Effect of Change in Shape Factor of a Single Crystal on Its Dissolution Behavior

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Purpose. To study the effect of change in the shape factor of real crystals on their dissolution behavior using a potassium dichromate crystal as a model for particulates in general.
Methods. A model geometry (parallelepiped) has been suggested for a dissolving particle. Single crystals of potassium dichromate which are monoclinic prisms were grown individually from supersaturated solutions at 40°C. Dissolution studies were carried out on five such crystals in 0.1N H_2SO_4 at 25°C and a stirrer speed of 50±1 rpm. The five crystals had different degrees of non-isometricity. Initial dimensions of the crystals were measured using image analysis techniques. The shape factor of the dissolving crystal as a function of time was obtained indirectly from the dissolution data.
Results. The shape factor of a single crystal changed significantly after about 50% dissolution. The nature of this change depended on the degree of non-isometricity of the crystal. The change in shape factor of the dissolving crystal was accounted for in the Hixson-Crowell cube root law, and a modified form of the cube root equation was developed. This equation for dissolution explained the observed upward curvature in the cube root law plot.
Conclusions. The shape factor for any non-isometric particle cannot be considered to be constant over the dissolution event, as is commonly assumed. This change has an appreciable effect on the dissolution behavior of crystals. This study is particularly of significance for elongated shapes like needles and platelets. By the methodology described here, it was possible to determine the initial shape factor of the crystal and the intrinsic dissolution rate constant.

KEY WORDS: single crystal dissolution; Hixson Crowell cube root law; shape factor; dissolution model; particle shape-parallelepiped; potassium dichromate.

INTRODUCTION

The subject of dissolution of particulates was, for many years, a main topic of pharmaceutical research. Once most of the practical problems (dissolution apparatuses) were solved, the theoretical aspects were abandoned as having been solved. However there are certain aspects of dissolution which are of interest from a preformulation standpoint, and the article to follow will deal with one of them, viz. particle shapes (shape factors).

The introductory statement is not meant to imply that *no* theoretical work has been done of late, and some recent articles in this area will be referred to in the following. In dissolution the governing equation is either the Noyes-Whitney equation (1) or the Levich equation (2). The former is of importance in the writing to follow and is stated as:

$$\frac{dm}{dt} = -kA(S - C) \tag{1}$$

where A is surface area (cm^2), k is intrinsic dissolution rate constant (cm/sec), S is solubility, m is mass of the undissolved particle, t is time and C is concentration at time t.

Under sink conditions C is sufficiently small so that $S - C \approx S$ and Eq. 1 becomes:

$$\frac{dm}{dt} = -kAS \tag{2}$$

Effect of Shape Factor

For any particle the relationship between area, volume, and shape factor is

$$A = \Gamma[V^{2/3}] = \Gamma\left(\frac{m}{\rho}\right)^{\frac{2}{3}} \tag{3}$$

where Γ is the shape factor, V is the volume of the particle, and ρ is its density. For a single particle dissolution under sink conditions Eqs. 2 and 3 yield

$$\frac{dm}{dt} = -k\Gamma\left(\frac{m}{\rho}\right)^{\frac{2}{3}} S \tag{4}$$

If there are N spherical particles of the same radius, then the mass at time t is Nm and initially is $M_O = Nm_O$ where the subscript refers to initial conditions. If these relations are introduced into Eq. 4 then

$$\frac{dM}{dt} = -k\Gamma N^{1/3}\left(\frac{M}{\rho}\right)^{\frac{2}{3}} S \tag{5}$$

Dividing through by $M^{2/3}$, integrating and imposing initial conditions then yields:

$$1 - \left(\frac{M}{M_0}\right)^{\frac{1}{3}} = \frac{kS\Gamma N^{1/3}t}{3(M_0)^{1/3}(\rho)^{2/3}}$$

$$1 - \left(\frac{M}{M_0}\right)^{\frac{1}{3}} = Kt \tag{6}$$

where

$$K = \frac{kS\Gamma N^{1/3}}{3(M_0)^{1/3}(\rho)^{2/3}} \tag{7}$$

is the so-called cube root dissolution rate constant. Eq. 6 is the mathematical statement of the Hixson Crowell cube root law for a monodisperse multiparticulate system (3). The cube root law plot is expected to be linear. However curvatures in such plots are not uncommon (4, 5); the extent of deviations from linearity depends on the validity of the several assumptions made in the derivation of the cube root law.

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In Eq. 7 Γ is assumed to be constant. Our objective is to decipher the contribution of the changing shape factor of a *real* crystal to its dissolution behavior.

