Dissolution Rates of Finely Divided Drug Powders II

Micronized Methylprednisolone

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The dissolution rate of micronized methylprednisolone in aqueous solutions was measured. Also, the particle size distribution was measured and an approximate distribution function was found. This function was incorporated into the theory for the diffusion-controlled dissolution of finely divided heterodisperse powders. The reasonably good agreement between experiment and theory suggests that the rate-determining step, in this instance, is diffusion of the drug in the aqueous phase. The possible effects of agitation, sedimentation, particle shapes, and the variation of solubility with particle size have been considered. The composite effects of these may account for the deviations between experiment and theory.

RECENTLY (1), the theoretical aspects of the liquid phase diffusion-controlled release characteristics of finely divided drug powders were examined in detail. The effects of particle size, size distribution, and drug solubility were considered in the formulation of a procedure for predicting the release *versus* time curves for powders in the region of particle size $\lesssim 25\,\mu$.

In this report, experimental studies of the dissolution rates of micronized methylprednisolone[1] in water are presented. The agreement of the data with theory is very satisfactory and demonstrates the usefulness of the theoretical procedure.

EXPERIMENTAL

Dissolution Rate Studies.—About 2.20 mg. of micronized methylprednisolone was added at zero time to 100 ml. of water in bottles which were rotated at 6 r.p.m. in a constant temperature bath maintained at 25°. The bottles were held in fixed positions on rotating wheels. Thus, mild agitation by tumbling action was achieved. Pure water was used in one set of experiments. In the other runs, the water was partially saturated with methylprednisolone to the extent of 30, 50, 70, and 90% of saturation so that a more rigorous test of the theory would be possible. At predetermined times bottles were removed and filtered rapidly, and then the filtrates were assayed spectrophotometrically.

Particle Size Analysis.—The Coulter counter[2] with the 100-μ aperture was used to determine the distribution of sizes. A 1% sodium chloride solution saturated with methylprednisolone was employed as the vehicle.

THEORETICAL CALCULATIONS

As before (1), we may write

$$a = \left(a_o^2 - \frac{2D\Delta Ct}{\rho}\right)^{1/2} \qquad \text{(Eq. 1)}$$

where a_o is the initial particle radius, a is the particle radius at time t, D is the diffusion coefficient of the drug molecule in water, ρ is the solid drug density, and $\Delta C = C_s - C_o$ where C_s is the solubility of the drug and C_o is the drug concentration in solution. While Eq. 1 applies strictly to the case where ΔC remains constant, it is easy to correct for the effects of the variation in ΔC, as will be shown later.

As most milled materials follow the log-normal distribution of sizes, Eq. 1 may be combined with a suitable function which approximates the log-normal function to give the expression for the dissolution rate of powders. This was done in the previous paper (1) and represents a generalization of the present treatment. Since in this study the initial size distribution of the methylprednisolone powder was determined with the Coulter counter, the present analysis utilizes the measured particle size distribution and constitutes a test of the applicability of the theory.

Equation 1 describes the dissolution of a single particle of initial size a_o. Consider now the situation in which there is initially a *distribution* of sizes. Let

$$n = n(a_o) \qquad \text{(Eq. 2)}$$

represent the measured distribution function. The quantity n is the initial ($t = 0$) number of particles between the sizes a_o and $a_o + da_o$. The total number of particles in the system at $t = 0$ is then

$$N = \int_{a_{so}}^{a_{lo}} n(a_o)da_o \qquad \text{(Eq. 3)}$$

where a_{lo} and a_{so} are the radii of the smallest and the largest particles, respectively, at $t = 0$.

The total mass of undissolved drug at $t = 0$ is

$$M_o = \int_{a_{so}}^{a_{lo}} \frac{4}{3}\pi a_o^3 \rho n(a_o)da_o \qquad \text{(Eq. 4)}$$

Now at any $t > \frac{a_{so}^2\rho}{2D\Delta C}$, the total amount of undissolved drug will be

$$M = \int_{a_{ot}}^{a_{lo}} \frac{4}{3}\pi\rho a^3 n(a_o)da_o \qquad \text{(Eq. 5)}$$

Here a is given by Eq. 1 and the lower limit of the integral, a_{ot}, is given by

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[1] Medrol, from The Upjohn Co.
[2] Marketed by Coulter Industrial Sales, Elmhurst, Ill.

$$a_{ot} = \left(\frac{2Dt\Delta C}{\rho}\right)^{1/2} \quad \text{(Eq. 6)}$$

This limit a_{ot} is the initial ($t = 0$) size of the particle which dissolves completely at time t.

