Does the Dose-Solubility Ratio Affect the Mean Dissolution Time of Drugs?

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Purpose. To present a new model for describing drug dissolution. On the basis of the new model to characterize the dissolution profile by the distribution function of the random dissolution time of a drug molecule, which generalizes the classical first order model.

Methods. Instead of assuming a constant fractional dissolution rate, as in the classical model, it is considered that the fractional dissolution rate is a decreasing function of the dissolved amount controlled by the dose-solubility ratio. The differential equation derived from this assumption is solved and the distribution measures (half-dissolution time, mean dissolution time, relative dispersion of the dissolution time, dissolution time density, and fractional dissolution rate) are calculated. Finally, instead of monotonically decreasing the fractional dissolution rate, a generalization resulting in zero dissolution rate at time origin is introduced.

Results. The behavior of the model is divided into two regions defined by q, the ratio of the dose to the solubility level: $q < 1$ (complete dissolution of the dose, dissolution time) and $q > 1$ (saturation of the solution, saturation time). The singular case $q = 1$ is also treated and in this situation the mean as well as the relative dispersion of the dissolution time increase to infinity. The model was successfully fitted to data (1).

Conclusions. This empirical model is descriptive without detailed physical reasoning behind its derivation. According to the model, the mean dissolution time is affected by the dose-solubility ratio. Although this prediction appears to be in accordance with preliminary application, further validation based on more suitable experimental data is required.

KEY WORDS: dissolution; model; fractional dissolution rate; mean dissolution time; relative dispersion.

INTRODUCTION

A fundamental feature of the drug dissolution theories, which were developed as an extension of the Noyes-Whitney model (2), is the constant proportionality of dissolution rate to the concentration difference ($C_s - C(t)$) between the solubility C_s and the concentration of drug in the dissolution medium at time t, $C(t)$ (see e.g., (3)). In the context of dissolution time distributions, this simple first order process implies exponentially distributed dissolution times, i.e., a time-constant fractional dissolution rate (well-mixed model). Furthermore, the mean dissolution time (MDT) is then independent of the dose-solubility ratio. We hereby propose a more flexible and natural extension of this model assuming the fractional dissolution rate is not constant, but a decreasing function of the amount dissolved. With regard to the underlying assumptions, this approach is analogous to the discrete time model developed by Dokoumetzidis and Macheras (4) and it can simply be considered as the continuous-time counterpart of their model.

It is the purpose of this report to show that this new empirical dissolution model, in contrast to the classical model, implies an increase in MDT if the dose gets near to the saturation (or solubility) level, reflecting the departure of the dissolution time distribution from the exponential distribution which is inherent for the classical model (denoted in the following by EX—exponentially distributed). The departure is also reflected by an increase of variability characterized by relative dispersion of the dissolution time which remains always greater than one. Both the new function and the conventional EX model are fitted to *in vitro* dissolution data of a poorly soluble drug (1). As expected, the new model is characterized by larger MDT.

THEORY AND RESULTS

The classical EX model (as extensions of the Noyes-Whitney equation) is characterized by a constant fractional (or relative) dissolution rate

$$k(t) = k_{EX} = \frac{\frac{d\Phi(t)}{dt}}{1 - \Phi(t)}, \tag{1}$$

where $\Phi(t) = A(t)/D$ denotes the fraction of drug dissolved up to time t (A denotes the amount of drug dissolved and D is the dose, which finally becomes completely dissolved). In probabilistic terms, the fractional dissolution rate is a conditional probability of being dissolved at time $[t, t + \Delta)$ under the condition that the dissolution has not taken the place before t. If we want to generalize this first order model, we can assume the fractional dissolution rate is a function of $\Phi(t)$, and consequently of time t, $k(t) = f[\Phi(t)]$. The simplest specification of f which contains the EX model as a limiting case is a linear function,

$$k(t) = f[\Phi(t)] = r(1 - q\Phi(t)), \tag{2}$$

where q is the dose-solubility ratio, $q = D/\theta$, denoting the amount of drug in the medium which corresponds to solubility by θ, and $r = k(0)$ represents the initial fractional dissolution rate. Now $k(t)$ approaches r for $\Phi(t) \to 0$ or $q \to 0$, which corresponds to the classical first order case where $r = k_{EX}$. If we substitute equation (2) into (I) we get

