total dose excreted can be used as indication of bioavailability. The data in Table V show that the percentage of the total dose recovered after 48 hr was similar for each drug and dosage form and that all were approximately 90–100% bioavailable. These findings are consistent with the results of other investigators (4–6, 12).

Renal clearances were calculated for each subject from the hourly urinary excretion rate data and the serum concentration at the midpoint of the collection period. Total body clearance was calculated from the volume of distribution and the elimination rate constant. Since no metabolites have been identified in humans for either cephalexin or cephradine (14), the renal and total body clearances would be expected to be identical. This expectation was found to be true (Table VIII). Renal and total body clearances of cephalexin and cephradine were also similar. Since both cephalexin and cephradine are eliminated by glomerular filtration and tubular secretion (14), clearances of greater than 125 ml/min were expected. This result is confirmed in Table VIII where it can be seen that the clearance values for these drugs are approximately 300 ml/min.

The present investigation, although not designed to investigate dose-dependent pharmacokinetics, firmly establishes in a carefully controlled manner that no difference exists in any measured parameter (Tables I–VIII) between cephradine and cephalexin in 1-g doses. This finding is consistent with previous pharmacokinetic analysis at low doses (0.25–0.50 g) (14). Rattie *et al.* (10) demonstrated that a linear relationship between dose (0.25–1.0 g) and both peak concentration and *AUC* exists for cephradine. Pfeffer *et al.* (9) reported that a linear relationship in peak concentration and *AUC* exists for cephalexin at doses of 0.25 and 0.5 g. The reported pharmacokinetic parameters from these studies are similar to the present findings; therefore, dose-dependent kinetics do not appear to exist with these drugs.

Since a 1-g tablet of cephalexin is available commercially, it was important to determine if the tablet and capsule dosage forms were equally bioavailable. Figure 1 and Tables II and III show that both the tablet and capsule yield similar serum concentration–time curves, indicating that no dosage form differences affecting the drug's pharmacokinetics exist. Statistical comparison of the *AUC*, percent of dose excreted, and all other pharmacokinetic parameters shown in Table V indicate that the bioavailability of the tablet and capsule dosage forms is similar. However, greater fluctuations in peak concentration and lag time were seen with the tablet dosage form. In addition, comparison of the cephalexin tablet to the cephradine capsules (Table V) reveals no statistically significant differences in any measured pharmacokinetic parameter.

The results of this study confirm that, from a pharmacokinetic view, these drugs in tablet or capsule form are essentially identical, both at low (0.25 g) and high (1.0 g) oral doses.

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Versatile Kinetic Approach to Analysis of Dissolution Data

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Received December 5, 1977, from the **Department of Pharmacy, School of Pharmacy, University of California at San Francisco, San Francisco, CA 94143,* and the ‡*National Center for Drug Analysis, Food and Drug Administration, St. Louis, MO 63101.* Accepted for publication February 14, 1978.

Abstract □ A new kinetically based dissolution equation is presented that considers dissolution of polydisperse systems and disintegrating solid dosage forms. The equation is applicable under sink as well as nonsink conditions and enables the specific dissolution rate parameter, the dispersion parameter, the disintegration lag time, and a newly introduced parameter, the dissolution availability, to be evaluated simultaneously and directly from percent of label claim dissolved *versus* time data. The equation showed excellent fit to dissolution data for aminophylline tablets. The kinetic significance of the estimated parameters of the equation is discussed. The method of analysis is compared to an approach employing an empirical equation based on a modified Weibull distribution function.

Keyphrases □ Dissolution—kinetically based equation considers polydisperse systems and solid dosage forms, various conditions □ Models, mathematical—kinetically based equation considers dissolution of polydisperse systems and solid dosage forms, various conditions □ Kinetic approach—mathematical model considers dissolution of polydisperse systems and solid dosage forms, various conditions

The extensive literature on dissolution testing of drugs contains many theories and equations to describe observed behavior (1, 2). The equations often have limited application because they are derived for specific experimental conditions such as sink or nonsink conditions or they are based on unrealistic assumptions such as an ideal monodisperse system. Such equations often do not agree adequately with observed dissolution data.

Consequently, there has recently been interest in empirical equations for obtaining a better, more flexible

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representation of dissolution profiles (3–5). However, although empirical equations may fit some dissolution data better than equations derived from kinetic principles, they are usually of limited kinetic significance. Empirical equations may describe the general shape or nature of a dissolution curve (4) but are unable to resolve the dissolution data to describe adequately the intrinsic dissolution properties of a drug.

A new dissolution kinetic equation for characterizing dissolution properties of disintegrating solid dosage forms and multiparticulate systems is presented and tested. It is generally more applicable than other published equations and more completely describes a drug's dissolution properties. The intrinsic dissolution rate, the particle distribution effect, the disintegration effect, and the amount of drug available for dissolution can be evaluated directly from percent dissolved *versus* time data in simple and meaningful terms. This equation considers dissolution under sink as well as nonsink conditions and can be applied using most dissolution apparatus available.