Inserting the expression for a from Eq. 1 into Eq. 5 gives

$$M = \int_{a_{ot}}^{a_{lo}} \frac{4}{3}\pi\rho\left(a_o^2 - \frac{2Dt\Delta C}{\rho}\right)^{3/2} n(a_o)da_o \quad \text{(Eq. 7)}$$

So the fraction, Q, of drug undissolved at time t is

$$Q = \frac{M}{M_o} = \frac{\int_{a_{ot}}^{a_{lo}} \left(a_o^2 - \frac{2Dt\Delta C}{\rho}\right)^{3/2} n(a_o)da_o}{\int_{a_{so}}^{a_{lo}} a_o^3 n(a_o)da_o} \quad \text{(Eq. 8)}$$

and hence the per cent release, R, is given by

$$R = 100\,(1 - Q) \quad \text{(Eq. 9)}$$

APPLICATION

Release Rate Data on Micronized Methylprednisolone.—In Fig. 1 we have the Coulter counter data for micronized methylprednisolone for which the dissolution rate studies were carried out. In the figure the smooth curve corresponds to the following empirical equation for the distribution function

$$n(a_o) = \frac{K}{a_o^2} \quad \text{(Eq. 10)}$$

where K is a constant. For a_{lo} and a_{so} the values of 0.5 μ and 9.0 μ were chosen respectively to give the good fit shown in Fig. 1. These limits correspond to a size range of 1–18 μ diameter and agree with microscopic sizing of micronized methylprednisolone.

We may now substitute Eq. 10 into Eq. 8 to get

$$Q = \frac{\int_{a_{ot}}^{a_{lo}} \frac{1}{a_o^2}\left(a_o^2 - \frac{2Dt\Delta C}{\rho}\right)^{3/2} da_o}{\int_{a_{so}}^{a_{lo}} a_o da_n} \quad \text{(Eq. 11)}$$

Integrating over the limits for both integrals in Eq. 11 and substituting for a_{ot} from Eq. 6, we obtain

$$Q = \frac{2}{(a_{lo}^2 - a_{so}^2)}\left[\left(\frac{a_{lo}}{2} + \frac{2Dt\Delta C}{\rho a_{lo}}\right)\left(a_{lo}^2 - \frac{2Dt\Delta C}{\rho}\right)^{1/2} + \frac{3Dt\Delta C}{\rho} ln\left\{\frac{\left(\frac{2Dt\Delta C}{\rho}\right)^{1/2}}{a_{lo} + \left(a_{lo}^2 - \frac{2Dt\Delta C}{\rho}\right)^{1/2}}\right\}\right] \quad \text{(Eq. 12)}$$

Now we have the following information on methylprednisolone: ρ = density = 1.28 Gm./ml.;[3] MW = molecular weight = 374; C_s = solubility = 7.4×10^{-5} Gm./ml. at 25°. We may calculate the diffusion coefficient, D, by means of the Stokes-Einstein relation

$$D = \frac{kT}{6\pi vs} \quad \text{(Eq. 13)}$$

where k = Boltzmann's constant = 1.37×10^{-16}; T = 300° Kelvin; v = viscosity $\simeq$ 0.01 poise for water; s = molecular diffusion radius for methylprednisolone, calculated from density and molecular weight = 4.7×10^{-8} cm. ±10%. Equation 13 then gives $D = 4.7 \times 10^{-6}$ cm.^{2} sec.$^{-1}$.

Inserting all of these values into Eq. 12 and combining with Eq. 9 gives the per cent released, R,

$$R = 100\left[1 - (1.12 \times 10^3 + 2.02 \times 10^4\, t\Delta C)(8.1 \times 10^{-7} - 7.34 \times 10^{-6}\, t\Delta C)^{1/2} - 62t\Delta C \log_{10}\left\{\frac{2.71 \times 10^{-3}\,(t\Delta C)^{1/2}}{9 \times 10^{-4} + (8.1 \times 10^{-7} - 7.34 \times 10^{-6}\, t\Delta C)^{1/2}}\right\}\right] \quad \text{(Eq. 14)}$$

Now in the derivation of Eq. 1 it was necessary to assume that ΔC was constant with time. Hence, Eq. 14 strictly applies only to the case of large undersaturation, *i.e.*, for $\Delta C \simeq C_s \gg C_o$. In order to apply Eq. 14 to the present release data (for which ΔC decreases with time), an approximation procedure was employed. The procedure may be carried out in the following manner: First, make a plot of R *vs.* $t\Delta C$ by means of Eq. 14. Then select R values from 0 to 100 so that ΔC does not change too greatly from one R value to the next (*i.e.*, changes in ΔC from one R value to the next must be small compared to ΔC itself). From the release rate experiments we know $\Delta C = C_s - C_o$ for any R value. Hence $\Delta t = t_{n+1} - t_n$ corresponding to R_{n+1} and R_n may be determined. Then finally, the sum of Δt values may be plotted against R to give the R *vs.* time curves.

Figure 2 shows the theoretical curves obtained by means of Eq. 14 and the approximation procedure just outlined. The experimental data are represented by the points in the figure. Because no empirical factor was used in the theoretical calculations, the agreement between the experiments and theory must be regarded as highly satisfactory

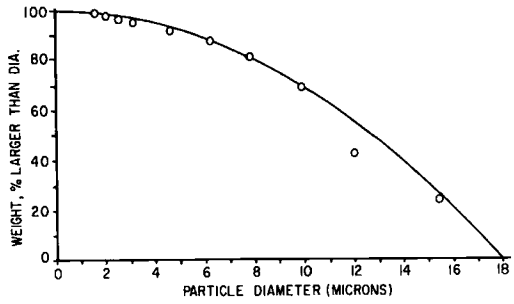

Fig. 1.—Distribution of particle sizes for micronized methylprednisolone obtained with the Coulter counter. Smooth curve is in accordance with $n = \frac{K}{a_0^2}$.