$$\frac{d\Phi(t)}{dt} = r(1 - \Phi(t))(1 - q\Phi(t)), \Phi(0) = 0. \tag{3}$$

Obviously for $q \to 0$, equation (3) describes a single-compartment model and all the conclusions for (3) have to have this limiting behavior. Intuitively, we may expect that for $q < 1$ all the dose can dissolve and for $q > 1$ the solution gets saturated. The case $q = 1$, which is singular from a practical point of view, is a limiting case for which the solution gets saturated when all the dose dissolves. The solution of equation (3) is

$$\Phi(t) = \frac{\exp(rt(1 - q)) - 1}{\exp(rt(1 - q)) - q}, \tag{4}$$

which is a monotonic function of t with two different asymptotes

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$$\Phi(\infty) = \begin{cases} 1 & \text{for } q \le 1 \\ 1/q & \text{for } q > 1 \end{cases} \quad (5)$$

Solution (4) takes the form

$$\Phi(t) = \frac{rt}{1 + rt} \quad (6)$$

for $q = 1$. The property (5) confirms that for $q \le 1$ all the amount is dissolved, while in the second case the saturation level $1/q$ is achieved. These are two qualitatively different situations and in the following text we treat them separately. An example of a mechanistic model which produces the non-classical behavior (Eq. 3) is presented in the Appendix.

Complete Dissolution ($q \le 1$)

The function Φ given by (4) behaves as a cumulative distribution function of a random variable denoted by T_d and called the dissolution time. It can be interpreted as a probability that a randomly selected molecule of the drug will be in dissolved form before time t. Solving (4) for unknown t and with left-hand-side equal to 1/2, the half-dissolution time, $t_{1/2}$, can be calculated,

$$t_{1/2} = \frac{1}{r(1 - q)} \ln(2 - q), \quad (7)$$

specially, for $q = 1$, $t_{1/2} = 1/r$. For $q \sim 1$ the dependency of half-dissolution time is approximately linear with respect to q and hyperbolic with respect to r, $t_{1/2} \sim 1/r - (1 - q)/(2r)$, see Fig. 1. In the same way as (7) other percentiles can be evaluated.

The probabilistic interpretation of (4) permits the calculation of all other commonly used characteristics. For the mean dissolution time, MDT_d, we have

$$\mathrm{MDT}_d = -\frac{1}{rq} \ln(1 - q), \quad (8)$$

which can be compared with the half-dissolution time given by (7), it holds that $t_{1/2} < \mathrm{MDT}_d$ for all q. For $q \to 1$, $\mathrm{MDT}_d \to \infty$ and the difference between the mean and the half-dissolution time is mostly pronounced in this region (see Fig. 2). For the second moment of the dissolution time, $E(T_d^2)$, holds

$$E(T_d^2) = \frac{2}{q(1 - q)r^2} \sum_{k=1}^{\infty} \frac{q^k}{k^2} \quad (9)$$

and using (8) and (9) the relative dispersion (coefficient of variation) can be calculated,

$$\mathrm{CV}_d^2 = \frac{2q \sum_{k=1}^{\infty} \frac{q^k}{k^2}}{(1 - q)\ln^2(1 - q)} - 1. \quad (10)$$

We see that CV_d^2 does not depend on r and after some calculation it can be shown that $\mathrm{CV}_d^2 > 1$ for any q (Fig. 3a). Brown (5) (see also (6)) proposed a measure $\Delta_{\exp}$ based on CV_d^2 which can be used for representing the departure of the distribution (4) from the exponential distribution (the single compartment model),

$$\Delta_{\exp} = \sup_{t \ge 0} |\Phi(t) - (1 - \exp(-t/\mathrm{MDT}_{EX}))| \le \frac{\mathrm{CV}_d^2 - 1}{\mathrm{CV}_d^2 + 1}. \quad (11)$$

The difference between the dependency on q of the distribution functions is illustrated in Fig. 3b.

