An analysis of the applications of dissolution efficiency

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Recently Khan (1975), Khan & Rhodes (1972) introduced the concept of 'dissolution efficiency' as a suitable parameter for the evaluation of *in vitro* dissolution. 'Dissolution efficiency' (DE) is defined as the area under the dissolution curve up to a certain time t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (see Fig. 1). 'Dissolution efficiency' is stated (Khan, 1975) to have the advantages that it enables ready comparisons to be made between a large number of formulations and that it can be theoretically related to *in vivo* data.

We have examined the meaning of 'dissolution efficiency' by reference to defined functions which describe drug release from a formulation as follows.

For a formulation which releases its drug in a dissolution test by a first-order process of rate K_r, the amount of drug (D) in the preparation at time t is given by

$$D = D_o e^{-K_r t} \quad .. \quad .. \quad .. \quad (1)$$

and the amount of drug (D_r) dissolved at time t is given by

$$D_r = D_o (1 - e^{-K_r t}) \quad .. \quad .. \quad (2)$$

In equations 1 and 2, D_o is the amount of drug in the formulation at t = 0. 'Dissolution efficiency, for this type of formulation is obtained by integration of equation 2 and dividing by the rectangular area defined by $D_o t$ (see Fig. 1), thus

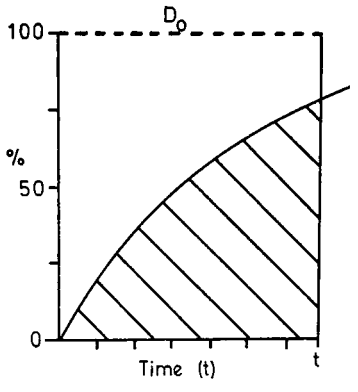

FIG. 1. Dissolution (%) of a drug as a function of time: $DE = \frac{\text{rectangle } D^{\circ\,100} \cdot t}{\text{shaded area}} 100.$

* Correspondence.

$$\text{'Dissolution efficiency' for first-order drug release (i.e. } DE_t) \equiv \frac{D_o \int_0^t (1 - e^{-K_r t})\, dt}{D_o t} \cdot 100 =$$

$$[1 + \frac{1}{K_r t}(e^{-K_r t} - 1)].100 \quad .. \quad .. \quad .. \quad 3$$

Time t in equation 3 is the time required for a percentage (f) of D_o to dissolve (i.e. $t \equiv t_f$), this time (t_f) is obtained by the application of equation 1 and is given by

$$t_f = \frac{4{\cdot}606 - \ln (100 - f)}{K_r} \quad .. \quad .. \quad 4$$

Substitution of t_f as given by equation 4 into equation 3 yields an expression for DE_f as a function of f, thus

$$DE_f \equiv 1 + \frac{1}{4{\cdot}606 - \ln (100 - f)} e^{-B} \quad .. \quad .. \quad 5$$

where $B = 4{\cdot}606 - \ln (100 - f)$.

For a formulation which releases its drug by a zero-order rate process of rate K_o the 'dissolution efficiency' is given as

$$\text{'Dissolution efficiency' for zero-order drug release (i.e. } DE_{t\text{-zero}}) = \frac{K_o t_f}{2D_o} . 100 \quad .. \quad .. \quad 6$$

However, the time required for a percentage (f) of D_o to dissolve is given by

$$t_f = \frac{D_o f}{100\, K_o} \quad .. \quad .. \quad .. \quad 7$$

and substitution of equation 7 into equation 6 yields an expression for

$$DE_{t\text{-zero}} = \frac{f}{2} \quad .. \quad .. \quad .. \quad 8$$

As is indicated by equations 5 and 8, DE values measured using a fixed percentage of a drug dissolved are independent functions of the release rate constants, consequently 'dissolution efficiency' should be measured using a fixed time, as indicated in the original definition. The latter is in contrast to the conventional parameter $1/t_f$ which is directly related to the release rate constants for both first-order and zero-order drug release (see equations 4 and 7).

