

Chapter 5

Drug Dissolution

The rate at which a solid substance dissolves in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution.

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The basic step in drug dissolution is the reaction of the solid drug with the fluid and/or the components of the dissolution medium. This reaction takes place at the solid–liquid interface and therefore dissolution kinetics are dependent on three factors, namely the flow rate of the dissolution medium toward the solid–liquid interface, the reaction rate at the interface, and the molecular diffusion of the dissolved drug molecules from the interface toward the bulk solution, Figure 5.1. As we stated in Section 2.4.2, a process (dissolution in our case) can be either diffusion or reaction-limited depending on which is the slower step. The relative importance of interfacial reaction and molecular diffusion (steps 2 and 3 in Figure 5.1, respectively) can vary depending on the hydrodynamic conditions prevailing in the microenvironment of the solid. This is so since both elementary steps 2 and 3 in Figure 5.1 are heavily dependent on the agitation conditions. For example, diffusion phenomena become negligible when externally applied intense agitation in in vitro dissolution systems gives rise to forced convection. Besides, the reactions at the interface (step 2) and drug diffusion (step 3) in Figure 5.1 are dependent on the composition of the dissolution medium. Again, the relative importance can vary according to the drug properties and the specific composition of the medium. It is conceivable that our limited knowledge of the hydrodynamics under in vivo conditions and the complex and position- and time-dependent composition of the gastrointestinal fluids complicates the study of dissolution phenomena in particular when one attempts to develop in vitro–in vivo correlations.

Early studies in this field of research formulated two main models for the interpretation of the dissolution mechanism: the diffusion layer model and the interfacial barrier model. Both models assume that there is a stagnant liquid layer in contact with the solid, Figure 5.2. According to the diffusion layer model (Figure 5.2A), the step that limits the rate at which the dissolution process occurs

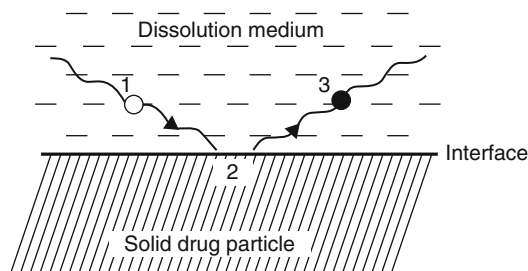


Fig. 5.1 The basic steps in the drug dissolution mechanism. (1) The molecules (\circ) of solvent and/or the components of the dissolution medium are moving toward the interface; (2) adsorption–reaction takes place at the liquid–solid interface; (3) the dissolved drug molecules (\bullet) move toward the bulk solution

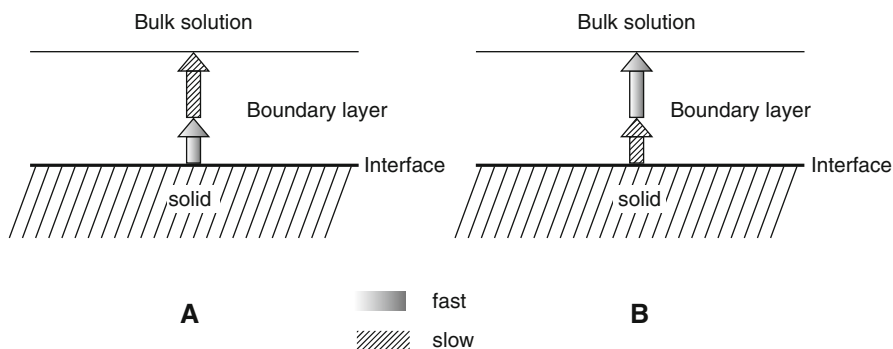


Fig. 5.2 Schematic representation of the dissolution mechanisms according to: (A) the diffusion layer model and (B) the interfacial barrier model

is the rate of diffusion of the dissolved drug molecules through the stagnant liquid layer rather than the reaction at the solid–liquid interface. For the interfacial barrier model (Figure 5.2B), the rate-limiting step of the dissolution process is the initial transfer of drug from the solid phase to the solution, i.e., the reaction at the solid–liquid interface.

Although the diffusion layer model is the most commonly used, various alterations have been proposed. The current views of the diffusion layer model are based on the so-called *effective diffusion boundary layer*, the structure of which is heavily dependent on the hydrodynamic conditions. In this context, Levich [104] developed the convection–diffusion theory and showed that the transfer of the solid to the solution is controlled by a combination of liquid flow and diffusion. In other words, both diffusion and convection contribute to the transfer of drug from the solid surface into the bulk solution. It should be emphasized that this observation applies even under moderate conditions of stirring.

5.1 The Diffusion Layer Model

Noyes and Whitney published [105] in 1897 the first quantitative study of a dissolution process. Using water as a dissolution medium, they rotated cylinders of benzoic acid and lead chloride and analyzed the resulting solutions at various time points. They found that the rate $\dot{c}(t)$ of change of concentration $c(t)$ of dissolved species was proportional to the difference between the saturation solubility c_s of the species and the concentration existing at any time t . Using k as a proportionality constant, this can be expressed as

$$\dot{c}(t) = k [c_s - c(t)] \quad c(0) = 0. \quad (5.1)$$

Although it was not stated in the original article of Noyes and Whitney, it should be pointed out that the validity of the previous equation relies on the assumption that the amount used, q_0 , is greater than or equal to the amount required to saturate the dissolution medium, q_s . Later on, (5.1) was modified [104, 106] and expressed in terms of the dissolved amount of drug $q(t)$ at time t while the effective surface area \mathcal{A} of the solid was taken into account:

$$\dot{q}(t) = \frac{\mathcal{D}\mathcal{A}}{\delta} \left[c_s - \frac{q(t)}{V} \right] \quad q(0) = 0, \quad (5.2)$$

where \mathcal{D} is the diffusion coefficient of the substance, δ is the effective diffusion boundary layer thickness adjacent to the dissolving surface, and V is the volume of the dissolution medium. In this case, the first-order rate constant k (dimension of time^{-1}) appearing in (5.1) and governing the dissolution process is

$$k = \frac{\mathcal{D}\mathcal{A}}{\delta V}. \quad (5.3)$$

The integrated form of (5.2) gives the cumulative mass dissolved at time t :

$$q(t) = c_s V [1 - \exp(-kt)]. \quad (5.4)$$

The limit $t \rightarrow \infty$ defines the total drug amount, $q_s = c_s V$, that could be eventually dissolved in the volume V assuming that the amount used q_0 is greater than q_s . Thus, we can define the accumulated fraction of the drug in solution at time t as the ratio $q(t)/q_s$. Equation (5.4) expressed in terms of concentration ($c(t) = q(t)/V$) leads to the most useful form for practical purposes:

$$c(t) = c_s [1 - \exp(-kt)]. \quad (5.5)$$

Equation (5.5) is the classical equation quoted in textbooks indicating the exponential increase of concentration $c(t)$ approaching asymptotically the saturation solubility c_s .

Also, (5.1) indicates that initially ($t \rightarrow 0$) when $c(t)$ is small ($c(t) \leq 0.15c_s$) in comparison to c_s :

$$\dot{c}(t) \Big|_{t \rightarrow 0} = kc_s.$$

If this applies then we consider that sink conditions exist. Under sink conditions the concentration $c(t)$ increases linearly with time,

$$c(t) = kc_s t \quad t \rightarrow 0, \quad (5.6)$$

and the dissolution rate is proportional to saturation solubility:

$$\dot{q}(t) \Big|_{t \rightarrow 0} = Vkc_s.$$

5.1.1 Alternative Classical Dissolution Relationships

The aforementioned analysis demonstrates that these classical concepts are in full agreement with Fick's first law of diffusion and the equivalent expressions in Sections 2.3 and 2.4. However, there are obvious deficiencies of the classical description of dissolution since the validity of (5.3) presupposes that all terms in this equation remain constant throughout the dissolution process. For example, the drug surface area \mathcal{A} of powders and immediate release formulations is decreasing as dissolution proceeds. In fact, a dramatic reduction of the surface area takes place whenever the dose is not used in large excess, i.e., the drug mass divided by product of the volume of the dissolution medium and the drug's solubility is less than 10. This problem has been realized over the years and equations that take into account the diminution of the surface area have been published. For example, Hixson and Crowell [107] developed the following equation, which is usually called the *cube-root law*, assuming that dissolution occurs from spherical particles with a mono-disperse size distribution under sink conditions:

$$q_0^{1/3} - [q(t)]^{1/3} = k_{1/3}t, \quad (5.7)$$

where q_0 and $q(t)$ are the initial drug amount and the drug amount at time t after the beginning of the process, respectively, and $k_{1/3}$ is a composite cube-root rate constant. Alternatively, when sink conditions do not apply, the following equation (usually called the law of 2/3) can be used:

$$[q(t)]^{-2/3} - q_0^{-2/3} = k_{2/3}t, \quad (5.8)$$

where $k_{2/3}$ is a composite rate constant for the law of 2/3.

