EFFECT OF SHAPE FACTOR ON CUBE ROOT DISSOLUTION BEHAVIOR

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SUMMARY

Crystalline particles that have needle or plate shapes can be approximated by long or shallow cylinders. By making such an approximation the cube root equation may be solved for non-isometric shapes and the effect of the degree of isometricity on the length of time the cube root dissolution equation will hold has been derived. A more exacting method of plotting is presented allowing calculation of the intrinsic dissolution rate constant from the slope of a plot of a reduced time plotted versus actual time.

INTRODUCTION

A substantial body of literature has been devoted in the past to dissolution of solids and this area of research and technology is, of course, of importance, since in certain domains of solubility and formulation characteristics, dissolution is the rate determining step in absorption of drugs (Lippold, 1977).

For dissolution of solids the so-called cube root law:

$$m_0^{1/3} - m^{1/3} = Kt \tag{1}$$

is frequently quoted, and often applies for substantial, if not the entire range of a dissolution situation for a powder dissolving in a liquid. m_0 is here the mass originally, m is the mass remaining undissolved at time t, and K is a cube root dissolution rate constant. The derivation of this equation will be demonstrated at a later point, but it should be emphasized that the assumption made in the derivation is the conventional assumptions in diffusion controlled dissolution, viz. constancy of diffusion layer thickness, isotropicity, independence of the solubility with regard to particle size, and smooth (geometric) surface areas. In addition the following specific assumptions are made: that sink conditions apply, that the powder is monodisperse and that the particles are isometric. Exten-

sion of the applicability into non-sink conditions have been made (Patel and Carstensen, 1975; Pothisiri and Carstensen, 1973), and extension of the applicability into polydisperse powder populations have also been successful (Carstensen and Musa, 1972; Brooke, 1973; Carstensen and Patel, 1975). The treatments to follow will assume that populations are monodisperse since, as just mentioned, applicability into the more realistic powder populations are assured.

For convenience one usually denotes the size by a length parameter of the particle, e.g. r, the radius, if it is assumed to be spherical, or the side of a cube if it is assumed to be cubical. The assumption of isometry is one which has not been dealt with in great detail in the past. Isometry is defined as 'length' independence of the shape factor, α, which is defined as:

$$\alpha = a \, v^{-2/3} \tag{2}$$

a is here the area of the individual particle and v is the volume of the individual particle. In the case of the total area of a particle population of N particles, the total area will be denoted A (=Na) and the total volume will be denoted V (=Nv). It is noted that for a sphere $\alpha = \pi^{1/3} \, 6^{2/3}$ and for a cube it equals 6, so that these two *shapes* are isometric. In contrast a cylinder is only isometric if its diameter, j, equals its height, h. The exact dissolution profiles of particular crystal shapes have been derived by Pedersen and Brown (1976 and 1977), but a broader treatment would seem to be of advantage for the explanation of why the cube root equation applies *in so many cases* for particle shapes which are not isometric. The article to follow presents such a broader (but at the same time approximate) approach, and the postulated views are substantiated by experimental findings.

MATERIALS AND METHODS

Tablets were made of oxalic acid dihydrate at 3000 kg force on a hydraulic press. The dimensions of the tablets were: height (thickness) 0.40 cm and diameter 1.10 cm. In one set of experiments 3 tablets were placed in the basket of a U.S.P. dissolution apparatus, and 900 ml of 0.1 N HCl were used at 25°C to conduct the dissolution experiment. The amount of material dissolved at time t was obtained by stopping and removing the basket and assaying an aliquot of the liquid after this had been further mixed for 2 min with a propeller mixer. In this fashion concentration gradient error as described by Carstensen et al. (1977) was avoided. The assay methology was as described by Carstensen and Patel (1975). The experiment was repeated for various time points, t. The same experiment was then carried out by placing the tablets directly outside the basket, i.e. under slightly different hydrodynamic conditions.

