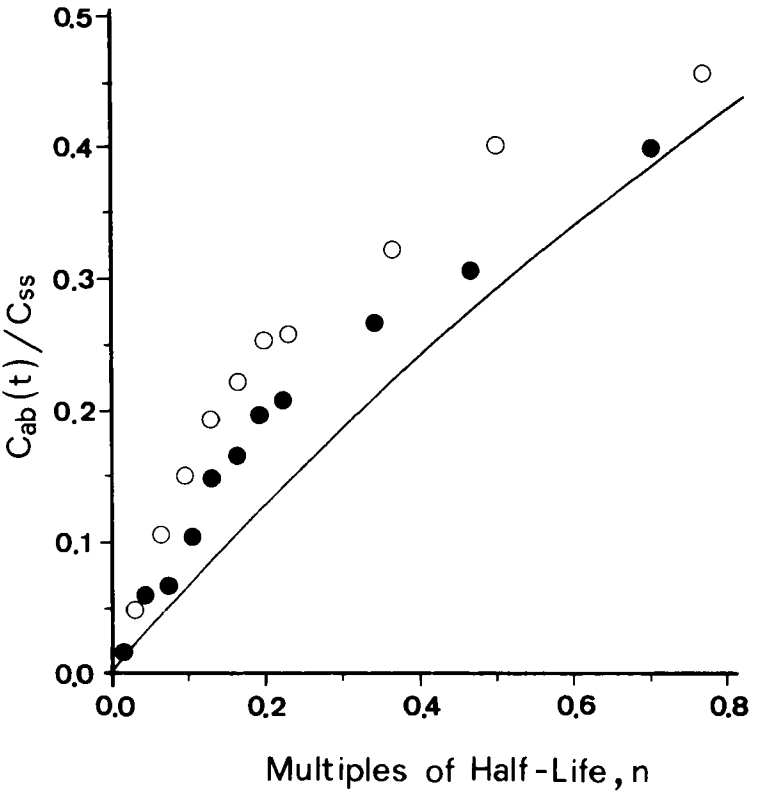

Figure 6. Fractional absorption profiles for the whole (●) and halved (○) tablets study of Simons *et al.*,[11] utilizing the absorption phase data with $t \leqslant 6$ h. The line corresponds to the theoretical curve of equation (7).

(Figure 5). As can be seen in Figure 5 the early data points have been moved towards the origin while the nonlinear character of the curve is maintained for both sets of data. Note that the initial steep increase in theophylline concentration for both data sets, is in accord with the initially high dissolution rate of drug (Figure 1 of Simons *et al.*[11]) However, the authors inferred from the initial portion of the per cent unabsorbed vs time plot (Figure 4 of Simons *et al.*[11]) that there is an apparent zero-order release of theophylline from tablets. The terminal nonlinear portion of this curve was ascribed to the fact that the fraction absorbed is approaching the asymptotic value. Although this could be true[12] for this type of graph, the plot of $C_{ab}(t)$ vs $1 - \exp(k_{el}t)$ does not suffer from this limitation. Figure 5 reveals that a constant rate of absorption can be considered only for the first 2 h.

To validate this conclusion, an analysis was attempted assuming that a zero-order input is actually operating but not evident due to experimental errors. Two alternatives were examined; first, the initial linear segment of Figure 5