THEORY

A previous paper (6) reported how the dissolution of multiparticulate systems under sink and nonsink conditions can be described rigorously according to a formula on the basis of the single-particle dissolution equation and the effective particle distribution (7). A mathematical model based on the well-established Noyes–Whitney kinetics (8) was derived for polydisperse systems with an effective particle distribution that is approximately log-normal (9). The mathematical model presented was:

$$\frac{W}{W_0} = \sum_{n=0}^{3} \binom{3}{n} (-G)^{(3-n)} \frac{F(T_2 - n\sigma) - F(T_1 - n\sigma)}{F(j - 3\sigma) - F(-i - 3\sigma)} \exp[(n^2 - 9)\sigma^2/2] \quad \text{(Eq. 1)}$$

where:

$$T_1 = \max(\ln G, -i\sigma)/\sigma \quad \text{(Eq. 2)}$$

$$T_2 = \max(\ln G, -j\sigma)/\sigma \quad \text{(Eq. 3)}$$

$$F(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} \exp(-u^2/2)\, du \quad \text{(Eq. 4)}$$

$$G = \frac{\alpha^3 K^*}{1 + \alpha^3} t + \frac{K^*}{1 + \alpha^3} \int_0^t \frac{W}{W_0} dt \quad \text{(Eq. 5)}$$

$$\binom{3}{n} = \frac{3!}{(3-n)!n!} \quad \text{(Eq. 6)}$$

and where W/W_0 is the fraction undissolved at time t; K^* is the specific dissolution rate parameter (dimension = time^{-1}); σ is the dispersion parameter, a dimensionless measure of "how polydisperse" the effective particle distribution is; i and j (dimensionless) are the lower and upper truncation parameters of the effective particle distribution, respectively; and α (dimensionless) is the dissolution capacity coefficient, a measure of the dissolution capacity of the experimental system (6).

Equation 1 describes a general class of multiparticulate dissolution models considering both monodisperse ($\sigma = 0$) and polydisperse ($\sigma > 0$) systems and nonsink ($\alpha < \infty$) as well as sink ($\alpha = \infty$) conditions. The effective particle distribution can be considered truncated ($i, j < \infty$) or ideal ($i = j = \infty$), in which case Eq. 1 is simplified to (6):

$$\frac{W}{W_0} = \sum_{n=0}^{3} \binom{3}{n} (-G)^{(3-n)} \left[1 - F\left(\frac{1}{\sigma} \ln G - n\sigma\right)\right] \exp[(n^2 - 9)\sigma^2/2] \quad \text{(Eq. 7)}$$

In a study of the dissolution of micronized gliburide under sink conditions ($\alpha = \infty$), Eq. 7 was more appropriate than Eq. 1 because it contained fewer parameters, had the same kinetic significance, and gave essentially as good a fit as Eq. 1 (10). Simulation studies also showed that the effect of i and j is insignificant as long as the effective particle distribution is not extremely truncated (7). Therefore, it is appropriate to develop Eq. 7 to consider more complex systems such as the dissolution of disintegrating tablets, capsules, and compounded powders.

Two problems must be considered. The first arises from the fact that the dissolution of such systems cannot be followed in terms of W/W_0 *versus* time as in Eqs. 1 and 7 because W_0, the initial amount available for dissolution, and, therefore, also $W = W_0 - W_d$, where W_d is the amount dissolved, are not known. There are two reasons for this problem: (*a*) the drug content in a unit dose is usually not equal to the label claim because of the limited precision of the manufacturing process; and (*b*) the amount of drug available for dissolution, W_0, may be less than the actual drug content because of formulation problems such as incomplete disintegration and complexation.

However, the dissolution of solid dosage forms can always be expressed in terms of p, the percent of label claim dissolved *versus* time:

$$p = 100 W_d/(W_0)_1 \quad \text{(Eq. 8)}$$

where W_d and $(W_0)_1$ are the amount dissolved and the label claim, respectively. This problem can then be solved by introducing an additional parameter, F_d; it will be called the dissolution availability and be defined as the percent of label claim available for dissolution:

$$F_d = 100 W_0/(W_0)_1 \quad \text{(Eq. 9)}$$

Since $W/W_0 = 1 - W_d/W_0$, it follows from Eqs. 8 and 9 that:

$$W/W_0 = 1 - p/F_d \quad \text{(Eq. 10)}$$

This expression can then be inserted in Eq. 7 to replace the unknown variable W/W_0 with the variable p, which can be measured.

The second problem concerns the disintegration process. On the basis of some assumptions about disintegration, extensions to the model can be developed so that the kinetics of the disintegration process are considered. However, this consideration may complicate the dissolution kinetic model unnecessarily. A simpler approach is to consider that the dosage form has an ideal, instantaneous disintegration. This ideal is never the case, so a disagreement will exist between the dissolution data and the ideal model in the initial phase of the dissolution where the disintegration takes place. However, if the disintegration process is relatively short compared to the dissolution process, then the model is expected to agree with the data after this initial phase when the model is corrected for the dissolution lag time caused by disintegration, *i.e.*, when t in Eq. 7 is substituted with the expression $\max(t - \tau, 0)$ defined by[1]:

$$\max(t - \tau, 0) = 0 \qquad \text{for } t \le \tau \quad \text{(Eq. 11)}$$

$$\max(t - \tau, 0) = t - \tau \qquad \text{for } t > \tau \quad \text{(Eq. 12)}$$

where τ is the dissolution lag time. The value determined for τ gives a simple measure of the effect of the disintegration process on the dissolution.

