Modeling Heterogeneity of Particles and Random Effects in Drug Dissolution

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Purpose. To investigate new models characterizing dissolution data obtained for heterogenous materials (model I) and under randomly time-varying conditions (model II).

Methods. In model I, the heterogeneity of the dissolving substance introduces variation of the fractional dissolution rate. In model II, the fractional dissolution rate evolves randomly, and thus the dissolution has the characteristics of a stochastic process. This situation is studied for the constant and time-dependent means of the dissolution rate.

Results. The time dynamics of the dissolved fraction is presented for model I. The standard characteristics of dissolution are derived under general conditions and for several examples. One of them is in accordance with a function found empirically (1). A duality between the time-dependency of the fractional dissolution rate and the heterogeneity of the substance is investigated. The mean and variance of the dissolved fraction are calculated for model II. A method for estimating the mean dissolution rate is proposed and illustrated using Monte-Carlo experiments.

Conclusions. It follows from model I that the heterogeneity, with the same mean properties, slows down the dissolution with respect to the homogeneous case. The second approach permits predictions about the role of the stochastic fluctuations of the dissolution rate and to establish the boundaries for the dissolution profiles.

KEY WORDS: dissolution; stochastic model; mean dissolution time; heterogeneity.

INTRODUCTION

Quantitative studies on the dissolution process have been performed for more than a century, and they range from empirical descriptions based on statistical fitting of a generic mathematical function to the experimental data to detailed biophysical investigations. For a review of the importance of dissolution tests for pharmaceutical studies see Dressman *et al.* (2). The relationship between *in vivo* and *in vitro* results is discussed in detail in Dunne *et al.* (3). The standard theory of dissolution was developed as an extension of the Noyes-Whitney model (4), and it is based on the assumption of a constant proportionality of the dissolution rate to the concentration difference $[C_s - C(t)]$ between the solubility C_s and the concentration $C(t)$ of the substance in the dissolution medium at time t (5). This assumption implies that the time dependency of the dissolution has an exponential profile and other basic models are the cubic root, two-thirds-root, and the square root time equations (6).

The dissolution process can be empirically described by quantifying the fraction of drug dissolved up to time t, $\phi(t) = A(t)/D$, where A denotes the amount of drug dissolved up to time t and D is the dose. The function $\phi(t)$ is monotonously increasing from zero to an asymptote lower than or equal to one, and thus it can be seen as a cumulative distribution function of a random variable T called the dissolution time. Having the function $\phi(t)$, we can define the fractional (relative) dissolution rate, which under the condition of complete dissolution of the applied dose, takes form

$$k(t) = \frac{\frac{d\phi(t)}{dt}}{1 - \phi(t)} \tag{1}$$

and is the conditional probability that a randomly selected molecule transfers from the solid state into the solution during time interval $< t, t + dt)$ under the condition that the dissolution has not taken place before t. As stressed above, Eq. (1) implicitly assumes that all the applied amount of drug is ultimately dissolved. Under this condition T is a proper random variable, $[\phi(\infty) = 1]$. If all of the drug does not become dissolved in the course of dissolution $[A(\infty) < D]$, then $\phi(\infty) = A(\infty)/D < 1$ and the fractional dissolution rate is

$$k(t) = \frac{\frac{d\phi(t)}{dt}}{\frac{A(\infty)}{D} - \phi(t)} \tag{1a}$$

By modifying the function $k(t)$ in Eqs. (1) or (1a), namely considering its time dependency, new variants of the model can be derived (7,8). In this article we concentrate on the model given by Eq. (1); analogous extensions of Eq. (1a) are straightforward.

There is an obvious variability in experimentally observed dissolution data, even if all the conditions are kept identical. This variability appears not only due to the measurement errors but also due to the fluctuations of the physical characteristics of the dosage-units and temporal variability of the conditions under which the dissolution takes place. A detailed list of possible sources of the variability of the dissolution environment is presented by Elkoshi (9). The author, in an attempt to include these random factors into a model of dissolution, took a Weibull function as one of the most common descriptors of dissolution and randomly varied its parameters. This approach appears more suitable for characterizing different experimental conditions rather than an influence of the environmental changes within a single experimental trial. Recently, Macheras and Dokoumetzidis (8) showed how the Weibull dissolution profile can be obtained from the assumption that the fractional dissolution rate is not constant during the whole process of dissolution but is a power function of time. This dependency was introduced to mimic the temporal changes of parameters of the dissolution (reduction of the effective surface area, nonhomogenous hydrodynamic conditions, etc.).