Not only the moments, but also the fractional dissolution rate (hazard function), $k_d(t)$ can be calculated using (4). The probability density of T_d is

$$\phi_d(t) = \frac{r(1 - q)^2 \exp(rt(1 - q))}{(\exp(rt(1 - q)) - q)^2}, \quad (12)$$

and $k_d(t) = \phi_d(t)/(1 - \Phi(t))$ implies

$$k_d(t) = \frac{r(1 - q)}{1 - q\exp(-rt(1 - q))}, \quad (13)$$

which is a decaying function of time originated at r that asymptotically approaches $(1 - q)r$. The shapes of the fractional dissolution rates are illustrated in Fig. 4a., where the time axis is normalized by r (the mean dissolution time for the classical model), and the axis for the fractional dissolution rate is normalized with respect to $1/r$ (the fractional dissolution rate for the classical model). Thus, the dependency on r in (13) is eliminated and we can observe the dependency on q. The curves always start at 1 and after a fast decay they slowly approach $(1 - q)$. For q close to zero the constant fractional dissolution rate is obvious.

For $q = 1$

$$k_d(t) = \frac{r}{1 + rt}, \quad (14)$$

which is decaying function of time starting from r and reaching asymptotically zero. In the normalized version, it can be seen in Fig. 4a.

Dunne *et al.* (7) introduced the odds function $g_d(t) = \Phi(t)/(1 - \Phi(t))$ which represents the ratio of the probability that a molecule will be dissolved before time t to the probability that it will not be dissolved and for (4) it takes the form,

$$g_d(t) = \frac{\exp(rt(1 - q)) - 1}{1 - q}. \quad (15)$$

Saturation ($q > 1$)

In this situation to speak about dissolution would be complicated because not all the administered amount dissolves and thus, T_d is not a proper random variable, $\mathrm{Prob}(T_d < \infty) = 1/q$. Therefore, it is more intuitive to study the saturation time T_s defined by the cumulative distribution function (4) normalized by $1/q$. T_s can be interpreted as the probability that a randomly selected molecule of the drug, from the part of the drug which will finally dissolve, will be dissolved before time t.

Using equation (4) with left-hand-side equal to $1/(2q)$, the half-saturation time $t_{1/2}$ can be calculated,

$$t_{1/2} = \frac{1}{r(1 - q)} \ln\left(\frac{q}{2q - 1}\right) \quad (7a)$$

and other percentiles can be evaluated, for illustration see Fig. 1. For the mean saturation time, MDT_s, we have

$$\mathrm{MDT}_s = \frac{1}{r} \ln\left(\frac{q}{q - 1}\right), \quad (8a)$$

which is illustrated in Fig. 2. The mean (8a) can be again compared with the half-saturation time given by (7a). It holds

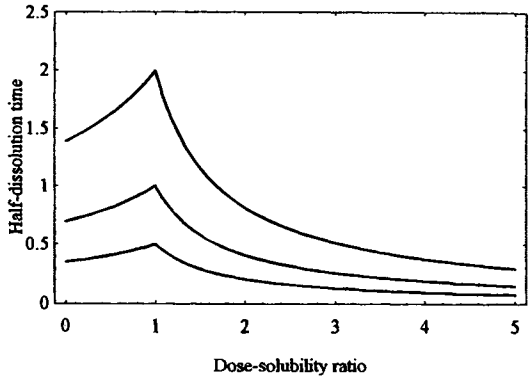

Fig. 1. Half-dissolution and saturation time given by (7) and (7a) for different values of r, from the top, $r = \frac{1}{2}$, 1, 2, in dependency on dose-solubility ratio q.

like in the previous section that, $t_{1/2} < \mathrm{MDT}_s$, which is mostly pronounced for q close to one. The second moment $E(T_s^2)$ is

$$E(T_s^2) = \frac{2}{(q-1)r^2} \sum_{k=1}^{\infty} \left(\frac{1}{q}\right)^k \frac{1}{k^2} \tag{9a}$$

and combining (8a) and (9a) the relative dispersion can be calculated,

$$\mathrm{CV}_s^2 = \frac{2}{(q-1)\ln^2\left(\frac{q}{q-1}\right)} \sum_{k=1}^{\infty} \left(\frac{1}{q}\right)^k \frac{1}{k^2} - 1. \tag{10a}$$

Analogous to (10), the value of (10a) does not depend on r and after some calculation we can show that $\mathrm{CV}_s^2 > 1$ for any q, Fig. 3a. The relative dispersion (10a) reflects the same departure (11) from the exponential distribution as (10) if expressed with respect to $1/q$ (see Fig. 3b).