When the expression for W/W_0 (Eq. 10) and the dissolution lag time τ is introduced in Eq. 7, it becomes:

$$p = F_d - F_d \sum_{n=0}^{3} \binom{3}{n} (-H)^{(3-n)} \left[1 - F\left(\frac{1}{\sigma} \ln H - n\sigma\right)\right] \exp[(n^2 - 9)\sigma^2/2] \quad \text{(Eq. 13)}$$

where:

$$H = K^* \max(t - \tau, 0) - \frac{K^*}{F_d(1 + \alpha^3)} \int_0^{\max(t-\tau,0)} p\, dt \quad \text{(Eq. 14)}$$

Equation 13 contains the normal probability integral F. This function is related to the error function, erf, and the complementary error function, erfc, by:

$$F(x) = \tfrac{1}{2}\left[\operatorname{erf}\left(\frac{x}{\sqrt{2}}\right) + 1\right] = 1 - \tfrac{1}{2} \operatorname{erfc}\left(\frac{x}{\sqrt{2}}\right) \quad \text{(Eq. 15)}$$

where:

$$\operatorname{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x \exp(-u^2)\, du \quad \text{(Eq. 16)}$$

Therefore, Eq. 13 can also be expressed in terms of the complementary error function, which may be computationally more convenient[2]:

[1] The expression $\max(x - y, 0)$ is frequently denoted by $(x - y)_+$ in the mathematical literature. The former way of writing is used here because it is less ambiguous.

[2] The complementary error function is available as a built-in Fortran library function, ERFC, in IBM's Fortran; the probability integral Eq. 4 is not.

$$p = F_d - \frac{F_d}{2}\sum_{n=0}^{3}\binom{3}{n}(-H)^{(3-n)}\,\mathrm{erfc}\left[\left(\frac{1}{\sigma}\ln H - n\sigma\right)\Big/\sqrt{2}\right] \exp[(n^2-9)\sigma^2/2] \quad \text{(Eq. 17)}$$

where H is the expression defined by Eq. 14.

Equation 17, which describes the variation of p, the percent of label claim dissolved, with time, is applicable under a wide range of conditions. It considers polydisperse ($\sigma > 0$) as well as monodisperse ($\sigma = 0$) systems dissolving under nonsink ($\alpha < \infty$) or sink ($\alpha = \infty$) conditions.

Polydisperse Systems Dissolving under Sink Conditions—A sink condition is described by letting $\alpha \to \infty$ for which:

$$H = K^* \max(t = \tau, 0) - \frac{K^*}{F_d(1+\alpha^3)}\int_0^{\max(t-\tau,0)} p\,dt \to K^* \max(t-\tau, 0) \quad \text{(Eq. 18)}$$

so that Eq. 17 (and, similarly, Eq. 13) becomes:

$$p = F_d - \frac{F_d}{2}\sum_{n=0}^{3}\binom{3}{n}[-K^* \max(t-\tau,0)]^{(3-n)} \mathrm{erfc}\left\{\left[\frac{1}{\sigma}\ln[K^* \max(t-\tau,0)] - n\sigma\right]\Big/\sqrt{2}\right\} \exp[(n^2-9)\sigma^2/2] \quad \text{(Eq. 19)}$$

If H in Eq. 14 is written in the form:

$$H = K^*\left[\max(t-\tau,0) - \frac{1}{F_d(1+\alpha^3)}\int_0^{\max(t-\tau,0)} p\,dt\right] \quad \text{(Eq. 20)}$$

the only difference between the equation for nonsink conditions (Eq. 17) and sink conditions (Eq. 19) is the expression:

$$-\frac{1}{F_d(1+\alpha^3)}\int_0^{\max(t-\tau,0)} p\,dt$$

which, according to Eq. 20, can be considered as a "time-correcting term" accounting for the nonsink conditions. This term vanishes as the sink condition is approached ($\alpha \to \infty$).

The sink condition was previously (6) defined as "an interparticle independent dissolution," *i.e.*, a dissolution where the dissolution of any one particle does not affect the dissolution of the other particles[3]. This condition can be approximated closely in a noncumulating, open flow-through system (*e.g.*, Refs. 11 and 12). The drug dissolution in such systems is often followed by an automatic, continuously recording technique that provides data of differential form, *i.e.*, dW_d/dt *versus* t. To apply Eq. 19 would require the experimental data to be integrated, which may introduce numerical integration errors. To avoid this problem, it is more convenient to use the following differential form of Eq. 19, which can be derived readily (10):

$$\frac{dW_d}{dt} = \frac{3(W_0)_1 F_d K^*}{200}\sum_{n=0}^{2}\binom{2}{n}[-K^* \max(t-\tau,0)]^{(2-n)} \mathrm{erfc}\left\{\left[\frac{1}{\sigma}\ln[K^* \max(t-\tau,0)] - n\sigma\right]\Big/\sqrt{2}\right\} \exp[(n^2-9)\sigma^2/2] \quad \text{(Eq. 21)}$$