Although these approaches demonstrate the important role of the drug material's surface and its morphology on dictating the dissolution profile, they still suffer from limitations regarding the shape and size distribution of particles as well as the assumptions on the constancy of the diffusion layer thickness δ and the drug's diffusivity \mathcal{D} throughout the process implied in (5.5), (5.6), (5.7), and (5.8). In reality, the parameters δ and \mathcal{D} cannot be considered constant during the entire course of the dissolution process when poly-disperse powders are used and/or an initial phase of poor deaggregation of granules or poor wetting of formulation is encountered. In addition, the diffusion layer thickness appears to depend on particle size. For all aforementioned reasons, (5.5), (5.6), (5.7), and (5.8) have been proven adequate in modeling dissolution data only when the presuppositions of constancy of terms in (5.3) are fulfilled.

5.1.2 Fractal Considerations in Drug Dissolution

Drug particles are classically represented as ideal smooth spheres when dissolution phenomena are considered. The surface area of a spherical smooth object is a multiple of the scale, e.g., cm^2 , and has a topological dimension $d_t = 2$. If one knows the radius ρ , the surface area of the sphere is $4\pi\rho^2$. However, many studies indicate that the surfaces of most materials are fractal [108]. The measured surface areas of irregular and rough surfaces increase with decreasing scale according to the specific surface structure. These surfaces have fractal dimensions d_f lying between the topological and the embedding dimensions: $2 < d_f < 3$.

Since the surface area of solids in dissolution studies is of primary importance, the roughness of the drug particles has been the subject of many studies. For example, Li and Park [109] used atomic force microscopy to determine the fractal properties of pharmaceutical particles. Moreover, analysis of the surface ruggedness of drugs, granular solids, and excipients using fractal geometry principles has been applied extensively [110–113]. Most of these studies underline the importance of surface ruggedness on dissolution. It is also interesting to note that considerations of the surface roughness are not restricted to the macroscopic level. The same concepts can also be applied to microscopic levels. A typical example is the importance of the surface roughness of proteins in binding phenomena [114].

Farin and Avnir [115] were the first to use fractal geometry to determine effects of surface morphology on drug dissolution. This was accomplished by the use of the concept of fractal reaction dimension d_r [116], which is basically the effective fractal dimension of the solid particle toward a reaction (dissolution in this case). Thus, (5.7) and (5.8) were modified [115] to include surface roughness effects on the dissolution rate of drugs for the entire time course of dissolution (5.9) and under sink conditions (5.10):

$$[q(t)]^{-\alpha} - q_0^{-\alpha} = \alpha k_{1/3}^* t, \quad (5.9)$$

$$q_0^{1-\alpha} - [q(t)]^{1-\alpha} = q_s (1 - \alpha) k_{1/3}^* t, \quad (5.10)$$

where $\alpha = d_r/3$ and q_s is the drug amount that could be dissolved in the volume of the dissolution medium and $k_{1/3}^*$ is the dissolution rate constant of the modified cube-root. Although the previous equations describe quantitatively the dissolution of solids with fractal surfaces, their application presupposes that the value of d_r is known.

According to the classical scaling laws, an estimate of d_r can be obtained from the slope of a log–log plot of the initial rate of dissolution $\dot{q}(t)\Big|_{t \rightarrow 0}$ vs. the radius ρ of the various particle sizes. This kind of calculation relies on the fundamental proportionality

$$\dot{q}(t)\Big|_{t \rightarrow 0} \propto \mathcal{A} \propto \rho^{d_r-3},$$

where \mathcal{A} is the effective surface area; the slope of $\log \dot{q}(t)\Big|_{t \rightarrow 0}$ vs. $\log \rho$ corresponds to $d_r - 3$, in agreement with the relationship for measurements regarding areas in Section 1.4.2. However, this approach for the calculation of d_r requires the execution of a number of experiments with a variety of particles of well-defined size and shape characteristics, which can also exhibit different d_r values.

For the aforementioned reasons, a simpler method requiring only a dissolution run with particles of a given size has been proposed for the estimation of d_r [117]. As can be seen from (5.9) and (5.10), on plotting the values of the left-hand side against time t , one can obtain the value of $k_{1/3}^*$ from the slope of the straight line. In practice, this involves choosing a starting value for d_r , e.g., 2, and, using an iterative method, searching for the linearity demanded by the previous equations for the experimental data pairs $(q(t), t)$. When this has been found, one knows values both for $k_{1/3}^*$ and d_r .

5.1.3 On the Use of the Weibull Function in Dissolution

In 1951, Weibull [118] described a more general function that can be applied to all common types of dissolution curves. This function was introduced in the pharmaceutical field by Langenbucher in 1972 [119] to describe the accumulated fraction of the drug in solution at time t , and it has the following form:¹

$$\frac{q(t)}{q_\infty} = 1 - \exp[-(\lambda t)^\mu], \quad (5.11)$$

¹In the pharmaceutical literature the exponential in the Weibull function is written as $\exp(-\lambda t^\mu)$ and therefore λ has dimension $\text{time}^{-\mu}$. In the version used herein (equation 5.11), the dimension of λ is time^{-1} .

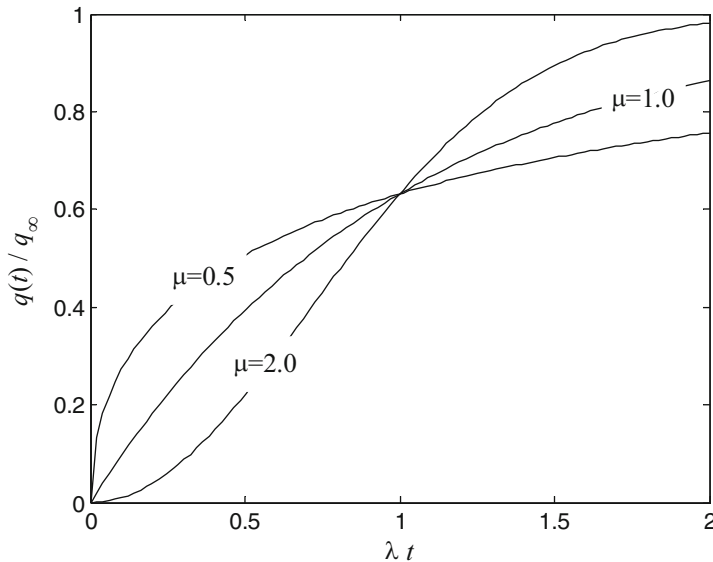


Fig. 5.3 Accumulated fraction of drug dissolved, $q(t)/q_\infty$ as a function of λt according to the Weibull distribution function (5.11)

where q_∞ is the total mass that can be eventually dissolved and λ , μ are constants. The *scale parameter* λ defines the time scale of the process, while the *shape parameter* μ characterizes the shape of the curve, which can be exponential ($\mu = 1$), S-shaped ($\mu > 1$), or exponential with a steeper initial slope ($\mu < 1$), Figure 5.3.

It is also worthy of mention that a gamma distribution function proposed by Djordjevic [120] for modeling in vitro dissolution profiles implies a relevant type of time dependency for the amount of drug dissolved.

