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EVALUATION OF PHARMACEUTICAL AVAILABILITY FROM THE CALCULATION OF DRUG LEVELS AND RELEASE PROFILES

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SUMMARY

An iterative procedure to simulate drug levels is described evaluating the pharmaceutical availability of drug preparations. The methematical technique is based on the assumption that the rate of release during any given time interval obeys zero-order kinetics. The model enables in vivo drug levels to be calculated from in vitro release profiles whose pharmacokinetics are based on single or multi-compartment systems. The use of the reverse technique for calculating in vitro release profiles from plasma levels is described using a single compartment model.

INTRODUCTION

The bioavailability of a preparation is particularly important in cases where the active ingredient is only sparingly soluble or where its release is delayed or sustained. In such instances, a preparation's therapeutic effectiveness is markedly affected by its formulation and the rate at which the active ingredient is released. Great importance must therefore be given to devising methods for measuring release of active ingredients from such preparations and to evaluating the results from them.

Techniques are required for the development and testing of drugs which enable the prediction of in vivo results from data obtained during studies in vitro. A mathematical model which could predict the shape of the blood level curve from in vitro release data would be extremely useful. Theoretical curves given by such a model could then be compared with those obtained from actual measurement of drug levels in vivo, and this comparison would in turn show how relevant the in vitro technique was to the in vivo situation. Application of this process in reverse would enable the calculation of 'ideal in vitro release profiles' from in vivo drug levels. By comparing such 'ideal' profiles with those previously obtained from in vitro studies, test conditions could then be made to reflect the in vivo situation as closely as possible.

The aims of the present investigation were to develop mathematical techniques to enable simulation of blood levels based on single or multi-compartment models, using in vitro data and known pharmacokinetic parameters and to devise a method for calculating in vitro release profiles from blood level curves.

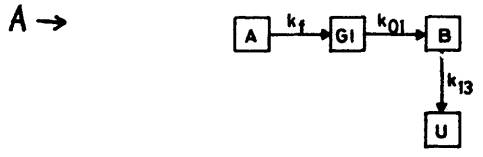
The model which has been developed uses pharmacokinetic parameters of pure substance, in particular the rate constants of absorption, distribution and elimination to simulate drug levels so that both the shape and the maxima of the blood level curve can be predicted. The concentration in the various body compartments can be correspondingly calculated from knowledge of the distribution volume, degree of absorption and the pattern of metabolism. It must however be remembered that such mathematical models can only give valid simulations if they are based on well-defined pharmacokinetic parameters and sufficient understanding of the model itself. Furthermore, the value of the information obtained from simulation studies is increased if it is known whether the kinetics are possibly independent of dose or if a first pass effect is present. Mathematical techniques for simulating drug levels which enable predictions to be made of the extent of absorption from depot preparations have already been described (Soliva and Speiser, 1966; Rowland and Beckett, 1964; Robinson and Eriksen, 1966; Wiegand and Taylor, 1960). It has usually been assumed that the rate of release over the entire curve obeys a certain order of kinetics. However the physicochemical properties of substances and drug forms make it fundamentally unlikely that there is strict accordance with a certain order or rate of reaction and the in vitro profile is better considered in small sections. Using this technique, drug levels based on a single compartment model have been simulated (Thoma and Gröning, 1978). In the present study, simulations are described based on both single and mutli-compartment systems, where small sections of the curve are considered in turn, and within which the rate of reaction can be defined by zero-order kinetics.

MODELS BASED ON THE RESULTS OF PHARMACEUTICAL AVAILABILITY STUDIES AND PHARMACOKINETIC DATA ENABLING CALCULATION OF DRUG CONCENTRATION VS TIME CURVES

Simulation of drug levels in vivo from in vitro data requires an understanding from model concepts, patterns of absorption, distribution, metabolism and elimination as well as knowledge of the volume of the individual compartments. The mathematical model we have developed is based on the assumption that the in vitro release of active ingredient between the two measuring points obeys zero-order kinetics. The rate constant of release is separately calculated for each time interval.

Simulation of drug levels using a single compartment model

The single compartment model can be schematically represented as follows:



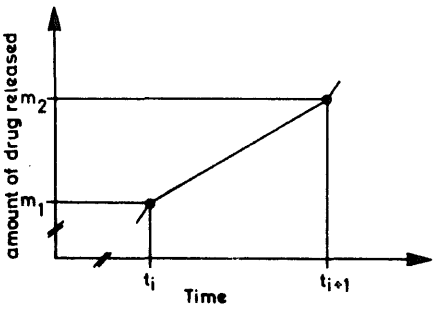


Fig. 1. Calculation of the release constant k_f.