Monodisperse Systems Dissolving under Nonsink Conditions—A monodisperse system dissolving under nonsink conditions is described by $\sigma \to 0$ and $\alpha < \infty$, for which Eq. 13 (and, similarly, Eq. 17) reduces to (6):

$$p = F_d - F_d\sum_{n=0}^{3}\binom{3}{n}(-H)^{(3-n)} = F_d[1-(1-H)^3] \quad \text{(Eq. 22)}$$

Differentiation and rearrangement of Eq. 22 followed by integration give:

$$p = F_d[1 - x(K^*, \tau, \alpha)^3] \quad \text{(Eq. 23)}$$

where $x(K^*, \tau, \alpha)$ is the root of the equation:

$$\phi(x, \alpha) - \phi(1, \alpha) + K^* \max(t-\tau, 0) = 0 \quad \text{(Eq. 24)}$$

where the function ϕ is defined by:

$$\phi(x,\alpha) = \frac{\alpha^3+1}{\alpha^2}\frac{1}{6}\ln\frac{(x+\alpha)^2}{x-\alpha x+\alpha^2} + \frac{1}{\sqrt{3}}\tan^{-1}\frac{2x-\alpha}{\alpha\sqrt{3}} \quad \alpha \neq 0 \quad \text{(Eq. 25)}$$

[3] The nonsink condition was defined as the condition in a solute cumulating, closed system where the particles are exposed to the same bulk concentration of solute.

Equation 23 is preferable compared to Eq. 22 because it can be evaluated faster and more accurately on a digital computer.

For the special case $\alpha = 0$, Eq. 22 becomes:

$$p = F_d\{1 - [1 + 2K^* \max(t-\tau, 0)]^{-3/2}\} \quad \text{(Eq. 26)}$$

Monodisperse Systems Dissolving under Sink Conditions—For sink conditions ($\alpha \to 0$), Eq. 22 becomes:

$$p = F_d\{1 - \{\max[1 - K^* \max(t-\tau, 0), 0]\}^3\} \quad \text{(Eq. 27)}$$

where the max relationship ensures that $p \to F_d$ for $t \to \infty$ as expected[4].

The differential form of Eq. 27 is:

$$\frac{dW_d}{dt} = 3(W_0)_1 F_d K^*\{\max[1 - K^* \max(t-\tau, 0), 0]\}^2 \quad \text{(Eq. 28)}$$

which may be more appropriate than Eq. 27 when the dissolution data obtained are of differential form. For the special case $\tau = 0$, Eq. 27 can, according to Eq. 10, be written:

$$(W/W_0)^{1/3} = \max(1 - K^* t, 0) \quad \text{(Eq. 29)}$$

which is the well-known Hixson–Crowell cube root law (13). However, it would be incorrect to apply this equation directly to the dissolution of compounded drugs because W_0 and W are usually not accurately known for such systems.

EXPERIMENTAL

Commercially available aminophylline tablets with a label claim of 97.2 mg (1.5 gr) of aminophylline (theophylline ethylenediamine) were used for the dissolution tests. A Hanson dissolution apparatus[5] modified to accommodate a round-bottom resin kettle (14) was used at a stirring speed of 50 rpm witn 900 ml of water at 37°. Filtered aliquots were automatically withdrawn every 10 min from 3 to 113 min and analyzed spectrophotometrically at 273 nm.

The dissolution data, expressed as percent of label claim dissolved *versus* time, were analyzed[6] by a nonlinear least-squares regression technique according to the mathematical models discussed using FUNFIT, an interactive time-sharing program for general nonlinear regression and curve fitting (15).

RESULTS AND DISCUSSION

Although the dissolution kinetic equation, Eq. 17, mathematically may seem difficult to apply because the dependent variable, p, appears in both explicit and integral form, it can readily be fitted to p *versus* t dissolution data using a digital computer. To do so, p must be expressed numerically as an explicit function of t and the parameters K^*, F_d, σ, τ, and α. This is done as follows. Define:

$$y = \int_0^{\max(t-\tau,0)} p\,dt \quad \text{(Eq. 30)}$$

Then:

$$\frac{dy}{dt} = p \quad \text{(Eq. 31)}$$

and Eq. 17 can be written:

$$\frac{dy}{dt} = F_d - \frac{F_d}{2}\sum_{n=0}^{3}\binom{3}{n}(-A)^{(3-n)} \mathrm{erfc}\left[\left(\frac{1}{\sigma}\ln A - n\sigma\right)\Big/\sqrt{2}\right] \exp[(n^2-9)\sigma^2/2] \quad \text{(Eq. 32)}$$

where:

$$A = K^* \max(t-\tau, 0) - \frac{K^*}{F_d(1+\alpha^3)}y \quad \text{(Eq. 33)}$$

and:

$$y = 0 \qquad \text{for } t \leq \tau \quad \text{(Eq. 34)}$$

Equations 32–34 constitute an initial value problem that can be solved

[4] It is also readily verified using L' Hospital's rule that $W/W_0 \to 0$ for $t \to \infty$ in Eqs. 1 and 7, that $p \to F_d$ for $t \to \infty$ in Eqs. 13, 17, 19, 22, and 23, and that $dW_d/dt \to 0$ for $t \to \infty$ in Eq. 21.

