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General Class of Multiparticulate Dissolution Models

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Abstract □ The dissolution of multiparticulate systems under sink and nonsink conditions can be described rigorously according to a generally applicable formula on the basis of the single-particle dissolution model and the initial particle distribution. The kinetic model for log-normal systems dissolving under sink conditions is extended to nonsink conditions as a specific example. The equation presented describes a general class of multiparticulate models for various values of the dispersion parameter and the dissolution capacity coefficient.

Keyphrases □ Dissolution model—multiparticulate systems under sink and nonsink conditions, generally applicable equations derived □ Models, dissolution—multiparticulate systems under sink and nonsink conditions, generally applicable equations derived □ Multiparticulate systems—dissolution model under sink and nonsink conditions, generally applicable equations derived

Characterization of dissolution behavior is often facilitated by the use of an appropriate mathematical model that enables the process to be summarized in terms of one or more parameters such as the dissolution rate constant. Since most dissolution tests are performed under nonsink conditions, the kinetics under such conditions are of interest. Various nonsink dissolution equations for multiparticulate systems have been derived (1–4), but they are based on monodisperse systems which are rarely met in practice (5).

A proper characterization of dissolution behavior must account for the particle-size distribution. This paper provides a general and rigorous description of dissolution under nonsink conditions on the basis of a single-particle dissolution model and the initial particle distribution. Log-normal powders are considered as a specific example. The equation presented describes a large class of multiparticulate dissolution models for various values of the dispersion parameter and the dissolution capacity coefficient.

THEORY

A previous publication (6) showed how the dissolution kinetics of a multiparticulate system can be rigorously described theoretically when the single-particle dissolution equation is known together with the initial particle-size distribution. Although equations for the general case (Eqs. 12 and 13 in Ref. 6) were derived assuming sink conditions, they can also be applied to nonsink dissolution.

In the current context, sink condition is defined as interparticle independent dissolution¹. This condition may be closely approximated in a noncumulating, open, flow-through system (7). A nonsink condition is defined as the condition in a solute-cumulating, closed system, where the particles are exposed to the same bulk concentration of solute. Dissolution according to the latter definition implies agitation that is intense enough to give a homogeneous bulk solute concentration and to suspend the dissolving particles freely in the vehicle.

The only difference between the mathematical description of the two systems is that, for nonsink conditions, dissolution is influenced by the bulk concentration of solute; therefore, the single-particle dissolution equation contains an additional time-dependent variable. Since this variable is a function of the total dissolution behavior of the system, mathematical analysis leads to an integral equation describing multiparticulate nonsink dissolution kinetics.

These principles can be illustrated on the basis of the well-known Noyes–Whitney kinetics (8) for log-normal powders and spherical particles without loss of generality. The choice of a log-normal distribution to approximate the initial particle distribution appears appropriate considering previous investigations (7, 9, 10).

Single-Particle Dissolution Equation—Consider a single spherical particle, in a polydisperse system, dissolving under nonsink conditions according to the Noyes–Whitney model:

$$dw/dt = -k_1s(c_i - c) = -k_2w^{2/3}[c_s - (W_0 - W)/V] \quad (\text{Eq. 1})$$

where w is the weight of the particle, s is its surface area, and c_i is the interfacial solute concentration which, in most cases, is close to the solubility concentration, c_s . Let it be assumed that k_1 and $k_2 = 4\pi(4/3\pi\rho)^{-2/3}k_1$ (ρ = density) are constants not dependent on the particle diameter. Such an assumption is reasonable, since it leads to the well-established cube root model (1) under sink conditions ($c = 0$). If the single-particle dissolution kinetics are different from the Noyes–Whitney kinetics (11) or if k (Eq. 1) is not constant, then the multiparticulate kinetics can still be treated similarly to the cases considered below. The bulk solute concentration, c (Eq. 1), is, according to the definition of nonsink conditions, equal to the ratio of the amount of powder dissolved, $(W_0 - W)$, to the vehicle volume, V .

