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A model independent method for estimating the *in vivo* release rate constant of a drug from its oral formulations

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A simple equation by which the first-order release rate constant of a drug from its oral formulation can be calculated is derived. The derivation is independent of any hypothetical concepts of drug distribution or elimination.

The *in vivo* release rate constant of a drug from its oral formulation is of considerable importance in pharmaceutics since this parameter can determine the time-course of drug action and markedly affects the drug's bioavailability. However, most methods of calculating the apparent first-order drug release rate constant require the assumption of a specific pharmacokinetic compartmental system to describe drug distribution and involve complicated computations (Loo & Riegelman 1968; Wagner 1974; 1975).

In the present text a general equation is derived, without recourse to hypothetical concepts of drug distribution, for estimating the apparent first-order release rate constant of a drug from an oral formulation.

THEORY AND DISCUSSION

The response of a linear system (i.e. one in which the principle of superposition applies) to a unit impulse input is defined as the weighting function (F_1) and the response (R) obtained with any other input is defined by the convolution integral so that

$$R = \int_0^t F_1(t-\tau)F_2(\tau)d\tau = F_1^* F_2 \quad .. \quad .. \quad (1)$$

In equation 1, F_2 is the input function. This time function is the first differential coefficient with respect to time of the cumulative input from $t = 0$ to t (i.e. the instantaneous input). Assuming the body behaves as a linear system then the plasma drug concentration-time curve obtained after the administration of a unit drug dose represents the weighting function.

Frequently, the plasma concentration-time function ($C_{p,\ soln}$) obtained after a single oral drug dose (D_1) in solution can be represented by a summation of exponential terms thus

$$C_{p,\ soln} = D_1 \sum A_1 e^{-\alpha_1 t} \quad .. \quad .. \quad .. \quad (2)$$

where A_1 and α_1 ($\alpha_1 > \alpha_{1+1}$) are constant coefficients. Division of equation 2 by D_1 defines the plasma concentration-time function for a unit drug dose. Defining this latter function as the weighting function for oral drug administration then the time function ($C_{p,\ form}$) describing plasma drug concentrations obtained after oral administration of a dosage form, which releases the drug dose (D_2) by a first-order rate process (K_r), is given by

$$C_{p,\ form} = fD_2K_re^{-K_rt} * \sum_{i=1}^{N} A_1e^{-\alpha_1 t} \quad .. \quad (3)$$

In equation 3, f represents the fraction of the drug dose (D_2) in the oral formulation that is absorbed (i.e. f = the biological availability of drug in a formulation relative to a solution drug dose). The convolution integral (eqn 3) can be evaluated by Laplace transformation of equation 3, expansion into partial fractions and inverse transformation of the resulting expression. Utilizing these methods equation 3 becomes.

$$C_{p,\ form} = fD_2K_r\left(\sum_{i=1}^{N} \frac{A_1}{(\alpha_1 - K_r)}\right) e^{-K_rt} + \sum_{i=1}^{N}\left(\frac{fD_2K_rA_1e^{-\alpha t}}{(K_r - \alpha_1)}\right) \quad .. \quad .. \quad .. \quad (4)$$

Provided K_r is greater than α_N then as time becomes large both $C_{p,\ soln}$ and $C_{p,\ form}$ will be described by single exponential functions which have a common exponential coefficient (α_N), thus for large values of time t

$$C_{p.\ form} \longrightarrow \frac{fD_2K_rA_Ne^{-\alpha_N t}}{(K_r - \alpha_N)} \quad .. \quad .. \quad .. \quad (5)$$

and

$$C_{p.\ soln} \longrightarrow D_1A_Ne^{-\alpha_N t} \quad .. \quad .. \quad .. \quad (6)$$

The t = 0 intercepts of the final exponential regression of $C_{p,\ soln}$ and $C_{p,\ form}$ are obtained from equation 5 and 6 as

t = 0 intercept of the final regression of

$$C_{p,\ soln}\ (\text{Int. } C_{p,\ soln}) = D_1A_N \quad .. \quad .. \quad (7)$$

and

t = 0 intercept of the final regression of

$$C_{p,\ form}\ (\text{Int. } C_{p,\ form}) = \frac{fD_2K_rA_N}{(K_r - \alpha_N)} \quad .. \quad (8)$$

Division of equation 7 by equation 8 on rearranging yields an expression for K_r

$$K_r = \frac{\alpha_N}{\left(1 - \frac{fD_2.\text{Int.}C_{p,\ soln}}{D_1.\text{Int.}C_{p,\ form}}\right)} \quad .. \quad .. \quad (9)$$

To evaluate the apparent first-order release rate constant (K_r) or an oral formulation by the application of equation 9 required the determination of α_N, $\text{Int.}C_{p,\ soln}$ and $\text{Int.}C_{p,\ form}$. The latter two can be obtained by plotting the logarithm of $C_{p,\ soln}$ and $C_{p,\ form}$ against time and extrapolating the final linear regressions to t = 0. The logarithmic plots can also be used to evaluate α_N. The ratio fD_2/D_1 is given by the ratio of areas under the plasma concentration-time curves.

Equation 9, with appropriate changes in nomenclature, is also applicable when using blood drug concentration or urinary excretion data.