[5] Hanson Research Corp., Northridge, CA 91324.

[6] The computations were done on an IBM 370/145 digital computer.

Table I—Dissolution Kinetic Parameters for Aminophylline Tablets Obtained by Nonlinear Least-Squares Regression Using Eq. 17

Tablet	Specific Dissolution Rate Parameter, $K^* \times 100$, min^{-1}	Dissolution Availability, F_d, %	Lag Time due to Disintegration, τ, min	Dispersion Parameter, σ	r
1	1.85	98.2	7.33	0.338	0.99882
2	1.96	99.9	6.19	0.302	0.99897
3	1.70	96.3	6.15	0.295	0.99854
4	2.25	96.5	6.71	0.431	0.99871
5	2.46	105	5.42	0.439	0.99848
6	1.82	98.3	6.20	0.374	0.99865
Mean	2.01	99.0	6.33	0.363	0.99870
CV, %	14.4	3.24	10.1	17.2	

numerically using a suitable integration algorithm such as a fourth-order Rhunge–Kutta method (16). The integration algorithm evaluates y as a function of time:

$$y(t) = \int_0^{\max(t-\tau,0)} p\,dt \qquad \text{(Eq. 35)}$$

which, when substituted into Eq. 32, gives p as a function of time, *i.e.*:

$$p = F_d - \frac{F_d}{2}\sum_{n=0}^{3}\binom{3}{n}(-A)^{(3-n)} \operatorname{erfc}\left[\left(\frac{1}{\sigma}\ln A - n\sigma\right)\Big/\sqrt{2}\right]\exp[(n^2-9)\sigma^2/2] \qquad \text{(Eq. 36)}$$

where:

$$A = K^*\max(t-\tau,0) - \frac{K^*}{F_d(1+\alpha^3)}y(t) \qquad \text{(Eq. 37)}$$

This procedure can be programmed and executed with a suitable nonlinear regression program to obtain the dissolution kinetic parameters K^*, F_d, τ, and σ directly from percent dissolved *versus* time dissolution data. The data treatment can readily be established as a simple routine procedure, either separately or directly in the form of a computer interface to a dissolution apparatus.

The practical value and power of Eq. 17 are substantiated by the significance and simplicity of its parameters. The specific dissolution rate parameter, K^*, is the most important parameter since it measures the dissolution rate. It has the remarkable property of not being dependent on the degree of sink or nonsink conditions in the dissolution or on the amount of drug used. It, therefore, allows a greater flexibility with respect to the design of the dissolution apparatus. This parameter can be interpreted as a dissolution rate parameter "extrapolated" to complete sink condition so it is automatically corrected for any degree of nonsink conditions (6). It gives a measure of the intrinsic dissolution rate properties of the drug.

A comparison of drug products on the basis of the K^* parameter is particularly simple and meaningful. For example, if $K_A^*/K_B^* = x$ in a comparison of Brand A and Brand B of tablets, capsules, or powders, then Brand A is x times faster dissolving than Brand B in the sense that it takes B x times as long to dissolve to the same extent (*e.g.*, 50, 95, or 100%) as Brand A. This is the case provided that the dissolution lag time, τ, and the dispersion parameter, σ, are not too different between the two products. This property is related to the concepts of intrinsic dissolution profiles and time scaling discussed previously (9).

In theory, the K^* ratio property extends over a wide range of experimental conditions. Therefore, the K^* parameter may be particularly valuable to consider in correlation analysis of *in vitro–in vivo* relationships.

The dissolution lag time, τ, is a more important and meaningful parameter to determine than the conventional disintegration time because it measures the effect of the disintegration on drug dissolution. This parameter is determined simultaneously with the other dissolution parameters and not in a separate "destructive" experiment as often is done in disintegration tests. This parameter is defined in a simple and meaningful way. It measures the time difference between the initial dissolution phase dominated by the disintegration reaction and the initial dissolution phase predicted under ideal conditions with instantaneous and complete disintegration.

Equation 17 appears to be the only kinetically based dissolution equation applicable under nonsink conditions that considers polydisperse systems. Other equations presented assume monodisperse systems that are never met in pharmaceutical preparations. For this reason, they are not able to describe or measure the distribution effect that shows up as a pronounced "tailing" in the later stage of dissolution if a fraction of the dispersed system is relatively slowly dissolving because it consists of particle aggregates, larger particles, or particles of a different crystal form (9). This inability is particularly unfortunate, because such dissolution behavior is important to detect and quantitate since it affects the systemic availability of drugs showing incomplete absorption due to dissolution rate-limited absorption.

Equation 17 does not have this deficiency. It is able to describe the distribution effect of polydisperse systems in terms of the dimensionless parameter σ, which is a measure of how "disperse" the effective particle distribution is. This parameter gives an intrinsic characterization of a particle system since it is essentially unaffected by experimental variables such as vehicle composition, pH, temperature, and agitation conditions (9).