The successful use of the Weibull function in modeling the dissolution profiles raises a plausible query: What is the rationale of its success? The answer will be sought in the relevance of the Weibull distribution to the kinetics prevailing during the dissolution process.

The basic theory of chemical kinetics originates in the work of Smoluchowski [121] at the turn of the twentieth century. He showed that for homogeneous reactions in three-dimensional systems the rate constant is proportional to the diffusion coefficient. In dissolution studies this proportionality is expressed with $k \propto \mathcal{D}$, where k is the intrinsic dissolution rate constant. In addition, both \mathcal{D} and k are time-independent in well-stirred, homogeneous systems. However, that is not true for lower dimensions and disordered systems in chemical kinetics. Similarly, homogeneous conditions may not prevail during the entire course of the dissolution process in the effective diffusion boundary layer adjacent to the dissolving surface. It is very difficult to conceive that the geometric and hydrodynamic characteristics of this layer are maintained constant during the entire course of drug dissolution.

Accordingly, the drug's diffusional properties change with time and the validity of use of a classical rate constant k in (5.1) is questionable. It stands to reason that an instantaneous yet time-dependent rate coefficient $k(t)$ governing dissolution under inhomogeneous conditions can be written as

$$k(t) = k_o \left(\frac{t}{t_o} \right)^{-\gamma} \quad \text{with} \quad t \neq 0, \quad (5.12)$$

where k_o is a rate constant not dependent on time, t_o is a time scale parameter, and γ is a pure number. In a simpler form ($t_o = 1$), the previous relation is used in chemical kinetics to describe phenomena that take place under dimensional constraints or under stirred conditions [17]. It is used here to describe the time dependency of the dissolution rate "constant" that originates from the change of the parameters involved in (5.3) during the dissolution process, i.e., the reduction of the effective surface area \mathcal{A} and/or the inhomogeneous hydrodynamic conditions affecting δ and subsequently \mathcal{D} .

Using (5.12) to replace k in (5.1), also changing the concentration variables to amounts $Vc(t) = q(t)$, $Vdc(t) = dq(t)$, and using, instead of $c_s V = q_s$, for generality purposes $c_\infty V = q_\infty$ (which applies to both $q_\infty = q_s$ and $q_\infty = q_0$), we obtain

$$\dot{q}(t) = k_o \left(\frac{t}{t_o} \right)^{-\gamma} [q_\infty - q(t)], \quad q(t_0) = 0,$$

and after integration,

$$\frac{q(t)}{q_\infty} = 1 - \exp \left\{ -\frac{k_o t_o}{1 - \gamma} \left[\left(\frac{t}{t_o} \right)^{1-\gamma} - \left(\frac{t_0}{t_o} \right)^{1-\gamma} \right] \right\}.$$

Taking the limit as t_0 approaches zero, for $\gamma < 1$ we get the following equation:

$$\frac{q(t)}{q_\infty} = 1 - \exp \left[-\frac{k_o t_o}{1 - \gamma} \left(\frac{t}{t_o} \right)^{1-\gamma} \right]. \quad (5.13)$$

This equation is identical to the Weibull equation (5.11) for

$$\lambda = \frac{1}{t_o} \left(\frac{k_o t_o}{1 - \gamma} \right)^{1/(1-\gamma)} \quad \text{and} \quad \mu = 1 - \gamma.$$

Furthermore, (5.13) collapses to the "homogeneous" (5.4) when $\gamma = 0$. These observations reveal that the parameter μ of (5.11) can be interpreted in terms of the heterogeneity of the process. For example, an S-shaped dissolution curve with $\mu > 1$ in (5.11) for an immediate release formulation can now be interpreted as a heterogeneous dissolution process (with $\gamma < 0$ in equation 5.13), whose rate

increases with time during the upwards, concave initial limb of the curve and decreases after the point of inflection. This kind of behavior can be associated with an initial poor deaggregation or poor wetting.

Most importantly, it was shown that the structure of the Weibull function captures the time-dependent character of the rate coefficient governing the dissolution process. These considerations agree with Elkoski's [122] analysis of the Weibull function and provide an indirect, physically based interpretation [123] for its superiority over other approaches for the analysis of dissolution data. In other words, drug dissolution is a typical example of a heterogeneous process since, as dissolution proceeds, homogeneous conditions cannot be maintained in the critical region of the microenvironment of drug particles. Thus, drug dissolution exhibits fractal-like kinetics like other heterogeneous processes (e.g., adsorption, catalysis) since it takes place at the boundary of different phases (solid–liquid) under topological constraints.

5.1.4 Stochastic Considerations

The dissolution process can be interpreted stochastically since the profile of the accumulated fraction of amount dissolved from a solid dosage form gives the probability of the residence times of drug molecules in the dissolution medium. In fact, the accumulated fraction of the drug in solution, $q(t)/q_\infty$, has a statistical sense since it represents the cumulative distribution function of the random variable *dissolution time* T , which is the time up to dissolution for an individual drug fraction from the dosage form. Hence, $q(t)/q_\infty$ can be defined statistically as the probability that a molecule will leave the formulation prior to t , i.e., that the particular dissolution time T is smaller than t :

$$q(t)/q_\infty = \Pr[\text{leave the formulation prior to } t] = \Pr[T < t].$$

Conversely,

$$1 - q(t)/q_\infty = \Pr[\text{survive in the formulation to } t] = \Pr[T \geq t].$$

Since $q(t)/q_\infty$ is a distribution function, it can be characterized by its statistical moments. The first moment is defined as the *mean dissolution time (MDT)* and corresponds to the expectation of the time up to dissolution for an individual drug fraction from the dosage form:

$$MDT = E[T] = \int_0^\infty t \frac{dq(t)}{q_\infty} = \frac{ABC}{q_\infty}, \quad (5.14)$$

where q_∞ is the asymptote of the dissolved amount of drug and ABC is the area between the cumulative dissolution curve and the horizontal line that corresponds to q_∞ , Figure 5.4.

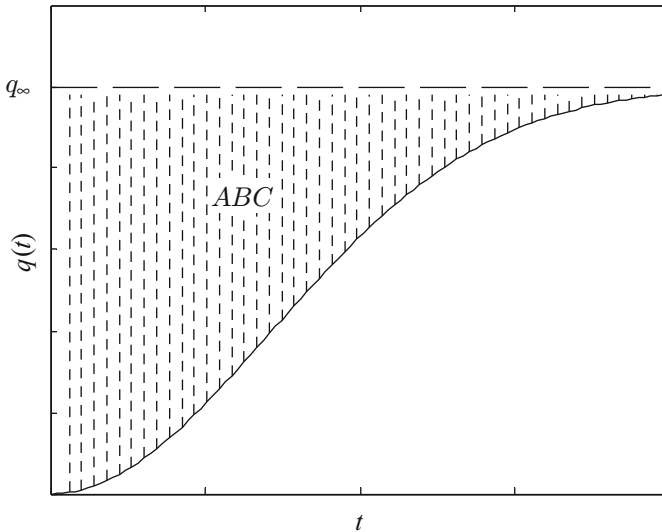


Fig. 5.4 The cumulative dissolution profile $q(t)$ as a function of time. The symbols are defined in the text

Since the fundamental rate equation of the diffusion layer model has the typical form of a first-order rate process (5.1), using (5.4) and (5.14), the *MDT* is found equal to the reciprocal of the rate constant k :

$$MDT = \frac{1}{k}. \tag{5.15}$$

As a matter of fact, all dissolution studies, which invariably rely on (5.1) and do not make dose considerations, utilize (5.15) for the calculation of the *MDT*. However, the previous equation applies only when the entire available amount of drug (dose) q_0 is dissolved. Otherwise, the mean dissolution time of the dose is not defined, i.e., *MDT* is infinite.