A purpose of this article is to study the dissolution variability as it follows classic deterministic dissolution models and their generalizations. Our approach is based on the situations in which the function $k(t)$ appearing in Eq. (1) is in-

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fluenced by the heterogeneity of the dissolving substance (polydispersity of the particles) or influenced by stochastic factors during the process of dissolution. First, we briefly summarize the relevant results for standard models. Variability arising from the initial heterogeneity of the dissolving compound is then investigated. In this situation, the variability is present only at the onset of the dissolution when the parameters are fixed and does not evolve in time. In the third subsection, the effect of random temporal variability of the dissolution rate is studied. Methods for parametric inference of the models are compared.

THEORY AND RESULTS

Deterministic Model with Homogeneous Particles

The classical model is characterized by a constant dissolution rate, $k(t) = r > 0$. Then, under the assumption of complete dissolution, $\phi(\infty) = 1$, T has an exponential distribution of probability,

$$\phi(t) = 1 - exp(-rt) \tag{2}$$

implying that for the mean dissolution time (MDT), its variance, and the relative dispersion (coefficient of variation) holds $E(T) = 1/r$, $Var(T) = 1/r^2$, and $CV^2 = 1$. Solving Eq. (2) for unknown t and with the left-hand side equal to 1/2, the half-dissolution time, $t_{1/2}$ is determined, $t_{1/2} = ln(2)/r$. These are the main properties characterizing Eq. (1) under the constant fractional dissolution rate. If the applied dose of a drug does not dissolve completely, as reflected by Eq. (1a), the properties of the dissolution time remain valid but only conditionally for the fraction that is finally dissolved. So, instead of asymptote $\phi(\infty) = 1$ in Eq. (2), the dissolution curve has the asymptote $A(\infty)/D$.

In our recent article (7), we proposed an extension of the first-order model [Eq. (2)] assuming that the fractional dissolution rate is not constant but a function of $\phi(t)$, and consequently of time t, $k(t) = f[\phi(t)]$. The simplest specification of f which contains the exponential model as a limiting case is a linear function, $k(t) = r[1 - q\phi(t)]$, where q is the dose-solubility ratio, $q = D/\theta$, denoting the amount of drug in the medium that corresponds to solubility θ, and $r = k(0)$ is the initial fractional dissolution rate. This approach is analogous to the discrete-time model developed by Dokoumetzidis and Macheras (10) and by Valsami *et al.* (11) and can be considered as the continuous-time counterpart of their model. Substituting $k(t)$ into Eq. (1) we get the differential equation:

$$\frac{d\phi(t)}{dt} = r[1 - \phi(t)][1 - q\phi(t)], \phi(0) = 0 \tag{3}$$

which has the solution:

$$\phi(t) = \frac{exp[rt(1-q)] - 1}{exp[rt(1-q)] - q} \tag{4}$$

having two different asymptotes, $\phi(\infty) = 1$ for $q \leq 1$ and $\phi(\infty) = 1/q$ for $q > 1$. The characteristics (MDT, CV and $t_{1/2}$) of dissolution profile [Eq. (4)] can be found in (7).

Another way to generalize the first-order model, as well as its modification Eq. (3), is to consider time-dependency of the dissolution rate r. We assumed in (7) a specific form of the fractional rate to reflect low dissolution close to the time origin:

$$r(t) = r[1 - exp(-t/\tau)] \tag{5}$$

where $\tau > 0$ is a time constant characterizing the speed at which $r(t)$ achieves the constant level r. The form of $r(t)$ ensures that the initial slope of $\phi(t)$ is not so steep as in the models with constant r (5). Independent of our investigations, Macheras and Dokoumetzidis (8) used the fractional dissolution rate:

$$k(t) = rt^{-h}, h < 1 \tag{6}$$

which can be either decreasing or increasing the function of time in dependency on parameter h. From experimental data, both negative and positive values of h were estimated.

We may conclude that whatever form of the above models is selected, the variability of the particles (or media) is not directly taken into account. A unique constant or time-dependent dissolution rate are determined at the initial moment and fixed throughout all the course of dissolution.

Deterministic Model with Heterogeneous Particles (Model I)

Let us assume that the drug is composed of n types of components/particles characterized by different dissolution rates r_i, $i = 1, \ldots, n$. Then, using the simplest model [Eq. (1)] with a constant rate for the fractions $\phi_i(t)$, dissolved up to time t, we can write

$$\frac{d\phi_i(t)}{dt} = r_i[1 - \phi_i(t)], \phi_i(0) = 0, i = 1, \ldots, n \tag{7}$$

with solutions given for each i by Eq. (2). If the initial doses are D_i ($D = \Sigma_{i=1}^{n} D_i$), then it implies that for the amounts, $A_i(t)$, dissolved up to time t, it can be written