The dissolution availability, F_d, measures a formulation's drug content in terms of the amount available for dissolution. In the biological context,

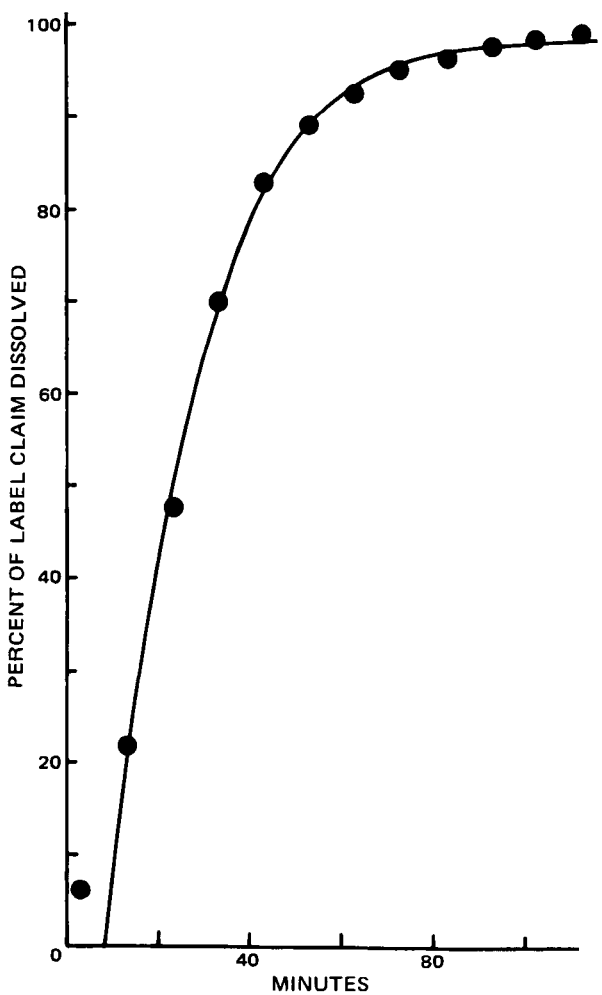

Figure 1—*Equation 17 fitted by nonlinear least-squares regression to dissolution data for an aminophylline tablet. The estimated dissolution kinetic parameters are given in the first row of Table I (Tablet 1).*

Table II—Dissolution Kinetic Parameters for Aminophylline Tablets Obtained by Nonlinear Regression Using Eq. 23 [a]

Tablet	Specific Dissolution Rate Parameter, $K^* \times 100$, min^{-1}	Dissolution Availability, F_d, %	Lag Time due to Disintegration, τ, min	r
1	2.04	110	9.43	0.99655
2	2.10	111	8.27	0.99790
3	2.17	107	8.90	0.99612
4	1.86	107	8.54	0.99787
5	1.84	116	7.17	0.99761
6	1.69	110	7.52	0.99832
Mean	1.95	110	8.305	0.997395
CV, %	9.37	3.01	10.19	

[a] Equation 23, which is identical to Eq. 17 with $\sigma = 0$, assumes that the dissolving particles are monodisperse.

this measure is more realistic than that obtained by conventional "drastic" analytical methods involving grinding followed by organic solvent extraction, which give an unrealistic measure of the amount available for dissolution *in vivo*.

The dissolution capacity coefficient, α, is a measure of the dissolution capacity of the experimental system. The parameter has a large value when the capacity is large, *i.e.*, when the solvent volume to drug weight ratio and the drug solubility are high. Its value decreases with the increasing degree of nonsink conditions (6). A flow-through system with complete sink conditions is described by letting $\alpha = \infty$. The dissolution capacity coefficient has the remarkable property that it provides an "automatic correction," so the other parameters, K^*, σ, τ, and F_d, can be determined unaffected by the degree of sink or nonsink conditions in the experimental design.

