International Journal of Pharmaceutics, 92 (1993) 115–122

IJP 03120

Modelling S-shaped dissolution curves

Lasse Kervinen [a] and Jouko Yliruusi [b]

[a] *Orion Corporation, Orion Pharmaceutica, R & D, Box 65, SF-02101, Espoo (Finland) and* [b] *University of Helsinki, School of Pharmacy, Pharmaceutical Technology Division, Fabianinkatu 35, SF-00170, Helsinki (Finland)*

(Received 7 September 1992)
(Accepted 17 November 1992)

Key words: Dissolution model; S-shaped dissolution; Dissolution probability; Control factor; Theophylline tablets; Nonlinear regression

Summary

Three models were derived for the analysis of S-shaped dissolution patterns. The models are applicable to systems containing drug substance from which the drug is dissolved under sink conditions. The models were based on the use of dissolution probability, which is assumed to be dependent on time. Several physical mechanisms are present in the dissolving system, which affect the dissolution probability and also the dissolution rate. Formally, the effect of these phenomena was taken into account with a control factor. Three simple approximations of the control factor were used in deriving the dissolution models, the exponential, the linear and the quadratic. The models were briefly tested with the dissolution data of theophylline tablets.

Introduction

In many cases tablet dissolution follows an S-shaped profile. However, in the practical work it is quite usual that this feature is not taken into account when explaining the experimental data. The standard methods in the dissolution data analysis are the cubic root law, the square root time equation and some modifications of the simple exponential function (Noyes et al., 1897; Hixon et al., 1931; Higuchi, 1967; Koch, 1984). These models are not able to describe S-shaped dissolution patterns. Wagner (1969) related the distribution of the available surface area to the dissolution rate. Simulations resulted to S-shaped dissolution patterns when the surface area was assumed to follow the logarithmic normal distribution function. Dissolution can be modelled using consecutive stages. For example the disintegration of tablet into particles and the dissolution of the particles can be separated. Such models have led to formulae which are applicable for S-shaped dissolution patterns (Leary and Ross, 1983). Also some experimental models have been used with S-shaped dissolution profiles. The Rosin-Rammler-Sperling-Weibull model as well as the Gompertz model can prove useful (Langenbucher 1972, 1976; Dawoodbhai et al., 1991). The disadvantage of these functions is that the model parameters are difficult to interpret. These models are not originally derived for dissolution data; therefore they usually lack the connection to the physical phenomenon of dissolution.

The purpose of this study is to derive and briefly to test new dissolution models for systems

Correspondence to: L. Kervinen, Orion Corporation, Orion Pharmaceutica, R & D, Box 65, SF-02101, Espoo, Finland.

from which the drug content is released in accordance with an S-shaped dissolution profile.

Theory

Let us study a system containing drug substance from which the drug is dissolved under sink conditions. Assuming the system is so homogeneous that all drug molecules have the same probability p to dissolve in unit time, the dissolution takes place according to

$$dN = -pN\,dt,\ t \geqslant t_0 \tag{1}$$

where dN is the number of molecules dissolved in time dt, N denotes the total number of undissolved molecules and t_0 is the lag time, during which no dissolution occurs. Rearranging and using mass units, we have

$$\frac{dG}{dt} = -sG,\ t \geqslant t_0 \tag{2}$$

where G represents the amount of undissolved drug and dG/dt is the dissolution rate. The factor s is the average probability that a unit amount of drug dissolves in unit time. Solving this equation we have, for the amount of dissolved drug, the formula

$$M(t) = \begin{cases} 0, & 0 \leqslant t \leqslant t_0, \\ M_0(1 - e^{-s(t-t_0)}), & t \geqslant t_0, \end{cases} \tag{3}$$

where $M(t)$ is the amount of dissolved drug after time t and M_0 denotes the total amount of drug. In the derivation of Eqn 3 we have the quite weakly supported assumption that all molecules have the same probability to dissolve, which means that the factor s is a constant (independent of time). In a real dissolution test this assumption is hardly true. For example, in the case of tablet dissolution there are several phenomena which have an effect on the dissolution probability s and also on the dissolution rate. The wetting of the tablet surface, the disintegration of the tablet core and the deaggregation of granules are such factors. They exert an effect in such a way that the dissolution probability s has a time dependence, which is for example mainly due to the slowly progressing disintegration of the tablet. Also, it is obvious that s has different values in different parts of the dissolving system. It is more probable that dissolution takes place near the tablet surface than deep inside the tablet core. These features of the system can be taken into account by replacing the constant s in Eqn 2 by the time dependent function $s(t)$. The value of the factor $s(t)$ reflects the dissolution probability on the average in the whole dissolving system. No attempt is made to discuss values of s in different parts of the system.