$$A_i(t) = D_i[1 - exp(-r_i t)], i = 1, \ldots, n \tag{8}$$

and thus, the total amount dissolved up to time t is

$$A(t) = \sum_{i=1}^{n} D_i[1 - exp(-r_i t)] \tag{9}$$

Therefore, for the fraction dissolved up to time t, $\phi(t) = A(t)/D$, holds

$$\phi(t) = \frac{1}{D}\sum_{i=1}^{n} D_i[1 - exp(-r_i t)] \tag{10}$$

The result given by Eq. (10) can be reinterpreted by taking into account that D_i/D reflects the probability that a randomly selected molecule of a drug comes from the group i, $p_i \approx D_i/D$, then:

$$\phi(t) = 1 - E[exp(-Rt)] \tag{11}$$

where R has multinomial distribution of probability, $Prob(R = r_i) = p_i$. Transition to any distribution of R, not only a discrete one, can be made by realizing that the proportions D_i/D represent the cumulative distribution function $F(r) \approx (1/D)\Sigma D_i$, where D_i are all sub doses with the rate constants lower or equal to r. Then, the general form, which is equivalent to Eq. (11) of the dissolution profile is

$$\phi(t) = 1 - \int_0^\infty exp(-rt)dF(r) \tag{12}$$

which means that ϕ is a complement to one of the Laplace-Stiltjes transformation of the distribution of R. The achieved results are illustrated below for several probability distributions of the rate constant R.

Examples

Figure 1 compares the dissolution profile given by Eq. (2) of a homogeneous drug with a dissolution profile given by Eq. (10) of a compound composed of two subpopulations. The mean dissolution rate of the heterogenous compound is the same as that of homogeneous drug (for details see text to the figure).

If R is exponentially distributed, $R \sim \lambda e^{-\lambda r}$ ($\lambda > 0$ is a constant, $E(R) = 1/\lambda$), then from Eq. (12) we have

$$\phi(t) = 1 - \int_0^\infty e^{-rt}\lambda e^{-\lambda r}dr = \frac{t}{\lambda + t} \tag{13}$$

and see Fig. 1 for comparison of $\phi(t)$ with that for the homogeneous drug. Following distribution [Eq. (13)], all of the drug is finally dissolved, $\phi(\infty) = 1$. The half-dissolution time is $t_{1/2} = \lambda = 1/E(R)$, however, MDT is infinity, and also the higher moments of Eq. (13) are infinite. Comparing, under the assumption $E(R) = r$, the half-dissolution time for model (13) with the half-dissolution time of the homogeneous drug, we can see that it is always in the ratio $1 : ln2$. How can the exponential distribution of R be interpreted? It means that the majority of drug molecules are characterized by low r (small r means large MDT) and this fact induces that $MDT = \infty$.

Model [Eq. (13)] can also be directly derived from Eq. (1) by assuming that $k(t) = 1/(\lambda + t)$, which is the time-dependent fractional dissolution rate. This is an example of how one can obtain formally identical models starting from very different assumptions. On one hand, it is time-dependent fractional dissolution rate, on the other hand it is time-constant dissolution rate, but the constants are different (random) for each molecule of the drug. This duality will also be shown in other situations.

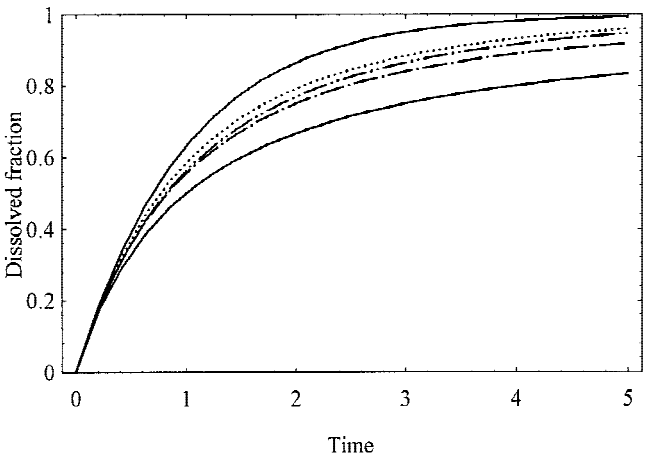

Fig. 1. The fraction of dissolved amount in dependency on time for different distributions of fractional dissolution rate R. The upper full line is for the deterministic model [Eq. (2)] with $r = 1$ (this can also be interpreted as delta distribution of R centered at 1), and the lower full line is for exponentially distributed dissolution rate [Eq. (13)] with mean rate $E(R) = 1$. The dotted curve is for a drug composed of two subcomponents [Eq. (10)], which are present at the same proportions ($D_1 = D_2$) with dissolution rates $r_1 = 0.5$ and $r_2 = 1.5$ (thus for the mean rate holds $E(R) = 1$). The dash-dot line [Eq. (14)] is for Erlang distribution of R, again with $E(R) = 1$ and $n = 2$, which implies $Var(R) = 1/2$. The dash-dot-dot line [Eq. (15)] is for inverse Gaussian distribution of R, again with $E(R) = 1$ and $Var(R) = 1/2$.