In fact, it will be shown below that *MDT* is dependent on the *solubility–dose ratio* if one takes into account the dose q_0 actually utilized [92]. Also, it will be shown that the widely used (5.15) applies only to a special limiting case. Multiplying both parts of (5.1) by V/q_0 (volume of the dissolution medium/actual dose), one gets the same equation in terms of the fraction of the actual dose of drug dissolved, $\varphi(t) \triangleq q(t)/q_0$:

$$\dot{\varphi}(t) = k \left[\frac{1}{\theta} - \varphi(t) \right], \varphi(0) = 0, \tag{5.16}$$

where θ is the *solubility–dose ratio*

$$\theta \triangleq \frac{q_0}{c_s V} = \frac{q_0}{q_s} \tag{5.17}$$

expressed as a dimensionless quantity. Equation (5.16) has two solutions:

- When $\theta \leq 1$ ($q_0 \leq q_s$), which means that the entire dose is eventually dissolved:

$$\varphi(t) = \begin{cases} \frac{1}{\theta} [1 - \exp(-kt)] & \text{for } t < t_o, \\ 1 & \text{for } t \geq t_o, \end{cases}$$

where $t_o = -\frac{\ln(1-\theta)}{k}$ is the time at which dissolution terminates ($\varphi(t_o) = 1$). Similarly to (5.14), the *MDT* is

$$MDT = \int_0^{t_o} t d\varphi(t) = \frac{\theta + (1-\theta) \ln(1-\theta)}{k\theta}. \quad (5.18)$$

This equation reveals that the *MDT* depends on both k and θ . Figure 5.5 shows a plot of *MDT* as a function of θ for three different values of the rate constant k . Note that (5.15) is obtained from (5.18) for $\theta = 1$ (the actual dose is equal to the amount needed to saturate the volume of the dissolution medium). In other words, the classically used (5.15) is a special case of the general equation (5.18).

- When $\theta > 1$ ($q_0 > q_s$), which means that only a portion of the dose is dissolved and the drug reaches the saturation level $1/\theta$:

$$\varphi(t) = \frac{1}{\theta} [1 - \exp(-kt)].$$

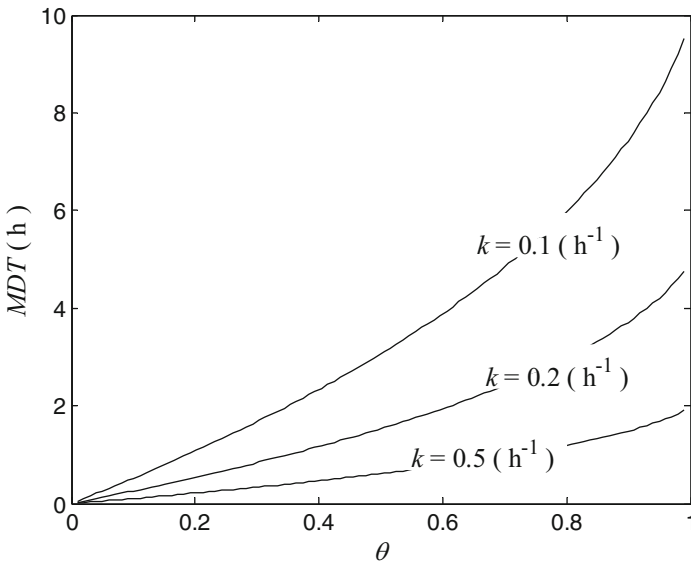


Fig. 5.5 Plot of *MDT* vs. θ using (5.18) for different values of k

The *MDT* is infinite because the entire dose is not dissolved. Therefore, the term mean saturation time, MDT_s , [124] has been suggested as more appropriate when we refer only to the actually dissolved portion of dose, in order to get a meaningful time scale for the portion of the dissolved drug dose:

$$MDT_s = \int_0^{\infty} t \frac{d\varphi(t)}{1/\theta} = \frac{1}{k}, \quad (5.19)$$

which is independent of θ .

This analysis demonstrates that when $\theta \leq 1$, solubility–dose considerations should be taken into account in accord with (5.18) for the calculation of *MDT*; the *MDT* is infinite when $\theta > 1$. Equation (5.15) can be used to obtain an estimate for *MDT* only in the special case $\theta = 1$. Finally, (5.19) describes the MDT_s of the fraction of dose dissolved when $\theta > 1$.

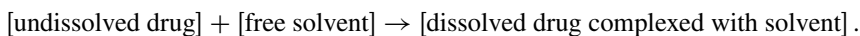
5.2 The Interfacial Barrier Model

In the interfacial barrier model of dissolution it is assumed that the reaction at the solid–liquid interface is not rapid due to the high free energy of activation requirement and therefore the reaction becomes the rate-limiting step for the dissolution process (Figure 5.1), thus, drug dissolution is considered as a reaction-limited process for the interfacial barrier model. Although the diffusion layer model enjoys widespread acceptance since it provides a rather simplistic interpretation of dissolution with a well-defined mathematical description, the interfacial barrier model is not widely used because of the lack of a physically based mathematical description.

In recent years three novel models [124–126] have appeared that were proposed to describe the heterogeneous features of drug dissolution. They are considered here as continuous (in well-stirred media) or discrete (in understirred media) reaction-limited dissolution models. Their derivation and relevance are discussed below.

5.2.1 Continuous Reaction-Limited Dissolution Models

Lansky and Weiss [124] proposed a novel model by considering the reaction of the undissolved solute with the free solvent yielding the dissolved drug complexed with solvent:



Further, global concentrations as a function of time for the reactant species of the above reaction were considered, assuming that the solvent is not in excess and applying classical chemical kinetics. The following equation was found to describe the rate of drug dissolution in terms of the fraction of drug dissolved:

$$\dot{\varphi}(t) = k^* [1 - \varphi(t)] [1 - \theta \varphi(t)], \varphi(0) = 0, \quad (5.20)$$

where $\varphi(t)$ denotes the fraction of drug dissolved up to time t , and θ is the dimensionless solubility–dose ratio (5.17); k^* is a fractional (or relative) dissolution rate constant with dimensions time^{-1} . The fractional dissolution rate is a decreasing function of the fraction of dissolved amount $\varphi(t)$, as has also been observed for the diffusion layer model (5.16). However, (5.20) reveals a form of second-order dependency of the reaction rate on the dissolved amount $\varphi(t)$. In reality, a classical second-order dependency is observed for $\theta = 1$. These are unique features, which are not encountered in models dealing with diffusion-limited dissolution. All the above characteristics indicate that (5.20) describes the continuous–homogeneous character of the reaction of the solid with the solvent or the component(s) of the dissolution medium, i.e., a reaction-limited dissolution process in accord with the interfacial barrier model.

The solution of (5.20) for $\theta \neq 1$ yields the monotonic function

$$\varphi(t) = \frac{\exp[k^*(1-\theta)t] - 1}{\exp[k^*(1-\theta)t] - \theta}, \quad (5.21)$$

and for $\theta = 1$,

$$\varphi(t) = \frac{k^*t}{k^*t + 1},$$

with the same asymptotes as found above for the diffusion layer model, i.e., $\varphi(\infty) = 1$ for $\theta \leq 1$ and $\varphi(\infty) = 1/\theta$ for $\theta > 1$. It is interesting to note that both MDT and MDT_s for the model of the previous equation depend on the solubility–dose ratio θ when $\theta \neq 1$. Thus, the MDT for $\theta < 1$ is

$$MDT = -\frac{1}{k^*\theta} \ln(1-\theta), \quad (5.22)$$

while the MDT_s for $\theta > 1$ is

$$MDT_s = \frac{1}{k^*} \ln\left(\frac{\theta}{\theta-1}\right). \quad (5.23)$$

For $\theta = 1$ the MDT is infinite. It should be noted that the MDT for the diffusion layer model depends also on θ for $\theta < 1$ while the MDT_s is equal to $1/k$ when $\theta \geq 1$, (5.18) and (5.19). However, this dependency is different in the two models, cf. (5.18), (5.19), and (5.22), (5.23).