As an example of the use of equation 9 the apparent first-order release rate constant for methylamphetamine from an oral formulation is now calculated. Tucker (1967) gives the urinary excretion rates of methylamphetamine, obtained under conditions of acidic urinary pH designed to minimize tubular reabsorption of unchanged drug, after administration of an aqueous drug dose (dose ≡ 15 mg (+)-methylamphetamine as the hydrochloride salt) and an equivalent oral dose as a tablet formulation (formulation D) in the same individual. The cumulative urinary excretion of unchanged methylamphetamine expressed as a percentage of the dose, after the solution and formulated drug doses were 50·4 and 50·9%. Consequently, the relative biological availability of the oral formulation can be regarded as unity (i.e. f = 1). The final linear regressions of the logarithm of urinary excretion rates against time have a half-life of 5 h. Consequently, α_N is given as 0·1386 h^{-1}. The ratio of the constant coefficients for the final exponential regressions is 0·7. Substitution of the above values into equation 9 gives K_r as 0·462 h^{-1}. This value corresponds to a half-life for *in vivo* drug release of 1·5 h. A similar half-life ($t_{\frac{1}{2}} = 2{\cdot}0$ h) for drug release is obtained *in vitro* (Tucker, 1967).

To demonstrate that the calculated value of K_r is a reasonable estimation of the *in vivo* release of methylamphetamine the urinary excretion rate for the oral formulation has been predicted and compared with the experimental data (see Fig. 1). The later prediction was achieved by defining the oral solution data by equation 10 (obtained by graphical analysis of the experimental data) and using the convolution integral in conjunction with the calculated value of K_r.

Urinary excretion of methylamphetamine after an oral solution dose

$$= 20{\cdot}5\ [e^{-0{\cdot}1386(t-0{\cdot}2)} - e^{-1{\cdot}54(t-0{\cdot}2)}]$$

$$(t < 0{\cdot}2,\ F\ (t) = 0 \quad .. \quad .. \quad .. \quad (10)$$

Applying the convolution integral then

urinary excretion of methylamphetamine after the formulation dose $= [-38{\cdot}08e^{-0{\cdot}462\ (t\ -\ 0{\cdot}2)}$

$$+29{\cdot}29e^{-0{\cdot}1386\ (t\ -\ 0{\cdot}2)} + 8{\cdot}76e^{-1{\cdot}54\ (t\ -\ 0{\cdot}2)}]$$

$$(t < 0{\cdot}2,\ F\ (t) = 0) \quad .. \quad .. \quad .. \quad (11)$$

Urinary excretion curves generated by equations 10 and 11 are compared with the experimental results in Fig. 1. The agreement between the predicted and experimentally observed urinary excretion rates for the oral formulation indicates that the release of methylamphetamine from its

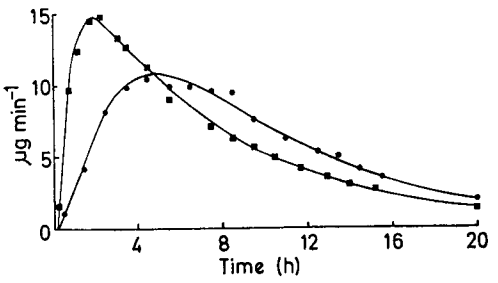

FIG. 1. Calculated and experimentally observed urinary excretion rates of methylamphetamine (μg min^{-1}), under conditions of controlled acidic urinary pH, after an oral solution dose (■) and oral formulation dose (●). Solid line represents the calculated excretion rates.

formulated dose can be reasonably represented by a first-order process of rate 0·462 h^{-1}.

Since α_N, Int. $C_{p,soln}$ and Int. $C_{p,form}$ are subject to errors in their determination, the calculated value of K_r (eqn 9) is also subject to statistical error. Analysis of plasma drug concentration data using non-linear least square computer programs will provide standard deviations for these parameters and consequently a standard deviation for K_r can be estimated.

The use of the final regression of blood or plasma concentration-time data for the determination of the apparent first-order drug release rate constant (K_r) from an oral formulation assumes that first-order drug release occurs *in vivo*. The validity of this assumption can be verified by generation of the oral formulation data by application of the convolution integral in conjunction with the calculated rate constant (K_r). Further verification can also be obtained from the analysis of *in vitro* dissolution data.

A major disadvantage of the above method for estimating K_r is that two drug trials in a single individual are required. However, alternative methods based on data from single drug-trials can only provided biased estimates.

In a previous communication (Vaughan, Mallard & Mitchard, 1974) an expression for estimating the first-order absorption rate constant (K_a) for a drug that is directly absorbed into the central compartment was derived.† The derivation of the latter expression, which is similar in format to equation 9, assumed that drug distribution within the body could be described by a linear mamillary compartmental model. However, such an assumption is unnecessary and an identical expression for K_a can be derived using the convolution integral, without recourse to compartmental concepts of drug disposition, in a manner analogous to the derivation of equation 9.

It should be stressed that the first-order absorption rate constant of an oral solution drug cannot be estimated from the final linear regressions obtained after intravenous and oral aqueous drug doses (i.e. using an equation similar to equation 9 or equation 9 in Vaughan & others, 1974), since the weighting functions for oral and intravenous drug doses are different when 'first-pass' hepatic metabolism is taken into account (see Vaughan & Trainor, 1975, for general oral and intravenous drug disposition functions).

In conclusion the application of equation 9 provides a rapid and simple method for estimating the apparent first-order release rate constant of a drug from an oral formulation. Since the derivation is independent of any concept concerning drug disposition or elimination the method is generally applicable to any drug provided the principle of superposition is applicable to that drug.

† Tucker, G. T., 1974; Notari, R., 1974 and Wijnand, H. P., 1974 (personal communications) have suggested that D_2 of equation 9 in Vaughan & others 1974 should be replaced by fD_2 where f is the relative biological availability of the drug dose that is directly absorbed into the central compartment.

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