Calculation of Absorption Rate Constants for Drugs with Incomplete Availability

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Abstract □ The absorption rate constant of a drug as determined by the Wagner–Nelson or Loo–Riegelman method, by nonlinear least-squares regression analysis, or by the method of residuals is in error when drug removal from the absorption site is due not only to absorption but also to other competing processes resulting in reduced availability, regardless of the kinetics of such processes. These methods overestimate the true absorption rate constant, the degree of overestimation increasing with decreasing bioavailability. Accordingly, calculation of absorption rate constants from plasma drug concentration–time data by commonly employed methods cannot be performed with any degree of confidence unless the drug is known to be completely absorbed as such.

Keyphrases □ Absorption rate constants, true, apparent—drugs with incomplete availability, calculation □ Drug absorption rate constants, true, apparent—calculation, incomplete drug availability □ Bioavailability—absorption rate constants for drugs with reduced availability, unreliability of plasma drug concentration–time data □ Plasma drug concentration–time profiles—unreliability for use in calculating absorption rate constants of drugs with reduced availability

Several methods have been commonly employed in pharmacokinetics for the calculation of drug absorption rate constants from plasma drug concentration–time data. Probably the most commonly used method for the determination of absorption rate constants is that of Wagner and Nelson (1, 2). The following relationship was developed to calculate the percent of an oral dose absorbed at various times after administration (2):

$$\text{percent absorbed} = \frac{A_T}{A_\infty} \cdot 100 = \frac{C_T + K_E \int_{t=0}^{t=T} C\,dt}{K_E \int_{t=0}^{t=\infty} C\,dt} \cdot 100 \qquad \text{(Eq. 1)}$$

where A_T is the cumulative amount of drug absorbed at any time T, A_∞ is the total amount of drug eventually absorbed, C_T is the drug concentration in the plasma at time T, K_E is the apparent first-order elimination rate constant for the drug, and $\int_{t=0}^{t=T} C\,dt$ and $\int_{t=0}^{t=\infty} C\,dt$ are the respective areas under the plasma concentration *versus* time curves from time $t=0$ to $t=T$ and $t=0$ to $t=\infty$. The utilization of this relationship is dependent upon the drug in question being distributed in the body according to a one-compartment model.

A similar approach was employed by Loo and Riegelman (3) for calculation of absorption rate constants for drugs distributed according to a two-compartment model. An equation analogous to Eq. 1 for a drug obeying two-compartment kinetics is:

$$\text{percent absorbed} = \frac{A_T}{A_\infty} \cdot 100 = \frac{C_T + \beta \int_{t=0}^{t=T} C\,dt + P_T}{\beta \int_{t=0}^{t=\infty} C\,dt} \qquad \text{(Eq. 2)}$$

where A_T, A_∞, C_T, $\int_{t=0}^{t=T} C\,dt$, and $\int_{t=0}^{t=\infty} C\,dt$ are as defined previously; β is the apparent first-order rate constant associated with the terminal exponential phase of drug elimination; and P_T represents the drug concentration in the tissue as defined in the original report (3). From Eqs. 1 and 2, percent drug absorbed–time data can be generated. These methods place no limitation on the order of the absorption rate process. However, semilogarithmic plots of percent drug remaining unabsorbed *versus* time are frequently linear and yield an apparent first-order absorption rate constant.

Nonlinear least-squares regression analysis has also been used to determine absorption rate constants from plasma drug concentration–time curves (4). Such curves are generally described by a one- or two-compartment model with first-order elimination and an apparent first-order absorption process. This method involves fitting a theoretical equation to the plasma drug concentration–time curves with the aid of a digital computer.

Employment of the method of residuals to calculate absorption rate constants from plasma drug concentration–time data was illustrated by Wagner (5). The residuals are generally plotted on semilogarithmic coordinates, with the slope of this plot yielding the apparent first-order rate constant.