In 2008 Dokoumetzidis et al. [126] published a complete analysis of a continuous reaction-limited model of dissolution based on a bidirectional chemical reaction of the undissolved drug species with the free solvent molecules yielding the dissolved species of drug complex with solvent. This bidirectional reaction governed by the k_{+1} and k_{-1} rate constants can be considered in either sink conditions, where it corresponds to the unidirectional case and the entire drug amount is dissolved, or reaching chemical equilibrium, which corresponds to saturation of the solution. The model equation derived for the drug concentration $y(t)$ in mass per volume units is

$$\dot{y}(t) = k_{+1} (w_0)^b \left[\frac{q_0}{V} - y(t) \right]^a - k_{-1} y(t) \quad (5.24)$$

where q_0 is the initial quantity (dose) in mass units, w_0 is the initial concentration of the free solvent species, a and b are exponents dependent on the stoichiometry of the reaction and/or the geometry (surface) of the solid particles, and V is the volume of the dissolution medium.

Simpler, special cases of the above equation can be considered. For example, when $a = 1$ the undissolved species have equal probability to dissolve, implying that they are in a form of a well-mixed dispersion. Upon integration of the above equation for $a = 1$ one ends up

$$\varphi(t) = \frac{1}{q_{ss}} \{1 - \exp[-(k_{+1} (w_0)^b + k_{-1}) t]\}$$

where $\varphi(t)$ is the fraction of dose dissolved and

$$q_{ss} = \frac{k_{+1} (w_0)^b + k_{-1}}{k_{+1} (w_0)^b}$$

is a dimensionless constant. Other simpler cases are also considered in [126]. The models derived were fitted successfully to dissolution experimental data sets. On the contrary, functions based on the diffusion layer model fitted to experimental data, failed to reveal the governing role of saturation solubility in the dissolution process. One of the most important results of this study is that the rate of dissolution of a reaction-limited approach is driven by the concentration of the undissolved species and solubility is considered to be the concentration when the reaction equilibrium is reached.

5.2.2 A Discrete Reaction-Limited Dissolution Model

Dokoumetzidis and Macheras [125] developed a population growth model for describing drug dissolution under heterogeneous conditions. In inhomogeneous media, Fick's laws of diffusion are not valid, while global concentrations cannot

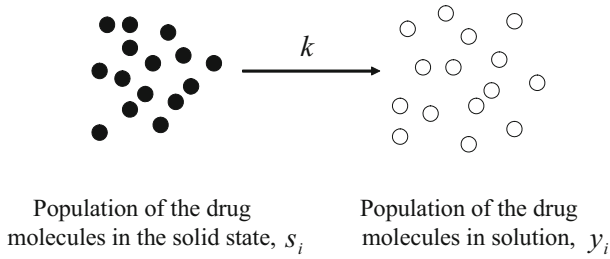


Fig. 5.6 A discrete, reaction-limited dissolution process interpreted with the population growth model of dissolution

be used in the dissolution rate equation. In order to face the problem of complexity and circumvent describing the system completely, the reaction of the solid with the solvent or the component(s) of the dissolution medium was described as the “birth” of the population of the dissolved drug molecules from the corresponding population of solid drug particles, Figure 5.6. In this context, only instants of the system’s behavior are considered and what happens in the meanwhile is ignored. The jump from one instant to the next is done by a logical rule, which is not a physical law, but an expression that gives realistic results based on logical assumptions. The variable of interest (mass dissolved) is not considered as a continuous function of time, but is a function of a discrete time index specifying successive “generations.”

Defining s_i and y_i as the populations of the drug molecules in the solid state and in solution in the i -th generation ($i = 0, 1, 2, \dots$), respectively, the following finite difference equation describes the change of y_i between generations i and $i + 1$:

$$y_{i+1} = y_i + ks_i = y_i + k(q_0 - y_i), y_0 = 0,$$

where k is a proportionality constant that controls the reaction of the solid particles with the solvent or the components of the dissolution medium, and q_0 is the population of the drug molecules in the solid state corresponding to dose (Figure 5.6). The growth of y_i is not unlimited since the solubility of drug in the medium restricts the growth of y_i . Thus, the rate of dissolution decreases as the population of the undissolved drug molecules decreases as reaction proceeds. For each one of the drug particles of the undissolved population, the solubility q_s (expressed in terms of the amount needed to saturate the medium in the neighborhood of the particle) is used as an upper “local” limit for the population growth of the dissolved drug molecules. Accordingly, the growth rate is a function of the population level and can be assumed to decrease with increasing population in a linear manner:

$$k \rightarrow k(y_i) = k \left(1 - \frac{y_i}{q_s} \right),$$

where q_s is the saturation level of the population, i.e., the number of drug molecules corresponding to saturation solubility. Thus, the previous recursion relation is replaced with the nonlinear discrete equation:

$$y_{i+1} = y_i + k (q_0 - y_i) \left(1 - \frac{y_i}{q_s}\right), y_0 = 0.$$

This equation can be normalized in terms of dose by dividing both sides by q_0 and written more conveniently using $y_i/q_0 = \varphi_i$, $y_{i+1}/q_0 = \varphi_{i+1}$, and $\theta = q_0/q_s$:

$$\varphi_{i+1} = \varphi_i + k (1 - \varphi_i) (1 - \theta\varphi_i), \varphi_0 = 0, \tag{5.25}$$

where φ_i and φ_{i+1} are the dissolved fractions of drug dose at generations i and $i + 1$, respectively. The previous discrete equation, if written as

$$\varphi_{i+1} - \varphi_i = k (1 - \varphi_i) (1 - \theta\varphi_i), \varphi_0 = 0, \tag{5.26}$$

becomes equivalent to its continuous analogue (5.20). As expected, (5.26) has the two classical fixed point, $\varphi_A^* = 1$ when $\theta \leq 1$ and $\varphi_B^* = 1/\theta$ when $\theta > 1$, Figure 5.7. All discrete features of (5.26) are in full analogy with the fractional dissolution rate differential equation (5.20), and it is for this reason that the two approaches are considered counterparts [124].

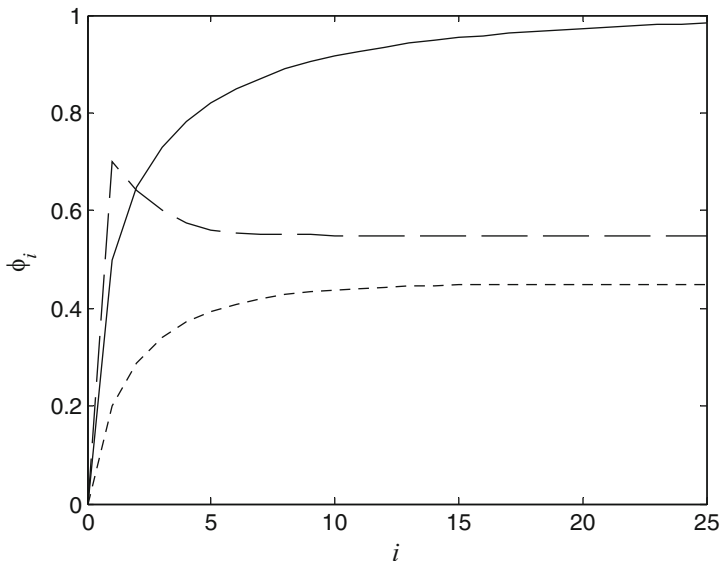


Fig. 5.7 Plot of the dissolved fraction φ_i as a function of generations i using (5.25) with $k = 0.5$, $\theta = 0.83$ (solid line); $k = 0.7$, $\theta = 1.82$ (dashed line); $k = 0.2$, $\theta = 2.22$ (dotted line)

Since difference equations exhibit dynamic behavior [127, 128], the stability of the fixed points of (5.25) is explored according to the methodology presented in Appendix A. The absolute value of the derivative of the right-hand side of (5.25) is compared with unity for each fixed point. There are the following cases:

- If $\theta < 1$, the derivative is equal to $1 - k(1 - \theta)$ and the condition for stability of the fixed point $\varphi_A^* = 1$ is

$$0 < k < \frac{2}{1 - \theta}.$$

- If $\theta > 1$, the derivative is equal to $1 - k(\theta - 1)$ and the condition for stability of the fixed point $\varphi_B^* = 1/\theta$ is

$$0 < k < \frac{2}{\theta - 1}.$$

- If $\theta = 1$, the derivative is equal to unity and therefore the fixed point $\varphi_A^* = 1$ is neither stable or unstable.

