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RESEARCH PAPER

Particle Size Distributions from Multiparticulate Dissolution

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ABSTRACT

It has been demonstrated theoretically that the particle size distribution of particles in a given sieve fraction of a powder may be assessed by means of short-term dissolution data. Theoretical considerations in this article show that by accounting for polydispersity in a powder sample, the cubic expression in time for amount undissolved and fraction undissolved gives rise to integrals that are essentially moments of the distribution function of one of the defining dimensions of the particle. The first and the second moments can be used to calculate the distribution parameters, (mean and standard deviation) of such a dimension of a crystalline powder. The theory is based on a model geometry, a parallelepiped, for the description of particles such as needles, plates, and prisms. The theory is substantiated by experimental data. A method for obtaining the particle size distribution parameters from the results of dissolution of three sieve fractions of oxalic acid dihydrate, and the general application of this to particle size determination is discussed. To validate the method, the distribution of lengths and breadths of oxalic acid dihydrate particles was obtained from microscopy. From actual powder dissolution data, an estimate of the mean height-to-breadth ratio of these particles belonging to a certain sieve fraction was obtained. With the knowledge of the dissolution rate constant, K, for oxalic acid dihydrate under specified hydrodynamic conditions, it was possible to evaluate the moments of the distribution function. The distribution parameters so obtained were in good agreement with the results obtained from microscopy.

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INTRODUCTION

In a different publication (1) we demonstrated how the average volume shape factor of particles from a sieve fraction can be obtained from powder dissolution data. The article to follow shows a method for obtaining particle size distributions of sieve fractions of crystalline solids from powder dissolution.

It is known that particulate solids resulting from unit processes such as crystallization, precipitation, and milling exhibit skewed particle size distributions (2–4). The importance of particle size distribution of powder substances in regard to dissolution rates has been well documented in the pharmaceutical literature (4–11). Simply said, smaller particles dissolve at a faster rate than larger particles.

Although very desirable from a theoretical point of view, practical problems are associated with particle size distribution and dissolution. Currently, virtually all solid dosage form products are routinely subjected to dissolution testing, and the most common cause for product recalls is failure of a product to meet dissolution specifications (12). Most often, particle size limits are included in drug substance specifications, because particle size affects both dissolution characteristics and machinability (flow and compression) of the substance. However, most particle size distributions are derived from volume-based measurements (e.g., Coulter-counter) of the particles from a random sample. Disadvantages of this method are that the volume is converted to an equivalent spherical radius and the sample size is always very small. Barnett and Nyström have cautioned researchers regarding the misuse of the spherical approximation by stating that, ". . . . direct comparisons between microscope-derived mean particle size parameters and Coulter-counter-derived data can lead to erroneous conclusions if no consideration is given to the shape of particles . . . ." (13). Size determination of needle-shaped particles by techniques such as the use of the Coulter-counter can lead to experimental difficulties such as "coincidence" of two or more particles at the orifice, which can lead to faulty results. This method also does not directly address the main reason for its execution, namely dissolution in a USP dissolution apparatus.

Microscopy is the only particle size analysis method that can provide an estimate of the *actual* dimensions of nonspherical particles. The major advantage of this method is that it can furnish size as well as shape information about nonisometric solids. On the other hand, the inherent tediousness and time-consuming nature of this method limits its use. The user is also restricted to a relatively small sample size on which the representativeness of the powder population has to be relied. Houghton and Amidon have suggested a microscopy-based image analysis routine procedure to determine the lot-to-lot variability in the particle size and shape characteristics of three lots of an investigational drug (14). Invariably, such methods rely on the particular software-defined size and shape parameters. It would be desirable to have a particle size determination method that can circumvent these shortcomings. This article shows that powder dissolution can be used successfully, with distinct advantage, to obtain meaningful information regarding particle size distribution of crystalline substances of nonspherical nature (15).

CONCEPTS

Rather than associating a particle with its spherical equivalent radius, it is useful to characterize the particle by a geometric means whereby the particle has a shape that might be characteristic of a crystal. In this article it is assumed that the shape of the crystal can be mimicked by a parallelepiped of height h, breadth b, and length l (16). The volume shape factor, α_v, correlates the volume, v, and the size, b, by the following relation (17):

$$v = \alpha_v b^3 \tag{1}$$

The initial volume of the particle before the advent of dissolution is

$$v_0 = \alpha_{v_0} b_0^3 \tag{2}$$

It can be shown that

$$\alpha_{v_0} = (l_0/b_0)(h_0/b_0) \tag{3}$$

The two shape ratios defined in Eq. (3) can be denoted by the following:

