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A new approach for the in vivo evaluation of sustained release dosage forms

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Summary

A new method utilizing the graphical measurement of the length, ℓ, above the occupancy time, Δt, of the minimum effective concentration was developed to aid in the quantification of the modified drug release of the sustained release formulations during the preformulation stages. Using simulated data, employing a conventional concentration/time plot in Cartesian coordinates, and expressing both parameters ℓ and Δt in units of distance, it was found that the ratio $\Delta t/\ell$ is related to the rate of release of drug from the formulation. This enabled the evaluation of the extent to which drug release is modified by the formulation.

Sustained release (SR) preparations offer the advantage of less frequent dosing with decreased fluctuation in the serum drug level during the dosing interval. In principle, the in vivo absorption of a drug from such a formulation occurs at a considerably slower rate than from an equivalent dose in a conventional dosage form. Recently, a great number of SR preparations have been developed and widely used in clinical therapy. The interest in the SR preparations imposed the necessity for the development of practical methods and criteria for the quantification of the modified drug release. With these approaches we can draw useful conclusions about the in vivo performance of a SR formulation in an early stage of development of dosage forms.

One of the methods, most frequently employed, is the area deviation method (Boxenbaum, 1984; Nimmerfall and Rosenthaler, 1986). It is based on the comparison of the area under the curves (AUC)s of the experimental curve and a standard curve used to describe quantitatively the release of drug. However, Pieters and Zuidema (1987) have shown that the applicability of the area deviation method is dependent on the duration of the time interval chosen for the comparison of formulations. Obviously, this happens because the AUC parameter is proportional to the extent and not the rate of absorption, and therefore, long time intervals are required to ensure the validity of the evaluation. Another approach, called the dosage form index method (Theeuwes and Bayne, 1977), utilizes the ratio of the maximum to minimum concentrations of the drug in plasma within each interdose interval at pseudo-steady state. The application of this method presupposes that the study

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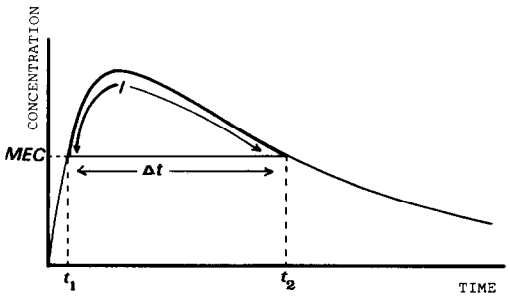

Fig. 1. Diagramatic illustration of a typical plasma concentration/time curve of the parameters: ℓ, Δt, and MEC.

has been properly designed and executed to obtain steady state plasma levels while the samples have been obtained at appropriate time intervals.

In this paper, we propose a new approach for the quantification of the modified drug release. It is based on the comparison of the length of the curve above the therapeutic occupancy time for the conventional and the rate-controlled system. The parameters of interest are presented schematically in Fig. 1.

The preferred therapeutic range is defined as the range above which unacceptable side effects are encountered and below which the desired effect is generally not achieved (minimum effective concentration or MEC). Thus, the basic reasons for developing SR formulations is the maintainance of concentration of drug within the desirable range and the avoidance of fluctuation in plasma levels. For chronic drug administration, drug delivery as close as possible to zero order rate is the theoretical goal, because it gives constant concentrations. In contrast, the result of repetitive dosing of conventional forms is a pattern of peaks and troughs in the concentration of drug in blood. Consequently, a parameter capable of quantifying the modified drug release should be sensitive enough to account for the changes of the shape of the concentration–time curves. We felt that the length of the curve, ℓ, above the occupancy time (Δt), in Fig. 1 can be used as a tool for such an evaluation either in single dosing or steady state conditions. This choice was based on the fact that the major determinant of the shape of plasma concentration/time curve for a hypothetical drug in a given formulation is the absorption rate constant. Conversely, when attempts are made in the preformulation stages to modify the rate of release of the drug, the associated changes in the parameter ℓ can be used to quantify the modifications in the rate of release.