It is useful to introduce the dissolution capacity coefficient defined by:

$$\alpha = [(c_sV - W_0)/W_0]^{1/3} = [(c_iV - W_0)/W_0]^{1/3} \quad (\text{Eq. 2})$$

Equation 1 then integrates to yield:

$$w = \left[w_0^{1/3} - \frac{3k_2W_0\alpha^3}{V}t - \frac{3k_2W_0}{V} \int_0^t \frac{W}{W_0} dt \right]^3 \quad (\text{Eq. 3})$$

For comparison with earlier derivations (6, 12), it is convenient also to

¹ This definition is different from the usual definition, which defines a sink condition as a condition where the solute bulk concentration does not increase beyond a small fraction (10–15%) of the solubility concentration.

present the single-particle dissolution equation derived for sink conditions ($c = 0$, Eq. 1):

$$w = (W_0^{1/3} - kt)^3 \quad (\text{Eq. 4})$$

where:

$$k = 3k_2c_s \quad (\text{Eq. 5})$$

According to Eqs. 2-5, Eq. 3 can be written in the following form:

$$w = (W_0^{1/3} - A)^3 \quad (\text{Eq. 6})$$

where:

$$A = \frac{\alpha^3 k}{1 + \alpha^3} t + \frac{k}{1 + \alpha^3} \int_0^t \frac{W}{W_0} dt \quad (\text{Eq. 7})$$

Multiparticulate Dissolution Equation—If log-normal powders are considered, the initial particle distribution is approximated by Eq. 15 from Ref. 6, which together with the single-particle dissolution model, Eq. 6, completely defines the multiparticulate dissolution according to Eq. 13 from Ref. 6. Equation 4 was used to derive the expression (Eq. 18 in Ref. 6) for dissolution of truncated log-normal powders under sink conditions. This equation was later presented in a more compact form (Eq. 15 in Ref. 12), which can be written using the notation defined previously (13):

$$\frac{W}{W_0} = \sum_{n=0}^3 \binom{3}{n} (-K^*t)^{(3-n)} \times \frac{F(T_2 - n\sigma) - F(T_1 - n\sigma)}{F(j - 3\sigma) - F(-i - 3\sigma)} \exp[(n^2 - 9)\sigma^2/2] \quad (\text{Eq. 8})$$

where:

$$T_1 = \max(\ln K^*t, -i\sigma)/\sigma \quad (\text{Eq. 9})$$

$$T_2 = \max(\ln K^*t, j\sigma)/\sigma \quad (\text{Eq. 10})$$

$$F(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^x \exp(-x^2/2) dx \quad (\text{Eq. 11})$$

The use of the max relationship (Eqs. 9 and 10) in this expression is related to the fact that a rigorous definition of the single-particle dissolution equation is not given by Eq. 4 but by:

$$w = [\max(w_0^{1/3} - kt, 0)]^3 \quad (\text{Eq. 12})$$

since it is required that $w \rightarrow 0$ for $t \rightarrow \infty$, which is not the case in Eq. 4. The operator P introduced earlier (6) automatically accounts for this lack of generality. The "switch" in T_1 (Eq. 9) occurs at the so-called critical time (14-17) when the smallest particles start disappearing. The switch in T_2 denotes the completion of dissolution. At that time and thereafter, $T_1 = T_2 [= \ln(K^*t)/\sigma]$, so $W/W_0 = 0$ as expected.

It is apparent from the the derivation of Eq. 8 (6, 13) that it can be readily extended to nonsink conditions. The only change in the derivation is that the single-particle dissolution equation (Eq. 6) is somewhat different from Eq. 4. However, this difference can be accounted for simply by substituting A for kt throughout. The following nonsink dissolution equation for log-normal powders results:

$$\frac{W}{W_0} = \sum_{n=0}^3 \binom{3}{n} (-G)^{(3-n)} \times \frac{F(T_2 - n\sigma) - F(T_1 - n\sigma)}{F(j - 3\sigma) - F(-i - 3\sigma)} \exp[(n^2 - 9)\sigma^2/2] \quad (\text{Eq. 13})$$

where:

$$T_1 = \max(\ln G, -i\sigma)/\sigma \quad (\text{Eq. 14})$$

$$T_2 = \max(\ln G, j\sigma)/\sigma \quad (\text{Eq. 15})$$

$$G = \frac{\alpha^3 K^*}{1 + \alpha^3} t + \frac{K^*}{1 + \alpha^3} \int_0^t \frac{W}{W_0} dt \quad (\text{Eq. 16})$$