Because of the discrete nature of (5.26), the first step always gives $\varphi_1 = k$; hence, k is always lower than 1, i.e., the theoretical top boundary of φ_i . Comparing the second step $\varphi_2 = k + k(1 - k)(1 - \theta k)$ with the first one $\varphi_1 = k$, one can obtain the conditions $k > 1/\theta$ and $\theta > 1$, which ensure that the first step is higher than the following steps (Figure 5.7B). The usual behavior encountered in dissolution studies, i.e., a monotonic exponential increase of φ_i reaching asymptotically 1, or the saturation level $1/\theta$, is observed when $\theta \leq 1$ (Figure 5.7A) or when $k < 1/\theta$ for $\theta > 1$ (Figure 5.7C), respectively.

As previously pointed out, when one uses (5.25) for $\theta > 1$ and values of k in the range $1/\theta < k < 2/(\theta - 1)$, the first step is higher than the plateau value followed by a progressive decline to the plateau (Figure 5.8A, B). For $1/\theta$ and k values close enough, the descending part of the dissolution curve is smooth, concave either upward (Figure 5.8B) or initially downward and then upward (Figure 5.8A); this decline can also take the form of a fading oscillation when k is close to $2/(\theta - 1)$ (Figure 5.8C, D). When k exceeds $2/|\theta - 1|$, the fixed points become unstable, bifurcating to a double-period stable fixed point. So we have both the unstable main point and the generated double-period stable point. This mechanism is called bifurcation and is common to dynamic systems (cf. Chapter 3).

Equation (5.26) can be used to estimate the proportionality constant k and θ from experimental data by plotting the fraction dissolved (φ_i) as a function of the generations i . Prior to plotting, the sampling times are transformed to generations defining arbitrarily a constant sampling interval as a “time unit.” By doing so, an initial estimate for k can be obtained by reading the value of φ_i corresponding to the first datum point. When $\theta > 1$ an initial estimate for θ can be obtained from the highest value of the dissolved fraction at the end of the dissolution run. However, an estimate for θ cannot be obtained from visual inspection when $\theta \leq 1$ since $\varphi_A^* = 1$

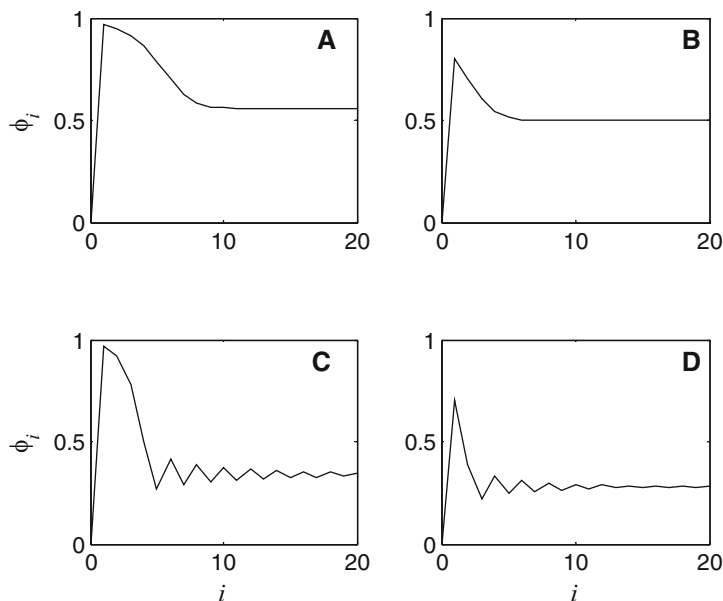


Fig. 5.8 Plots of the dissolved fraction ϕ_i as a function of generations i using (5.25) with k and θ values satisfying the inequality $1/\theta < k < 2/(\theta - 1)$: (A) $k = 0.97$, $\theta = 1.79$; (B) $k = 0.8$, $\theta = 2.0$; (C) $k = 0.97$, $\theta = 2.94$; (D) $k = 0.7$, $\theta = 3.57$

in all cases. The initial estimates for k and θ can be further used as starting points in a computer fitting program to obtain the best parameter estimates.

The population growth model of dissolution utilizes the usual information available in dissolution studies, i.e., the amount dissolved at certain fixed intervals of time. The time points of all observations need to be transformed to equally spaced values of time and furthermore to take the values $0, 1, 2, \dots$. Since the model does not rely on diffusion principles it can be applied to both homogeneous and inhomogeneous conditions. This is of particular value for the correlation of in vitro dissolution data obtained under homogeneous conditions and in vivo observations adhering to the heterogeneous milieu of the gastrointestinal tract. The dimensionless character of k allows comparisons to be made for k estimates obtained for a drug studied under different in vitro and in vivo conditions, e.g., various dissolution media, fasted, or fed state.

Example 2. Danazol Data

For the continuous model, a fitting example of (5.21) to actual experimental data of danazol [129] is shown in Figure 5.9. For the discrete model, a number of fitting examples are shown in Figure 5.10 for danazol dissolution data obtained by using 15 minutes as a “time unit.” Table 5.1 lists the estimates for k and θ obtained from the computer analysis of danazol data utilizing an algorithm minimizing the sum of squared deviations between experimental and theoretical values obtained from (5.25). ■

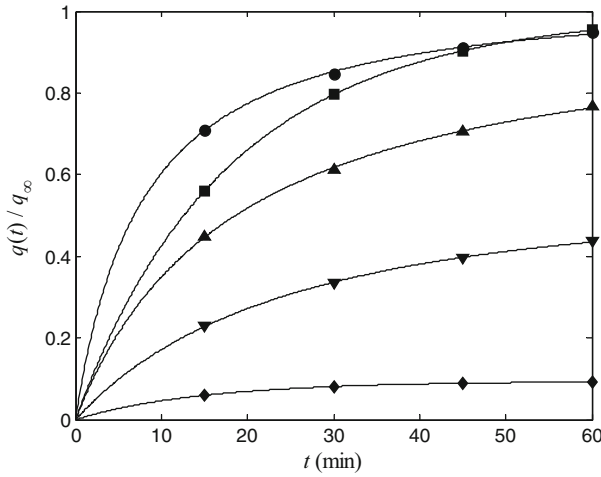


Fig. 5.9 The fraction of dose dissolved as a function of time for the danazol data [129]. Symbols represent experimental points and the lines represent the fittings of (5.21) to data. Key (% sodium lauryl sulfate in water as dissolution medium): ● 1.0; ■ 0.75; ▲ 0.50; ▼ 0.25; ◆ 0.10

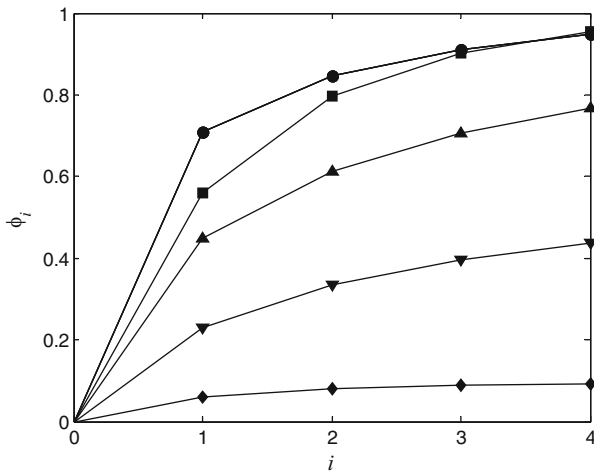


Fig. 5.10 The fraction of dose dissolved ϕ_i as a function of generations i , where the *solid line* represents the fittings of (5.25) to danazol data [129]. Symbols represent experimental points transformed to the discrete time scale for graphing and fitting purposes assigning one generation equal to 15 minutes. Key (% sodium lauryl sulfate in water as dissolution medium): ● 1.0; ■ 0.75; ▲ 0.50; ▼ 0.25; ◆ 0.10

Table 5.1 Estimates for k and θ obtained from the fitting of (5.24) to danazol data, Figure 5.10. (a) Percentage of sodium lauryl sulfate in water, (b) Determination coefficient.