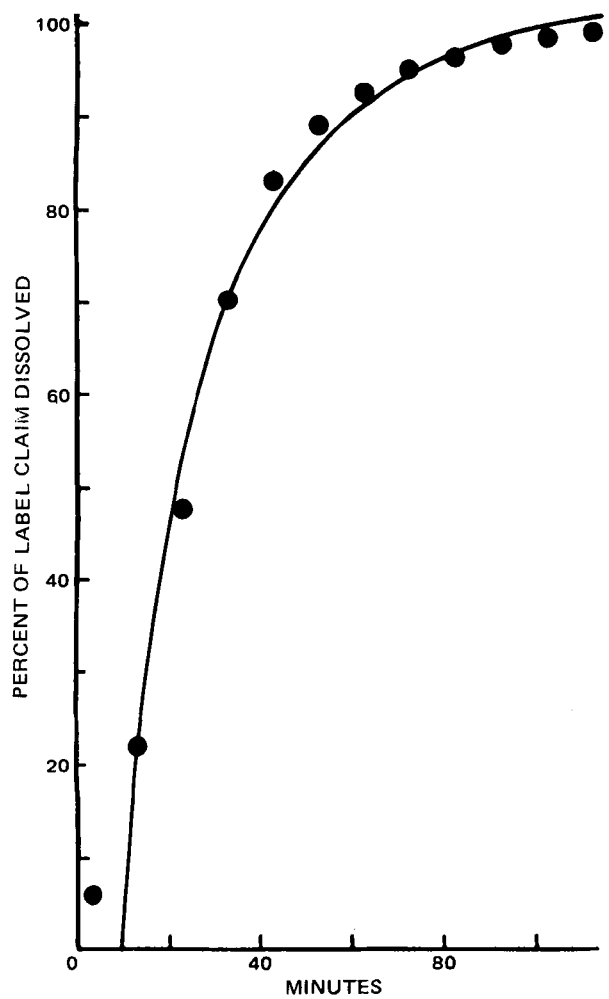

Figure 2—*Equation 23 fitted by nonlinear least-squares regression to dissolution data for an aminophylline tablet. Equation 23 is identical to Eq. 17 with $\sigma = 0$ and assumes a monodisperse particle system. The estimated dissolution kinetic parameters are given in the first row of Table II (Tablet 1).*

Characterization of Aminophylline Tablet Dissolution Properties—The dissolution data for six aminophylline tablets agreed well ($r = 0.99870$) with the kinetic model, Eq. 17 (Table I and Fig. 1). The agreement was consistent from tablet to tablet as reflected in the r values. The variability of each parameter appears to be of a magnitude that can be expected from the variation in physical properties and content uniformity caused by the limited reproducibility of the tablet manufacturing process. The variability is fairly small for F_d, as may be expected since the tablet size and the drug to excipient ratio facilitate a good drug uniformity in the manufacturing process.

The variability of the other parameters (K^*, τ, and σ) is considerably greater. These parameters are expected to be more dependent on the tablet's physical properties that mainly depend on the composition of the excipients and the compression dynamics. However, the variability does not seem to be greater than the mean values of the parameters, which can be considered to give a good representation of the overall dissolution properties of the batch from which the tablets are drawn.

There are ample opportunities for extensive statistical comparisons of brands and batches of tablets on the basis of the kinetic parameters given in Table I. With established statistical tests, it can be concluded whether tablets differ with respect to dissolution rate (K^*), disintegration (τ), drug uniformity (F_d), or dispersibility and particle aggregation (σ). The information may be used ultimately for more detailed analysis of *in vitro–in vivo* correlation than is possible using approaches based on "one-point" *in vitro* methods (*e.g.*, $t_{1/2}$), which give an incomplete characterization and ignore important aspects of the dissolution behavior.

It is of interest to investigate how well Eq. 17 fits the dissolution data if it is assumed that the dissolving particles are monodisperse, *i.e.*, $\sigma = 0$, which leads to Eq. 23 as a special case. Although the mean value for K^* obtained using Eq. 23 (Table II) does not differ significantly from that obtained using Eq. 17 (Table I), a pairwise comparison of the individual K^* values shows little agreement. This result seems to indicate that the assumption $\sigma = 0$ leads to a somewhat erratic determination of K^*. Judged from the r values, Eq. 17 also appears to fit the data significantly better than Eq. 23. Equation 23 tends to give significantly higher values for F_d and τ than Eq. 17 (Tables I and II). This bias is reflected in the definite consistent trend in the fitted curves as shown by Fig. 2, which clearly demonstrates the inadequacy of the model that assumes $\sigma = 0$. Thus, the size distribution effect must be considered to get a proper characterization of the drug's dissolution properties.

Comparison with an Empirical Equation—It is of interest to compare Eq. 17 with what appears to be the most flexible or versatile empirical dissolution equation presented:

$$p = p_\infty \{1 - \exp[-\max(t - T, 0)^b/a]\} \qquad \text{(Eq. 38)}$$

where p_∞ is the limit for p as $t \to \infty$, T is the location parameter, a is the scale parameter, and b is the shape parameter. This equation is a modification of the Weibull distribution function; it has been presented in various forms (3–5) and received much attention primarily because it has the ability to summarize dissolution profiles of pronounced sigmoid shape and of more regular shapes (3). However, because it is an empirical equation not derived from kinetic principles, it has several deficiencies:

1. The equation has no kinetic basis and can only summarize, but not adequately characterize, the dissolution kinetic properties of a drug.
2. It does not contain a single parameter that gives a simple measure

Table III—Dissolution Kinetic Parameters for Aminophylline Tablets Obtained by Nonlinear Least-Squares Regression Using Eq. 38

Tablet	p_∞, %	Location Parameter, T, min	Shape Parameter, b	Scale Parameter, a	r
1	97.9	4.89	1.28	58.8	0.99890
2	99.3	0[a]	1.36	92.3	0.99933
3	96.3	3.74	1.29	59.5	0.99863
4	95.6	4.09	1.16	43.2	0.99824
5	104	0[a]	1.20	56.9	0.99883
6	97.1	0[a]	1.26	74.8	0.99896
Mean	98.4	2.12	1.26	64.3	0.99882
CV, %	3.09	111	5.60	26.5	

[a] The fit is constrained by the lower limit (= 0) assigned to this parameter.

of the intrinsic drug dissolution rate. Instead, the rate is determined by a, b, and T in a way that seems extremely difficult to interpret.