The above refers to a monodisperse powder consisting of N particles of initial weight m_O and if polydisperse powder dissolution is studied, the sum of the fractions can be studied and, for instance Brooke (6) and Carstensen and Musa (7) have studied this situation for spheres (where $\Gamma = \pi^{1/3}6^{2/3}$).

Lai and Carstensen (4) studied the effect for isotropically dissolving oxalic acid in order to establish the effect of shape factor on cube root dissolution behavior. In this case non-isotropic shapes were simulated by cylindrical tablets. The shape factor of the dissolving cylinder was calculated from the dissolution data at every time point. They observed that Γ changed significantly after about 50% of total dissolution time. Also, they could show by graphical integration that as the degree of non-isometricity of the cylinder increased, this "cut-off" time shifted to a lower value. It is only when a particle is isometric (i.e. when Γ is independent of dimension) that Γ is constant. The goal of the present work is to study this concept for a *real* crystal, and to develop a dissolution equation that takes into account its changing shape factor.

Lu et al. (8) have extended the concept proposed by Lai and Carstensen (4), and have shown that the cylindrical model yields a better fit of dissolution data for hydrocortisone particles than a sphere as a model for the same. However, in their paper there was no account of changing shape factor *as described* by Lai and Carstensen (4).

Pederson and Brown (9) carried out a systematic study on the dissolution of a 60-85 mesh fraction of tolbutamide in a flow through dissolution apparatus by using a time-scaling approach. They too have assumed the shape factor to be constant. Understandably so, they made this simplification because their aim was to assess the three models for dissolution viz., the cube root law model (3), the square root law model (10), and the squared cube root law model (11).

It is, however, not only the effect of the shape factor which is of importance. The intrinsic dissolution rate constant, k, is assumed to be a constant for the substance. In this discussion we do not intend to address this issue and in the derivation to follow, isotropicity is assumed. Much dissolution work has been done with this assumption, with specific reference to the thorough work of Pedersen and Brown (12), who derived dissolution equations for several crystal systems. Our interest in this lies in studying the shape factor as a function of dissolution time, and the derivation below is based with this aim in mind. It should be pointed out that the equations developed here are in agreement with those derived by Pedersen and Brown (12), and that the shape factor calculations are the ones that make our theme unique.

The Hixson-Crowell cube root law for powder dissolution makes the following assumptions: (i) the shape of dissolving particles is predominantly spherical and hence they are isometric (ii) isotropicity (iii) independence of solubility with respect to particle size, and (iv) sink conditions. Extensive work has been done to study the dissolution kinetics of polydisperse powders (5,6,7,11,13), and the extension of the applicability of this law to non-sink conditions has been demonstrated (14,15). *Real* particles are not spherical hence the shape factor of such particles is a function of their dimensionality. As a particle dissolves its dimensions change and a change in its shape factor occurs. Thus to take into consideration the changing shape factor is to account for the non-isometricity of the dissolving particle.

In the derivation to follow, a model for the dissolving particle will be considered keeping in mind that many crystalline substances exist as needles, flakes, platelets, prisms, etc. The simplest non-isometric geometry that can be perceived along these lines is a parallelepiped. So the immediate goal is to develop an expression for the shape factor of such a particle as a function of dissolution time.

Most crystalline solids can be classified into seven different crystals systems depending on the respective dimensions of the crystal faces and the angles between them. (16). These seven crystal systems are: regular, tetragonal, orthorhombic, monoclinic, triclinic, trigonal, and hexagonal. The choice of potassium dichromate as the model compound is justified in three respects: (i) It has a high aqueous solubility therefore the assumption of sink conditions is valid, (ii) It is feasible to grow large crystals, and (iii) It has a prismatic crystal habit and a triclinic pinacoidal crystal system, which closely approximates a parallelepiped.

THEORY

Consider a parallelepiped of length l, breadth b, and height h as shown in Fig. 1. The area A and volume V of a particle with such a geometry are given by the following equations.

$$A = 2(lb + bh + lh) \tag{8}$$

$$V = lbh \tag{9}$$

Noyes-Whitney equation under sink conditions is:

$$\frac{dm}{dt} = -kAS \tag{10}$$

where the symbols carry their usual meaning.