A recent report by Notari *et al.* (6) considered the application of the Wagner–Nelson and Loo–Riegelman methods to a situation where there is parallel first-order absorption and loss of a drug from the absorption depot. It was shown that the apparent first-order absorption rate constant obtained is the sum of the true absorption rate constant and the rate constant for the parallel first-order loss of drug from the absorption site. These authors pointed out that simultaneous first-order "nonabsorption" processes, such as chemical degradation, biotransformation by enzymes or intestinal bacteria, or the transfer of a drug to a compartment other than the blood, which compete for a drug at the absorption site may influence the calculated value of the absorption rate constant. These findings are contrary to the prevailing view that employment of the Wagner–Nelson method to calculate absorption rate constants requires no knowledge of the fraction of a dose absorbed (1, 2). Therefore, it was of interest to consider from a general point of view the influence of incomplete availability,

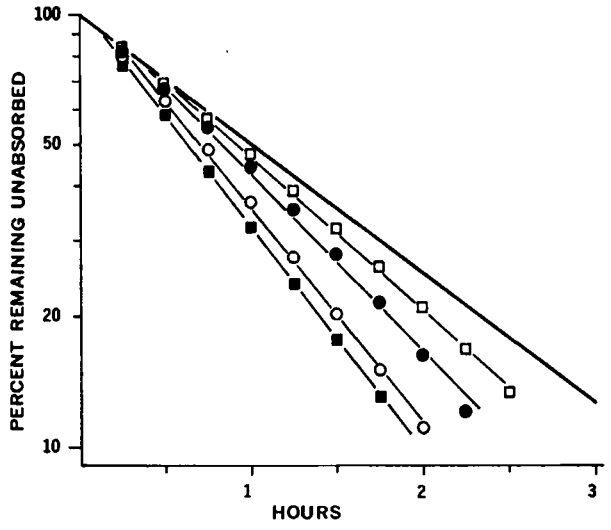


Figure 1—*Semilogarithmic plots of percent drug remaining unabsorbed* versus *time. Data were simulated according to Scheme I for a competing first-order process* ($K = 0.5\ hr.^{-1}$) *with various lag times. Slope* $= -K_A/2.3$. *Key:* ——, *control,* $K_A = 0.693\ hr.^{-1}$; ■, *lag time = 0.5 hr., 70% available,* $K_A = 1.195\ hr.^{-1}$; ○, *lag time = 1.0 hr., 79% available,* $K_A = 1.136\ hr.^{-1}$; ●, *lag time = 2.0 hr., 90% available,* $K_A = 0.936\ hr.^{-1}$; *and* □, *lag time = 3.0 hr., 95% available,* $K_A = 0.806\ hr.^{-1}$.

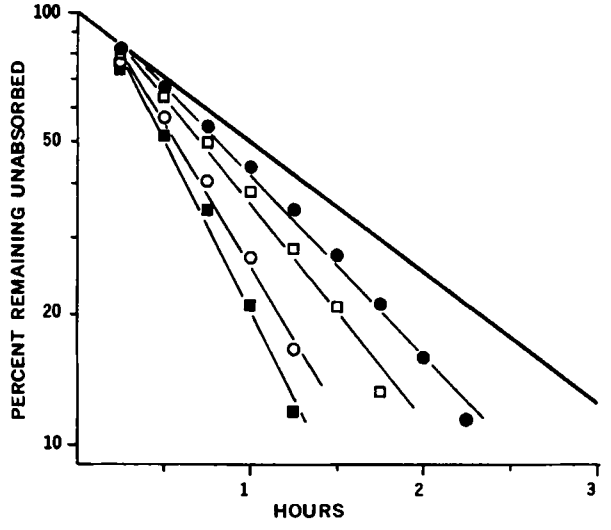


Figure 3—*Semilogarithmic plots of percent drug remaining unabsorbed* versus *time. Data were simulated according to Scheme I for a competing zero-order process* ($K_0 = 25.0$ *weight units/hr.*) *with various lag times. Slope* $= -K_A/2.3$. *Key:* ——, *control,* $K_A = 0.693\ hr.^{-1}$; ■, *lag time = 0.5 hr., 61% available,* $K_A = 1.824\ hr.^{-1}$; ○, *lag time = 1.0 hr., 69% available,* $K_A = 1.540\ hr.^{-1}$; □, *lag time = 2.0 hr., 81% available,* $K_A = 1.155\ hr.^{-1}$; *and* ●, *lag time = 3.0 hr., 89% available,* $K_A = 0.949\ hr.^{-1}$.

irrespective of whether this is due to competing processes or to limited duration of drug at the absorption site, on the estimation of apparent first-order absorption rate constants.