The most common generalization of the exponential distribution is the Erlang distribution, $R \sim \lambda^n r^{n-1}e^{-\lambda r}/(n-1)!$, ($\lambda > 0$ is a constant, $n \in N$), for which $E(R) = n/\lambda$. Now the dissolution profile is

$$\phi(t) = 1 - \left(\frac{\lambda}{\lambda + t}\right)^n \tag{14}$$

(see Fig. 1). We can calculate all the moments for Eq. (14), namely $E(T) = \lambda/(n-1)$, for $n \geq 2$], for $n \geq 3$. Thus $CV^2 = n/(n-2)$, which tends to one as n increases and distribution (14) gets closer and closer to the exponential one. The half-dissolution time is $t_{1/2} = \left\{\lambda\left(1 - \sqrt[n]{1/2}\right)\right\}/\sqrt[n]{1/2}$, which can be related to the mean of R. The results are analogous for Gamma distribution which is characterized by non-integer parameter n. Again, we can ask the question what form of the fractional dissolution rate would imply this dissolution profile. Using formula (14) in Eq. (1), we get $k(t) = n/(\lambda + t)$.

For the inverse Gaussian distribution of the fractional rate constant, $R \sim \sqrt{\kappa/2\pi}r^{-3/2}exp\left[-\kappa(r-\mu)/2\mu^2 r\right]$, for which $E(R) = \mu$, we have

$$\phi(t) = 1 - exp\left[\frac{\kappa}{\mu}\left(1 - \sqrt{\frac{2\mu^2 t}{\kappa} + 1}\right)\right] \tag{15}$$

We can see from Fig. 1 that for R, either with Erlang or inverse Gaussian distribution (with the same means and variances), the dissolution profiles are rather close. One can expect such a result taking into account similarity of these two distributions (12). To calculate $t_{1/2}$ for dissolution profile [Eq. (15)] is an easy task, however, the moments are difficult to obtain.

R is uniformly distributed in an interval (a,b), $R \sim 1/(b-a)$, $(b > a > 0)$ for which $E(R) = (b+a)/2$, ϕ yields

$$\phi(t) = 1 - \frac{e^{-at} - e^{-bt}}{t(b-a)} \tag{16}$$

Obviously, with a decreasing range of R, $(b-a) \to 0$, while centered around r, $\phi(t)$ converges to $1 - e^{-rt}$ as given by Eq. (2). For Eq. (16) calculation of $t_{1/2}$ and of the moments is a tractable task. The uniform distribution of R would reflect equal proportions of all subpopulations in the compound.

A natural question arises whether we can decide which dissolution is faster, the homogenous drug with a fixed fractional rate r or the nonhomogeneous one if the mean rate is the same, $E(R) = r$. This question is meant not only in average or in the half-dissolution time but along all the dissolution process. In the context of the above example with an exponential distribution of R, we are interested in the relationship between $1 - \lambda/(\lambda + t)$ and $1 - exp(-t/\lambda)$ (see Fig. 1). In general, the function $g(r) = exp(-rt)$ is convex and by using *Jensen's inequality* (e.g., 13, p. 120) we can prove that for any t:

$$1 - E[exp(-Rt)] \leq 1 - exp[-E(R)t] \tag{17}$$

which permits us to conclude: The dissolution of a homogeneous substance is always faster than that of nonhomogeneous compound for which the mean rate is the same as the rate of the homogeneous one.

In the same way as for the simple exponential model, we can propose an analogous generalization for Eq. (3). Then, the system of Eqs. (7) is replaced by equations:

$$\frac{d\phi_i(t)}{dt} = r_i[1 - q\phi(t)][1 - \phi_i(t)], \phi_i(0) = 0, i = 1, \ldots, n, \quad (18)$$

where $\phi(t) = (1/D) \Sigma_{i=1}^{n} D_i \phi_i(t)$. Equation (18) can be derived in an analogous way to model (3), see (7). The intuitive reason for the term $[1 - q\phi(t)]$ in model (18) follows from the fact that the dissolved drug forms identical complexes with water irrespectively from which component/particle it comes. Whereas Eqs. (7) are mutually independent and thus the system is easily tractable, there is a common term in Eqs. (18) which is influenced by all the components and thus we are not able to find an analytical solution. Therefore, further analyses of Eqs. (18) are restricted to the numerical methods only.