The probability density of saturation time is $\phi_s(t) = q\phi_d(t)$ where ϕ_d is given by (12). Combining $\phi_s(t)$ and the scaled version of (4), the fractional dissolution rate can be calculated,

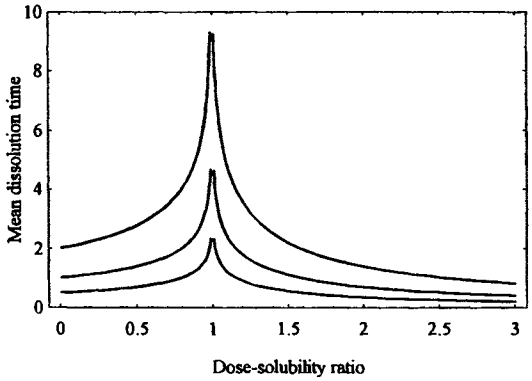

Fig. 2. Mean dissolution and saturation time given by (8) and (8a) for different values of r, from the top, $r = \frac{1}{2}$, 1, 2, in dependency on dose-solubility ratio q. The initial point, at $q = 0$, gives the mean dissolution time for the classical model ($\mathrm{MDT}_{\mathrm{EX}}$). The dependency is pronounced only in the vicinity of the singular point $q = 1$ for which MDT $= \infty$, MDT is almost constant for other values of q.

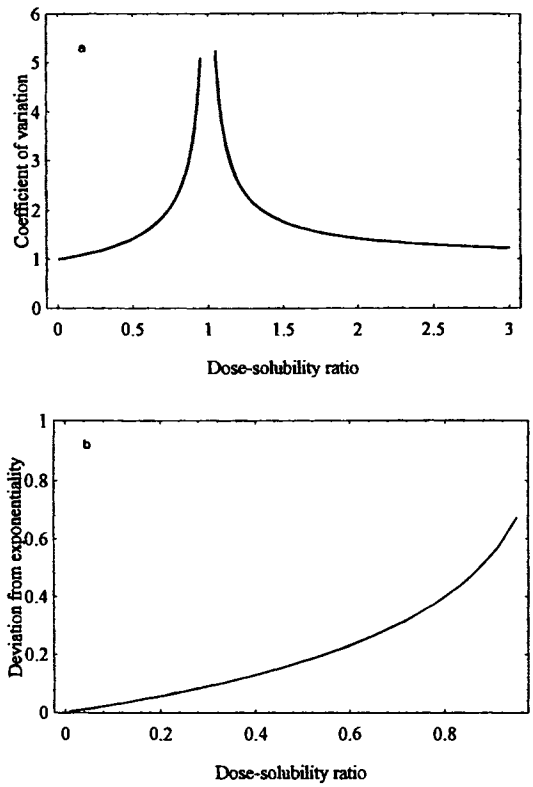

Fig. 3. (a) Relative dispersion for dissolution and saturation time given by (10) and (10a) in dependency on dose-solubility ratio q. The values are always bigger than one and for q between 0.75 and 1.25 the dependency becomes highly nonlinear. (b) The deviation of model (3) from the classical model (EX) reflected by the bound (11) for both $q < 1$ and $q > 1$ (presented as $1/q$ on the abscissa). We can see that for $q < 0.6$ ($q > 10/6$) the difference is less than 20%.