Expressing mass in terms of volume, and density

$$m = \rho V$$

$$\therefore \frac{dm}{dt} = \rho \frac{dV}{dt} \tag{11}$$

Substituting Eqs. 8, and 11 in Eq. 10 gives:

$$\rho \frac{dV}{dt} = -2kS(lb + bh + lh) \tag{12}$$

Since V is a composite function of l, b, and h, the rate of change of volume w.r.t. time can be written as

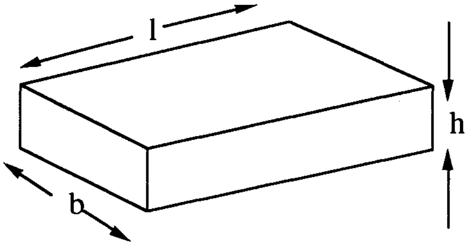

Fig. 1. Model for the dissolving particle-parallelepiped.

$$\frac{dV}{dt} = \left(\frac{dV}{dl}\right)\left(\frac{dl}{dt}\right) + \left(\frac{dV}{db}\right)\left(\frac{db}{dt}\right) + \left(\frac{dV}{dh}\right)\left(\frac{dh}{dt}\right)$$

Treating these as partial derivatives the following equation is obtained:

$$\frac{dV}{dt} = bh\left(\frac{dl}{dt}\right) + lh\left(\frac{db}{dt}\right) + lb\left(\frac{dh}{dt}\right) \qquad (13)$$

From Eqs. 12 and 13

$$bh\left(\frac{dl}{dt}\right) + lh\left(\frac{db}{dt}\right) + lb\left(\frac{dh}{dt}\right) = -\frac{2kS}{\rho}[lb + bh + lh]$$

or

$$\frac{1}{l}\left(\frac{dl}{dt}\right) + \frac{1}{b}\left(\frac{db}{dt}\right) + \frac{1}{h}\left(\frac{dh}{dt}\right) = -\frac{2kS}{\rho}\left[\frac{1}{l} + \frac{1}{b} + \frac{1}{h}\right]$$

let $\frac{2kS}{\rho} = K$

where K is a constant.

$$\frac{1}{l}\left(\frac{dl}{dt}\right) + \frac{1}{b}\left(\frac{db}{dt}\right) + \frac{1}{h}\left(\frac{dh}{dt}\right) = -\frac{K}{l} - \frac{K}{b} - \frac{K}{h}$$

In this differential equation the variables are in the separate variable form. Hence it follows that,

$$\frac{dl}{dt} = -K, \frac{db}{dt} = -K, \text{and } \frac{dh}{dt} = -K$$

This implies isotropic dissolution. These expressions can be integrated to obtain relationships between the crystal dimensions and time of dissolution. If l_0, b_0, and h_0 are the initial length, breadth and height of the crystal,

$$\int_{l0}^{l} dl = -K\int_0^t dt, \int_{bo}^{b} db = -K\int_0^t dt,$$

$$\text{and } \int_{ho}^{h} dh = -K\int_0^t dt$$

Then the following relationships are obtained:

$$l_0 - l = Kt \qquad (14)$$

$$b_0 - b = Kt \qquad (15)$$

$$h_0 - h = Kt \qquad (16)$$

Consider

$$h_0\left[1 - \frac{h}{h_0}\right] = Kt$$

$u = (1 - h/h_0)$ is defined as the "reduced time". However since u is a dimensionless quantity, the labeling of the name "reduced length" is also acceptable. It should be pointed out that the definition of u is based on the smallest dimension of the crystal.

It is obvious that just before dissolution starts $h = h_0$, and at the point when the crystal completely dissolves $h = 0$. Hence the domain of u is [0,1].

$$\therefore u = \frac{Kt}{h_0} \qquad (17)$$

Substituting for Kt in Eqs. 14, 15, and 16:

$$l = l_0 - uh_0 \qquad (18)$$

$$b = b_0 - uh_0 \qquad (19)$$

$$h = h_0 - uh_0 \qquad (20)$$

Substituting for K in Eq. 17 we get,

$$u = \left(\frac{2kS}{\rho h_0}\right)t \qquad (21)$$

In order to determine u, we consider the fraction of amount undissolved ($F = m/m_0$). F can be expressed as the ratio of instantaneous volume of the dissolving particle to its initial volume, density being constant:

$$F = \frac{lbh}{l_0b_0h_0} = \frac{(l_0 - uh_0)(b_0 - uh_0)(h_0 - uh_0)}{l_0b_0h_0}$$

Two shape ratios p and q are defined which are indicative of the degree of non-isometricity of the crystals.

$$p = \frac{l_0}{b_0} \text{ and } q = \frac{l_0}{h_0}$$

Rearranging the above equation using these two ratios gives the following result

$$F = [1 - u]\left[1 - \frac{u}{q}\right]\left[1 - \frac{pu}{q}\right] \qquad (22)$$

This is a third degree equation in u. The criteria for choosing the "correct" root of the possible three is that it should be a real number between 0 and 1. F can be obtained from dissolution data which enables one to solve Eq. 22 for u. From Eq. 21 a linear relationship between u and t should result. Adequate linearity for a plot of u versus t has been demonstrated by Lai and Carstensen for cylindrical tablets of oxalic acid (4). The slope of such a plot gives the value of the intrinsic dissolution rate constant if the solubility, density and initial dimensions of the dissolving particle are known.

