

Dissolution Rates of Finely Divided Drug Powders I

Effect of a Distribution of Particle Sizes in a Diffusion-Controlled Process

By W. I. HIGUCHI† and E. N. HIESTAND

An equation is derived to describe the dissolution rate of a particle with time in a diffusion-controlled dissolution process. This is applied to a hypothetical powder whose particles are approximately log-normally distributed. The change in size distribution with time is shown. Also, the dissolution rate of such a powder is compared with that of a monosized powder whose radius equals the mass median radius of the powder.

THE dissolution rate of many finely divided powders is diffusion controlled. In addition to the diffusion rate constant, the effect of the size distribution must be included in order to calculate the dissolution rate. This paper discusses the use of equations suitable for making these calculations.

THEORY

The Dissolution of a Single Particle.—Several simplifying assumptions enable one to describe the dissolution of a single particle. These assumptions are: (a) The dissolution rate is diffusion controlled. (b) The diffusion layer thickness is always the same for all particles of the same size and is comparable to or greater than the particle radius. (c) The concentration change of dissolved solid in the bulk solution is negligible at all times. (d) The effective particle shape approximates a sphere.

From Fick's law of diffusion,

$$\frac{dm}{dt} = D4\pi r^2 \frac{dC}{dr} \quad (\text{Eq. 1})$$

where m is the weight of a solid particle, D is the diffusion rate constant, C is the concentration of dissolved solid, t is time, and r is the radius of an imaginary sphere through which the diffusion occurs.

If a is the radius of the particle at time t , then $r > a$. The second assumption, (b), implies a quasi-steady state condition in the diffusion layer. Hence, the time required to establish this steady state condition is neglected (see the Appendix). Therefore, one may write

$$\frac{dm}{dt} \int_a^\infty \frac{dr}{r^2} = 4\pi D \int_{C_s}^{C_0} dC$$

C_s is the saturation concentration and C_0 is the concentration in the bulk of the solution. Upon integration one obtains

$$\frac{dm}{dt} = -4\pi D a \Delta C \quad (\text{Eq. 2})$$

where $\Delta C = C_s - C_0$.

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† Present address: School of Pharmacy, University of Michigan, Ann Arbor.

Since it has been assumed that ΔC is independent of time, particle size, a , is the only variable with time. From the volume of the particle, v , and density, ρ

$$\frac{dm}{dt} = \frac{d(v\rho)}{dt} = 4\pi\rho a^2 \frac{da}{dt} \quad (\text{Eq. 3})$$

Equating 2 and 3

$$a\rho \frac{da}{dt} = -D\Delta C$$

Let $a = a_0$ at $t = 0$, then

$$\int_{a_0}^a a da = -\frac{D\Delta C}{\rho} \int_0^t dt$$
$$a^2 = a_0^2 - \frac{2D\Delta C t}{\rho} \quad (\text{Eq. 4})$$

Equation 4 provides a means of calculating any particle diameter at time t if its radius at zero time is known.

The Total Dissolution Rate.—Let the particle size distribution at zero time be characterized by some function of a_0

$$n = n(a_0) \quad (\text{Eq. 5})$$

then the total number of particles, N , in any increment of sizes is

$$N = \int_{a_{s0}}^{a_{l0}} n(a_0) da_0 \quad (\text{Eq. 6})$$

where a_{l0} and a_{s0} are the largest and smallest particles at zero time in the increment; and by defining a_{s0} and a_{l0} as the extremes of the size distribution, N becomes the total number of particles in the entire sample.

The total mass of undissolved drug at

$$t < \frac{a_{s0}^2 \rho}{2D\Delta C}$$

is

$$M = \int_{a_{s0}}^{a_{l0}} 4/3\pi\rho a^3 n(a_0) da_0 \quad (\text{Eq. 7})$$

where a in the integral is given by Eq. 4.