During the beginning of the dissolution process there usually is a lag phase. In the case of tablet dissolution the surface is intact, possibly covered by an undissolved coating or there is some surface potential which prevents the beginning of wetting and also dissolution. During the lag phase the dissolution probability s is zero and hence there is practically no dissolution. After the lag time t_0 the probability is non-zero and the dissolution rate starts to increase. In the case of a coated tablet the coating is partly or totally dissolved or diffusion of drug substance through the wetted coating starts. Tablet disintegration begins. As a whole, the tablet undergoes a variety of physical changes, which control the value of the dissolution probability s. Therefore, this phase will referred to in this presentation as the control phase. During the control phase the average probability of dissolution increases. After a certain time t_e the system is supposed to reach the status, in which the probability s has the constant value σ, the final dissolution probability. The physical changes in the system have ended excluding the dissolution of the drug. Hence, after the control phase end time t_e the system is in such a state that all remaining drug molecules have the same probability to dissolve.

Formally, introducing a control factor $\varphi(t)$ with the restrictions $0 \leqq \varphi(t) \leqq 1$, $\varphi(t)$ increasing, we may write $s(t) = \sigma\varphi(t)$ and the differential formula, Eqn 2, becomes

$$\frac{dG}{dt} = -\sigma\phi(t)G,\ t \geqslant t_0 \tag{4}$$

The control factor $\varphi(t)$ should be given an explicit form in order to solve Eqn 4. The factor $\varphi(t)$ is dependent on all the mechanisms which are present during the control phase and which affect the dissolution probability. All these or at least the most governing ones should be modeled if a more accurate or thorough dissolution model is to be derived. In this study we omit detailed models and use some simple approximation forms of the control factor $\varphi(t)$. Possible approaches are the use of the exponential function, as well as the linear and quadratic approximations of $\varphi(t)$.

Model I: The exponential control factor

Thus, there is supposed to exist a group of physical phenomena in the dissolving system which affect the dissolution probability s through the control factor $\varphi(t)$. It is assumed that their combined effect can be approximated with one time dependent function, the control factor. The value of $\varphi(t)$ reflects the amount of changes which have occurred in time t. The total amount of changes is Ψ. Suppose the changes in the system take place with the rate $\mathrm{d}\varphi/\mathrm{d}t$, which is proportional to the amount of changes which are still to take place. Hence, the rate of changes is

$$\frac{\mathrm{d}\varphi}{\mathrm{d}t'} = \lambda(\Psi - \varphi(t')),\ t' \geqslant 0, \tag{5}$$

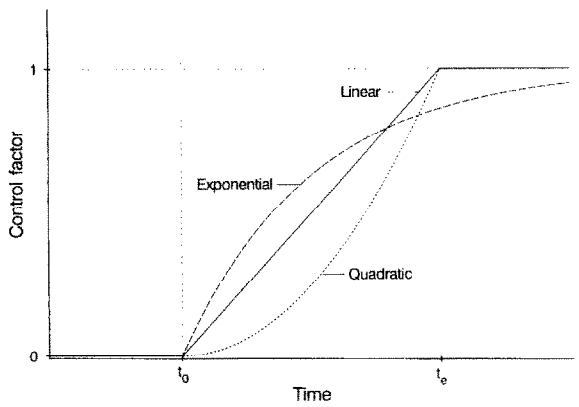


Fig. 1. Different forms of the control factor vs time: the exponential (– – – – –), the linear (———) and the quadratic control factor (------). The time symbols are the lag time t_0 and the control phase end time t_e.