[3] Courtesy of Dr. J. W. Shell.

despite some deviations. Clearly, the most likely rate-determining step is the rate of diffusion of methylprednisolone in water. It is possible that other processes such as surface nucleation or surface orientation might contribute to the dissolution rate, but certainly, even if they do, they are not very important for micronized methylprednisolone.

It is apparent that the experimental release rates are always somewhat greater than theory at small values, and always somewhat less at large t. Several possible reasons may be put forward to explain these deviations.

Firstly, it is worthwhile to mention that if a particle size-distribution function corresponding to a somewhat broader distribution were employed in the theoretical calculations, an almost perfect agreement would be obtained for cases A through D. It is possible that the distribution curve (Fig. 1) determined with the Coulter counter does not exactly represent the true initial size distribution, particularly for the smaller sizes. This might be attributed to the tendency for small particles to be more soluble than the larger ones. Thus, if the vehicle were saturated with a sample of methylprednisolone, it might have been undersaturated with respect to the small particles of a subsequently added sample. In case E (see Fig. 2), for which the dissolution medium was initially 90% saturated, the final concentration of methylprednisolone exceeded the solubility (7.40 mg. per 100 ml.) of prednisolone by about 3 or 4%.[4] This might also be explained by the greater solubility of the smaller particles. It was furthermore noted that in the determination of the methylprednisolone solubility, which was found by adding a three-fold excess of methylprednisolone to water and following the methylprednisolone concentration as a function of time, a maximum value several per cent greater than the final constant value was observed. This is consistent with the behavior in case E and with the possibility that the Coulter counter did not give correct weighting to the small particles.

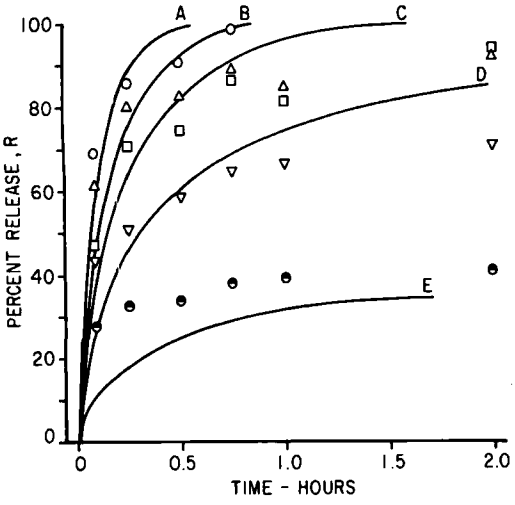

Fig. 2.—Experimental and theoretical release of drug from micronized methylprednisolone. Theory A, pure water, experiment ○; theory B, 30% presaturation, experiment △; theory C, 50% presaturation, experiment □; theory D, 70% presaturation, experiment ▽; theory E, 90% presaturation, experiment ●.

The theory assumes that the particles are spheres. The influence of shape variations may be estimated from the electrostatic theory (2) of conducting ellipsoids. Ellipsoids with axial ratios of two or so will dissolve at about a 5% greater rate than spheres of the same volume. Since the micronized methylprednisolone particles were found to be relatively isometric under the microscope, the shape effects were probably unimportant.

Occasionally, clumping of some of the particles was observed during the dissolution experiments. Some of the scatter as well as the low rates at large t values may be explained on this basis. In general, however, the methylprednisolone samples dispersed readily.

Another factor contributing to the deviations is the Stokes law calculated value for the diffusion coefficient. The uncertainty here is estimated to be around 10–20%. If a smaller value for D were used, the theoretical curves in Fig. 2 would be expanded in proportion to t along the t-axis, or if a larger D value were employed, the curves would be linearly contracted.

Finally, the effects of stirring and the sedimentation of particles will affect the dissolution rate to a certain extent. Recent studies by Nielsen (3) show that for methylprednisolone particles in the size range $\lesssim 25\ \mu$, the hydrodynamic effects arising from sedimentation should be small, the order of a few per cent, insofar as the dissolution rate is concerned. Furthermore, the effects due to moderate stirring should have been also small for these particle sizes since the local accelerations and decelerations in the medium probably were at most only comparable to that due to gravity, and since velocity gradients were probably $\lesssim 1.0\ \text{sec.}^{-1}$.

Thus, the composite effect of these uncertainties may very well account for the deviations. Future experiments will dwell upon these factors more thoroughly.

REFERENCES

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(2) See, e. g., Smythe, W. R., "Static and Dynamic Electricity," McGraw-Hill Book Company, Inc., New York, N. Y., 1950.

(3) Nielsen, A. E., *J. Phys. Chem.*, **65**, 46(1961).

[4] In the other series saturation was never reached.