$$k_s(t) = \frac{qr(1-q)}{\exp(rt(1-q)) - q} \tag{13a}$$

being a decaying function of time starting at rq and reaching asymptotically $(q-1)r$. The shape of the fractional dissolution rates are illustrated in Fig. 4b., where the time axis is normalized by r (the mean dissolution time for the classical model), and the axis for the fractional dissolution rate is normalized with respect to $1/r$ (the fractional dissolution rate for the classical model). Again, this eliminates the dependency on r in (13a) and we can study the dependency on $1/q$. The curves always start at q and after a decay they approach $q - 1$. For q close to one, the behavior is the same as in Fig. 4a. For the odds function we have,

$$g_s(t) = \frac{1 - \exp(rt(q-1))}{1-q}. \tag{15a}$$

Nonmonotonic Fractional Dissolution Rate

Equation (2) expresses that the fractional dissolution rate monotonically decreases from $k(0) = r$ to $k(\infty)$, which implies the dissolution rate is maximal at the time origin. A more realistic picture would be an initial slow increase of the dissolution rate. A possible way how to describe this phenomenon

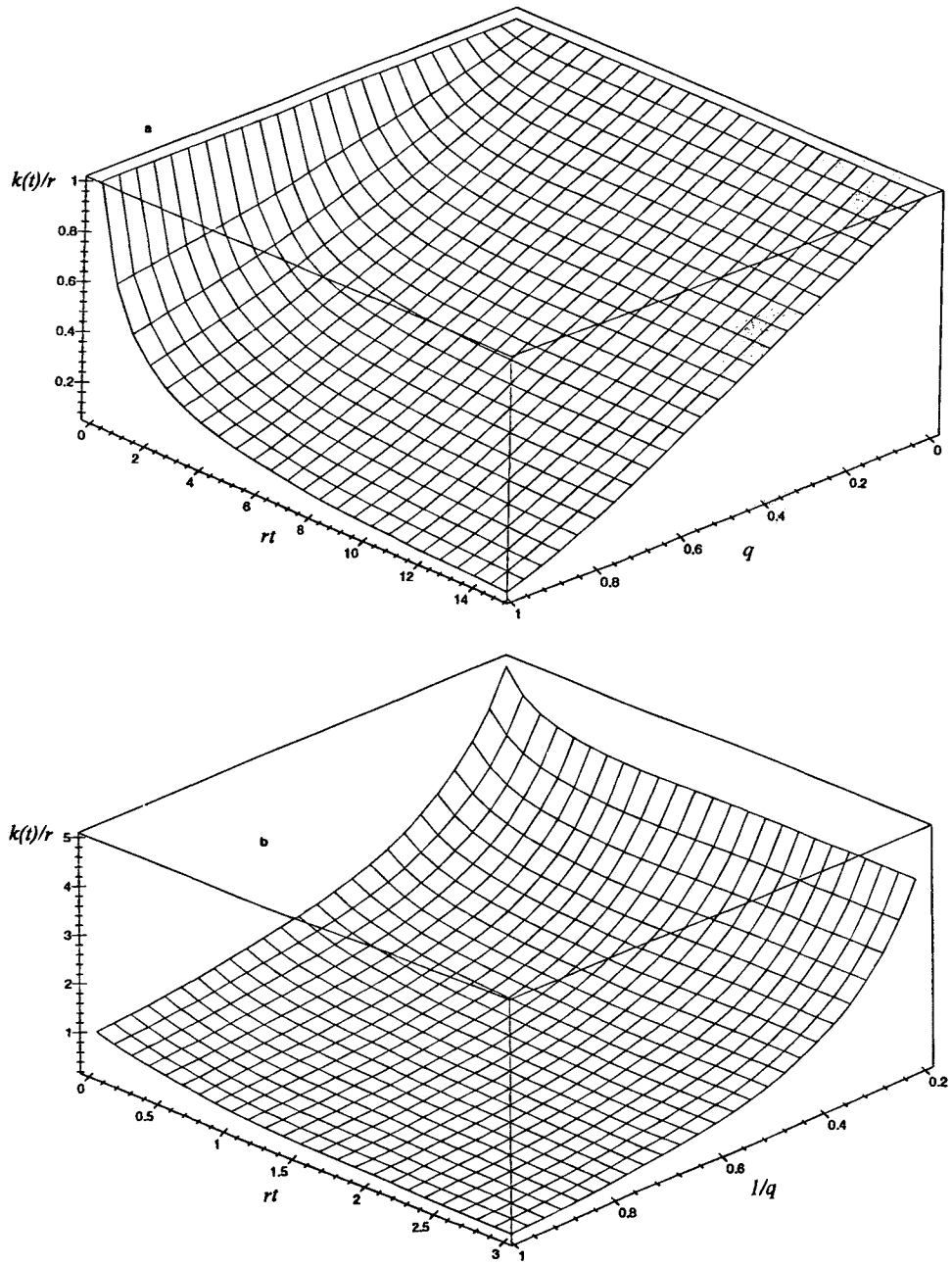

Fig. 4. Normalized fractional dissolution rates, $k(t)/r$, as a function of normalized time, tr, and dose-solubility ratio, q; 4a. $q < 1$, 4b. $q > 1$, for details see the text.