If the truncation parameters i and j are more than 3, then the particle distribution can be just as well approximated by an "ideal" distribution ($i = j = \infty$), which leads to (13):

$$\frac{W}{W_0} = \sum_{n=0}^3 \binom{3}{n} (-G)^{(3-n)} \left[1 - F\left(\frac{1}{\sigma} \ln(G) - n\sigma\right) \right] \times \exp[(n^2 - 9)\sigma^2/2] \quad (\text{Eq. 17})$$

Equation 13 describes a general class of multiparticulate dissolution

models for both mono- and polydisperse systems and nonsink and sink conditions (Table I). A monodisperse powder is described by letting $\sigma = 0$; the sink condition is described by letting $\alpha = \infty$. For closed systems ($V = \text{constant}$), α always is finite, so a sink condition can only be approached when $\alpha \rightarrow \infty$. Although α is not defined by Eq. 2 for open systems operating under sink conditions, it is meaningful and mathematically correct to define the dissolution capacity coefficient to be infinite ($\alpha = \infty$) for such systems. For example, according to Eq. 16, $G \rightarrow K^*t$ for $\alpha \rightarrow \infty$; i.e., for $c_i V \gg W_0$, Eqs. 13 and 17 approach the equations valid for sink conditions as expected. A monodisperse system is described by letting $\sigma \rightarrow 0$, which leads to:

$$\frac{W}{W_0} = \sum_{n=0}^3 \binom{3}{n} (-G)^{(3-n)} = (1 - G)^3 \quad (\text{Eq. 18})$$

or:

$$f = 1 - G \quad (\text{Eq. 19})$$

where $f = (W/W_0)^{1/3}$ is introduced for convenience. Differentiation and rearrangement of Eq. 19 give:

$$(\alpha^3 + 1) \frac{df}{\alpha^3 + f^3} = -K^*dt \quad (\text{Eq. 20})$$

which, for $\alpha \neq 0$, integrates to:

$$\phi(f) = \phi(1) - K^*t \quad \max(-\alpha, 0) \leq f \leq 1 \quad (\text{Eq. 21})$$

where:

$$\phi(f) = \frac{\alpha^3 + 1}{\alpha^2} \left[\frac{1}{6} \ln \frac{(f + \alpha)^2}{f^2 - \alpha f + \alpha^2} + \frac{1}{\sqrt{3}} \tan^{-1} \frac{2f - \alpha}{\alpha\sqrt{3}} \right] \quad (\text{Eq. 22})$$

For $\alpha = 0$, Eq. 20 integrates to:

$$f^{-2} = 1 + 2K^*t \quad 0 < f \leq 1 \quad (\text{Eq. 23})$$

Furthermore, it can be seen (Eq. 19) that if a monodisperse system ($\sigma = 0$) is exposed to a large excess of solvent so that $c_i V \gg W_0$ ($\alpha \rightarrow \infty$), the dissolution kinetics approach the Hixson-Crowell cube root law:

$$f = (W/W_0)^{1/3} = 1 - K^*t \quad (\text{Eq. 24})$$

RESULTS AND DISCUSSION

Effective Particle Distribution—The description of the kinetics of polydisperse systems presented is based on a log-normal, spherical approximation to the initial particle distribution, the simplest approximation in most cases (7, 9, 10). Even if particle-size analysis reveals a significant deviation from log-normality and the particle shapes are considerably different from spherical, the effective size distribution may still be close to log-normal with respect to dissolution behavior. *The effective particle distribution is defined as the distribution of a hypothetical system of spherical particles where each individual spherical particle best approximates the real particle according to the single-particle dissolution equation expressed on a w/w_0 versus time basis.*

Most particle-size distributions are characterized by a pronounced skewness to the right (5, 9). The dispersion parameter, σ , takes into account not only how broad a distribution is but also such skewness. This single parameter, therefore, appears to be the simplest, general measure of the distribution effect. The value of K^* and σ in characterizing dissolution behavior was discussed previously (13). The equations summarized in Table I have considerable practical value, since they enable dissolution behavior to be characterized in terms of these parameters. Evaluation can be made under sink as well as nonsink conditions, thus making the approach generally applicable and feasible using almost any dissolution apparatus.