Our primary objective is to investigate the change in shape factor of *real* crystals as a function of dissolution time. Isotropicity and isometricity are some of the basic assumptions in the derivation of the Hixson-Crowell cube root law. A cube, a sphere, and a right circular cylinder are some examples of isometric geometries because their shape factors are independent of their dimensions. *Real* particles are usually not isometric. The shape factor of any particle is defined as

$$\Gamma = AV^{-\frac{2}{3}}$$

For the parallelipiped model

$$\Gamma = 2(lb + bh + lh)(lbh)^{-\frac{2}{3}}$$

Inserting Eq. 18, 19, and 20 in the above equation yields

$$\Gamma = 2\left\{\frac{(l_0 - uh_0)(b_0 - uh_0) + (b_0 - uh_0)(h_0 - uh_0) + (l_0 - uh_0)(h_0 - uh_0)}{[(l_0 - uh_0)(b_0 - uh_0)(h_0 - uh_0)]^{\frac{2}{3}}}\right\}$$

Rearranging this equation so as to write it in terms of the shape ratios p and q,

$$\Gamma = 2\left\{\frac{\left[(q-u)\left(\frac{q}{p}-u\right)\right]^{\frac{1}{3}}}{1-u} + \frac{\left[(1-u)\left(\frac{q}{p}-u\right)\right]^{\frac{1}{3}}}{q-u} + \frac{[(q-u)(1-u)]^{\frac{1}{3}}}{\left(\frac{q}{p}-u\right)}\right\} \quad (23)$$

Eq. 23 expresses the shape factor for the parallelepiped geometry considered here, as a function of reduced time. Lai and Carstensen (4) followed a similar approach for cylindrical tablets with different radius to height ratios. They derived an expression for shape factor in terms of the ratio of radius of the cylinder to its height, and the reduced time. By graphical integration they could show that for an isometric tablet (ratio = 1) there was no change in the shape factor as a function of reduced time. However, significant changes in the shape factor were predicted as this ratio deviated from unity. For a ratio of 2.75 for an actual tablet they observed that Γ changed significantly after 50% of the material had dissolved. The intent in this study was to examine the change in shape factor of *real* crystals by the approach spelt above.

MATERIALS AND METHODS

Potassium dichromate (EM Science, Gibbstown, New Jersey) was used as supplied to grow single crystals for dissolution studies. Concentrated sulfuric acid 98% (Aldrich Chemical Co., Milwaukee, Wisconsin) was used in preparation of the dissolution medium. Deionized water was obtained by using a Barnstead PCS cartridge water filter system (The Barnstead Co., Boston, Massachusetts). Dissolution studies were carried out in Distek Inc. model 2000 paddle dissolution apparatus (Distek Inc., New Brunswick, New Jersey) at a stirrer speed of 50 ± 1 rpm. 0.1N Sulfuric acid served as the dissolution medium and all studies were carried out at 25°C. The volume of dissolution medium was varied according to the weight of individual crystal. The range was 750 ml to 1000 ml so as to have a final dichromate concentration of about 400 mcg/ml after complete dissolution. 5 ml aliquots were withdrawn at regular intervals without replacement. The change in total volume of dissolution medium after successive withdrawals was accounted for in concentration computations. Samples were withdrawn until the crystal dissolved completely. Potassium dichromate solutions were analyzed at 457 nm using a Perkin Elmer 559A UV/Vis spectrophotometer.

Potassium Dichromate Crystals

A saturated solution of potassium dichromate was prepared at 25°C. This solution was placed in a large porcelain dish and was allowed to evaporate in a room whose temperature was maintained at 25±1°C. Fine prismatic crystals (length 2-3 mm) were obtained within 24 hours. These crystals were further grown individually, by suspending them with a thread in jacketed glass jars containing a supersaturated solution (degree of supersaturation 1.05) of potassium dichromate at 40°C(16). During crystal growth, the temperature was maintained by circulating water at 40°C from a thermostated water bath. Typically, it took about 24 hours for the crystals to grow to a length of around 9 mm. The crystals so grown retained their prismatic crystal habit. Finally, these crystals were dried under vacuum.