RESULTS AND DISCUSSION

Results of the dissolution tests are plotted according to Eqn. 1 in Fig. 1. It is noted that the cube root law is adhered to for the initial period, up to a value of $-\Delta(M^{1/3})$ of 3, where M denotes total mass undissolved (i.e. M = N m). Since M_0 is 1500 mg, a value of $-\Delta(M^{1/3})$ of 3 denotes about 50% of the material is dissolved, hence Eqn. 1 is adhered to
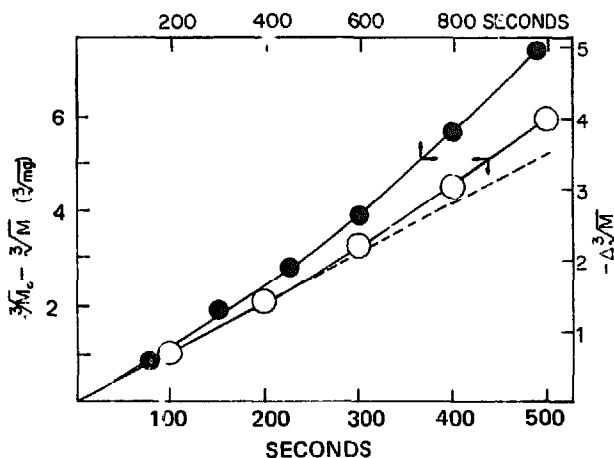
Fig. 1. Cube root plotting of dissolution of cylinders of oxalic acid, 1.1 cm in diameter and 0.4 cm in height under two different hydrodynamic conditions.

through a substantial part of the entire dissolution. The dimensions of the tablet (cylinder) used is such that it is far from rendering it isometric and it is used here to exemplify the effect of non-isometry on the dissolution equations.

The reason a cylinder is used in the following is that it approximates crystal shapes, which are most commonly either 'needles' or 'plates'. If the initial diameter, j_0, is larger than the height, h_0, then the shape will approximate that of a plate, and in this case use is made of the ratio

$$b = j_0/h_0 \qquad (j_0 > h_0) \tag{3}$$

In the case of a needle, this may be approximated by a cylinder where $h_0 > j_0$, and in this case use is made of the ratio

$$e = h_0/j_0 \qquad (h_0 > j_0) \tag{4}$$

The derivations to follow will be carried out for $j_0 > h_0$, but entirely parallel treatment for $h_0 > j_0$ leads to identical equations where b is simply permuted with e. It should be noted too, that shapes that are neither needles or plates are covered in the treatment by $h_0 \sim j_0 \sim 1$.

The derivation of Eqn. 1 for $j_0 > h_0$ can be carried out in a more general form than what is usually done, by utilizing Eqn. 2. The general diffusionally controlled dissolution equation for a particle with solubility S and intrinsic dissolution rate constant k is given by:

$$dm/dt = -k \, a \, S \tag{5}$$

when sink conditions apply. If the density of the material is ρ then $m = \rho \, v$, i.e.

$$dm/dt = \rho \, dv/dt \tag{6}$$

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The area of the particle is given by:

$$a = \pi jh + \pi j^2/2 \tag{7}$$

and introducing Eqns. 6 and 7 into Eqn. 5 then gives

$$dv/dt = -K\,\pi(jh + [j^2/2]) \tag{8}$$

where

$$K = kS/\rho \tag{8}$$

v is a function of h and j, i.e.

$$\frac{dv}{dt} = \frac{dv}{dj}\frac{dj}{dt} + \frac{dv}{dh}\frac{dh}{dt} \tag{9}$$

The equation for the volume is

$$v = \pi j^2 h/4 \tag{10}$$

When Eqn. 10 is inserted in Eqn. 9 the following equation ensues:

$$\frac{dv}{dt} = (\pi jh/2)\frac{dj}{dt} + (\pi j^2/4)\frac{dh}{dt} \tag{11}$$

Combining Eqns. 11 and 8 and dividing through by $\pi j^2 h$ then gives:

$$-\frac{K}{j} - \frac{K}{2h} = \frac{1}{2j}\frac{dj}{dt} + \frac{1}{4h}\frac{dh}{dt} \tag{12}$$

Separation of variables then gives:

$$dj/dt = -2K \tag{13}$$

$$dh/dt = -2K \tag{14}$$

Introducing now the 'reduced time', u, given by

$$u = 2Kt/(h_0) \tag{15}$$

Eqns. 13 and 14 may be written:

$$j_0 - j = h_0 - h = 2Kt = uh_0 \tag{16}$$

It is noted that h = 0 implies u = 1, so that the domain of u is [0|1]. At time t the frac-

tion of material yet undissolved, f, is given by:

$$f = \frac{v}{v_0} = \frac{j^2 h}{j_0{}^2 h_0} = \frac{(j_0 - u h_0)^2 (h_0 - u h_0)}{j_0{}^2 h_0} = \left(1 - \frac{u}{b}\right)^2 \cdot (1 - u) \tag{17}$$

f, of course, equals m/m_0, M/M_0 and V/V_0 as well. Eqn. 17 is a cubic equation with one real and two imaginary roots, and since, in a dissolution test, f can be calculated at any time, u can be found as a real root of Eqn. 17 at that f-value.