Numerical Treatment—The experimental determination of K^* and σ under sink conditions was described previously (13). A method for simultaneous determination of σ and K^* from nonsink dissolution data for polydisperse systems, employing Eq. 13 or 17, is described in the Appendix.

Effect of Dispersion Parameter—Theoretical dissolution profiles were calculated according to Eq. 17, with $\alpha^3 = 5$, using the numerical approach in the Appendix, to evaluate the effect of the dispersion parameter σ (Fig. 1). A cube root representation is used for a better comparison with the dissolution of monodisperse systems ($\sigma = 0$) dissolving under sink conditions (Eq. 24). Only a slight deviation from linearity is observed due to the nonsink conditions ($\alpha^3 = 5$) for the monodisperse systems (second curve from left). An increasing deviation from linearity is observed for increasing values of the dispersion parameter as expected.

Table I—A General Class of Multiparticulate Dissolution Models Based on Eq. 13

Dissolution Capacity Coefficient ^a , α	Dispersion Parameter, σ	Truncation Parameters ^b , i and j	Particle Distribution	Condition	Dissolution Model
$-1 < \alpha < \infty$	$\sigma > 0$	i and $j < \infty$	Truncated log-normal	Nonsink	Eq. 13
$-1 < \alpha < \infty$	$\sigma > 0$	$i = j = \infty$	Ideal log-normal	Nonsink	Eq. 17
$-1 < \alpha < \infty$	$\sigma = 0$	$i = j = 0$	Monodisperse	Nonsink	Eq. 21 ($\alpha \neq 0$), Eq. 23 ($\alpha = 0$)
$\alpha = \infty$	$\sigma > 0$	i and $j < \infty$	Truncated log-normal	Sink	Eq. 8
$\alpha = \infty$	$\sigma > 0$	$i = j = \infty$	Ideal log-normal	Sink	Eq. 17 with $G = K^*t$
$\alpha = \infty$	$\sigma = 0$	$i = j = 0$	Monodisperse	Sink	Eq. 24

^a When $\alpha < 0$, dissolution will be incomplete: $\min(W/W_0) = -\alpha^3$ [in general, $\min(W/W_0) = \max(-\alpha^3, 0)$]. ^b The cases for semiideal distributions; i.e., $i = \infty, j < \infty$ or $i < \infty, j = \infty$ can similarly be described (13).

The numerical solution of Eq. 17 closely approached the numerical solution of Eq. 21 as $\sigma \rightarrow 0$, thus indicating satisfactory accuracy in the numerical technique used².

Deviations from Linearity in $\phi, (t)$ Plot for Polydisperse Systems—For monodisperse systems, Eq. 21 predicts a linear relationship between $\phi(f)$ and t , enabling K^* to be determined by linear regression. However, a deviation from linearity is expected in practice, since most systems are not monodisperse. The extent to which such deviations depend on σ is of interest. The exact theoretical curves in Fig. 1 for the nonsink dissolution of polydisperse systems were plotted according to Eq. 21, using K^*t instead of t as the independent variable for generality (Fig. 2)³.

The deviation from linearity is not greatly affected by σ in the initial dissolution phases, but it becomes more pronounced toward the end for σ values greater than about 0.2. This result indicates the need to follow dissolution to completion or near completion to get a reliable estimate of the degree of dispersion of a multiparticulate system.

Dissolution of Dosage Forms—The given equations are derived for multiparticulate systems of pure compounds. Particle systems produced by fast disintegrating tablets and capsules are multiparticulate, although perhaps not as well defined as those considered. The equations presented should be valuable to characterize the dissolution behavior of such dosage forms.

If the disintegration time, τ , is significant compared to the dissolution

time, the variable t in the equations presented should be redefined as:

$$t = \max(t - \tau, 0) \tag{Eq. 25}$$

for a better description of the kinetics. In such cases, τ may be treated as an additional parameter that can be determined from the dissolution data.