EXPERIMENTAL

A drug that is being removed from the site of absorption in the GI tract by an apparent first-order absorption process and by a second process that renders it unavailable for absorption may be described by Scheme I, where X_u and X_G are the respective amounts of drug unabsorbed and at the absorption site; X_A, the total amount of drug absorbed, is the sum of the amounts of drug in all "body" compartments plus drug that has been eliminated from the body; and K_A is the apparent first-order rate constant associated with the absorption process.

A drug is usually incompletely absorbed due to poor permeability characteristics of the drug itself and/or incomplete release of drug from the formulation. When either of these conditions is operative, a portion of the administered dose is removed from the absorption site by some process, resulting in the appearance of drug in the feces. Although the exact kinetic process by which a drug leaves an absorption site and is thereby rendered unavailable does not appear to be known, several possibilities exist. Grevsten *et al.* (7) administered a test solution of radioactive material by gavage and suggested that the movement of radioactivity down the GI tract could be described

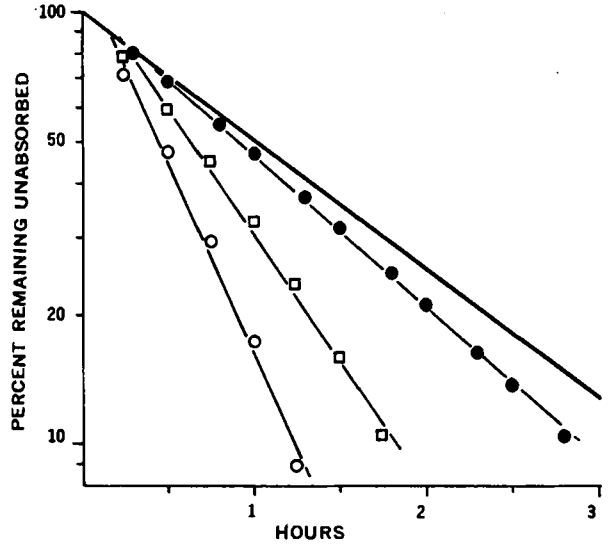


Figure 2—*Semilogarithmic plots of percent drug remaining unabsorbed* versus *time. Data were simulated according to Scheme I for competing simultaneous parallel zero-order processes* (K_0). *Slope* $= -K_A/2.3$. *Key:* ——, *control,* $K_A = 0.693\ hr.^{-1}$; ○, $K_0 = 25.0$ *weight units/hr., 52% available,* $K_A = 2.038\ hr.^{-1}$; □, $K_0 = 10.0$ *weight units/hr., 70% available,* $K_A = 1.359\ hr.^{-1}$; *and* ●, $K_0 = 1.0$ *weight unit/hr., 94% available,* $K_A = 0.806\ hr.^{-1}$.