The data from Fig. 1 have been plotted according to Eqn. 17 in Fig. 2. Linearity through the entire range is apparent, i.e. Eqn. 15 is obeyed and the slope of the line is given by

$$\text{Slope} = 2K/h_0 = 2kS/(\rho h_0) \tag{18}$$

Since all quantities with the exception of k are known, this latter can be calculated Fig. 2 supports the assumption made, so that it is rational to proceed to investigate the change of the shape factor with time. The area and volume of the cylinder as a function of u are obtained via Eqns. 7, 10 and 16 and are:

$$a = \pi(j_0 - u h_0)(h_0 - u h_0) + \pi(j_0 - u h_0)^2/2 \tag{19}$$

$$v = \pi(j_0 - u h_0)^2(h_0 - u h_0)/4 \tag{20}$$

Eqns. 2, 19 and 20 then give the expression for the shape factor

$$= a\, v^{-2/3} = \frac{\pi}{1}\left(\frac{4}{\pi}\right)^{2/3} \frac{(j_0 - u h_0)(h_0 - u h_0)}{(j_0 - u h_0)^{4/3}(h_0 - u h_0)^{2/3}} +$$

$$\frac{\pi}{2}\left(\frac{4}{\pi}\right)^{2/3} \frac{(j_0 - u h_0)^2}{(j_0 - u h_0)^{4/3}(h_0 - u h_0)^{2/3}}$$

$$= 3.69 \left\{ \frac{1}{2}\left(\frac{b - u}{1 - u}\right)^{2/3} + \left(\frac{1 - u}{b - u}\right)^{1/3} \right\} \tag{21}$$

The shape factor at a particular time, t', averages

$$\alpha' = \frac{1}{t'} \int_0^{t'} \alpha(t)\, dt \tag{22}$$

One may introduce u via Eqn. 15. It should be noted that for the limits:

$$t = 0 \rightarrow u = 0 \tag{23}$$

and
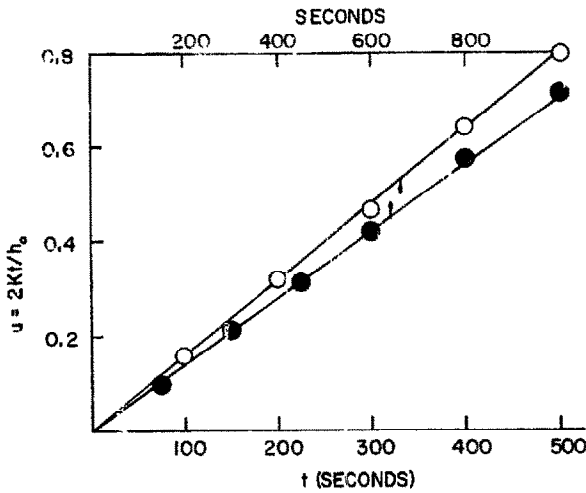
$$t = t' \rightarrow u = u' = (2K/h_0)t' \tag{24}$$

Fig. 2. Plotting of the data in Fig. 1 via Eqn. 15.

and also that

$$(1/t')dt = (1 = u')du \tag{25}$$

so that Eqn. 22 may be written:

$$\alpha' = \frac{1}{u'} \int_0^{u'} \alpha(u)\,du \tag{26}$$

α' can then be found for any value of t', u' or f.