Dissolution medium ^a	k	θ	R^{2b}
0.10	0.06	10	0.993
0.25	0.23	1.82	0.9993
0.50	0.45	0.75	0.9999
0.75	0.56	0.08	0.9995
1.00	0.71	0.47	0.9996

5.2.3 Modeling Supersaturated Dissolution Data

The dissolution data are basically of monotonic nature (the drug concentration or the fraction of drug dissolved is increasing with time) and therefore the corresponding modeling approaches rely on monotonic functions. However, nonmonotonic dissolution profiles are frequently observed in studies dealing with co-precipitates of drugs with polymers and solid dispersion formulations [130, 131]. The dissolution profiles in these studies usually exhibit a supersaturation phenomenon, namely, an initial rapid increase of drug concentration to a supersaturated maximum followed by a progressive decline to a plateau value. This kind of behavior cannot be explained with the classical diffusion principles in accord with the diffusion layer model of dissolution. It seems likely that the initial sudden increase is associated with a rapid reaction of the solid particles with the dissolution medium. The dynamics of the difference equation for the population growth model of dissolution, (5.25), can capture this behavior and therefore can be used to model supersaturated dissolution data [132].

Example 3. Nifedipine Data

An example of fitting (5.25) to experimental data of a nifedipine solid dispersion formulation [131] is shown in Figure 5.11. Initially, the drug concentration values are transformed to the corresponding dissolved fractions of dose φ_i and plotted as a function of the generations i , obtained by using a “time unit” of 5 minutes. The transformation of sampling times to generations i is achieved by adopting the time needed to reach maximum concentration (equivalent to maximum fraction of dose dissolved) as the time unit of (5.25). Reading the maximum and lowest values of φ_i , one obtains initial estimates for parameters k and $1/\theta$, respectively. These values are further used as starting points in a computer program minimizing the sum of squared deviations between observed and predicted values to determine the best parameter estimates. The estimated parameter values for k and θ were found to be 0.323 and 4.06, respectively. The value of k denotes the maximum fraction of dose that is dissolved in a time interval equal to the time unit used. The value of θ corresponds to the reciprocal of the plateau value, which is the fraction of dose remaining in solution at steady state. ■

However, the use of (5.25) should not be considered as a panacea for modeling nonmonotonic dissolution curves. Obvious drawbacks of the model (5.25) are

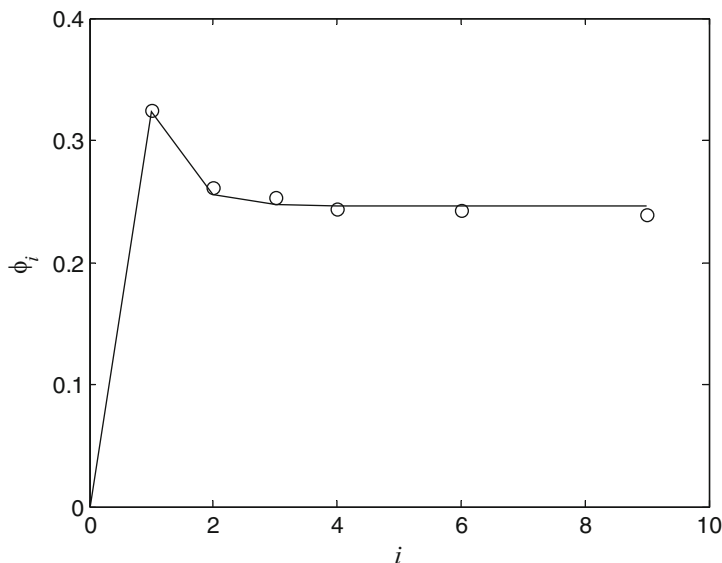


Fig. 5.11 Plot of the dissolved fraction ϕ_i as a function of generations i (time step 5 min) using (5.25) for the dissolution of nifedipine solid dispersion with nicotinamide and polyvinylpyrrolidone (1 : 3 : 1), in 900 ml of distilled water. Fitted line of (5.25) is drawn over the experimental data

1. The data on the ascending limb of the dissolution curve, if any, should be ignored.
2. The time required to reach the maximum value of the dissolved fraction of drug should be adopted as the time interval between successive generations.
3. The time values of the data points that can be used for fitting purposes should be integer multiples of the time unit adopted.

Further, when k takes values much larger than $1/\theta$, (5.25) exhibits chaotic behavior following the period-doubling bifurcation (cf. Chapter 3). For example, (5.25) leads to chaos when $1/\theta = 0.25$ and k is greater than 0.855. Despite the aforementioned disadvantages, the model offers the sole approach that can be used to describe supersaturated dissolution data. In addition, the derivation of (5.25) relies on a model built from physical principles, i.e., a reaction-limited dissolution model. Other approaches based on empirical models, e.g., polynomial functions, could provide better fittings for supersaturated dissolution data but these approaches will certainly lack in physical meaning.

In 2011 Charkoftaki et al. [133] modified the continuous reaction-limited model of dissolution [126] to describe classical experimental supersaturated dissolution data of carbamazepine in presence of d-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). The model developed was based on a time-dependent expression for the forward microconstant of the bidirectional reaction carbamazepine-TPGS at the solid-liquid interface. The following modified version of equation 5.24 was

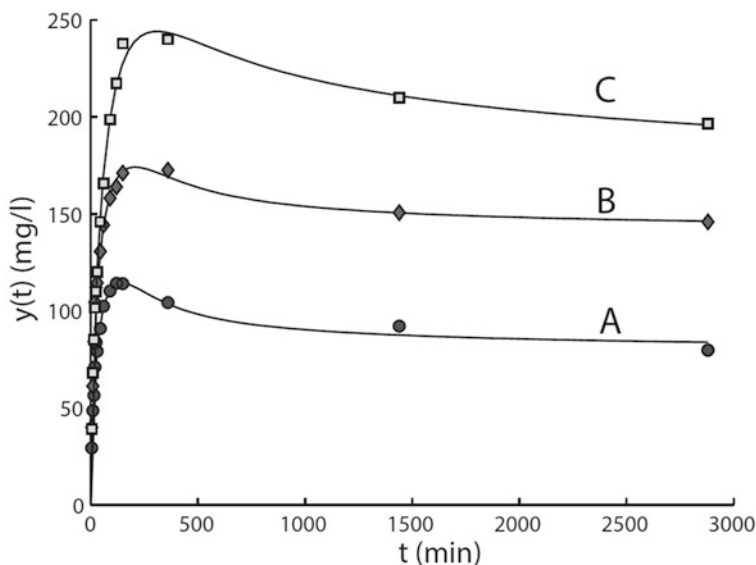


Fig. 5.12 Fittings of equation 5.27 to three data sets of carbamazepine tablets in presence of TPGS at 10° C exhibiting supersaturated dissolution profiles. Key: (A) 0.5 mM TPGS; (B) 2 mM TPGS; (C) 4 mM TPGS

fitted to the experimental data of carbamazepine dissolution in presence of TPGS at 10° C:

$$\dot{y}(t) = k[\lambda + (1+t)^{-h}] \left[\frac{q_0}{V} - y(t) \right]^a - k_{-1}y(t) \quad (5.27)$$

where k is a constant in $(\text{time})^{b-1}$ units and λ is a constant in $(\text{time})^{-h}$ units. Figure 5.12 shows the fittings of the above equation to three data sets of carbamazepine dissolution.

5.3 Modeling Random Effects

In all previous dissolution models described in Sections 5.1 and 5.2, the variability of the particles (or media) is not directly taken into account. In all cases, a unique constant (cf. Sections 5.1, 5.1.1, and 5.1.2) or a certain type of time dependency in the dissolution rate “constant” (cf. Sections 5.1.3, 5.2.1, and 5.2.2) is determined at the commencement of the process and fixed throughout the entire course of dissolution. Thus, in essence, all these models are deterministic. However, one can also assume that the above variation in time of the rate or the rate coefficient can take place randomly due to unspecified fluctuations in the heterogeneous properties

of drug particles or the structure/function of the dissolution medium. Lansky and Weiss have proposed [134] such a model assuming that the rate of dissolution $k(t)$ is stochastic and is described by the following equation:

$$k(t) = \bar{k} + \sigma \xi(t),$$

where \bar{k} is the deterministic part of the dissolution rate “constant,” $\xi(t)$ is Gaussian white noise, and $\sigma > 0$ is its amplitude. According to the definition of this equation, the “constant” \bar{k} represents the mean of $k(t)$.