When

$$t > \frac{a_{s0}^2 \rho}{2D\Delta C}$$

the lower limit of integration must be changed to correspond to the zero time radius of the particle that has just dissolved at time t , viz. a_{0t} :

$$a_{0t} = \left(\frac{2D\Delta Ct}{\rho} \right)^{1/2} \quad (\text{Eq. 8})$$

Combining Eqs. 4 and 7, and using the lower limit defined in Eq. 8, the amount of undissolved drug at time t is

$$M = \int_{a_{0t}}^{a_{10}} 4/3\pi\rho \left(a_o^2 - \frac{2D\Delta Ct}{\rho} \right)^{3/2} n(a_o) da_o \quad (\text{Eq. 9})$$

so the fraction undissolved, Q , at time t is

$$Q = \frac{\int_{a_{0t}}^{a_{10}} 4/3\pi\rho \left(a_o^2 - \frac{2D\Delta Ct}{\rho} \right)^{3/2} n(a_o) da_o}{M_o} \quad (\text{Eq. 10})$$

or

$$Q = \frac{\int_{a_{0t}}^{a_{10}} \left(a_o^2 - \frac{2D\Delta Ct}{\rho} \right)^{3/2} n(a_o) da_o}{\int_{a_{30}}^{a_{10}} a_o^3 n(a_o) da_o}$$

where M_o is the total weight of solid at zero time.

The Cumulative Distribution Curve.—The use of the cumulative plot of per cent of sample above a given size *vs.* the size is most convenient, especially when the particles are approximately log-normally distributed as they usually are when produced by milling. The fraction larger than a_{i0} is given by

$$f > a_{i0} = \frac{\int_{a_{i0}}^{a_{10}} 4/3\pi\rho a_o^3 n(a_o) da_o}{M_o} \quad (\text{Eq. 11})$$

The Change in Size Distribution with Time.—It is possible to evaluate the size distribution at times after the dissolution has started. When

$$t \leq \frac{a_{10}^2 \rho}{2D\Delta C}$$

$$f > a_i = \frac{\int_{a_{i0}}^{a_{10}} \left(a_o^2 - \frac{2D\Delta Ct}{\rho} \right)^{3/2} n(a_o) da_o}{\int_{a_{30}}^{a_{10}} \left(a_o^2 - \frac{2D\Delta Ct}{\rho} \right)^{3/2} n(a_o) da_o} \quad (\text{Eq. 12})$$

or when

$$t > \frac{a_{10}^2 \rho}{2D\Delta C}$$

$$> a_i = \frac{\int_{a_{i0}}^{a_{10}} \left(a_o^2 - \frac{2D\Delta Ct}{\rho} \right)^{3/2} n(a_o) da_o}{\int_{a_{0t}}^{a_{10}} \left(a_o^2 - \frac{2D\Delta Ct}{\rho} \right)^{3/2} n(a_o) da_o} \quad (\text{Eq. 13})$$

Obviously the integrals in Eqs. 12 and 13 are the same form as in Eq. 9 and may be evaluated if Eq. 9 may be evaluated.

The Size Distribution Function.—Equation 5 states that the size distribution is some function of a_o . Equation 9 is sufficiently complex that the integration becomes difficult if the distribution function is not simple. In practice, many materials have particle size distributions that correspond to a relatively simple function of a_o . Such a case will be described in a later publication which gives a test of the theory presented here.

Because many materials when milled produce a size distribution that approximates a log-normal distribution, it would be useful to substitute for $n(a_o)$ the log-normal distribution function. However, this becomes a somewhat complex case.

A log-normal distribution when plotted as n *vs.* a_o gives a skewed curve with the long tail toward the large diameters. In such a case the mass median diameter is much larger than the diameter corresponding to the mode of the histogram. Consequently, most of the mass is present in the region of the distribution where n is increasing as a_o is decreasing. Therefore, distributions approximately log-normal may also be approximately characterized over the region accounting for most of the mass by some inverse power of the radius. Figure 1 shows the reasonable correlation of such a case. This case corresponds to a distribution according to the equation

$$\frac{nv_o}{V_o} = \frac{K'}{a_o} \quad (\text{Eq. 14})$$

where $v_o = 4/3\pi a_o^3$; $V_o = \sum_{a_{30}}^{a_{10}} nv_o$ and K' is a constant. Hence

$$n = \frac{K}{a_o^4} \quad (\text{Eq. 15})$$

where K is another constant.