where $t' = t - t_0$ and λ is the change coefficient. When Eqn 5 is solved with the constraint $\varphi(0) = 0$, we have

$$\varphi(t) = \Psi(1 - e^{-\lambda(t-t_0)}),\ t \geqslant t_0. \tag{6}$$

The resulting function is non-negative, increasing and it also has a limiting value Ψ, when time t goes to infinity. When we select $\Psi = 1$, the function fulfills the restrictions given to the control function $\varphi(t)$ above and we have

$$\varphi(t) = 1 - e^{-\lambda(t-t_0)},\ t \geqslant t_0. \tag{7}$$

The behaviour of the control factor is depicted in Fig. 1. Combining Eqns 4 and 7, and solving the differential equation, the amount of undissolved drug $G(t)$ is given by

$$G(t) = M_0 \exp\left\{-\sigma\left[t - t_0 - \frac{1}{\lambda}(1 - e^{-\lambda(t-t_0)})\right]\right\},$$
$$t \geqslant t_0, \tag{8}$$

where M_0 is the total amount of drug. The fraction of dissolved drug can be written as $M(t) = M_0 - G(t)$. Hence, the final form of the dissolution model with the exponential control factor (model I) is

$$M(t) = \begin{cases} 0, & 0 \leqslant t \leqslant t_0, \\ M_0\left(1 - \exp\left\{-\sigma\left[t - t_0 - \frac{1}{\lambda}(1 - e^{-\lambda(t-t_0)})\right]\right\}\right), \\ t \geqslant t_0, \end{cases} \tag{9}$$

where t_0 is the lag time, M_0 represents the total amount of drug, σ is the final dissolution probability and λ denotes the change coefficient of the dissolving system. Comparison of Eqns 3 and 9 shows that the physical changes in the system associated with the dissolution probability are expressed in an extra exponential term. If in the case of tablet dissolution the tablet disintegration and other phenomena occur very rapidly compared to the dissolution time, the coefficient λ is much greater than unity and the extra term is

small compared to the term $t - t_0$. In this case the extra term vanishes and the double exponential model (Eqn 9) is reduced into the simple form (Eqn 3). The effect of the parameter λ on the dissolution pattern is presented in Fig. 2.

Model II: The linear control factor

In model I (Eqn 8) it is assumed that the changes in the dissolving system associated with the dissolution probability occur according to an exponential curve. As can be seen from Fig. 1 the system is supposed to change rapidly after time t_0. It can also be noted that the control factor reaches a value of unity asymptotically. These features seem to be reasonable. However, in some situations it is probable that all changes in the system which affect the dissolution probability take place in time t_e, i.e., $\varphi(t) = 1$ when $t \geqq t_e$. The behaviour of the control factor φ between the lag time t_0 and the control end time t_c can be presented by many formulae, but the linear and quadratic functions are unquestionably the simplest ones (Fig. 1). If the function is linear, the changes are assumed to occur at a constant rate. In terms of the control factor,

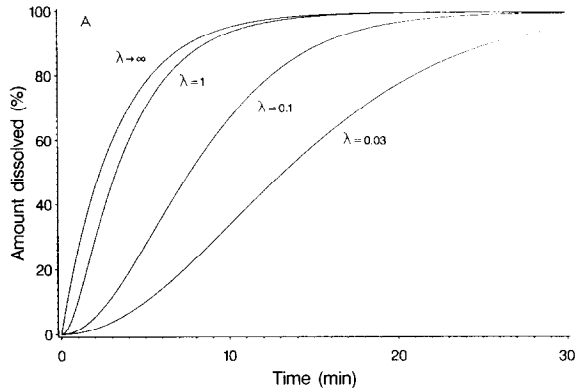
$$\frac{d\varphi}{dt} = \phi, \tag{10}$$

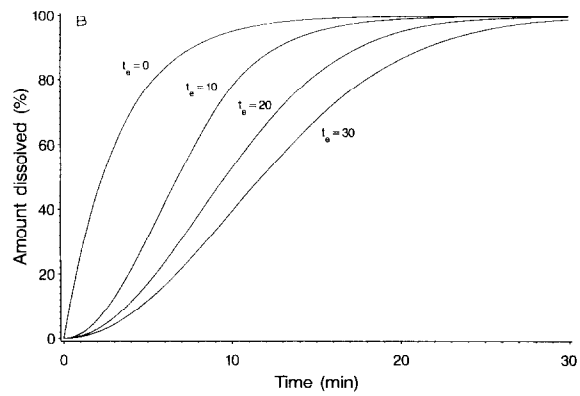
where ϕ is a constant. Assuming the system has a lag time t_0, we can use a new time coordinate $t' = t - t_0$ and also a constant $t'_e = t_e - t_0$, which leads to the segmented formula for the control factor

$$\varphi(t') = \begin{cases} \dfrac{t'}{t'_e}, & 0 \leqslant t' \leqslant t'_e, \\ 1, & t \geqslant t'e. \end{cases} \tag{11}$$