Experimental analysis of dissolution kinetics of polydisperse systems under nonsink conditions considering those models is in progress.

APPENDIX

Equations 13 and 17 appear somewhat complex to evaluate because the dependent variable, W/W_0 , occurs in implicit, nonlinear, integral form. A general numerical approach for nonlinear integral equations (18) is too complex for practical purposes. Fortunately, however, the problem can be transformed into an initial value problem, which can be solved readily using established numerical techniques (19) as follows. Let:

$$y = \int_0^t \frac{W}{W_0} dt \tag{Eq. A1}$$

$$y' = W/W_0 \tag{Eq. A2}$$

Substitution of these equations into Eqs. 13 and 17 yields the initial value problem:

$$y' = h(t, y) \quad y(0) = 0 \tag{Eq. A3}$$

The function h is simply the right-hand side of Eq. 13 (or 17), where $\int_0^t W/W_0 dt$ has been substituted by y . The $y(t)$ values obtained using a suitable integration algorithm will, when substituted into Eq. A3, give the required explicit functional relationship between the variables W/W_0 and t :

$$W/W_0 = y'(t) = h[t, y(t)] \tag{Eq. A4}$$

Once this relationship is defined, the parameters σ and K^* (as well as i ,

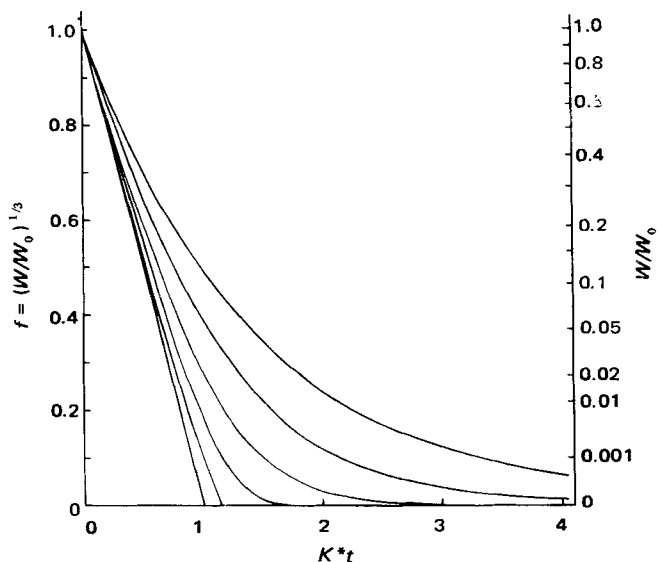


Figure 1—Effect of the dispersion parameter, σ , on the intrinsic dissolution profile of log-normal powders dissolving (Eq. 17) under nonsink conditions with a dissolution capacity coefficient $\alpha^3 = 5$. The straight line at the far left (Eq. 24), representing a monodisperse system ($\sigma = 0$) dissolving under sink conditions ($\alpha = \infty$), is included for comparison. The other five curves represent, from left to right, $\sigma = 0, 0.1, 0.2, 0.3$, and 0.4 , respectively.