Identifying parameters of the models is crucial for verification and applications. Obviously, the main parameter in the dissolution models is the rate constant *r,* and we further focus our attention on it. Any parameter in a deterministic model can be sensibly estimated from time series data only by embedding the model in a statistical framework. It is usually performed by assuming that instead of exact measurements on ϕ, we have these values blurred by observation errors which are independent and normally distributed. The parameter r in the deterministic dissolution Eqs. (2) or (4) is estimated by linear [after log transformation in Eq. (2)], or nonlinear least squares method with observation on concentration of dissolved drug, $C(t)$, further transformed into $\phi(t)$ and serving as "dependent variable".

Let us point out the meaning of estimation in the models with heterogenous particles. The situation is qualitatively different from that described by Eq. (2) because the constant r has been replaced by a random variable R. Now, by fitting the curve $\phi(t)$ to the observed data we obtain estimates of the parameters of the distribution of R. In the simple example given by Eq. (13), where we assumed the exponential distribution of R, the estimate of λ is calculated, and we know that it is the inverse value of the mean of R. The same procedure can be applied in all of the Eqs. (13)–(16) and their modifications.

Stochastic Model with Homogeneous Particles (Model II)

The heterogeneity of the drug has been reflected in the model introduced above by the fact that the rate constants are different for different particles and thus, from the population point of view, it is a random variable. After determining the rate constants at the beginning of the dissolution process, the dissolution itself behaves in the deterministic manner. However, one can also expect that the rate constant varies in time, not only deterministically as mentioned before, but in a random way due to the unspecified fluctuations (e.g., heterogenous properties of dissolution media or of the substance). In such a case, the rate becomes a stochastic process and consequently also the fraction dissolved up to time t is a random process; to distinguish between stochastic and deterministic dissolutions, the symbol ϕ is further replaced by Φ. If the changes of the rate are smooth and without any dominant component, it can be represented by equation:

$$R(t) = r + \sigma\xi(t) \quad (19)$$

where $\xi(t)$ is the Gaussian white noise (a formal derivative of the Brownian motion $dB(t)/dt$, sometimes also called Wiener process), $\sigma > 0$ is its amplitude and $r > 0$ is the deterministic part of the noisy dissolution rate. Now, the constant r is only the mean of R, $E[R(t)] = r$. For physical reasons we should require condition $R(t) \geq 0$, however, it would mean a formal restriction and consequently decreased tractability of the model. Therefore, we continue to control positivity of $R(t)$ only through the amplitude of noise.

Considering the basic exponential model with complete dissolution and under Eq. (19), we can write it in the form of a stochastic differential equation:

$$d\Phi(t) = r[1 - \Phi(t)]dt + \sigma\xi(t)[1 - \Phi(t)]dB(t), \Phi(0) = 0 \quad (20)$$

which in Ito-sense has solution (14):

$$\Phi(t) = 1 - exp\left[-\left(r + \frac{1}{2}\sigma^2\right)t - \sigma B(t)\right] \quad (21)$$

which is know as the geometric Brownian motion. Now, when the dissolution profile is a random process only its statistical properties can be analyzed. However, formulation of the model via a stochastic differential equation permits us to perform Monte-Carlo experiments with it [for details on simulation of biological diffusion see (15)]. The discretized version of Eq. (20) with the time step Δ and notation $\Phi_j = \Phi(j\Delta)$ is

$$\Phi_{j+1} = \Phi_j + r(1 - \Phi_j)\Delta + \sigma n_j \sqrt{\Delta}(1 - \Phi_j), \Phi_0 = 0 \quad (22)$$

where $n_j \sim N(0,1)$ are independent realizations of standard Gaussian random variable. Trajectories of the process [Eq.(21)] are illustrated in Fig. 2 for different values of σ. It is apparent that with increasing noise, locally negative values of the dissolution rate appears and the model would require further modification.

Using Eq. (21), the moments of the random function Φ can be calculated. We can show (16) that as expected

$$E[\Phi(t)] = 1 - exp(-rt) \quad (23)$$

which means that the mean of the dissolution process behaves as deterministic [Eq. (2)] and for the variance of the dissolved fraction holds

$$Var[\Phi(t)] = [exp(\sigma^2 t) - 1]exp(-2rt) \quad (24)$$

It follows from Eq. (23) that $E[\Phi(\infty)] = 1$, so the drug is ultimately dissolved, but only as the mean of the dissolution curves is concerned. To prove that the complete dissolution arises with probability one, we have to show that $Var[\Phi(\infty)] = 0$ holds. As it follows from Eq. (24), this is true only for $2r \geq \sigma^2$ and otherwise $Var[\Phi(\infty)] = \infty$ and this result has an intuitive interpretation. If the amplitude of the noise σ is too large with respect to the mean dissolution rate constant r, then the stochastic rate [Eq. (19)] often achieves negative values; and this is responsible for infinite dispersion of Φ. Therefore only relatively small fluctuations of r are practically acceptable but even under this condition a temporal negativity of $R(t)$ can arise.