Solubility Studies

Excess potassium dichromate was suspended in 0.1N sulfuric acid in stoppered vials. These were mounted on a motor-driven rotating shaft assembly placed in a water bath, and the temperature was controlled at 25°C by a thermostat. Samples were withdrawn after 48 hours and were filtered through Nylon 66 (0.2 microns) filters. The solutions were analyzed spectrophotometrically after proper dilution.

Measurement of Crystal Dimensions

The length, breadth, and height of the crystals as depicted in Fig. 2 were measured by making use of the "object measurement" mode of an Image-1/AT image analysis and data acquisition system. This image analysis system comprises of a Javelin Ultrachip™ CCD camera bearing a 55 mm f/2.8 Nikon lens which feeds digital information to a Trinitron SONY® color video monitor (complete assembly was supplied by Fryer Co. Inc., Huntley, Illinois). Data acquisition and processing from the video camera is facilitated by having an interface via a Gateway 2000 P4D-66 PC (North Sioux City, South Dakota) and software (Image-1 version 4.0) from Universal Imaging Corporation (West Chester, Pennsylvania). The instrument was calibrated with the help of a ruler prior to use. A series of measurements along faces of the crystals were made to determine their respective dimensions and an average length, breadth and height was used in each experiment.

Computer Programs

The third degree equations in u were solved by using two independent mathematical programs viz., Mathematica (version 2.2 for Macintosh) and Student MATLAB (DOS version). Modeling and statistical treatment of the acquired data was accomplished using the statistical program Scientist (Micromath Scientific Software, Salt Lake City, Utah).

RESULTS AND DISCUSSION

In order to determine the shape factor Γ of a single crystal, as a function of time, the fraction undissolved was calculated from the amount dissolved (Fig. 2). The transformation of actual time t to reduced time u is a convenient way to normalize all dissolution runs. There is a one to one correspondence between u and t. There was no ambiguity in selection of the "correct" root of Eq. 22 because in all the

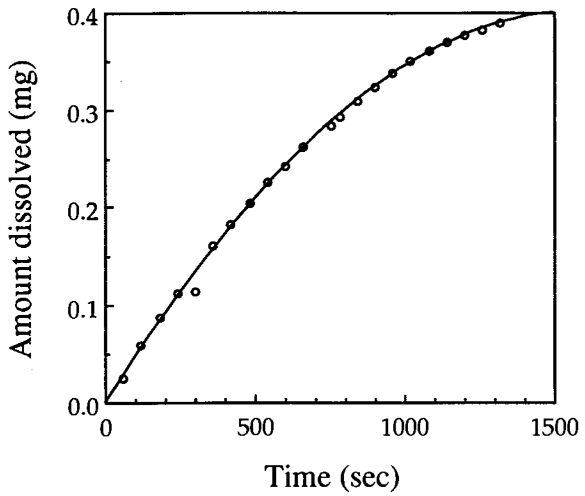

Fig. 2. Dissolution curve for potassium dichromate crystal no. 2 in 0.1N H_2SO_4 at 25°C and 50 rpm stirrer speed.

cases that were studied, two of the three roots were either imaginary or were greater than unity.

The linearity in the plot shown in Fig. 3 for crystal no. 2 with dimensions $l_0 = 1.120$ cm, $b_0 = 0.518$ cm, and $h_0 = 0.299$ cm confirms the validity of Eq. 21. Knowing the saturation solubility at 25°C (0.1397 g/ml), density at 25°C (2.676 g/ml), and h_0 one could estimate the intrinsic dissolution rate constant from the slope of the graph shown in Fig. 3. For this crystal it was found to be 2.14×10^{-3} cm/sec. A similar study was done on four other crystals of potassium dichromate and all the u vs t plots were linear. The intrinsic dissolution rate constants so obtained are given in Table I. The mean of these values with 95% confidence limits was found to be $2.74 \pm 0.62 \times 10^{-3}$ cm/sec.

Table I. Intrinsic Dissolution Rate Constants for the Five Potassiun Dichromate Crystals

Crystal no.	h_0 cm	$q/p = b_0/h_0$	$c_3 \times 10^4$ sec^{-1}	$k \times 10^3$ cm/sec
1	0.400	1.60	9.76	3.74
2	0.299	1.73	7.47	2.14
3	0.373	1.18	7.31	2.61
4	0.173	3.09	13.61	2.25
5	0.304	1.68	10.22	2.97

The shape factor at each time point was calculated for this crystal via Eq. 23. A plot of Γ versus u is shown in Fig. 4. It must be mentioned that the nature of this plot is in concordance with the one reported by Lai and Carstensen (4) for the cylindrical tablets. One salient feature of this plot is that in the initial phases of dissolution the shape factor increases only marginally, and after about u = 0.5 there is a significant change in Γ. Physically this implies that as the particle dissolves, the volume of the crystal decreases at a faster rate than the surface area. Hence at relatively smaller particle sizes, surface area is the dominant factor.