The stochastic nature of $k(t)$ allows the description of the fraction of dose dissolved, $\varphi(t)$, in the form of a stochastic differential equation if coupled with the simplest dissolution model described by (5.16), assuming complete dissolution ($\theta = 1$):

$$d\varphi(t) = \bar{k}[1 - \varphi(t)] dt + \sigma \xi(t)[1 - \varphi(t)] dB(t), \quad (5.28)$$

where the symbol $\varphi(t)$ is used here to denote the random nature of the process, while $dB(t)$ comes from the Brownian motion since the noise $\xi(t)$ is the formal derivative of the Brownian motion, $\dot{B}(t)$. The solution of (5.28) gives

$$\varphi(t) = 1 - \exp\left[-\left(\bar{k} + \frac{1}{2}\sigma^2\right)t - \sigma B(t)\right].$$

A discretized version of (5.28) can be used to perform Monte Carlo simulations using different values of σ and generate $\varphi(t)$ -time profiles [134]. The random fluctuation of these profiles becomes larger as the value of σ increases.

Stochastic variation may be introduced in other models as well. In this context, Lansky and Weiss [134] have also considered random variation for the parameter k^* of the interfacial barrier model (5.20).

5.4 Homogeneity vs. Heterogeneity

Lansky and Weiss defined [135] the classical dissolution first-order model in terms of the fraction of dose dissolved, $\varphi(t)$ (equation 5.16 assuming $\theta = 1$),

$$\dot{\varphi}(t) = k[1 - \varphi(t)], \quad \varphi(0) = 0,$$

as the simplest homogeneous case, since the fractional dissolution rate function $k(t)$ derived from the above equation,

$$k(t) = \frac{\dot{\varphi}(t)}{1 - \varphi(t)},$$

is constant throughout the dissolution process. In physical terms, the homogeneous model dictates that each drug molecule has equal probability to enter solution during the entire course of the dissolution process. Plausibly, the various dissolution models have different time-dependent functional forms of $k(t)$. Accordingly, all these models were termed heterogeneous since the time dependence of the functions $k(t)$ denotes that the probability to enter solution is not identical for all drug molecules. To quantify the departure from the homogeneous case, Lansky and Weiss proposed [135] the calculation of the Kullback–Leibler information distance $Dist(f, \varphi)$ as a measure of heterogeneity of the function $f(t)$ from the homogeneous exponential model $\varphi(t)$ derived from the previous equation:

$$Dist(f, \varphi) = \int_0^{\infty} f(t) \ln \frac{f(t)}{\varphi(t)} dt.$$

This measure of heterogeneity generalizes the notion of heterogeneity as a departure from the classical first-order model initially introduced [123] for the specific case of the Weibull function. In addition, the above equation can also be used for comparison between two experimentally obtained dissolution profiles [135].

The comparison of dissolution curves based on the calculation of $Dist(f, \varphi)$ is model-independent; however, other model-dependent comparative approaches have been proposed [136]. Caution should be exercised, though, when comparison of estimates of the parameters obtained from various models is attempted in the context of heterogeneity assessment. For example, the valid use of (5.15) for the homogeneous case presupposes that the amount needed to saturate the medium is exactly equal to the dose used in actual practice, i.e., $\theta = 1$ [136]. Recently, Lansky and Weiss presented [137] in a concise form the results of their recent studies [124, 134]. The empirical and semiempirical models for drug dissolution were reviewed and classified in five groups: first-order model with a time lag, models for limited solubility of drug, models of heterogeneous compound, Weibull and inverse Gaussian models, and models defined on a finite time window. In this contribution, the properties of models were investigated, the parameters were discussed, and the role of drug heterogeneity was studied.

5.5 Comparison of Dissolution Profiles

The comparison of dissolution profiles is of interest for both research and regulatory purposes. Several methods, which can be roughly classified as (1°) statistical approaches, (2°) model-dependent, and (3°) model-independent methods, have been reported in the literature for the comparison of dissolution profiles [138–140]. The statistical approaches are based on the analysis of variance, which is used to test the hypothesis that the two profiles are statistically similar. The model-dependent methods are mainly used for clarifying dissolution or release mechanisms under various experimental conditions and rely on the statistical

comparison of the estimated parameters after fitting of a dissolution model (e.g., the Weibull model) to the raw data. The model-dependent methods can be applied to dissolution profiles with nonidentical dissolution sampling schemes, while the model-independent methods require identical sampling points since they are based on pairwise procedures for the calculation of indices (factors) from the individual raw data of two profiles. Two of these factors, namely, the *difference factor* f_1 and the *similarity factor* f_2 , have been adopted by the regulatory agencies and have been included in the relevant dissolution Guidances for quality control testing [141–143]. Each one of these factors is calculated from the two mean dissolution profiles and is being used as a point estimate measure of the (dis)similarity of the dissolution profiles.

The difference factor f_1 [141] measures the relative error (as a percentage) between two dissolution curves over all time points:

$$f_1 = 100 \frac{\sum_{i=1}^m |R_i - T_i|}{\sum_{i=1}^m R_i}. \quad (5.29)$$

where m is the number of data points, R_i and T_i are the percentage of drug dissolved for the reference and test products at each time point i , respectively.

The similarity factor f_2 [141–143] is a logarithmic reciprocal transformation of the sum of squared errors and is a measurement of the percentage similarity in the dissolution between the two dissolution curves:

$$f_2 = 50 \log \left\{ 100 \left[1 + \frac{1}{m} \sum_{i=1}^m (R_i - T_i)^2 \right]^{-0.5} \right\}. \quad (5.30)$$

Both factors take values in the range 0 – 100 assuming that the percentage dissolved values for the two products are not higher than 100%. When no difference between the two curves exist, i.e., at all time points $R_i = T_i$, then $f_1 = 0$ and $f_2 = 100$. On the other hand, when the maximum difference between the two curves exists, i.e., at all time points $|R_i - T_i| = 100$, then $f_1 = 100$ and $f_2 = 0$.

The calculation of the factors from the mean profiles of the two drug products presupposes that the variability at each sample time point is low. Thus, for immediate release formulations, the FDA guidance [141] allows a coefficient of variation of no more than 20% for the early data points (e.g., 10 or 15 min), while a coefficient of variation less than 10% is required for the other time points. According to the guidances [141, 143], when batches of the same formulation are compared, a difference up to 10% at all sample points is considered acceptable. On the basis of this boundary, the acceptable range of values derived from (5.29) and (5.30) for f_1 is 0 – 15 [141] and for f_2 is 50 – 100 [141, 143]. From a technical point of view, the following recommendations are quoted in the guidances [141, 143] for the calculation of f_1 and f_2 as point estimates:

1. a minimum of three time points (zero excluded),
2. 12 individual values for every time point for each formulation,
3. not more than one mean value of $> 85\%$ dissolved for each formulation.

Note that when more than 85% of the drug is dissolved from both products within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation. For the sake of completeness, one should add that some concerns have been raised regarding the assessment of similarity using the direct comparison of the f_1 and f_2 point estimates with the similarity limits [144–146]. Attempts have been made to bring the use of the similarity factor f_2 as a criterion for assessment of similarity between dissolution profiles in a statistical context using a bootstrap method [145] since its sampling distribution is unknown.

Although there are some differences between the European [143] and the US guidance [141, 142], e.g., the composition of the dissolution media, it should be pointed out that both recommend dissolution studies as quality assurance tests as well as for bioequivalence surrogate inference. The latter aspect is particularly well developed in the FDA guidance [142] in the framework of the Biopharmaceutics Classification System (BCS), which is treated in Section 6.6.1.