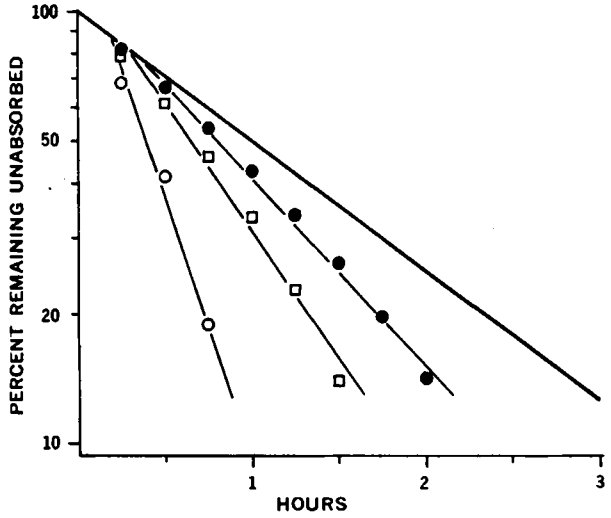


Figure 4—*Semilogarithmic plots of percent drug remaining unabsorbed* versus *time. Data were simulated according to Scheme I for an all or none process (see text) with various lag times. Slope* $= -K_A/2.3$. *Key:* ——, *control,* $K_A = 0.693\ hr.^{-1}$; ○, *lag time = 1.0 hr., 50% available,* $K_A = 2.888\ hr.^{-1}$; □, *lag time = 2.0 hr., 75% available,* $K_A = 1.386\ hr.^{-1}$; *and* ●, *lag time = 3.0 hr., 88% available,* $K_A = 0.990\ hr.^{-1}$.

Table I—Nonlinear Least-Squares Regression Analysis of Plasma Concentration–Time Data According to Scheme III (Data for Regression Analysis Obtained from Simulations According to Scheme II)

Condition Imposed on Drug Being Absorbed[a]	K_A	K_E	Coefficient of Determination[b]
Complete absorption	0.693 (0.000)[c]	0.0693 (0.000)[c]	1.0000
Parallel first-order loss (K = 0.5 hr.$^{-1}$) after 1-hr. lag	0.980 (0.066)	0.0716 (0.0016)	0.9997
Absorption terminated at 2 hr.	1.075 (0.090)	0.0755 (0.0048)	0.9979
Parallel zero-order loss (K_0 = 25 units/hr.)	1.576 (0.087)	0.0731 (0.0027)	0.9992
Parallel zero-order loss (K_0 = 25 units/hr.) after 1-hr. lag	1.221 (0.216)	0.0750 (0.0105)	0.9985

[a] Dose = 100 units. [b] $(\Sigma obs^2 - \Sigma dev^2)/\Sigma obs^2$. [c] Parenthetic values denote the standard error of the estimate.

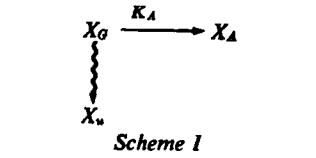
by an exponential function. If this were the case, removal of the drug from the absorption site (which can be considered as a finite length of the GI tract) could probably be approximated by an apparent first-order process. Since a certain period of time would be expected to elapse before this finite length of GI tract is traversed by the drug, a number of simulations were performed by initiating a competing first-order process at various time intervals after administration. These time intervals are referred to as lag times.

Another possibility for the removal of drug is by a zero-order process. Sikov *et al.* (8) suggested that the velocity at which a material passes through any one segment of the intestine is constant throughout that segment. Therefore, several simulations were undertaken employing simultaneous, competing, parallel, zero-order processes as well as a competing zero-order process with various lag times.

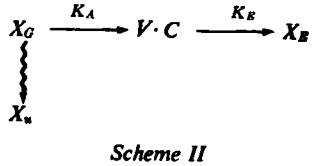
There may also be instances where a drug passes down the GI tract as a nondisintegrating unit. An example of this may be a timed-release dosage form where the drug is dispersed in an insoluble matrix. In such a case the drug is continually released until it passes out of the absorption site, at which time the drug is no longer absorbed even though it is still being released from the dosage form. This type of process is referred to as an "all or none" phenomenon. To simulate this pattern, the absorption process was halted at various times after administration.

Initially, the effect of incomplete availability (due to the various competing processes mentioned above) on the apparent first-order absorption rate constant of a drug was determined using the Wagner–Nelson and Loo–Riegelman methods. Simulations of the processes were obtained by generating amounts of drug absorbed as a function of time after oral administration using the appropriate differential equations and rate constants, according to Scheme I, as input data for the "MIMED" digital computer analog simulation program (9). Semilogarithmic plots of percent drug remaining unabsorbed *versus* time were prepared.