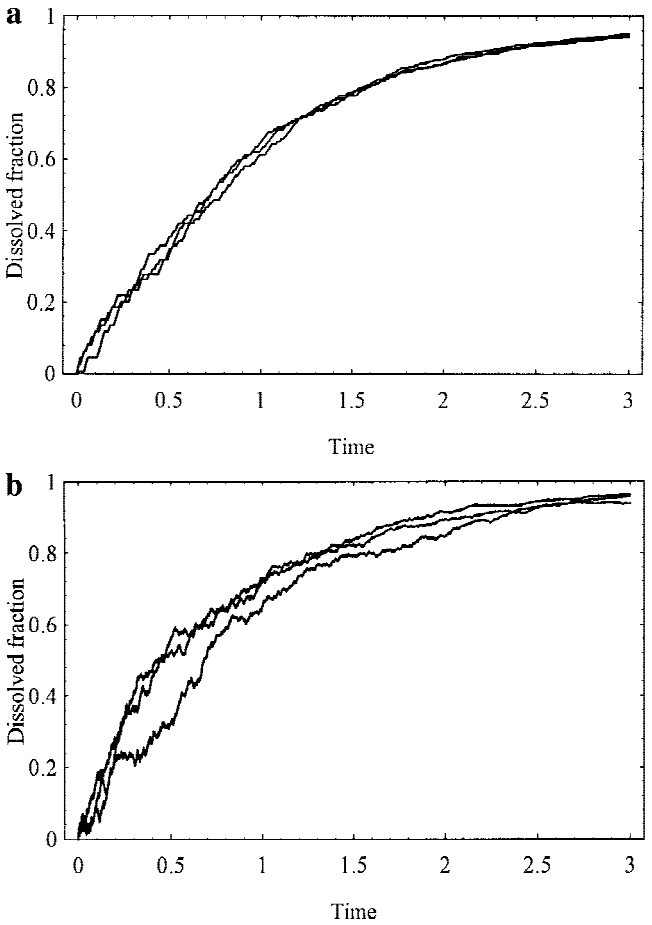

Fig. 2. Profiles of the fraction of the dissolved amount in dependency on time for stochastic model [Eq. (21)] with parameter $r = 1$ and different variability of the dissolution rate (a) $\sigma = 0.1$, and (b) $\sigma = 0.2$ where locally negative profiles of the dissolution arises.

Having at disposal variance [Eq. (24)] of the dissolved fraction we can plot a confidence region in which most of the trajectories of $\Phi(t)$ can be expected, $E[\Phi(t)] \pm 2\sqrt{Var[\Phi(t)]}$, (Fig. 3). Further, from Eq. (23) we can estimate the half-dissolution time of the mean trajectory by solving it for unknown t and with the right-hand-side equal to 1/2. We obtain the formula for the exponential model and by solving analogous equations for $E[\Phi(t)] \pm 2\sqrt{Var[\Phi(t)]}$ the boundaries for $t_{1/2}$ can be determined (see text to Fig. 3). Under the condition $2r \geq \sigma^2$ and using Eq. (24), we can determine the time instant of maximum variance:

$$t_m = \frac{1}{\sigma^2} ln\left(\frac{2r}{2r-\sigma^2}\right) \tag{25}$$

The random fluctuation of the dissolution constant as described by Eq. (19) can also be introduced in models with nonconstant r. For Eq. (3) this stochastic variation yields

$$d\Phi(t) = r[1-\Phi(t)][1-q\Phi(t)]dt + \sigma\xi(t)[1-\Phi(t)] \\ [1-q\Phi(t)]dB(t) \tag{26}$$

with initial condition $\Phi(0) = 0$. Solution of this stochastic differential equation is

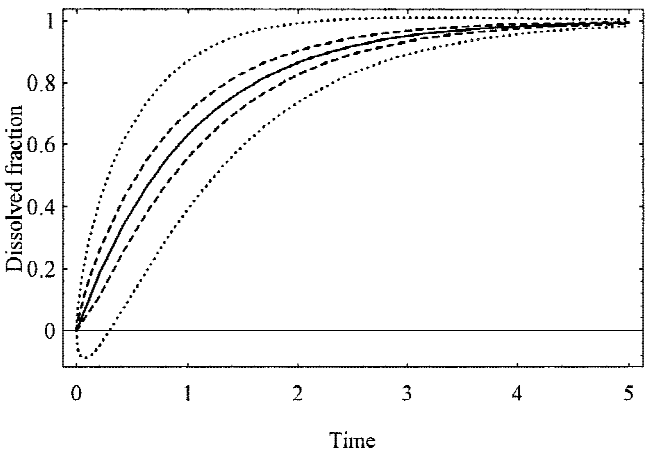

Fig. 3. Mean of $\Phi(t)$ given by Eq. (23) together with confidence region calculated from Eq. (24) are plotted against time. The full line is the mean calculated for $r = 1$, the dashed lines gives the confidence region calculated for $\sigma^2 = 0.01$, the dotted lines were calculated by using $\sigma^2 = 0.1$. The half-dissolution time for the deterministic model (full line) is 0.69, the ranges calculated for the confidence regions are (0.53, 0.86) for $\sigma^2 = 0.01$ and (0.28, 1.24) for $\sigma^2 = 0.1$.