Khan (1975) suggests that 'dissolution efficiency' can be used as a comparative parameter in *in vitro* dissolution tests. Consequently when determining the 'dissolu-

tion efficiencies' of a series of formulations a dissolution time is chosen at which one preparation (designated the standard) has released f_s percentage of its drug and all other 'dissolution efficiencies' are determined by reference to this time (see Fig. 1). For first-order drug release all 'dissolution efficiencies' (DE_j) are functions of K_j/K_s and f_s, where K_j and K_s are the first-order release rate constants for formulation j and the standard formulation respectively. The values of DE_j are obtained by the application of equations 3 and 4 and are given by

$$DE_j = \left\{ 1 + \frac{1}{A}(e^{-A} - 1) \right\} .100$$

where $A = K_j . [4{\cdot}606 - \ln (100 - f_s)]/K_s$ .. 9

Similarly for zero-order drug release DE_{j-zero} is a function of K_{oj}/K_{os} and f_s where K_{oj} and K_{os} are the zero-order release rate constants for formulations j and the standard formulation respectively. Values of DE_{j-zero} are given by

$$DE_{j-zero} \quad (0 < DE_{j-zero} \leqslant 50) = \frac{K_{oj} f_s}{K_{os}.2}$$

$$DE_{j-zero} \quad (50 < DE_{j-zero} \leqslant 100) = \left\{ 1 - \frac{50K_{os}}{K_{oj} f_s} \right\} .100 \ldots 10$$

As is indicated by equation 9 the 'dissolution efficiency' for first-order drug dissolution is not a linear function of the rate constant K_j, whereas for zero-order drug dissolution (see eqn 10) DE_{j-zero} is a linear function of K_{oj} for values less than 50 but is non-linear for values greater than 50. The functional relationships between DE_j and K_j/K_s and DE_{j-zero} and K_{oj}/K_{os} when f_s equals 90% are shown in Fig. 2.

In contrast to the above, the conventional parameter of drug dissolution $1/t_f$ (f = 50, 90, etc.) is linearly related to the first-order and zero-order dissolution rate constants.

Since 'dissolution efficiency' is a non-linear function of the first-order release rate constant, the functional relationship between 'dissolution efficiency' and biological availability is complicated and dependent on the biological availability of the standard formulation. The relationships between 'dissolution efficiency' and biological availability for first-order drug release when the standard formulation is 30, 60 and 90% available is illustrated in Fig. 3. The curves depicted in Fig. 3 were calculated (eqns 1, 4 and 9) assuming identical *in vitro* and *in vivo* drug dissolution and that drug absorption occurs for a finite time (i.e. the time (t_f) for the standard to release f_s).

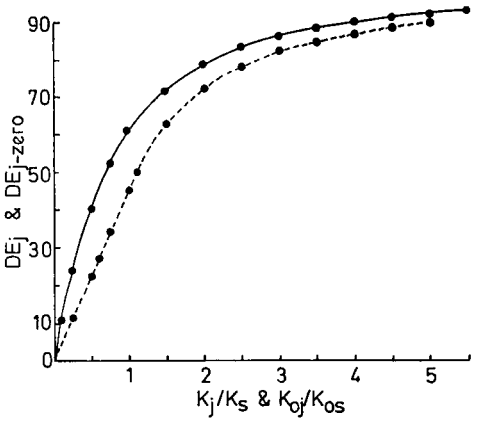

FIG. 2. 'Dissolution efficiency' as a function of the drug release rate constant, first-order drug dissolution —●—, zero-order drug dissolution - - -●- - -.

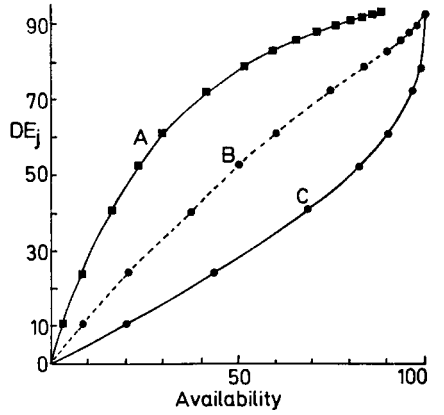

FIG. 3. 'Dissolution efficiency' as a function of biological availability (% of dose) for first-order drug dissolution, when the standard formulation is 30 (A), 60 (B) and 90% (C) available.

As is indicated in Fig. 3 'dissolution efficiency' is not a linear function of the biological availability and the shape of the functional curve is determined by the availability of the standard formulation.

In conclusion the parameter 'dissolution efficiency' is a complicated function and even for defined dissolution functions its relation to biological availability is difficult to predict. For inexact dissolution profiles its relation to biological availability will be obsecure. Consequently the predictive value of this parameter is of limited value.

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