Hence we obtain for the differential formula (Eqn 3) the segmented form

$$\begin{aligned} \frac{dG}{dt'} &= -\sigma G \frac{t'}{t'_e}, \quad 0 \leqslant t' \leqslant t'_e, \\ \frac{dG}{dt'} &= -\sigma G, \qquad t' \geqslant t'_e. \end{aligned} \tag{12}$$





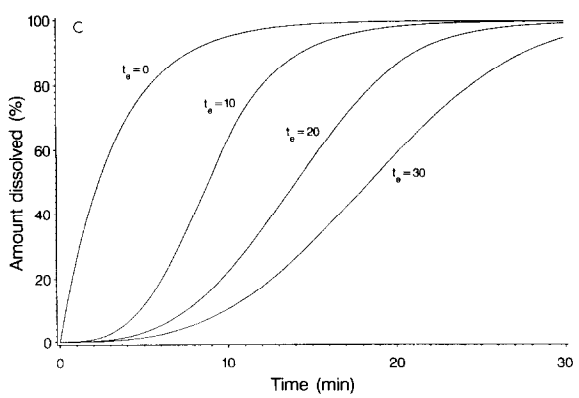


Fig. 2. Dissolution profiles with different forms of the control factor. The final dissolution probability $\sigma = 0.3$ min^{-1}, and the lag time t_0 is assumed to be zero. Panel a shows the exponential control factor with the change coefficient λ varying from 0.03 min^{-1} to infinity; (b) the linear; and (c) the quadratic control factor. In panels b and c the control end times t_c are 0, 10, 20 and 30 min.

These equations have two restrictions. The resulting function $G(t')$ should be continuous at t'_e and the value of G at zero should be equal to M_0, the total amount of drug to be dissolved. Solving the equations, moving back from the t'-coordinate system to the t-coordinate system, and replacing the amount of undissolved drug G with the amount of the dissolved drug M, we obtain for the dissolution model with linear control factor (model II) the segmented formula

$$M(t) = \begin{cases} 0, & 0 \leqslant t \leqslant t_0, \\ M_0\left\{1-\exp\left(-\dfrac{\sigma(t-t_0)^2}{2(t_e-t_0)}\right)\right\}, & t_0 \leqslant t \leqslant t_e, \\ M_0\left\{1-\exp\left[-\sigma\left(t-t_0-\dfrac{t_e-t_0}{2}\right)\right]\right\}, & t \geqslant t_e. \end{cases} \tag{13}$$

Model III: The quadratic control factor

As previously stated, the quadratic function is the third in the set of simple approximations for the control factor $\varphi(t)$. Formally, if the rate change is proportional with time, the differential equation for the control factor is

$$\frac{d\varphi}{dt} = \phi' t, \tag{14}$$

where ϕ' is a constant. Eqn 14 is valid between time t_0 and time t_e. Applying the same method as above, we find

$$\varphi(t') = \begin{cases} \dfrac{t'^2}{t'^2_e}, & 0 \leqslant t' \leqslant t'_e, \\ 1, & t' \geqslant t'_e. \end{cases} \tag{15}$$

Eqn 15 is substituted in the differential formula (Eqn 4), and the resulting equations are solved. As a result we obtain for the dissolution model with the quadratic control factor (model III) the segmented formula

$$M(t) = \begin{cases} 0, & 0 \leqslant t \leqslant t_0, \\ M_0\left\{1-\exp\left(-\dfrac{\sigma(t-t_0)^3}{3(t_e-t_0)^2}\right)\right\}, & t_0 \leqslant t \leqslant t_e, \\ M_0\left\{1-\exp\left[-\sigma\left(t-t_0-\dfrac{2(t_e-t_0)}{3}\right)\right]\right\}, & t \geqslant t_e. \end{cases} \tag{16}$$

The close relationship between the linear model (Eqn 13) and the quadratic model (Eqn 16) is clearly seen. Both can be compared to Eqn 3, which is due to the assumption that under certain conditions all drug molecules have the same probability to dissolve and the dissolution profile is a simple exponential function. The effects of the physical mechanisms which affect the dissolution probability are expressed in the presence of the second segment and in extra terms inside the exponential of the third segment in Eqns 13 and 16.