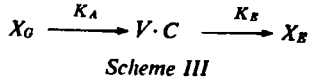
Apparent first-order absorption rate constants were also calculated for representative examples of each type of competing process simulated according to Scheme II, where X_G, X_u, and K_A are as defined previously; V is the apparent volume of distribution; C is the plasma drug concentration, the product of V and C gives the amount of drug in the body; and X_E and K_E are the amount of drug eliminated and the apparent first-order rate constant for elimination, respectively. The plasma drug concentration data simulated according to Scheme II were given equal weight and used as input for the digital computer program of Marquardt (10) to obtain a nonlinear least-squares regression fit of these data to Scheme III, where all terms are as defined previously. This treatment yielded estimates of the apparent first-order absorption rate constants for the models studied.



Scheme I



Scheme II



Scheme III

Data generated according to Scheme II were also plotted on semilogarithmic coordinates, and the apparent first-order absorption rate constants were determined by the method of residuals. This method involves extrapolating the linear elimination phase of the semilogarithmic plasma concentration–time plot to $t=0$ and subtracting the plasma drug concentrations in the absorption phase from the corresponding time–concentration values on the extrapolated line. The apparent first-order absorption rate constant was determined from the slope of a semilogarithmic plot of the values obtained by subtraction *versus* time.

RESULTS AND DISCUSSION

An overestimate in the apparent first-order absorption rate constant, as illustrated by the increase in the slopes of the percent drug remaining unabsorbed *versus* time plots in Figs. 1–4, occurred in all instances where there was a lack of availability due to a competing

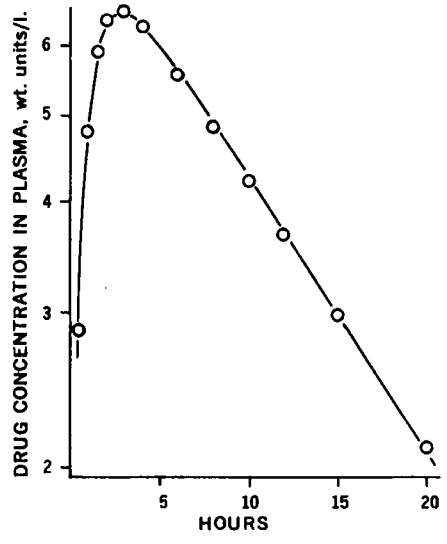


Figure 5—*Semilogarithmic plot of plasma drug concentration* versus *time after oral administration of 100 weight units of a drug. Key:* O, *data simulated according to Scheme II for a first-order absorption process* (K_A = *0.693 hr.*$^{-1}$) *and a competing first-order process* (K = *0.5 hr.*$^{-1}$) *with a lag time of 1 hr.;* ——, *biexponential least-squares fit of the simulated plasma drug concentration–time data to Scheme III,* K_A = *0.980 hr.*$^{-1}$.

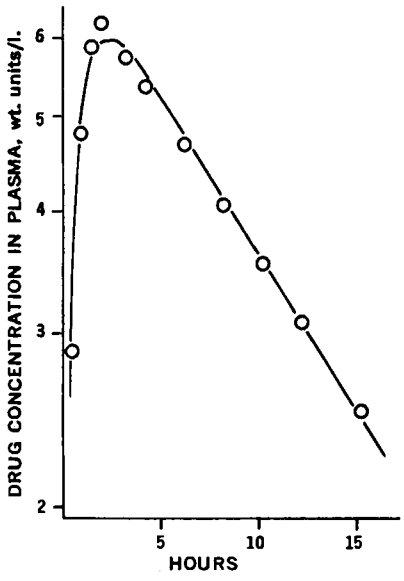


Figure 6—*Semilogarithmic plot of plasma drug concentration* versus *time after oral administration of 100 weight units of a drug. Key:* O, *data simulated according to Scheme II for a first-order absorption process* (K_A = *0.693 hr.*$^{-1}$) *and a competing zero-order process* (K_0 = *25.0 weight units/hr.*) *with a lag time of 1 hr.;* ——, *biexponential least-squares fit of the simulated plasma drug concentration–time data to Scheme III,* K_A = *1.221 hr.*$^{-1}$.