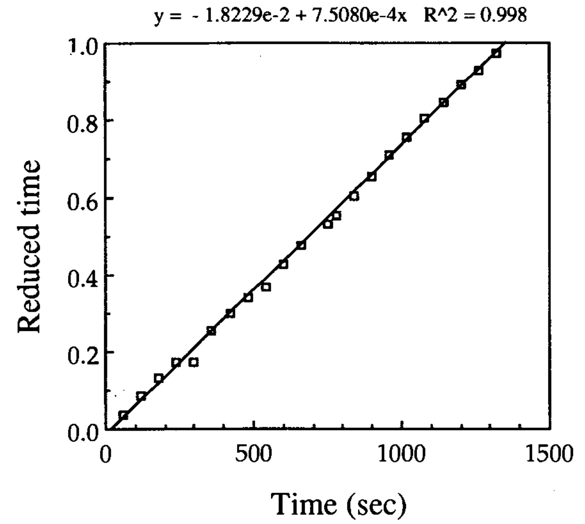

Fig. 3. Reduced time versus actual time data for crystal no. 2.

Empirically the following equation describes the data in Fig. 4:

$$\Gamma = c_1 + \frac{c_2}{(u^* - u)} \tag{24}$$

where c_1, c_2, and u^* are parameters that can be determined from a nonlinear regression fit to the data. To be consistent with the curve in Fig. 4 the value of u^* must be very close to unity. For an isometric particle such as a sphere or a cube or a right circular cylinder one would expect c_2 to be zero so that the shape factor would be independent of u, i.e. time.

In an attempt to fit the shape factor data other functions were used viz., polynomials, logarithmic function in u, exponential function in u, and a combination of polynomial and logarithmic function in u. None of them gave good fits. The nature of the curve in Fig. 4 suggests an inverse functionality in (1-u). The goodness of fit of all the functions mentioned here was determined on the basis of a statistical parameter called the Model Selection Criterion (MSC). This is a part of the data fitting statistical program Scientist™. It is given by the following expression:

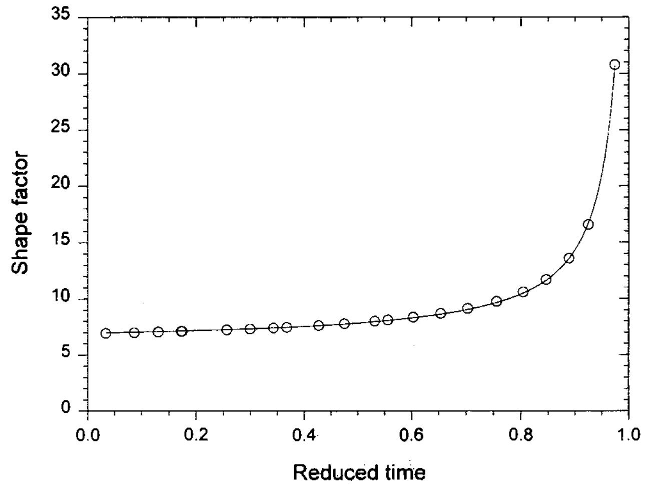

Fig. 4. Shape factor versus reduced time for crystal no. 2. The open circles represent the experimental data points and the curve is a least square fit to the data.

$$MSC = \ln\left\{\frac{\sum_{i=1}^{n}(Y_{obs_i} - \overline{Y}_{obs})^2 w_i}{\sum_{i=1}^{n}(Y_{obs_i} - \overline{Y}_{cal_i})^2 w_i}\right\} - \frac{2p}{n} \qquad (25)$$

where w_i are the weights applied to each point in a set of data, n is the number of points, and p is the number of parameters in the model equation. Y represents the dependent variable and "obs" and "cal" indicate the observed and calculated values for that variable. This parameter is particularly useful in comparing two different models with different number of parameters. Larger the value of MSC greater is the information content of the model, and better is the fit. It was found that this value was largest for Eq. 24 as the model as compared to other functions used.

The data in Fig. 4 were least square fitted using non-linear regression with the following outcome: $c_1 = 6.021$, $c_2 = 0.930$, and $u^* = 1.012$, $R^2 = 0.999$. Dissolution studies were carried out on four other crystals of potassium dichromate with different dimensions. The pertinent data and parameters are given in table II. In all the cases the value of u^* was close to unity. Substituting $u = 0$ in Eq. 24 yields the value of initial shape factor (Γ_0). For all the five crystals (within experimental errors) these values were in good agreement with the ones calculated from their initial dimensions (columns 10 and 11 in table II).