$$\Phi(t) = 1 - \frac{exp\left[\left(r(q-1) - \frac{1}{2}\sigma^2\right)t - \sigma B(t)\right]}{1 + qr\int_0^t exp\left[\left(r(q-1) - \frac{1}{2}\sigma^2\right)s - \sigma B(s)\right]ds} \tag{27}$$

which for $\sigma \to 0$ tends to the solution given by Eq. (4). Unfortunately, Eq. (27) does not help to calculate the moments of $\Phi(t)$.

The regression method, which is used for the deterministic exponential model blurred by measurement errors, does not lead to a good estimate of the parameter r of model (26) because it is based on the assumptions of normality and independence, which are not valid here. Variability of the rate does not result in the same type of error as measurement variability. Therefore a different method should be devised. The maximum likelihood estimate of r based on a continuous observation of the process Φ given Eq. (20) in the time $(0,T)$ is

$$\hat{r} = \frac{1}{T}\int_0^T \frac{d\Phi(t)}{1-\Phi(t)} \tag{28}$$

(e.g., 17). Of course, for $\sigma \to 0$, substituting the exponential model into Eq. (28), we have $\hat{r} = r$. Eq. (28) can be transformed into a form suitable for discrete time observations obtained at instances $t_1, \ldots, t_n$, as available in the dissolution experiments:

$$\hat{r} = \frac{1}{T}\sum_{j=1}^{n-1} \frac{\Phi(t_{j+1}) - \Phi(t_j)}{1-\Phi(t_j)} \tag{29}$$

The statistical properties of the estimate $\hat{r}$ are well known (e.g., 17). Formula (29) can be compared with the results obtained by linear regression used on transformed Eq. (2). For example, for computerized experiments presented in Fig. 2a., the estimates of r obtained by formula (29) are 0.99 (0.94), 1.02 (0.99), and 1.00 (0.97) where the numbers in parentheses are the estimates obtained from regression. We used the

simulated values Φ_j obtained from Eq. (22) instead of the observed values $\Phi(t_j)$, assuming equidistant sampling step Δ, $t_j = j\Delta$. The estimates of the parameters of the model given by Eq. (26) can be derived analogously to the above procedure.

DISCUSSION

We have shown that heterogeneity of the particles, which is reflected by variation of the dissolution rate constant *r,* induces that dissolution profiles can be described by a wide class of functions. For example, Bohner *et. al.* (1) successfully fit the dissolution curve of β-Tricalcium phosphate powder by $y(t) = t/(a + bt)$. The authors claim that the equation has been used to estimate the initial dissolution rate ($= 1/a$) and not to provide a mechanistic description of dissolution. Model [Eq. (13)] derived from the heterogeneity assumptions results in the same form at the time origin and if model (1a) is employed, we have exactly the same curve as the model prediction. Of course, as mentioned before, specific form of time dependency of $k(t)$ in Eq. (1) gives the same result. To solve this duality problem whether variability of k in time or variability of r at the initial moment is responsible for the effect cannot be successfully answered theoretically but only from experiments. On the other hand, Eq. (12) permits us to solve an inverse problem—what distribution of the rate constant R corresponds to the observed dissolution profile ϕ.

The conjecture arising from the assumption about the heterogeneity of the particles predicts the slower dissolution of nonhomogeneous compounds. As it follows from Fig. 1, this result is not so striking as the difference of *MDTs* which under some conditions can be even infinitely large. The question that remains open is to decide which distribution of R is realistic and under which conditions. In addition, the same development can be applied to more detailed models as, for example, those which consider the geometrical properties of the particles (6). In this way, heterogeneity of the particles would be introduced into models that take into account the difference between surface and volume dissolution and other specific biophysical characteristics. We should note that our approach to the dissolution of heterogeneous particles if formally analogous to the method used by Gross *et al.* (18) and Donbrow *et al.* (19) in describing the kinetics of the release of material from populations of microcapsules.