The drug from A contains a certain dose of active ingredient which is released in the gastrointestinal tract (GI) at a rate independent of concentration, i.e.

$$k_f = \frac{m_2 - m_1}{t_{i+1} - t_i}$$

k_f is a zero order rate constant which can be calculated from in vitro experiments to determine drug release profiles, as shown in Fig. 1. k_f can vary over the total curve, but is assumed to be constant between any two measuring points, i.e. it corresponds to the slope of the release profile within each chosen interval. By introducing compartment A into the model the expression:

$$a(t = 0) = D$$

where a is the amount of drug compartment A and D is the dose administered, and this can be used instead of the usual condition

$$g(t = 0) = D$$

where g is the amount of drug in GI. Knowledge of kinetics of pure drug will provide data on V (distribution volume) k_{01} and k_{13} the rate constants of absorption and elimination for first-order reactions.

The model described above is based on the following differential equations:

$$\frac{da}{dt} = -k_f$$

$$\frac{dg}{dt} = k_f - k_{01}g$$

$$\frac{db}{dt} = k_{01}g - k_{13}b$$

$$\frac{du}{dt} = k_{13}b$$

where,

a = amount of drug in form A at time t
g = amount of drug in gastrointestinal tract (GI) at time t
b = amount of drug in the central compartment B at time t
u = amount of drug in the elimination compartment U at time t
k_{01} = rate constant of absorption
k_{13} = rate constant of elimination
k_f = rate constant of release
m_1 = amount of drug released at time t_i
m_2 = amount of drug released at time t_{i+1}
A = drug from compartment
GI = gastrointestinal compartment
B = central compartment
U = elimination compartment
D = dose administered

Since k_f as a function of time is not known, a_t, g_t, b_t and u_t can be determined from the appropriate equations by iteration.

Transport from A to GI. At time t = 0, the amount of drug in compartment A is a_0. From the differential equation $da/dt = -k_f$, with initial conditions t = 0 and $a = a_0$:

$$s\bar{a} - a_0 = -\frac{k_f}{s}$$

$$a = a_0 - k_f \cdot t$$

where s = Laplace operator and $\bar{a}$ = Laplace transformation of a. Similarly,

$$\frac{dg}{dt} = k_f - k_{01}g$$

$$s\bar{g} - g_0 = \frac{k_f}{s} - k_{01}g$$

$$\bar{g} = \frac{g_0 s + k_f}{s(s + k_{01})}$$

$$g = \frac{k_f}{k_{01}}(1 - e^{-k_{01}t}) + g_0 e^{-k_{01}t}$$

Transport from GI to B. At time t = 0, the amount of drug in compartment B is b_0.

$$\frac{db}{dt} = k_{01}g - k_{13}b$$

$$s\bar{b} - b_0 = k_{01}\bar{g} - k_{13}\bar{b}$$

$$\bar{b} = \frac{b_0 s^2 + s k_{01}(b_0 + g_0) + k_{01} \cdot k_f}{s(s + k_{01})(s + k_{13})}$$

By integrating, one obtains

$$b = \frac{k_f}{k_{13}} + \frac{k_f}{k_{13} - k_{01}} \left(\frac{k_{01}}{k_{13}} e^{-k_{13}t} - e^{-k_{01}t} \right) + g_0 \frac{k_{01}}{k_{13} - k_{01}} (e^{-k_{01}t} - e^{-k_{13}t}) + b_0 e^{-k_{13}t}$$

b represents the amount of drug which is present in blood at time t. The equation for u can be similarly deduced.

Calculation of the drug level. The calculation begins with $T_0 = 0$ and ends at $t = T_n$. For each interval (T_i, T_{i+1}) the amounts of drug at time T_i in each compartment are a_0, b_0, g_0 and u_0. Intermediate values within an interval can be calculated since t from 0 to $T_{i+1} - T_i$ is chosen in arbitrary increments. There is a specific k_f for each interval.

After the entire amount of active ingredient has been released, the drug level is influenced exclusively by the pharmacokinetic parameters of the pure substance.

a_0 = amount of drug in compartment A at time t = 0
b_0 = amount of drug in compartment B at time t = 0
g_0 = amount of drug in compartment G at time t = 0
u_0 = amount of drug in compartment U at time t = 0
t = time from beginning to end of an iteration interval
T = duration of the period under investigation

From the distribution volume V and the degree of absorption f, the concentrations of drug in plasma can also be simulated by multiplying the amount of drug b by the factor f/V.