$$m = l_0/b_0 \tag{4}$$

and

$$n = h_0/b_0 \tag{5}$$

Note that a shape factor may be used in conjunction with any dimension as long as it is consistently chosen throughout, and in this publication it is the breadth which is used as the dimension to arrive at the volume via Eq. (1). An estimate of an average volume shape factor for a set of particles from a sieve fraction can be obtained from powder dissolution data (1). Microscopy, at best, yields an estimate of the mean length-to-breadth ratio for such an ensemble of particles, because it is not possible

to measure the smallest dimension, h. In other words, α_{v_0} from microscopy would correspond to the shape ratio, m, whereas α_{v_0} obtained from dissolution corresponds to the product of the ratios m and n. Although there is no direct means of measuring the height of the particles, an estimate of the mean height of the particles within a distribution can be obtained from the following relationship:

$$\text{Mean of height} = \left(\frac{\alpha_{v_{0\,\text{dissolution}}}}{\alpha_{v_{0\,\text{microscopy}}}} \right) \text{mean of breadth} \quad (6)$$

Microscopy has been used for many years to obtain particle distributions (4,18) and is still used today (14), but the method suffers from the disadvantage of small sample sizes. Electronic means of counting have the same drawback. Sieve analyses allow larger sample sizes, but suffer from lack of definition, in that the aperture of the smaller confining sieve may not necessarily conform with the smallest dimension of the particles sieved. Furthermore, in cases in which aggregation is a problem, if it is not minimized, results from sieving may be misleading (19).

This article describes an approach in which dissolution is used to gauge particle size distributions. Because analysis of dissolution is one of the purposes of carrying out particle size distribution analyses, it first constitutes a meaningful measure, and furthermore has the advantage that the sample size may be substantial.

MATERIALS AND METHODS

Oxalic acid dihydrate (97%) was obtained from Aldrich Chemical Co., Milwaukee, WI. Deionized water was obtained by using a Barnstead PCS cartridge ion exchange water filtration system (The Barnstead Co., Boston, MA). HCl (0.1 N) was used as the dissolution medium for oxalic acid dihydrate and was prepared by diluting 8.3 ml concentrated HCl to 1 liter with deionized water.

Recrystallization

Eight hundred milliliters water at 60°C was used to dissolve 350 g oxalic acid. The solution was filtered and slowly cooled to 25°C and then allowed to stand at 25°C for 24 hr. To avoid vitrification, after filtration the crystals were stored in a desiccator over sodium chloride suspension (4). A Thomas Hoover capillary melting point apparatus (Arthur H. Thomas Company, Philadelphia, PA) was used to obtain the melting point which compared well with the reported value (20).

Density Measurement

The density of the oxalic acid dihydrate was obtained by employing pycnometry in a solution saturated at 25°C with oxalic acid. Density was found to be 1.63 g/ml.

Solubility Measurement

The solubility in 0.1 N HCl at 25°C of oxalic acid dihydrate was obtained by suspending excess solid in the medium and using 10-ml vials. The vials were arranged on a rotating assembly in a thermostated water bath. Samples were removed after 48 hr and the supernatant filtered through 0.2-μm nylon-66 filters. Analysis was done by spectrophotometry. The saturation solubility in 0.1 N HCl of oxalic acid dihydrate was 0.1443 g/ml.

Sieve Analysis

The recrystallized oxalic acid dihydrate was size-separated using US standard sieves using the following mesh sizes: 30 (600 μm), 40 (425 μm), 50 (300 μm), and 60 (250 μm). These sieves were mounted on a sieve shaker (CSC Scientific Co.) and the sieving was carried out for 30 min.

Particle Size Analysis

The breadths and lengths of samples from the mesh fractions were determined by means of a microscope coupled with image analysis (Nikon microscope, Image-1/AT image analyzer, Fryer Co., Inc., Huntley, IL). Calibration employed a 1-mm stage micrometer. Representative samples were obtained by coning and quartering (21). Three hundred particles was assumed to be a representative sample of the population. The observed lengths and breadths were grouped into a number of class intervals (such as determined by Sturge's rule). A frequency distribution was obtained from this (22). The total number of particles in a sample for dissolution (from a mesh cut) was obtained from the weight of 300 particles from that fraction.

Powder Dissolution Studies

A USP apparatus method II (paddle) was used at 25°C and 50 rpm. Three grams of oxalic acid dihydrate was introduced into the apparatus containing 800 ml of

0.1 N HCl. The amount of solid employed was so chosen such that sink conditions would prevail throughout the dissolution. Samples (4 ml) were removed at fixed intervals. The samples were analyzed without further dilution by spectrophotometry at 255 nm (Varian DMS 500 UV/VIS spectrophotometer, Palo Alto, CA).