Note that Fig. 1 was plotted on log-probability paper; a straight line represents a material that is log-normally distributed. A plot of values cal-

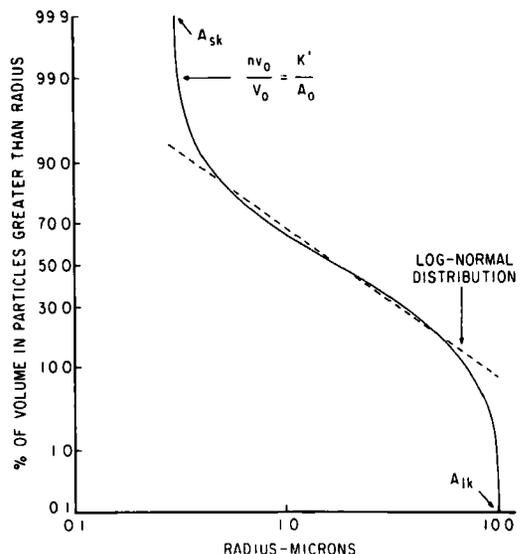


Fig. 1.—Comparison of the log-normal distribution with a simpler case, $n = \frac{K}{a_o^4}$.

culated using Eqs. 1 and 15 fits the log-normal line very closely except for the upper and lower 10% by volume. The contribution of the larger radius 10% to the dissolution will be small except at the very end of the dissolution process and the particles at the small end of the distribution will dissolve very rapidly. Consequently, after they have dissolved completely, these smallest particles will contribute nothing to the solution of Eq. 9. Therefore, deviations from the log-normal case resulting from the use of Eq. 15 are modest, and the general conclusions from its use may be considered to also be approximately true for the log-normally distributed case.

The Dissolution Rate of Powder when $n = K/a_o^4$.—Substituting from Eq. 15 into Eq. 10 and integrating gives

$$Q = \frac{4K\pi\rho}{3M_o} \left(\ln \frac{a_{i0} + a_i}{a_{oi}} - \frac{a_i}{a_{i0}} - \frac{a_i^3}{3a_{i0}^3} \right) \quad (\text{Eq. 16})$$

where

$$a_i = \sqrt{a_{i0}^2 - \frac{2D\Delta C t}{\rho}}$$

In our hypothetical case we do not have an experimental value for M_o so we must use Eq. 7, which gives

$$M_o = 4/3\pi\rho K \ln \frac{a_{i0}}{a_{o0}} \quad (\text{Eq. 17})$$

and

$$Q = \frac{1}{\ln \left(\frac{a_{i0}}{a_{o0}} \right)} \left(\ln \frac{a_{i0} + a_i}{a_{oi}} - \frac{a_i}{a_{i0}} - \frac{a_i^3}{3a_{i0}^3} \right) \quad (\text{Eq. 18})$$

In a real case it might be better to evaluate K to give the best fit to the real size distribution and use the experimental value of M_o in the equation. Of course this leads to some hypothetical values of the largest and smallest radii that correspond with the selected value of K . These we may designate a_{iK} and a_{oK} , respectively. It is necessary that $a_{iK} \geq a_{i0}$ and that $a_{oK} \leq a_{o0}$ where a_{i0} and a_{o0} now define the experimental largest and smallest particle in the real sample.