Models II and III (Eqns 13 and 16) assume that the physical changes affecting the dissolution probability occur between the lag time t_0 and the control end time t_e. In the limiting case $t_0 = t_e$, which in the case of dissolving tablets means that the tablet practically explodes into fine particles at the moment t_0. Now the second segments of models II and III vanish and the models are simplified into the form of Eqn 3. This can also be seen in Fig. 2, where dissolution profiles according to the models with the linear (model II)

TABLE 1

The model parameters and the squared sum of errors of the fitted dissolution models

Dissolution model	Type of control factor	Final dissolution probability σ (min^{-1})	Lag time t_0 (min)	Change constant λ (min^{-1})	Control end time t_e (min)	Sum of squared errors SSE
Model I	Exponential	1.223	1.10	0.183	–	83.7
Model II	Linear	0.803	0.83	–	5.99	65.2
Model III	Quadratic	0.996	−0.62	–	6.00	19.0

and the quadratic control factor (model III) are presented in addition to the model with the exponential control factor (model I). If it is assumed that there is no control phase ($t_e = t_0$ or $\lambda \to \infty$), the dissolution profiles are consistent with the pattern of the simple exponential function (Eqn 3). If the length of the control phase is significant, the dissolution pattern is S-shaped and the dissolution is retarded.

Materials and Methods

The derived dissolution models were briefly tested using the dissolution data of tablets containing theophylline as active substance. It has been reported previously that the dissolution profile of theophylline tablets is S-shaped (Dawoodbhai et al., 1991).

The active drug substance in the test formulation was anhydrous theophylline (Ph.Eur.). The particle size distribution of the active substance was determined by the laser light diffraction method (Malvern 2600C Droplet and Particle Sizer, Malvern Instruments, Malvern, U.K.). The 10, 50 and 90% fractiles were 62, 140 and 470 μm, respectively, the relative standard deviations being less than 3%. In addition to the active drug the composition contained 20% commonly used tablet excipients. The active substance and the main excipients were granulated in an instrumented fluidized bed granulator (Glatt WSG-5, W. Glatt, Haltingen, Germany). The binder solution contained 10% of Kollidon K 25 and 20% of Eudragit NE 30 D in purified water. The batches contained 4.0 kg dry material. The final granules were dried in an oven at 40 ± 2°C for 24 h.

Before tablet compression, 0.7% of magnesium stearate was added to the granules as a lubricant. The concave tablets, size 7.5 × 19.2 mm, average weight 650 mg, were compressed using a production scale rotatory press (Fette P2000, Wilhelm Fette GmbH, Hamburg, Germany). The compression speed was 30 000 tablets per h. The relative humidity and the temperature of the air during compression were 40 ± 1% and 23 ± 1°C, respectively. The tablet machine was adjusted so that the target hardness of the tablets was 15 kp (Schleuniger Hardness Tester, Dr. Schleuniger Productronic AG, Solothurn, Switzerland). This was achieved using the maximum precompression force of 0.4 kN and the maximum main compression force of 6.2 kN.

The dissolution measurements were made using an automated dissolution tester and a standard USP XXII paddle method. The dissolution medium was 900 ml of thermostated (37°C) phosphate buffer solution (pH 7.5) and the speed of rotation used was 50 rpm. The sampling times were 0, 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h. Six tablets were used in all dissolution studies. The means of the measured dissolution values were used in the data analysis. The experimental data were fitted to the dissolution models with the exponential (model I), linear (model II) and quadratic control factor (model III) using the non-linear regression procedure of the MathCAD program (Version 3.0, MathSoft Inc, Cambridge, MA, U.S.A.). The MathCAD algorithms are available from the authors upon request. The estimated parameters were the final dissolution probability σ and the lag time t_0, as well as the change coefficient λ and the control end time t_e where applicable. The end value of the dissolution M_0 was estimated graphically to be 102%. The sum of squared errors (SSE) was calculated for all models in order to evaluate the goodness of fit.

Results and Discussion

The measured dissolution values (mean ± SD) and the fitted dissolution profiles are presented in Fig. 3. The estimated parameter values and the values of sum of squared errors (SSE) of the fitted dissolution models are listed in Table 1.