process at the absorption site. Employment of the Wagner–Nelson or Loo–Riegelman method results in an incorrect estimate of the true absorption rate constant whenever a drug is less than 100% available. While the percent remaining unabsorbed–time plots are actually slightly curvilinear rather than linear (Figs. 1–4), it is quite likely in our view that such data would normally be fit to a straight line with a lag time, considering the normal scatter and limited number of data points generally available in the absorption phase of a plasma concentration–time curve, the lag time being associated perhaps with gastric emptying.

When data simulated according to Scheme II were fit to Scheme III by a nonlinear least-squares method, a substantial overestimate of the apparent first-order absorption rate constant was again observed whenever a decrease in the availability occurred (Table I). Reasonable fits to the simulated plasma concentration–time data were obtained in all cases, as shown by the high coefficient of determination and low standard error of the estimate and as illustrated by Figs. 5 and 6. Similar results were arrived at when the absorption rate constants were calculated by the method of residuals (Fig. 7). It is quite clear that the commonly employed methods for the estimation of first-order absorption rate constants from plasma concentration *versus* time data all overestimate the true first-order absorption rate constant when there is a decrease in drug availability.

In two instances, corrections may be made for the lack of availability when determining absorption rate constants. As discussed by Notari *et al.* (6), if a drug is removed from the site of absorption by a mechanism that is first-order and occurs parallel to the absorption process, the true first-order absorption rate constant may be obtained by multiplying the apparent first-order absorption rate constant, as arrived at by the Wagner–Nelson or Loo–Riegelman method, by the fraction of the orally administered dose absorbed. Also, if the drug is less than fully available solely due to an all or none phenomenon, the percent of drug absorbed can be calculated relative to the total dose administered rather than relative to the total amount of drug eventually absorbed, A_∞. Theoretically, such corrections are feasible but practically it would be virtually impossible to determine the kinetic characteristics of the process responsible for the competitive removal of a drug from the site of absorption.

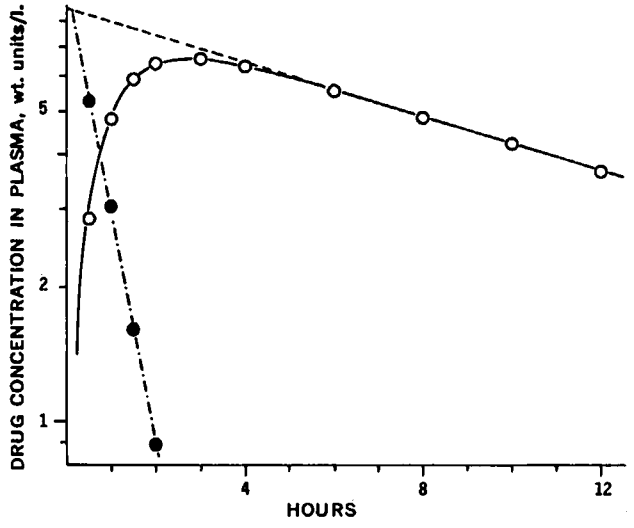


Figure 7—*Semilogarithmic plot of plasma drug concentration* versus *time after oral administration of 100 weight units of a drug. Key:* O, *data simulated according to Scheme II for a first-order absorption process* (K_A = *0.693 hr.*$^{-1}$) *and a competing first-order process* (K = *0.5 hr.*$^{-1}$) *with a lag time of 1 hr.; and* ●, *semilogarithmic plot of residuals, the slope of which yields the apparent first-order absorption rate constant* (K_A = *1.260 hr.*$^{-1}$).

Therefore, it appears that in all cases where a drug is less than completely absorbed as such, true absorption rate constants cannot be calculated. Apparent absorption rate constants that are calculated where there is less than complete availability may be used to describe the time course of drug in the plasma after single or multiple doses, but they cannot be used for quantitating the absorption characteristics of a drug.

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