An Illustrative Example.—Figure 2 represents a plot of Eq. 18 when the following values are used: $a_{i0} = 10\mu$; $a_{o0} = 0.3\mu$; $\rho = 1.3 \text{ Gm./ml.}$; $\Delta C =$

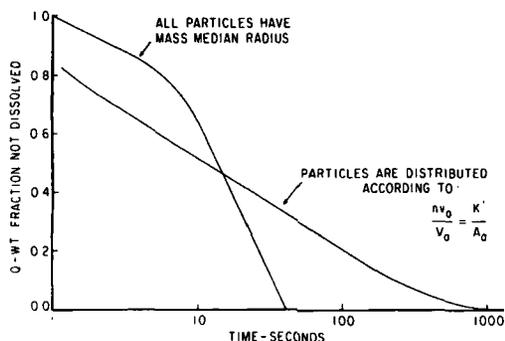


Fig. 2.—Comparison of the dissolution rate of a polydispersed powder with a monodispersed powder.

$1 \times 10^{-4} \text{ Gm./ml.}$; $D = 5 \times 10^{-6} \text{ cm}^2/\text{sec.}$ Note that Q vs. $\log t$ gives a nearly linear plot over much of the dissolution time.

According to Eq. 4, a_{o0} will dissolve completely when

$$t = \frac{(3 \times 10^{-6})^2 1.3}{2 \times 5 \times 10^{-6} \times 1 \times 10^{-4}} = 1.17 \text{ sec.}$$

and a_{i0} will dissolve completely when

$$t = \frac{(10 \times 10^{-4})^2 1.3}{2 \times 5 \times 10^{-6} \times 1 \times 10^{-4}} = 1300 \text{ sec.} = 21 \text{ min. and } 40 \text{ sec.}$$

Also, Fig. 2 shows the dissolution rate of a material if the entire material is assumed to have the radius of the mass median radius. Obviously, the results of a calculation based on a single particle size do not produce rates similar to those that include the entire size range.

Figure 3 shows the change of a_i and a_{oi} during the dissolution process.

Figure 4 represents the size distributions at the time when approximately half of the solid has dissolved. Obviously, the smallest particles are dissolving most rapidly and the size distribution changes accordingly.

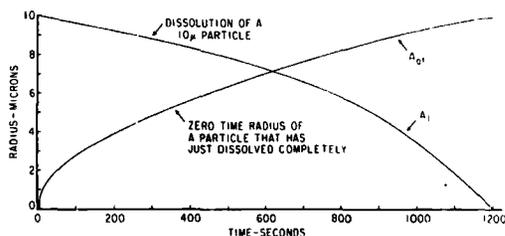


Fig. 3.—Changes in a_i and a_{oi} with time.

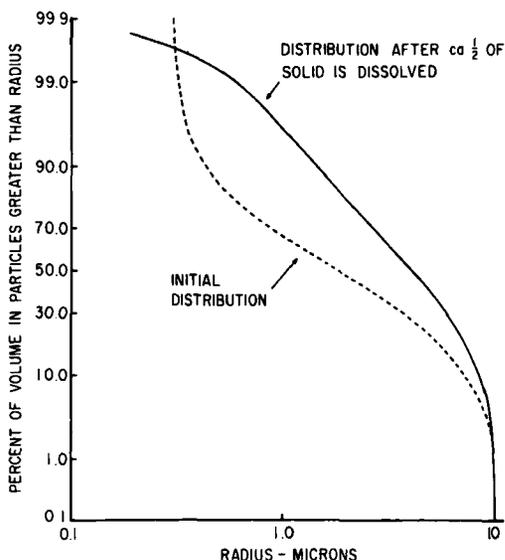


Fig. 4.—Illustration of size distribution changes during dissolution of powder.

Equations 13, 15, and 18 are combined to obtain Eq. 19.

$$a > a = \frac{\ln \frac{a_{10} + a_i}{a_0 + a} + \frac{a}{a_0} - \frac{a_i}{a_{10}} + \frac{a^3}{3a_0^3} - \frac{a_i^3}{3a_{10}^3}}{Q \ln \frac{a_{10}}{a_0}} \quad (\text{Eq. 19})$$

which was used to calculate this plot.