Restricting our discussion to formulations exhibiting the same extent of absorption it can be argued that when a certain Δt is considered, then the lower the value of ℓ, the more sustained is the release of drug. However, when a comparison of two or more formulations is made, the corresponding values of Δt should also be taken into account. To this end, it is advisable to consider the magnitude of the ratio $\ell/\Delta t$ as a basis for the quantification of modified drug release; again, the lower the value of $\ell/\Delta t$ the more sustained release of drug from the formulation. Obviously, the lower limit of the parameter $\ell/\Delta t$ is one i.e. $\ell = \Delta t$ * which happens at the steady state of a perfect zero-order release of drug when the time interval (τ) of dosing and the time span of the zero-order delivery are identical.

In theory, the length of the curve, ℓ, for a given MEC (Fig. 1) is calculated from the equation:

$$\ell = \int_{t_1}^{t_2} \sqrt{\left(\frac{dC}{dt}\right)^2 + 1} \cdot dt \qquad (1)$$

where dC/dt is the first derivative of the function $C = f(t)$ describing the kinetics of the drug in the body; the time limits t_1 and t_2 are defined in Fig. 1. As is implicit from Eqn. 1 the units of the length of the curve, ℓ, have no physical meaning. In reality, ℓ is a hybrid of the time and concentration units i.e. $[(\text{concentration})^2 + (\text{time})^2]^{-1/2}$. In spite of this, it can be utilized as such since its absolute value is of no use and its exclusive application is restricted to comparative studies. The same is applicable to the term $\ell/\Delta t$ with units $[(\text{concentration})^2 + (\text{time})^2]^{-1/2}/(\text{time})$. However, when $\ell = \Delta t$, the parameter $\ell/\Delta t$ becomes unitless and equal to one.

This work as well as the relevant methods are confined to evaluations of the individual experi-

* Measured in the same units e.g. units of distance.

mental plasma level–time profiles plotted on Cartesian coordinates. Thus, a graphical iteration is suggested by Boxenbaum (1984) and a transformation of the concentration/time curve to a rectangle of equal area is proposed by Nimmerfall and Rosenthaler (1986). In the present method, the scaling of the axes employed for the plotting of data can be used to permit the calculation of ℓ and Δt to equivalent units of distance, e.g. cm. Analogously, this transformation will make the parameter $\ell/\Delta t$ a unitless quantity. Consequently, the quantification of the modified drug release can be based on the units of distance for ℓ and unitless numbers for $\ell/\Delta t$. This procedure coincides with the fact that the actual application of the method will be accomplished graphically by measuring the approximate length of the curve, ℓ, and the occupancy time, Δt, in units of distance.

Relying on the above syllogisms it is conceivable that the reciprocal of the parameter $\ell/\Delta t$ can be expressed as a dimensionless quantity obeying the inequality: $0 < (\Delta t/\ell) \leqslant 1$. This feature allows the quantification of the modified drug release as percent improvement, I, based on the equation:

$$I = \frac{(\Delta t/\ell)_s - (\Delta t/\ell)_r}{(\Delta t/\ell)_r} \cdot 100 \qquad (2)$$

where s and r stand for the sustained release and the reference formulation, respectively.

Eqn. 2 can be applied to single dose studies and steady state conditions. When an ideal zero order delivery is achieved and the time interval of dosing is equal to time span of zero order delivery then $(\Delta t/\ell)_s$ becomes maximum and equal to one at steady state *. Under these circumstances, the improvement, I, depends on the original value of $(\Delta t/\ell)_r$. In general, the more abrupt the release of drug from the reference formulation, the lower the value of $(\Delta t/\ell)_r$; accordingly a big improvement is expected when a delivery close to zero order is achieved. For example, if the value of $(\Delta t/\ell)_r$ is 0.4, the maximum possible improvement with an ideal zero order rate can be estimated:

$$I = \frac{1 - 0.4}{0.4} \cdot 100 = 150\%$$

In order to demonstrate the application of the method and test its validity, a number of pharmacokinetic data were simulated using the following equation (Gibaldi and Perrier, 1982):

$$C_n = \frac{FK_aD}{V(K_a - K)}\left[\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right) \cdot e^{-Kt} - \left(\frac{1 - e^{-nK_a\tau}}{1 - e^{-K_a\tau}}\right) \cdot e^{-K_at}\right] \qquad (3)$$