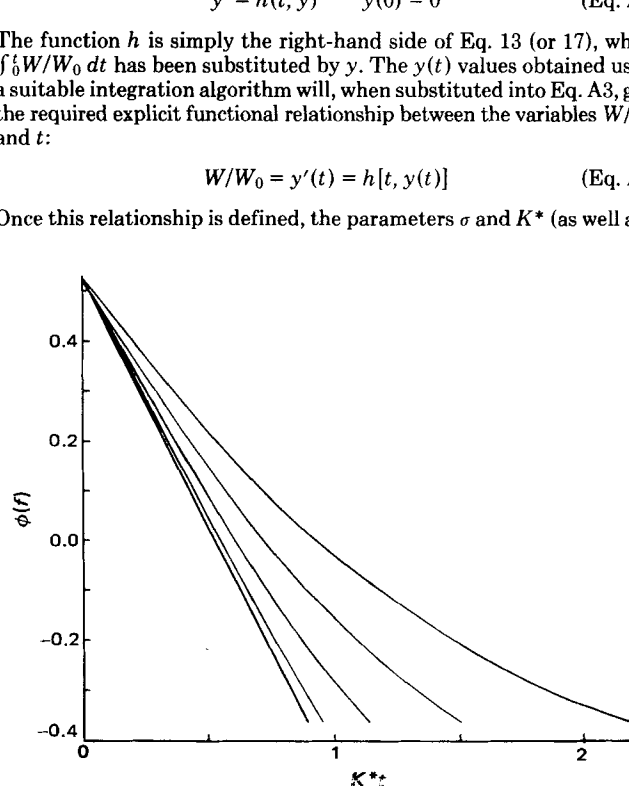


Figure 2—Effect of the dispersion parameter, σ , on linearity when nonsink ($\alpha^3 = 5$) dissolution data from log-normal powders (Eq. 17 and Fig. 1) are plotted according to Eq. 21, which is based on monodisperse systems. From left to right, $\sigma = 0, 0.1, 0.2, 0.3$, and 0.4 , respectively.

² A fourth-order Runge-Kutta method was used to solve the initial value problem.

³ Because Eq. 17 is based on an ideal distribution, the dissolution data are only plotted in Fig. 2 until 99% has dissolved to disregard approximation errors originating from the infinite tails of the untruncated distribution.

j , α , and τ) can then be determined directly from nonsink dissolution data (W/W_0 versus t) using a suitable nonlinear regression program.

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Bioavailability of Sulfadiazine in Rabbits Using Tablets Prepared by Direct Compression and Fluidized-Bed Granulation

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Abstract □ Experimental sulfadiazine tablets prepared by direct compression, using a commercially available direct compression tablet mass, were compared with experimental sulfadiazine tablets prepared by fluidized-bed granulation and commercially available sulfadiazine tablets USP. The values for friability and the time required to release 10 and 50% of the direct compression tablets were between those of the fluidized-bed tablets and the commercial product. With the commercial tablet as a standard, the extent of bioavailability was determined in rabbits; it was slightly higher for both the direct compression and fluidized-bed tablets. A statistically significant difference was found between the direct compression tablets and the standard with respect to the extent of bioavailability and the time of the peak.

Keyphrases □ Sulfadiazine—bioavailability of tablets prepared by direct compression and fluidized-bed techniques compared to commercial product, rabbits □ Bioavailability—sulfadiazine, tablets prepared by direct compression and fluidized-bed techniques compared to commercial product, rabbits □ Tablets—sulfadiazine, prepared by direct compression and fluidized-bed techniques, bioavailability compared to commercial product, rabbits □ Antibacterials—sulfadiazine, bioavailability of tablets prepared by direct compression and fluidized-bed techniques compared to commercial product, rabbits

Sulfadiazine tablets are considered to present actual or potential bioequivalence problems (1). The use of a direct compression technique for their preparation seemed of particular interest, since numerous formulation factors influencing the *in vitro* dissolution rate and bioavailability previously were studied with sulfadiazine as a model

substance. The compression pressure and binder concentration of acacia affected the dissolution rate of sulfadiazine tablets (2). The effects of disintegration agents, binders, fillers, and lubricants on the *in vitro* disintegration time and dissolution rate and the *in vivo* availability of various formulations were investigated (3). The highest blood levels in rabbits were found with formulations that did not contain magnesium stearate as the lubricant and lactose as the filler.

The influence of different lubricants in various concentrations on dissolution rate and bioavailability was studied (4). The highest bioavailability was obtained when the lubricant was kept at the minimum concentration with improved flow properties; a lubricant concentration resulting in optimum flow properties resulted in decreased bioavailability. Increasing amounts of starch paste, carboxymethylcellulose sodium, gelatin, or polyethylene glycol decreased *in vitro* drug release, whereas increasing amounts of povidone increased sulfadiazine release (5). Increasing amounts of carboxymethylcellulose sodium resulted in decreased bioavailability in rabbits (5).

The influence of the granulation method on the *in vitro* drug release and bioavailability of sulfadiazine tablets in rabbits was studied (6, 7). *In vitro* drug release decreased in the following order of granulation method: fluidized bed, nodulation, shaking, sieve pressure, and hole disk. *In vivo*