3. The equation is of limited use for establishing *in vitro–in vivo* correlations.

4. Although the location parameter, T, gives an indication of when dissolution starts, the equation provides no measure of the effect of the disintegration reaction on the drug release. In fact, a negative value would have been obtained for T in two of the three cases if the lower limit was not set to zero for this parameter (Table III).

5. Equation 38 is not able to measure the distribution effect. It is not possible, from any of its parameters, to see whether some fraction of the particle system dissolves considerably slower than the rest.

The only advantages of Eq. 38 seem to be that it can summarize a great variety of dissolution curves and that it, because of its asymptotic property, can give an estimate of F_d by the parameter p_∞. Although Eq. 38, judged from the mean r value in Table III, appears to give a slightly better fit to the dissolution data than Eq. 17 (Table I and Fig. 3), this is not significant when compared by a t test (<0.05).

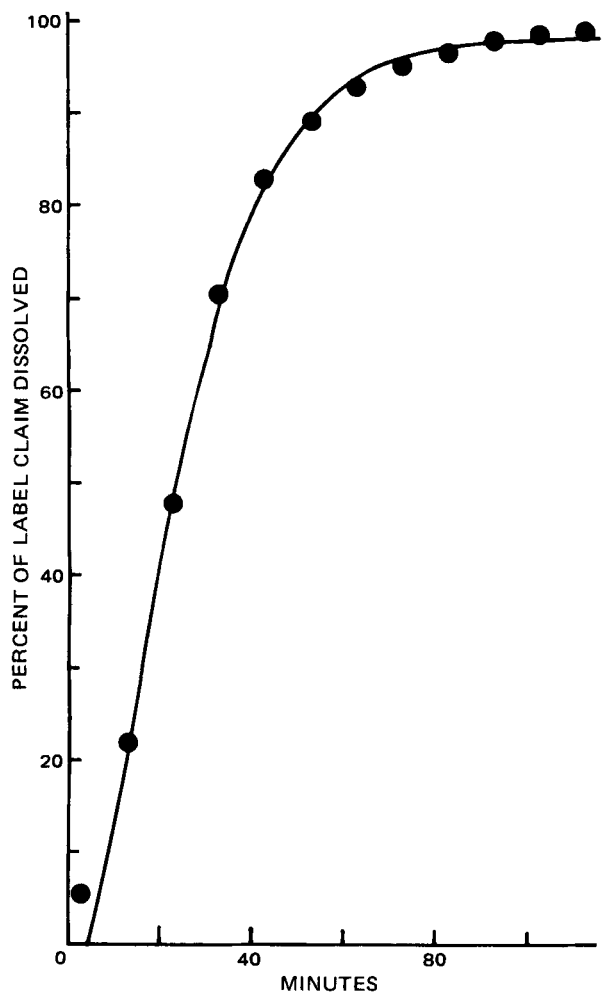

Figure 3—*Equation 38 fitted by nonlinear least-squares regression to dissolution data for an aminophylline tablet. The estimated parameters of the equation are given in the first row of Table III (Tablet 1).*

Among the many kinetically based dissolution equations published, there may well be some that fit the present dissolution data as well as Eq. 17. However, the adequacy of such equations for general usage can first be established when they are tested over a wide range of conditions and the kinetic significance of the parameters in the equation can be verified. Equation 17 in the form $\alpha = \infty$, $\beta = 100$, and $\tau = 0$ already has described accurately dissolution of the 60–85-mesh fraction of tolbutamide (12) and dissolution of micronized gliburide (10). Thus, with the present dissolution data included, the equation has accurately described the dissolution of a broad range of drug systems with widely different particle sizes, shapes, degrees of dispersity, and solubilities, dissolving under sink as well as nonsink conditions at various agitation conditions.

Although the approach presented provides a powerful tool for analysis of drug dissolution, the experimental requirements for its use can readily be met. For dissolution under nonsink conditions, the dissolving particles must be dispersed evenly in the dissolution liquid and be exposed to constant agitation, temperature, and pH. The sampling procedure must not significantly disturb the dissolution process and should be extensive enough to represent properly the complete dissolution process. For dissolution under sink conditions using a dissolution cell, the dissolving particles must be evenly dispersed over the cross section of the cell in a thin layer. Such conditions can be established readily for pure drug powders (10, 12). However, some engineering problems are expected for disintegrating dosage forms because of the possibility of uneven distribution and agitation conditions for the disintegrated particles. For such drug systems, it seems more appropriate to use a nonsink, constant volume-type dissolution apparatus.

Equation 17 shows great potential in characterizing the dissolution properties of disperse systems and disintegrating solid dosage forms with relevance to dosage form development and quality control. In future investigations, it would be valuable to investigate the biological significance of the dissolution kinetic parameters for drug systems showing dissolution rate-limited absorption. Hopefully, such investigations will lead to quality control standards of documented biological significance.

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