α' has been found by graphical integration as a function of u for various values of b, and these curves are shown in Fig. 3. It is noted that for $b = 1$, α is time independent, i.e.
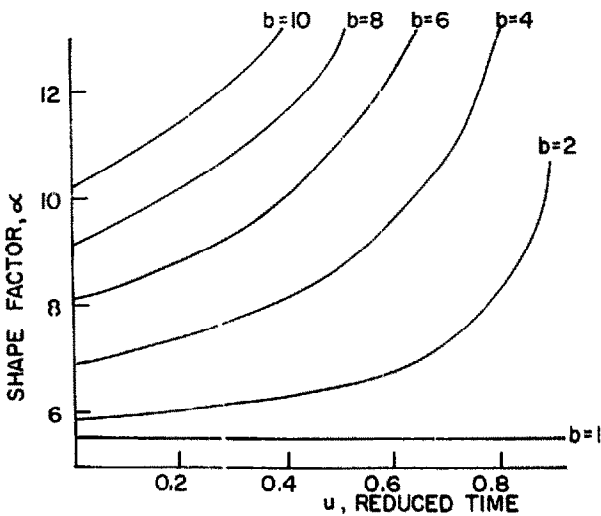

Fig. 3. The shape factor as a function of reduced time for various diameter to height ratios.
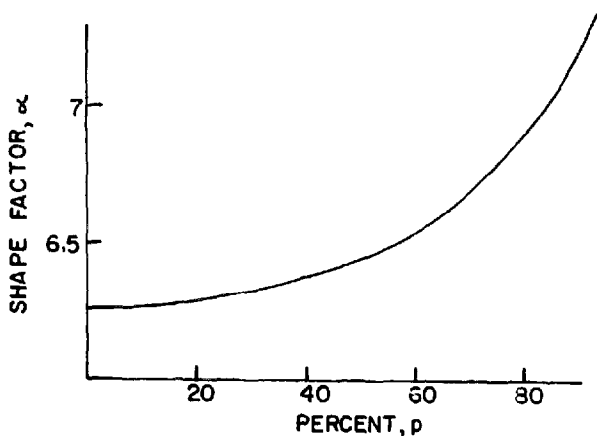
Fig. 4. The shape factor as a function of percent of oxalic acid dissolved for oxalic acid cylinder, 1.1 cm in diameter and 0.4 cm high.

the cylinder is isometric. u can be converted to fraction dissolved via Eqn. 7 and α then plotted versus f, or the percent, p, dissolved (i.e. p = 100f). Such a graph is shown for the cylinder in question, i.e. where j_0 = 1.1 and h_0 = 0.4 in Fig. 4. In this case b = 1.1/0.4 = 2.75 so that α = 6.25, and in this case Eqn. 1 holds up to 50% dissolved. At this point, as shown in Fig. 4, α has risen to 6.55, so that an increase in α of 5% does not cause an experimentally detectable deviation from linearity of the cube root plot. Of course, better analytical precision might alter this figure, but in general, in dissolution work, precisions better than titrimetric are not encountered. In the following it shall be assumed that a change in α of 5% will not cause deviation from linearity of a cube root plot. The percent, L, at which the deviation from the original α-value is indeed 5% has been computed
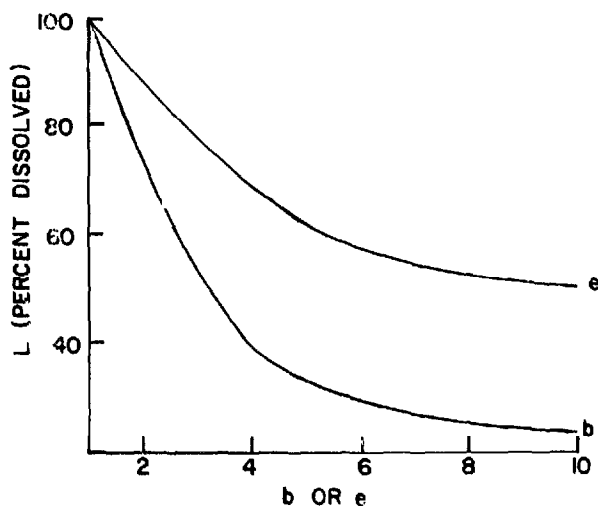

Fig. 5. The critical percent, L, as a function of height to diameter ratio (e) for needle-shaped crystals or diameter to height ratio (b) for plate-shaped crystals.

from Fig. 3, and the value of L as a function of b is plotted in Fig. 5. The value of L as a function of e has been computed in exactly similar fashion and is shown in this figure as well. This graph shows how far one may proceed in dissolution without expected deviation of linearity of a cube root plot for a needle (e-curve) and plate (b-curve). The graphs shows that for particles which are not too far removed from very elongated or very flat, the dissolution follows Eqn. 1 for substantial parts of the dissolution process. This is comforting, since many of the basic equations in pharmacy rest on the validity of Eqn. 1.

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