in which t is time, K_a and K are absorption and elimination rate constants, respectively, F is the fraction of dose D absorbed, V is the apparent volume of distribution of the drug, n is the dose number, and τ is the dosing interval. The values of the following population pharmacokinetic parameters were considered common in all cases examined: $F = 1$, $V = 10$ litres, $K = 0.15\ h^{-1}$; the dose, D, and the time interval, τ, were kept also constant and equal to 100 mg and 12 h, respectively. The values of K_a were varied to simulate data from different formulations and assuming that drug release rate is rate-limiting for absorption. A 12-h zero-order absorption from an ideal SR formulation of the hypothetical drug considered was also simulated using the equation (Gibaldi and Perrier, 1982):

$$C_n = \frac{K_0}{V \cdot K}(1 - e^{-(n-1)K\tau})\, e^{-Kt} + \frac{K_0}{VK}(1 - e^{-Kt}) \qquad (4)$$

where $K_0 = D/\tau = 100/12 = 8.33$ mg/h. The values assigned to K_0 and τ imply that the zero-order delivery lasts for 12 h and when abruptly ends the next dose is administered. A MEC value equal to 3 μg/ml was considered. The values of ℓ were calculated by a numerical integration method while the lower, t_1, and the upper, t_2, limit were obtained from Eqns. 3 and 4 substituting $C = 3$

* The concentration/time profile becomes a straight line parallel to the concentration axis. Whatever the values of Δt and MEC chosen, $\Delta t = \ell$.

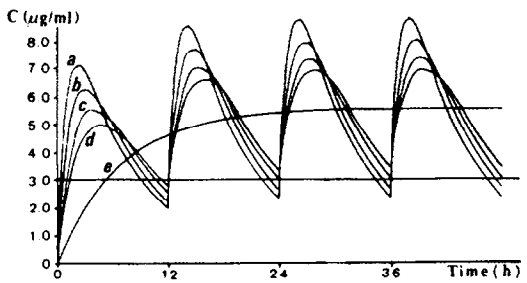

Fig. 2. Plasma level–time curves resulting from administration of 5 formulations of the hypothetical drug. The values of the absorption rate constants utilized for the generation of the curves were: **a**, 1 h^{-1}; **b**, 0.6 h^{-1}; **c**, 0.4 h^{-1}; **d**, 0.3 h^{-1}; **e** (zero order), 8.33 mg/h. See text for the values assigned to other parameters.

μg/ml and solving the resulting equations with an iteration method.

The plasma level–time profiles constructed from the data are illustrated in Fig. 2. For our purposes, formulation **a** with the fastest rate of release is postulated as the reference formulation and all others represent various preparations with slower rates of release. The quantification of the modified release of the hypothetical drug from formulations **b**–**e** in relation to formulation **a** is presented in Table 1. As can be seen the more sustained release of drug from the formulations, **b**, **c**, and **d**, delivering the drug in a first order fashion, the higher the improvement according to Eqn. 2 (Table I, column 4). The improvement follows the relative changes of the ratio $\Delta t/\ell$ and is higher in single dosing than under steady state conditions. In contrast, formulation **e** with the zero-order delivery of drug exhibits the greatest improvement under steady-state conditions. This happens because the concentration of drug in plasma reaches a plateau after repetitive administration of formulation **e**, maximizing, thus, the ratio $\Delta t/\ell$. It is advisable, therefore, to apply the approach developed in steady-state conditions. Another reason for suggesting application of the methodology to steady state conditions is the quite possible non-ideal frequency of administration in relation to the time span of zero order delivery. For example if for formulation **e** a higher value for the zero order constant, $K_0 = 10$ mg/h was assumed, while all other parameters were kept constant, then the improvement under single dosing and steady-state considerations would be 82.8 and 167.3%, respectively. Evidently, the "low" value of improvement in the single dose study is linked with the longer declining phase since the delivery of drug from the formulation ends at 10 h. Under steady state conditions the fluctuations of drug concentration produces a value for $\Delta t/\ell$ equal to 0.72 which results in a lower value of improvement (167.3%) in comparison to the ideal

TABLE 1

*Comparison of formulations **b**–**e** with formulation **a**, utilizing single dose and steady state parameters calculated from simulated data*

Formulation	ℓ (cm)	$\Delta t/\ell$ (unitless)	I (%)	BEF ($\mu g \cdot ml^{-1} \cdot h$)
a	6.68–9.20	0.32–0.27	–	19.85–31.28
b	5.57–8.11	0.40–0.33	26.9–22.4	17.76–30.84
c	4.65–7.30	0.51–0.40	59.5–47.8	15.02–30.67
d	4.01–6.30	0.60–0.46	89.5–71.3	12.34–30.67
e	3.48–2.93 *	0.68–1.00	113.7–268.4	8.73–30.67

For each parameter, the left hand column gives single dose simulated values while the right hand column gives simulated values at steady state.