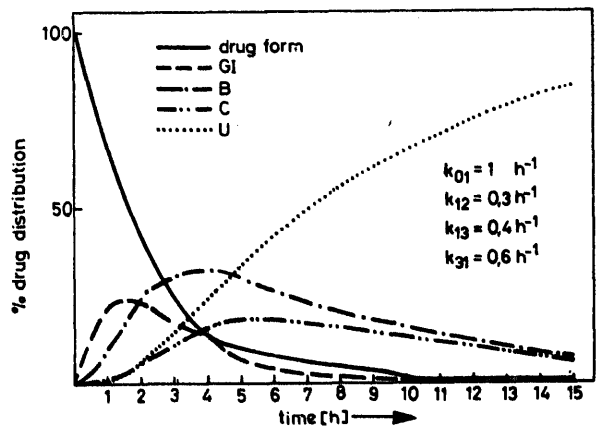


Fig. 2. Selection of possible in vitro availability curves (A–E).

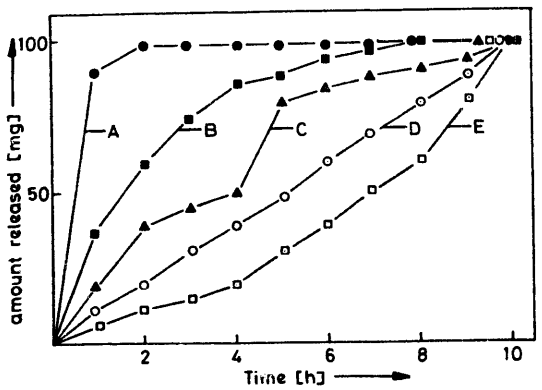


Fig. 3. Simulation of drug levels from the release profiles A–E.

Simulation of drug levels from various release profiles

Some commonly encountered release profiles are shown in Figs. 2 and 3. By taking the rate constants of absorption and elimination as 1 (h^{-1}), a distribution volume V of 100 liters and a dose D of 100 mg, the course of the drug level curves can be calculated as shown in Fig. 3.

Rapid release of active ingredient in vitro produces curves which rise steeply to their respective maxima (profiles A and B). In example C, the effect of stepwise discontinuous release of active substance can be seen, which is reflected in the presence of two maxima. With preparation D, the release profile is linear and the simulated drug levels show a corresponding concentration plateau – precisely what is desirable for a sustained drug effect. Example E shows a release profile where the maximum is markedly delayed.

Calculation of 'ideal release profiles' from measured plasma levels

By reversing the technique, 'ideal release profiles' can be calculated from plasma levels measured after administration of preparations, using pharmacokinetic data of the pure substance. Bearing in mind the scatter inherent in studies in vivo, this method enables the biological relevance of various in vitro methods to be determined and compared.

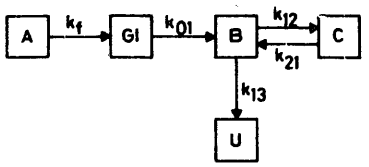
For a single compartment model when $k_f = f(T)$:

$$k_f = \frac{bk_{13}(k_{13} - k_{01}) + g_0k_{01}k_{13}(e^{-k_{13}t} - e^{-k_{01}t}) + b_0k_{13}(k_{01} - k_{13})\,e^{-k_{13}t}}{k_{13}(1 - e^{-k_{01}t}) + k_{01}(e^{-k_{01}t} - 1)}$$

This 'ideal release' can be similarly estimated for multicompartment models using a search method for k_f (Himmelblau, 1972).

Drug level simulation using a two compartment model

The two compartment model can be schematically represented as follows:



C = peripheral compartment
k_{12} = rate constant of distribution from the central to the peripheral compartment
k_{21} = rate constant of distribution from the peripheral to the central compartment

The appropriate differential equations are as follows:

$$\frac{da}{dt} = -k_f$$

$$\frac{dg}{dt} = k_f - k_{01}g$$

$$\frac{db}{dt} = k_{01}g - (k_{13} + k_{12})b + k_{21}c$$

$$\frac{dc}{df} = k_{12}b - k_{21}c$$

$$\frac{du}{dt} = k_{13}b$$

At time $T_0 = 0$, $a = D$, $g = b = c = u = 0$

By taking arbitrary small increments on the curve, the iterative calculation of the individual levels in the various compartments is carried out after solving the following equations by the technique of stepwise integration.