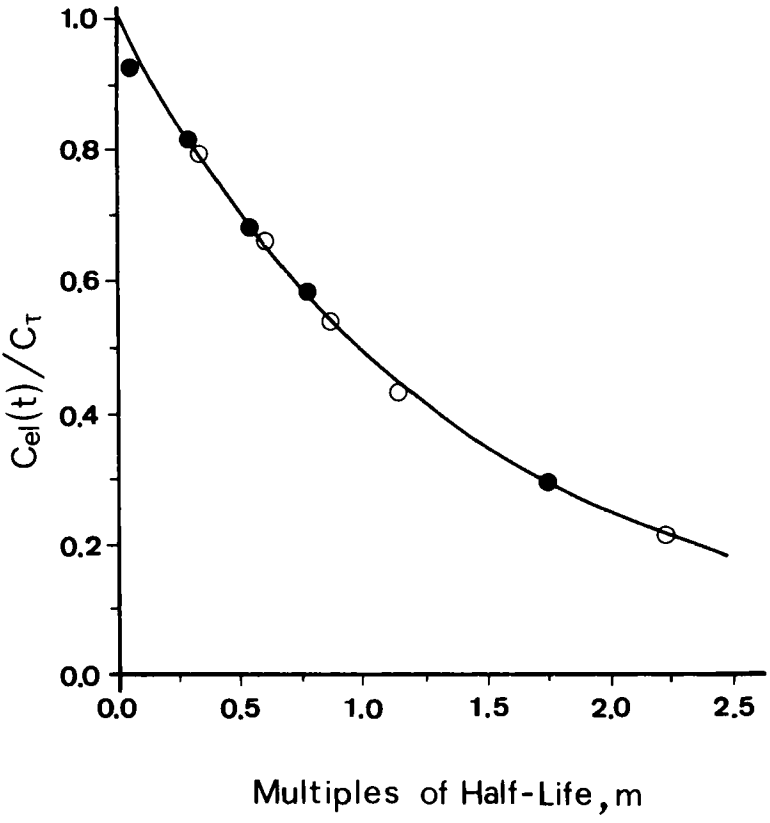

Figure 7. Fractional elimination profiles for the whole (●) and halved (○) tablets study of Simons *et al.*[11] The line corresponds to the theoretical curve of equation (8). The estimates for C_τ were obtained from equation (A2) and found to be 5·93 and 6·72 μg ml^{-1} for the whole and halved tablets study, respectively

($t \leqslant 2$ h) corresponds to the zero-order input throughout the absorption phase and, second, the zero-order absorption process is described adequately by all absorption phase data ($t \leqslant 6$ h). The first alternative is completely ruled out for both sets of data on the basis of the estimates for τ, 5·6 and 4·9 h (Table 3), which yield values for C_τ from equation (A2), 8·00 and 8·32 μg ml^{-1} for the whole and halved tablets study, respectively. These values are not relevant to the experimental profile (Figure 2 and Table 2 of Simons *et al.*[11]) The second assumption should be also rejected in spite of the fact that the values of τ estimated (Table 3), are in the neighbourhood of experimental t_{max} values (Figure 2 of Simons *et al.*[11]). The rejection is justified because the fractional absorption data do not fit the theoretical profile (Figure 6). On the other hand, the experimental fractional elimination profiles are identical to the theoretical profile (Figure 7). This observation supports the view that the calculation of k_{el} from all elimination phase data ensures a conformity of experimental to

the theoretical profile once the estimate for C_τ is in the neighbourhood of experimental C_{max}. Nevertheless, the data should obey *both* fractional plots in order to reach a conclusion for a zero-order absorption process.

In summary, methods for the estimation of the duration of the zero-order absorption for drugs following either one or two-compartment model kinetics have been developed. In addition, for drugs obeying one-compartment model disposition the use of the fractional absorption and elimination plot provides an accurate means for ascertaining the absorption kinetics. These developments are certainly of value for the evaluation of controlled release dosage forms during the preformulation stage. Furthermore, an estimate for the duration of input process will facilitate the use of NONLIN in analysing data according to the one- or two-compartment model with zero-order absorption.

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APPENDIX

Derivation of equation (5)

Re-arrangement of the terms of equation (2) and logarithmic transformation yields

$$\ln C_{el}(t) = \ln(C_\tau \cdot e^{k_{el}\tau}) - k_{el}t \qquad \text{(A1)}$$

Linear regression analysis of the elimination phase data according to equation (A1) yields

$$\ln(C_{\tau} . e^{k_{el}\tau}) = (\text{intercept})_{el} \tag{A2}$$

$$-k_{el} = (\text{slope})_{el} \tag{A3}$$

Since k_{el} is known (equation (A3)), a plot of $C_{ab}(t)$ vs $1 - \exp(-k_{el}t)$ can be constructed. According to equation (4), a linear plot should be obtained with a slope equal to:

$$\frac{Fk_0}{V_1 k_{el}} = (\text{slope})_{ab} \tag{A4}$$

Substituting equations (3) and (A4) into equation (A2) yields

$$\ln[(\text{slope})_{ab} . (1 - e^{-k_{el}\tau}) . e^{k_{el}\tau}] = (\text{intercept})_{el} \tag{A5}$$

Substitution of k_{el} from equation (A3) into equation (A5) and solution of the resulting equation in terms of τ yields equation (5).

Derivation of equation (14)

Rearrangement of equation (10) yields

$$C_{el}(t) = M(e^{\lambda_1\tau} - 1) . e^{-\lambda_1 t} - N(e^{\lambda_2\tau} - 1) . e^{-\lambda_2 t} \tag{A6}$$

Simplification of equation (A6) gives

$$C_{el}(t) = M_1 . e^{-\lambda_1 t} + N_1 . e^{-\lambda_2 t} \tag{A7}$$

where $M_1 = M . (e^{\lambda_1\tau} - 1)$ (A8)

$$N_1 = N . (1 - e^{\lambda_2\tau}) \tag{A9}$$

Equation (A7) is the typical equation of the sum of two exponentials which can be solved using NONLIN.[5] Estimates for M_1, N_1, λ_1, λ_2 can be thus derived. Substituting M and N from equations (A8) and (A9), respectively, into equation (11) yields equation 14.