Fig. 5 illustrates the effect of the degree of non-isometricity on the extent of change in the shape factor during dissolution of the crystals. For convenience the ratio q/p which is equal to b_0/h_0 can be used to quantify the degree of non-isometricity of a crystal. Accordingly crystal no. 4 exhibits the highest degree of non-isometricity. It is also the one which experiences the earliest and most significant change in the shape factor. The observation is particularly relevant to extreme elongated shapes like needles and flakes. The nature of the curves in Fig. 5 is in agreement with those obtained by graphical integration for non-isometric cylinders, as reported by Lai and Carstensen (4).

Derivation of the Modified Cube Root Equation for Dissolution

Since

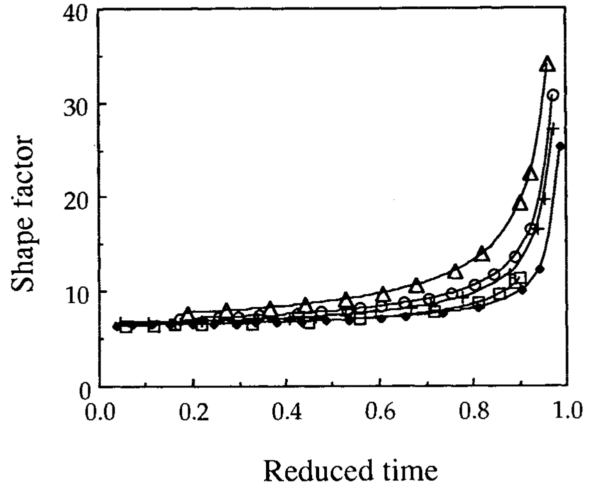

Fig. 5. Shape factor versus reduced times for crystals 1-5. Crystal no. 1: **squares** ($q/p = 1.60$); crystal no. 2: **circles** ($q/p = 1.73$); crystal no.3:**diamonds** ($q/p = 1.18$); crystal no. 4: **triangles** ($q/p = 3.09$); crystal no. 5: + ($q/p = 1.68$).

$$u = \left(\frac{2kS}{\rho h_0}\right) t = c_3 t \qquad (26)$$

it follows from Eq. 24 that

$$\Gamma = c_1 + \frac{c_2}{(u^* - c_3 t)} \qquad (27)$$

Eq. 2 may now be written as

$$\frac{dm}{dt} = -kS\left[c_1 + \frac{c_2}{(u^* - c_3 t)}\right]\left(\frac{m}{\rho}\right)^{\frac{2}{3}} \qquad (28)$$

Eq. 28 may be integrated to give:

$$\int_{m_0}^{m} \frac{dm}{m^{2/3}} = -\frac{kS}{\rho^{2/3}} \int_0^t \left\{c_1 + \frac{c_2}{(u^* - c_3 t)}\right\} dt \qquad (29)$$

or

$$m_0^{1/3} - m^{1/3} = \frac{kS}{3\rho^{2/3}}\left[c_1 t - \frac{c_2}{c_3} \ln\left(\frac{u^* - c_3 t}{u^*}\right)\right] \qquad (30)$$

or

Table II. Initial Dimensions of Five Different Crystals of Potassium Dichromate, Their Respective Shape Ratios, and Parameters for the Shape Factor of the Dissolving Crystal

Crystal no.	l_0 cm[a]	b_0 cm[a]	h_0 cm[a]	p	q	c_1[b]	c_2[b]	u^*[b]	Γ_0[c] from fit	Γ_0[d] actual
1	0.902	0.642	0.400	1.406	2.252	5.753	0.578	1.008	6.33	6.34
2	1.120	0.518	0.299	2.161	3.738	6.021	0.930	1.012	6.94	6.88
3	0.876	0.441	0.373	1.987	2.306	6.072	0.394	1.008	6.46	6.39
4	0.712	0.535	0.173	1.330	4.117	5.915	1.549	1.016	7.44	7.31
5	0.912	0.511	0.304	1.784	2.999	5.909	0.756	1.009	6.65	6.61

[a] Determined by image analysis technique with prior calibration.

[b] Obtained from non-linear regression fit of shape factor as a function of reduced time.

[c] Calculated from c_1, c_2, and u^*.