$$a_{i+1} = a_i - k_f\Delta t \quad (1)$$

$$g_{i+1} = g_i + k_f\Delta t - k_{01}g\Delta t \quad (2)$$

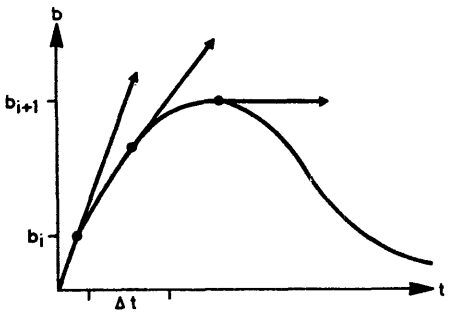
$$b_{i+1} = b_i + k_{01}g_i\Delta t - (k_{13} + k_{12})b_i\Delta t + k_{21}c_i\Delta t \quad (3)$$

$$c_{i+1} = c_i + k_{12}b_i t - k_{21}c_i\Delta t \quad (4)$$

$$u_{i+1} = u_i + k_{13}b_i\Delta t \quad (5)$$

By taking infinitesimally small parts of the curve it is thus possible to linearize the level at any point, where the slope of the tangent is given by the appropriate differential equation (Fig. 4). By substituting experimentally determined values of k_f, the value of a_{i+1} etc. can be calculated according to Eqn. 1 above. Taking $g_i = 0$, the initial g_{i+1} value can be calculated and then other values of g_i at different time intervals. Similarly, Eqns. 2 to 5 can be solved to obtain values for b_i, c_i and u_i at different time intervals. This technique can also be used for systems of more than two compartments. The greatest source of error lies in the choice of increment size.

Using a two compartment model, the percentage distribution of drug in each com-



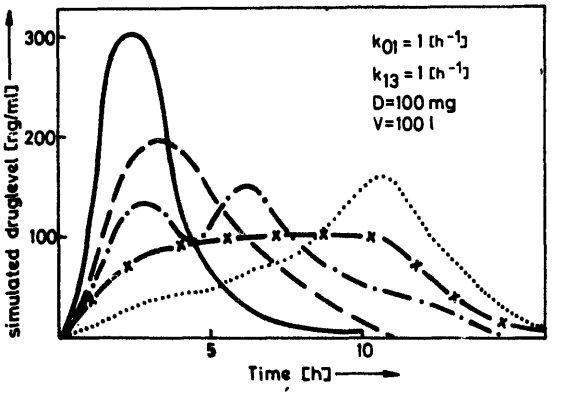


Fig. 4. Linearization of the plasma level.

Fig. 5. Time course of % drug distribution in the various compartments.

partment can be calculated as shown in Fig. 5, from the release profile B depicted in Fig. 2. The constants shown in Fig. 5 were chosen arbitrarily. At time T = 0, 100% of the drug is found in the actual form it is administered, e.g. coated tablet. As shown in Fig. 5 the drug is subsequently distributed between the various compartments depending on the time, and at approximately 15 h after administration it is only present in the elimination compartment. The percentage distribution of the drug at any time can be read off the curves shown in Fig. 5.

Application of the simulation procedure for a two compartment model to a phenobarbital preparation

To test applicability of the simulation procedure for a two compartment model,

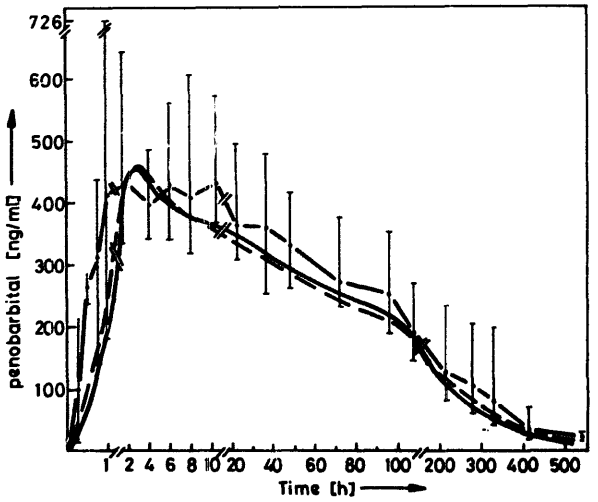


Fig. 6. Simulation of drug levels from the release profiles of two in vitro models and plasma level of Segontin S. · – · – ·, plasma level Segontin S; - - - - - -, predicted drug level – column method; ———, predicted drug level – Sartorius method. Each point represents the mean and standard deviation of 6 subjects.

plasma levels of phenobarbital have been calculated using the procedure described above (Steinbach et al., 1978). The pattern of release of phenobarbital from tablets of Segontin S containing 15 mg phenobarbital was firstly determined using two different in vitro methods. The experimental values obtained were then substituted in the appropriate equations and theoretical in vivo levels calculated. These predicted values were then compared with plasma levels measured after oral administration of the preparation, as shown in Fig. 6. Results showed good reasonable agreement between predicted and measured plasma levels of phenobarbital.

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