The calculation of ℓ and Δt in units of distance (cm) was accomplished by equating one unit of time (1 h) and concentration (1 μg/ml) to 0.244 and 0.739 cm, respectively (Fig. 2). I was calculated from Eqn. 2. BEF, bioequivalence factor, defined by Macheras and Rosen (1983); calculated by integrating Eqn. 3 or 4 with t_1 and t_2 as lower and upper limit, respectively, and then subtracting the rectangular area below the MEC between t_1 and t_2.

* The length of the declining part of the curve (not shown in Fig. 2) corresponding to the single dose of the zero-order delivery was taken into account; it was calculated by applying Eq. 1 with limits 0 and 2.90 hours to the function $C = 4.64 \exp(-0.15t)$ where 4.64 μg/ml is the concentration reached when absorption abruptly ends at 12 hours while the time required for the diminution of concentration to 3 μg/ml is 2.90 hours.

observed (268.4%, Table 1) when the drug is administered every 12 h.

Needless to say, that the calculated percentages of improvement are linked with the plot utilized (Fig. 2) and the specific transformation of concentration and time units to units of distance (see Table 1). It is necessary, therefore, whenever the method is applied for transformation of the scaling of axes to units of distance to be reported. This will make the literature data meaningful, comprehensible and comparable.

The discussion so far was confined to formulations having the same extent of absorption. When bioinequivalent products are considered, differences in the magnitudes of ℓ and Δt arising from their bioinequivalency in terms of extent rather than rate of absorption will be observed. However, the comparison of the extent of absorption of the formulations examined is an equally important but *independent* consideration. This has been also supported by Vallner et al. (1983). In this context, we propose that the evaluation of the extent of absorption for SR formulations can be based on the bioequivalence factor, BEF, introduced by Macheras and Rosen (1983) and applied to SR formulations by Dowse and Kanfer (1986). In Table 1 the BEF values of the formulations considered are listed. Slight changes were noted as a result of the changes of absorption rate constant since the overall bioavailability of formulations was considered constant ($F = 1$). In fact, under the steady state conditions the values of BEF were almost identical for all formulations. These differences are inherent with the concept of BEF and the chosen MEC and should not be an additional concern for the physical pharmacist working with the SR formulations.

The results obtained from the simulated data indicate that the approach developed is capable of quantifying the modification of the rate of release. The method is simple and rapid and is relying on the presupposition of equivalency in the extent of absorption of the preparations examined. The application of the method in practice requires only the graphical measurement of the parameters of interest ℓ and Δt for a MEC value chosen in accord with the literature data of the drug formulated. Consider, for example, the dapsone concentration/time curves given in Fig. 1 of Pieters and Zuidema (1987); since the minimum inhibitory concentration of dapsone in man for *M. leprae* has been estimated to be approximately 30 ng/ml (Martindale, 1982), an evaluation was attempted comparing curves 1 and 8 of Fig. 1 of their paper assuming a MEC bar coinciding with the time axis. According to the graph (1 μg/ml and 1 day are "equivalent" to 0.15 cm), curve 8 shows a 105.2% improvement vs curve 1 for the time interval of 28 days considered with the assumption of equivalency in the extent of absorption for curves 1 and 8.

In conclusion, the method developed utilizes the length of curve ℓ above the occupancy time Δt for a chosen MEC, Fig. 1, to quantify the modified drug release. The latter two parameters are inextricably linked with the strategy of design of SR formulations. This means that the specific values assigned to MEC and Δt and defined as target values during the preformulation stages are simultaneously the key elements for the method developed. However, when the MEC value is neither known or applicable, the method proposed cannot be applied.

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