[d] Calculated from l_0, b_0, and h_0.

$$m_0^{1/3} - m^{1/3} = Bt - D \ln\left(\frac{u^* - c_3 t}{u^*}\right) \qquad (31)$$

where

$$B = \frac{c_1 k S}{3\rho^{\frac{2}{3}}} \qquad (32)$$

$$D = \frac{c_2 \rho^{\frac{1}{3}} h_0}{6} \qquad (33)$$

and

$$c_3 = \frac{2kS}{\rho h_0} \qquad (34)$$

Knowing the values of the constants ρ, S, k and the parameters c_1, c_2, c_3, and u^* the cube root differences can now be calculated from Eq. 30. These would be the predicted values from our model. These values for crystal no. 2 are represented by open squares in Fig.6 and the open circles represent the actual experimental values for the same crystal. For an isometric particle c_2 and hence D would be zero. In such cases Eq. 31 reduces to the usual cube root law. Both these instances are depicted in Fig.6. The straight line is the prediction from the Hixson Crowell cube root law ($D = 0$). It can be seen that the model equation derived here explains the upward curvature in the plot. The differences in the observed values and the ones calculated from the model are less than those from the predictions of Hixson Crowell cube root law. Similar behavior was exhibited for all the other crystals, in that an upward curvature was seen in the cube root law plots and the predicted values were always higher than the predicted values.

One could speculate several reasons for the observed differences in the experimental values and the predicted values from the model. Firstly, potassium dichromate belongs to a triclinic pinacoidal crystal system. None of the three angles between the three defining axes are equal to 90°. Secondly, by visual inspection during dissolution runs it was observed that towards the end of the dissolution event the dissolving crystals assumed irregular shapes thereby making it more difficult to approximate the model geometry. Obviously this ties in with non-isotropicity. There are active sites on the crystal which may be unevenly placed leading to preferential dissolution from a corner or an edge of the crystal.

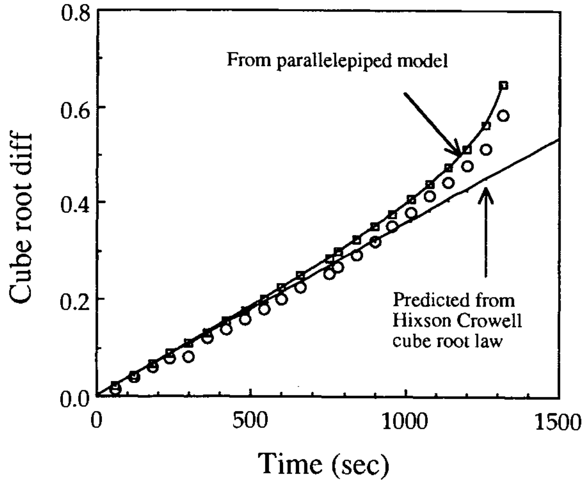

Fig. 6. Cube root difference values plotted against time for crystal no. 2. Circles represent experimental data points, squares are the values calculated from our model equation, and the straight line represents predictions of the Hixson Crowell cube root law.

The work done by Lai and Carstensen (4) dealt with oxalic acid tablets and the simulation model for a *real* particle was a cylinder. Their conclusions regarding effect of non-isometricity on the change in shape factor was based on results obtained from graphical integration. Only two lengths are necessary to define the shape of a cylinder, namely height and the base radius. Although this, to some extent, mimics the overall shape of a needle or a platelet, it lacks the third dimension. Hence an extension of their work was deemed to be in order.

All the same, the model underlines the importance of shape factor and hence surface area of the dissolving particle in the manifestation of its dissolution behavior. It can be concluded that amongst other variables, the shape factor of *real* particles is critical in determining their dissolution behavior. This study is particularly relevant to shapes like needles and platelets because they are characterized by high degrees of non-isometricity. This treatise will be extended to multiparticulate systems by considering separate sieve fractions of crystalline substances (17) in a study that is presently underway.

SYMBOLS

A = surface area of dissolving solid (cm^2), C = concentration (mg/ml) at time t, M = mass of monodisperse powder not dissolved (mg or g) at time t, M_O = Initial mass of monodisperse powder (mg or g), m = mass of a single particle remaining at time t, m_O = initial mass of a single crystal (mg or g). k = intrinsic dissolution rate constant (cm/sec), S = saturation solubility (g/ml solvent), t = time (sec), Γ = shape factor, ρ = true density of the solid (g/cm^3), l_0 = initial length of the crystal (cm), b_0 = initial breadth of the crystal (cm), h_0 = initial height of the crystal (cm), l = length of the dissolving crystal at any time t (cm), b = breadth of the dissolving crystal at any time t (cm), h = height of the dissolving crystal at any time t (cm), p,q = shape ratios for a crystal

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