DISCUSSION

In the derivation of Eq. 18, ΔC was considered constant both with time and with particle size. The first requires that the liquid phase be large so that no significant change in concentration results from the dissolved solid. A later communication (1) describes a method of handling this problem when a correction is needed.

The particle size effect on solubility cannot be easily included since many sizes are present at any given time. If one assumes the interfacial tension to be about 50 ergs/cm.², then a 0.1 μ particle would have a solubility approximately 1.1 times that of a large particle. Usually this does not become significant except when dissolving in a nearly saturated vehicle. Such small particles dissolve so rapidly even when the change in ΔC is neglected that this effect cannot significantly alter the dissolution characteristics of the powder.

APPENDIX

Considerations on the Validity of Equation 2.—The use of the steady state equation to describe this case seems to be justified. The arguments used by Nielsen (2) for the case of crystal growth may be applied here since the growth and dissolution expressions are identical except for sign, as becomes evident in the following:

Fick's law of diffusion is

$$\frac{\partial C}{\partial t} = D\nabla^2 C \quad (\text{Eq. 1a})$$

When solved for the boundary conditions for growth it gives

$$C(r,t) = C_0 \left[1 - \frac{a}{r} \operatorname{erfc} \frac{r-a}{2\sqrt{Dt}} \right] \quad (\text{Eq. 2a})$$

where

$$\operatorname{erfc} y = \frac{2}{\sqrt{\pi}} \int_y^\infty e^{-E^2} dE$$

and when solved for the boundary conditions for dissolution it gives

$$c(r,t) = C_0 \left[\frac{a}{r} \operatorname{erfc} \frac{r-a}{2\sqrt{Dt}} \right] \quad (\text{Eq. 3a})$$

and from Eq. 1 the gradient across the boundary sphere at $r = a$ is

$$\frac{dm}{dt} = 4\pi a^2 D \left(\frac{\partial C}{\partial r} \right)_{r=a}$$

Obviously, $\partial c/\partial r$ for the two cases differ only in sign.

Equation 2 may be written to include the time dependent term. It becomes

$$\frac{dm}{dt} = 4\pi D \Delta C a \left(1 + \frac{a}{\sqrt{\pi D t}} \right) \quad (\text{Eq. 4a})$$

where the second term in the parenthesis represents the non-steady part, *i.e.*, the time dependent rate. If this term becomes much less than the first term before any significant material has dissolved then the steady state case is a very good approximation.

An estimate of the time, t' , required for this term to be negligible is obtained when

$$\int_0^{t'} dt \gg \int_0^{t'} \frac{adt}{\sqrt{\pi D t}} \quad (\text{Eq. 5a})$$

which gives

$$t' \gg 2a \left(\frac{t'}{\pi D} \right)^{1/2}$$

or

$$t' \gg \frac{4a^2}{\pi D} \quad (\text{Eq. 6a})$$

When $a = 1 \times 10^{-4}$ cm. and $D = 5 \times 10^{-6}$ cm.²/sec. as before, then

$$t' \gg 2 \times 10^{-3} \text{ sec.}$$

is the criterion of the time in which very little dissolution should occur if the steady state equation is to be sufficient.

Both Eqs. 4 and 6a involve a^2 , so the time criterion changes with the radius in the inverse direction to the rate of change of radius by dissolution. Thus, the effects are compensating.

Equation 4a rigorously applies only when a is constant. Obviously a is constant only when $\Delta C = 0$ and in a real case $\Delta C \neq 0$. Therefore, one must determine how large ΔC may be before the change in a is important.

The steady state diffusion layer will have a thickness at least equal to a . A significant change in a might be set at level where the change in a is 1% or more of the diffusion layer thickness, *i.e.*, approximately 0.01 a . The change in a necessary to establish the diffusion layer may be estimated by estimating the amount of solid required to form the diffusion layer. Of course, this varies with the magnitude of ΔC . In the case considered here, values of $\Delta C < 1 \times 10^{-2}$ Gm./ml. seem to be sufficient for the constancy of a to be a good approximation for calculating t' .