theoretically is to replace the constant r in equation (3) by a time variable $r(t)$. To satisfy the condition $\Phi'(0) = 0$, we may assume in the model that $r(t)$ starts at the time origin (the beginning of dissolution process) from being initially equal to zero and gradually reaches its asymptotic level r. An example of a function fulfilling such a requirement is

$$r(t) = r(1 - \exp(-t/\tau)), \tag{16}$$

where $\tau > 0$ is a time constant characterizing the speed of $r(t)$ in achieving the constant level r. Solving (3) in which constant r is replaced by time the varying function $r(t)$ given by (16), we obtain

$$\Phi(t) = \frac{\exp\{r(t + \tau(e^{-t/\tau} - 1))(1 - q)\} - 1}{\exp\{r(t + \tau(e^{-t/\tau} - 1))(1 - q)\} - q}. \tag{17}$$

In Fig. 5a. there are examples of the shape of $\Phi(t)$ given by (17) and we can see that by increasing τ the initial slow dissolution is more pronounced. Of course, for large t with respect to τ (17) and (4) behave identically, but they are shifted with respect to the time axis. Due to the delay of the dissolution caused by

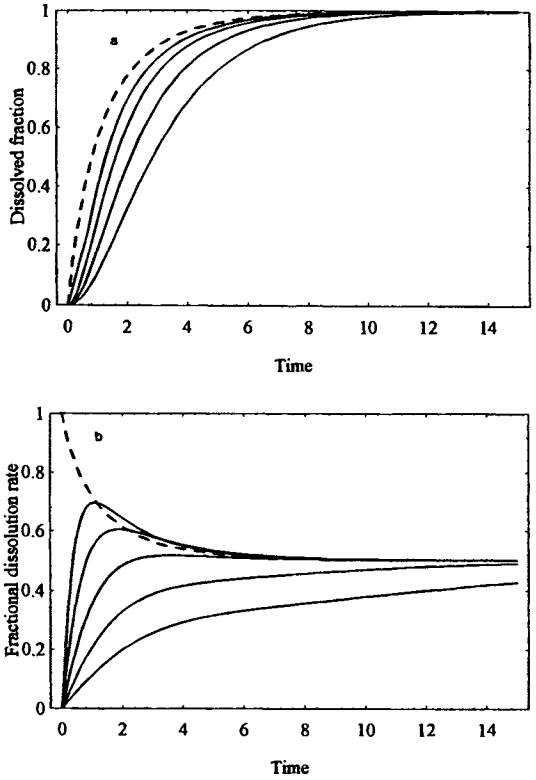

Fig. 5. (a) Profiles of the fraction of the dissolved amount given by (17), for $r = 1$ and $q = 0.5$, in dependency on time. The dashed curve is for constant r ($\tau = 0$), the full line curves from the left to the right correspond to the values of time constant $\tau = 0.5$, 1, 2, 4 and 8. (b) Fractional dissolution rates corresponding to $\Phi(t)$ presented in Fig. 5a.

the fact that $r(t) < r$ for all t, the mean dissolution time will always be larger for (17) than for (4).