The stochastic variation of the fractional dissolution rate can also be interpreted in the context of articles (8) and (9). To get the Weibull dissolution profile from Eq. (1), it is sufficient to assume that $k(t) = a\beta t^{\beta-1}$ [see Eq. (6)]. As mentioned, the variability of conditions can be reflected by statistical variation of the constants appearing in the model as well as by their time dependency. However, both approaches lead to different interpretations and predictions. In particular, the deterministic model always predicts the same dissolution profile with measurement error being the only source of variability, whereas the stochastic approach has variability as its intrinsic property. Under this scenario there is no unique dissolution profile (for examples see Fig. 2), but their families have some probabilistic properties. As mentioned, stochastic variation of the rate constant may result in locally nonmonotonous dissolution profiles (Fig. 2b). See Valsami *et al.* (11) for treatment of this type of experimental data by a stochastic model with discrete time step.

The intrinsic variability of the rate reflected by stochasticity of the dissolution profile implies that the random variable T cannot be defined as it was done in the case of ϕ, even the term half-dissolution time loses its sense and only the boundaries for such a quantity can be determined. In Fig. 3 we presented regions in which the realizations of the dissolution profile will be confined with a prescribed probability, but it does not mean that a single realization could not be completely or partly outside such a region. As given by Eqs. (24) and (25), the maximum of the dissolution variance is reached at the middle of the profiles and this result corresponds to the cases presented in (9, Figs. 2 and 3).

Presenting dissolution as a stochastic process has substantial advantages. First of all, it is more realistic because one can expect that even under identical physical and chemical conditions the dissolution profiles will not be the same as predicted by deterministic models. Further, this approach offers new and probably more efficient methods for parametric inference based on the experimental data compared to the classical regression methods.

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REFERENCES

1. M. Bohner, J. Lemaître, and T. A. Ring. Kinetics of dissolution of β-Tricalcium phosphate. *J. Colloid Interface Sci.* **190**:37–48 (1997).
2. J. B. Dressman, G. L. Amidon, C. Reppas, and V. P. Shah. Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms. *Pharm. Res.* **15**:11–22 (1998).
3. A. Dunne, T. O'Hara, and J. Devane. A new approach to modelling the relationship between *in Vivo* and *in Vitro* drug dissolution/absorption. *Stat. Med.* **18**:1865–1876 (1999).
4. A. A. Noyes and W. R. Whitney. Über die Auflösungsgeschwindigkeit von festen Soffen in ihren eigenen Lösungen. *Z. Physik. Chemie* **13**:689–692 (1897).
5. P. Macheras, C. Reppas, and J. B. Dressman. *Biopharmaceutics of Orally Administered Drugs.* Ellis Horwood, London, 1995.
6. J. Wang and D. R. Flangan. General solution for diffusion-controlled dissolution of spherical particles. 1. Theory. *J. Pharm. Sci.* **88**:731–738 (1999).
7. P. Lánský and M. Weiss. Does the Dose-Solubility Ratio Affect the Mean Dissolution Time of Drugs? *Pharm. Res.* **16**:1472–1478 (1999).
8. P. Macheras and A. Dokoumetzidis. On the heterogeneity of drug dissolution and release. *Pharm. Res.* **17**:108–112 (2000).
9. Z. Elkoshi. On the variability of dissolution data. *Pharm. Res.* **14**:135–1362 (1997).
10. A. Dokoumetzidis and P. Macheras. A population growth model of dissolution. *Pharm. Res.* **14**:1122–1126 (1997).
11. G. Valsami, A. Dokoumetzidis, and P. Macheras. Modeling supersaturated dissolution data. *Int. J. Pharm.* **181**:153–157 (1999).
12. C. E. Smith, P. Lánský, and T.-H. Lung. Cycle-time and residence-time density approximations in a stochastic model for circulatory transport. *Bull. Math. Biol.* **59**:1–22 (1997).
13. C. R. Rao. *Linear Statistical Inference and its Applications,* Willey, New York, 1965.
14. L. M. Ricciardi. *Diffusion Processes and Related Topics in Biology,* Springer, Berlin, 1977.

15. H. C. Tuckwell and P. Lánský. On the simulation of biological diffusion processes. *Comp. Biol. Med.* **27**:1–7 (1997).
16. B. Øksendal. *Stochastic Differential Equations,* Springer, Berlin, 1998.
17. B. L. S. Prakasa Rao. *Statistical Inference for Diffusion Type Processes,* Arnold, London, 1999.
18. S. T. Gross, A. Hoffman, M. Donbrow, and S. Benita. Fundamentals of release mechanisms interpretation in multiparticulate systems: the prediction of the commonly observed release equations from statistical population models for particle ensembles. *Int. J. Pharm.* **29**:213–222 (1986).
19. M. Donbrow, A. Hoffman, and S. Benita. Variation of poluation release kinetics in polydisperse multiparticulate systems (microcapsules, microspheres, droplets, cells) with heterogeneity of one, two or three parameters in the population of individuals. *J. Pharm. Pharmacol.* **40**:93–96 (1988).