DEFINITIONS OF SYMBOLS

- a = radius of a particle at time t .
- a_0 = radius of a particle at zero time.
- a_{10} = radius of largest particle at zero time.
- a_{s0} = radius of smallest particle at zero time.
- a_{0t} = zero time radius of largest particle that has completely dissolved at time t .
- a_i = $\left(a_{10}^2 - \frac{2D\Delta C t}{\rho} \right)^{1/2}$
- a_{iK} = hypothetical values of the largest particle corresponding to the value of K .
- a_{sK} = hypothetical values of the smallest particle corresponding to the value of K .

- a_t = any chosen value of a in the range present.
 a_{10} = the zero time radius of a_t .
 C = concentration.
 C_s = saturation concentration.
 C_o = concentration of bulk of solution.
 D = diffusion coefficient.
 $f > a_0$ = fraction larger than radius, a_0 , at zero time.
 $f > a$ = fraction larger than radius, a , at time t .
 K = a proportionality constant.
 $K' = \frac{4\pi K}{3V_o}$
 m = mass of a single particle.
 M = total mass of undissolved solid.
 M_o = total mass of solid at zero time.
 n = number of particles of a given size.
 N = total number of particles.
- Q = fraction of undissolved solid at time t ;
 M/M_o .
 r = radius of imaginary sphere through which diffusion occurs.
 t = time.
 v = volume of a single particle.
 $V_o = \frac{M_o}{\rho}$
 v_o = volume of a particle of a_o radius at zero time.
 $\pi = 3.1416$.
 ρ = density.

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Hypotensive Activity of Certain Diquaternarized Ammonium Compounds as Influenced by Administration Route and Anesthesia

By DAVID W. COATES†, JOSEPH P. BUCKLEY, and WILLIAM J. KINNARD

A three-way crossover experimental design demonstrated that urethan anesthesia enhanced the hypotensive responses of certain diquaternarized ammonium compounds in normotensive rats. The test showed that cardiovascular responses were more significant in hypertensive than in normotensive rats. Barbiturate anesthesia potentiated the hypotensive responses of certain of the compounds in normotensive dogs. Intravenous infusion of two of the compounds into anesthetized normotensive dogs produced a maximum hypotensive effect in 2 minutes with no further lowering of the blood pressure as the infusion was continued.

THE INCOMPLETE absorption following the oral administration of bisquaternary ammonium compounds has long been considered one of the main factors contributing to the erratic results produced by these ganglionic blocking agents in the treatment of arterial hypertension, and strong support for this view was provided by the absorption studies of Levine, *et al.* (1), and Schanker, *et al.* (2). Maxwell, *et al.* (3), reported the relative ineffectiveness of chlorisondamine in lowering the blood pressure of unanesthetized normotensive rats and dogs following intravenous administration. Haas and Goldblatt (4) obtained slight pressor responses in mean femoral arterial blood pressure following the intravenous infusion of tetraethylammonium, hexamethonium, pentolinium,

chlorisondamine, and mecamlamine in unanesthetized normotensive dogs. However, these same investigators demonstrated a depressor response with pentolinium during an intermediate period of renal hypertension in dogs (5).

This report deals with the attempt to evaluate several bisquaternary ammonium compounds (Fig. 1) for their oral hypotensive activity in unanesthetized normotensive rats and dogs and in unanesthetized renal hypertensive rats. The experiment was designed to allow comparisons between oral and parenteral administration of the compounds to unanesthetized animals and between parenteral administration to unanesthetized and anesthetized animals.

METHOD

Hypotensive Activity in Normotensive Rats.—Normotensive Wistar rats were trained for indirect systolic blood pressure determinations using the photoelectric tensometer.¹ These rats were then divided into five groups of eight animals each. One of the following compounds was assigned to each

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† Present address: University of Rhode Island, College of Pharmacy, Kingston.

¹ Metro Industries.