As seen in Fig. 3, all three models are able to describe the S-shape of the dissolution data. The results of all fittings are acceptable, but slight differences can still be seen between the models. The models with the exponential (model I) and the linear control factor (model II) fit to the experimental data quite identically. However, the SSE is lower when model II is used (Table 1). In this test case the model with the quadratic control factor (model III) has the best fit to the data

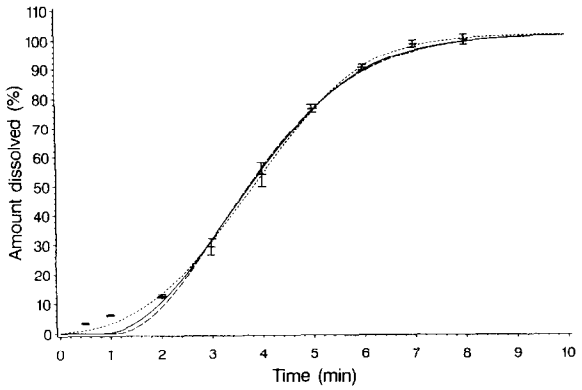


Fig. 3. Measured dissolution values of theophylline tablets (mean ± SD, $N = 6$) and fitted dissolution profiles with the exponential (– – – – –), the linear (———) and the quadratic control factor (------).

compared to the other models. The SSE is significantly lower, and the fitted curve in Fig. 3 can be ranked the best also visually. Model III best decribes the test data if the negative lag time $t_0 = -0.62$ min can be given a reasonable interpretation. One explanation is the presence of loose powder on the surface of the tablets, which in view of the model means that the disintegration of the tablet structure has begun before the dissolution test had started.

Parameters common to all three models are the total amount of drug M_0, the final dissolution probability σ and the lag time t_0. These parameters have the same interpretation as in the case of the simple exponential function (Eqn 3). In addition to these parameters we have the change coefficient λ and the control end time t_e, which provide information about the control phase. When the model with the exponential control factor is used, this phase can be described with the half-time $t_{1/2} = \ln(2)/\lambda$. Time $t_{1/2}$ is defined as the time during which half of the remaining changes occur. In the test case $t_{1/2} = 3.8$ min. The models with the linear and the quadratic control factor have as a parameter the control end time t_e after which no control effect on the dissolution rate is present and the dissolution probability is a constant. Hence the length of the control phase Δt_C can be estimated with $\Delta t_C = t_e - t_0$. The tested theophylline tablets have the Δt_C values of 5.2 min in the case of the linear control factor and 6.6 min with the quadratic control factor, respectively. The length of the control phase Δt_C gives an estimation of how long the physical phenomena affecting the dissolution probability are present in the dissolving system.

Simple approximations of the control phase are used in deriving the three dissolution models presented in this study. It is evident that the models can be developed further if more specific formulae for the control factor can be derived. For example, in the case of tablet dissolution the effect of disintegration, deaggregation and wetting on the dissolution probability should be separated.

In the experimental part of this study the derived dissolution models were tested on the data of uncoated tablets. Another application of the models might be the dissolution studies of coated tablets, in which case the coating acts as the retarding factor of the dissolution. It may also be useful to apply the models to dissolution studies of capsules, suspensions, suppositories, and even for drug release of transdermal products. The model parameters can give information about the fine structure of the dissolving system, which can be useful in the formulation of new products. In general, the models can be used for comparing quantitatively the dissolution behaviour of different batches of products.

References

Dawoodbhai, S., Suryanarayan, E.R., Woodruff, C.W. and Rhodes, C.T., Optimization of tablet formulations containing talc. *Drug Dev. Ind. Pharm.*, 17 (1991) 1343–1371.

Higuchi, W., Diffusional models useful in biopharmaceutics: Drug release rate processes. *J. Pharm. Sci.*, 56 (1967) 315–324.

Hixson, A.W. and Crowell, J.H., Dependence of reaction velocity upon surface and agitation. I: Theoretical consideration. *Ind. Eng. Chem.*, 23 (1931) 923–931.

Koch, H.P., Die Technik der Dissolutionsbestimmung (Teil 2). *Pharm. Acta Helv.*, 59 (1984) 130–139.

Langenbucher, F., Linearization of dissolution rate curves by the Weibull distribution. *J. Pharm. Pharmacol.*, 24 (1972) 979–981.

Langenbucher, F., Parametric representation of dissolution-rate curves by the RRSBW distribution. *Pharm. Ind.*, 38 (1976) 472–477.

Leary, J.R. and Ross, S.D., Mathematical expression of tablet dissolution profiles. *Int. J. Pharm.*, 17 (1983) 193–201.

Noyes, A.A. and Whitney, W.R., The rate of solution of solid substances in their own solutions. *J. Am. Chem. Soc.*, 19 (1897) 930–934.

Wagner, J.G., Interpretation of percent dissolved-time plots derived from in vitro testing of conventional tablets and capsules. *J. Pharm. Sci.*, 58 (1969) 1253–1257.