The result given by equation (17) can be generalized for any non-negative integrable function $r(t)$ describing the evolution of the time variable rate in (3). Let $R(t) = \int_0^t r(s)ds$, ($R(\infty) = \infty$ is only a formal requirement), then

$$\Phi(t) = \frac{\exp(R(t)(1-q)) - 1}{\exp(R(t)(1-q)) - q}. \tag{18}$$

In this way statistical characteristics derived in Sections 1.1 and 1.2 can be easily expressed. For $q < 1$, the probability density of T_d is

$$\phi_d(t) = \frac{r(t)(1-q)^2 \exp(R(t)(1-q))}{(\exp(R(t)(1-q)) - q)^2}, \tag{19}$$

and the fractional dissolution rate is

$$k_d(t) = \frac{r(t)(1-q)}{1 - q\exp(-R(t)(1-q))}. \tag{20}$$

Similarly for $q > 1$, the fractional dissolution rate can be calculated,

$$k_s(t) = \frac{qr(t)(1-q)}{\exp(R(t)(1-q)) - q}. \tag{20a}$$

In both these cases, the fractional dissolution rate starts from zero. However, their complete profile depends on the detailed

Table 1. Model Given by Equation (3)

%LS in W	q	r	MDT	MSC
0.25	1.996	0.024	29.50	7.58
0.50	1.016	0.053	78.30	9.21
0.75	0.268	0.060	19.45	8.81
1.00	0.880	0.144	16.75	8.15
Model EX				
%LS in W	q	k_{EX}	MDT	MSC
0.25	2.180	0.045	22.17	7.44
0.50	1.287	0.054	18.62	5.68
0.75	1.028	0.056	17.73	9.38
1.00	1.081	0.094	10.57	5.26

properties of the function $r(t)$, see Fig. 5b. There it is shown that the shapes of $k_d(t)$ given by (20) range from monotonic decay through non-monotonic behavior to monotonic growth.

APPLICATION AND DISCUSSION

We applied model (3) to the *in vitro* dissolution data (1) of danazol capsules in different media (different θ and constant D), which were also used by Dokoumetzidis and Macheras (4). The model, when fitted to the data, results in two independent dimensionless parameters r and q, see Table 1. Further, the new model was compared with the classical approach given by equation (1) with $k(t) = k_{EX}$, which predicts the following dissolution profile,

$$\Phi(t) = 1 - \exp(-tk_{EX})$$

implying that MDT $= 1/k_{EX}$,

$$A(t) = A(\infty)(1 - \exp(-t/\text{MDT})).$$

Figure 6. shows the fits obtained with the new model; the parameter estimates and the goodness of fit obtained with both

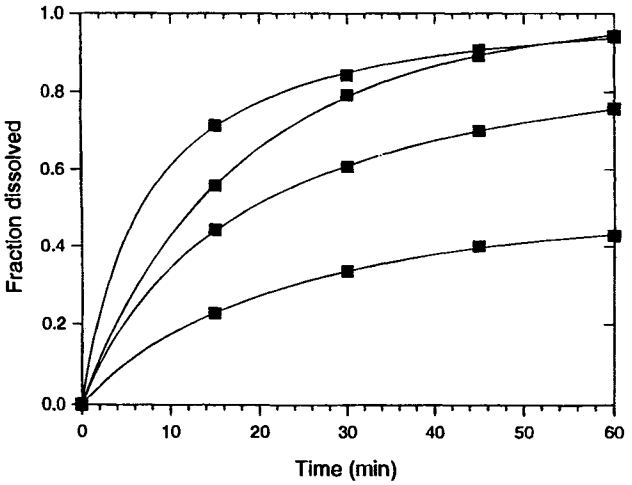

Fig. 6. The fraction of dose dissolved as a function of time for data Shah *et al.* (1995). The squares are the danazol data (1, 0.75, 0.50, 0.25 % sodium lauryl sulfate in water as dissolution medium; from top to the bottom). The lines obtained from the fit of the model (3) to the data, for details see text.

models, equations (1) and (3), are summarized in Table 1. With one exception the fits provided by the new model were superior to those of the classical approach. The fit was evaluated by nonlinear regression method using software package SCIENTIST (MicroMath Scientific Software, Salt Lake City, UT) and the goodness of fit assessed using the model selection criterion of SCIENTIST (MSC-criterion) which is a modified AIC-criterion. As expected, the difference between the MDT estimates are pronounced near the solubility limit (saturation level) and the classical case is per definition restricted to $q > 1$.

Note that all classical descriptions of dissolution, which are based on the proportionality of dissolution rate to the concentration difference $(C_s - C(t))$, share the assumption that the particle environment (dissolution medium) is homogeneous (well-stirred). Further, note that the homogeneity or well-stirred assumption implies a time-constant fractional dissolution rate and the relative dispersion of dissolution time distribution $CV^2 = 1$ (e.g., 8). The present model aims to overcome these restrictions. The model is empirical in so far that a physical interpretation of the approximation of $k(\Phi)$ by a linear decreasing function (2) is lacking. The fact that the new model allowed a better fit of the dissolution data in the present example is of course not a proof of its correctness; it simply means that the model could not be rejected on the basis of the available data. An important consequence is that MDT exceeds MDT_{EX} if D is not much less than θ.

Recently Oh *et al.* (9) defined fundamental dimensionless parameters to estimate the fraction of a dose absorbed under in vivo conditions, *Do* and *Dn*. Note that our parameter θ corresponds to the parameter *Do*, which is the ratio of dose concentration to solubility and that MDT is an important determinant of *Dn* defined as the ratio between the residence time of the drug in the intestine and MDT. Thus it may be interesting to ask whether the values of MDT obtained by the present model could be useful for prediction of *in vivo* drug absorption, (10).

Finally, it should be stressed the aim of the above model is different from a statistical approach where various dissolution curve-models are compared without making assumptions about the dissolution process (11) as well as from more detailed geometrical models of drug release from special dosage forms of water-soluble compounds (e.g., 12).

APPENDIX

The following model is intended to give an example of a possible mechanism which may cause the non-classical behavior (i.e., the deviation from Noyes-Whitney equation). Many aspects of the dissolution process (e.g., surface changes) are not taken into account by this largely simplified model.

Let us assume that in a reaction vessel of volume V, at time t, we have the concentrations (number of molecules per unit volume) $w(t)$ of free solvent molecules each taking a volume v_w; $s(t)$ of undissolved molecules of solute, each with effective volume v_s and $c(t)$ of dissolved molecules of the drug complexed with solvent, each complex with effective volume v_c. So, it holds,

$$w(t)v_w + s(t)v_s + c(t)v_c = 1. \tag{A1}$$

An obvious condition is that the complex molecule has a larger volume than its components, namely $v_s < v_c$ and $v_w < v_c$. Let us further assume that the dissolution process follows the chemical kinetics reaction $s + w \rightarrow c$, with the rate k^* and taking into account that the solvent is initially free of the solute, $c(0) = 0$. So, the equation describing the complex formation is

$$\frac{dc(t)}{dt} = k^* w(t)s(t), \quad c(0) = 0. \tag{A2}$$

From conservation of matter law follows

$$s(t) + c(t) = D/V \tag{A3}$$

and substituting it into (A2) we have

$$\frac{dc(t)}{dt} = k^* w(t)\left(\frac{D}{V} - c(t)\right), \quad c(0) = 0. \tag{A4}$$

From (A4), for the fraction of drug dissolved at time t ($\Phi(t) = c(t)V/D$) holds

$$\frac{d\Phi(t)}{dt} = k^* w(t)(1 - \Phi(t)), \; \Phi(0) = 0. \tag{A5}$$

If $w(t)$ is sufficiently large that it is practically constant during the dissolution process, $w(t) = w$, we obtained the classical exponential law, in which $k = k^* w$. However, if due to the creating the complex the amount $w(t)$ changes, then it has to be taken into account in (A5). Combining (A1) and (A3) we have,

$$w(t) = \frac{1}{v_w}\left(1 - v_s\frac{D}{V} - (v_c - v_s)c(t)\right) \tag{A6}$$

and after substitution into (A4) we obtain

$$\frac{d\Phi(t)}{dt} = \frac{k^*(V - v_sD)}{V v_w}\left(1 - \frac{(v_c - v_s)D}{V - v_sD}\Phi(t)\right) \times (1 - \Phi(t)), \quad \Phi(0) = 0. \tag{A7}$$

Defining $r = (k^*(V - v_sD)/Vv_w)$ and $q = ((v_c - v_s)D/V - v_sD)$ we arrived to dissolution equation (3). Obviously, both constants r and q are positive and $q > 1$ is equivalent to $v_cD > V$, in other words, the completely dissolved amount does not fit to the vessel volume.

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