RESULTS AND DISCUSSION

Particle size analysis of the lengths and breadths of oxalic acid dihydrate particles was done *a priori*, to validate the results obtained from powder dissolution. The number distribution of breadths of these particles within the different class intervals, for a –40/+50 sieve fraction, is shown in Table 1. The frequency distribution function is obtained from the fractional number frequency and is shown in column 6 of Table 1. The normalized ordinate values, $Y = f(b_0)$, are obtained from the frequency, F, by noting that normalization (dictating unit area under the curve) requires that

$$Y = F/(b_u - b_l) \tag{7}$$

where b_u is the upper limit and b_l the lower limit of the interval.

The probability density function, $f(b_0)$ plotted versus the midpoint of the frequency interval is shown in Fig. 1. The data can be approximated to a normal distribution, and from a least-squares fit to the data, an estimate of the mean and standard deviation of the breadth of the particles can be obtained. Similar analysis can be done for the length of these particles, and the distribution parameters for the same were obtained. The ratio of the mean of the length to the mean of the breadth gives an estimate of $\alpha_{v0microscopy}$.

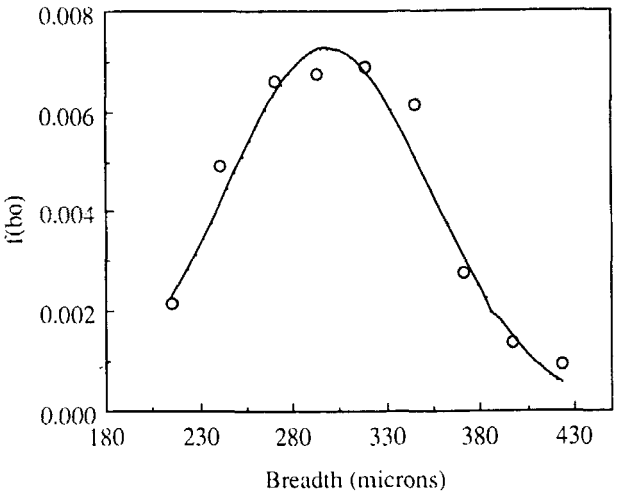

Figure 1. Frequency distribution function of a –40/+50 sieve fraction of oxalic acid dihydrate.

The method of normalization is obvious and it is emphasized that the distribution function is logically truncated between the smallest breadth b_{min} and the largest breadth b_{max} in the distribution.

$$\int_{b_{min}}^{b_{max}} f(b_0)db_0 = 1 \tag{8}$$

If a particle has an initial breadth, b_0, then the original mass, m, of that particle is given by

Table 1

Calculation of the Probability Density Function from the Number Frequency for a –40/+50 Mesh Fraction of Oxalic Acid Dihydrate

Lower Limit of Interval, b_l	Upper Limit of Interval, b_u	Midpoint of Interval	Number Frequency N	$F = N/N_{total}$	$Y = f(b_0) = F/26$ (interval = 26)
202	228	215	14	0.0558	0.00214
228	254	241	32	0.1275	0.0049
254	280	270	43	0.1713	0.00659
280	306	293	44	0.1753	0.00674
306	332	319	45	0.1793	0.00689
332	358	345	40	0.1594	0.00613
358	384	371	18	0.0717	0.00276
384	410	397	9	0.0358	0.00138
410	436	423	6	0.0239	0.00092

$$m = \rho v = \rho(\alpha_{v_0})b_0^3 \quad (9)$$

where v is volume, and ρ is particle density. The dimensions are distributed by a normalized frequency function $f(b_0)$, so the number fraction, N_b, of particle between the infinitesimally small interval $(b_0, b_0 + db_0)$ would be given by

$$N_b = f(b_0)db_0 \quad (10)$$

Denoting the mass of the whole powder population by M_0, it would given by

$$M_0 = \int_{b_{min}}^{b_{max}} \{N\rho\ f(b_0)(\alpha_{v_0})b_0^3\}db_0 \quad (11)$$

where b_{max} and b_{min} denote the largest and smallest dimension of the particles in the powder population, and b_0 refers to the fact that the particles will be placed in a dissolution medium at a given time of zero. Equation (11) applies to a polydisperse system of particles (for instance, a sieve fraction), and in this regard an average value for the initial volume shape factor has been ascribed to that particular sieve fraction.

If the powder is dissolved under sink conditions, then the dimensions of the particle will decrease linearly with respect to time (5,16,23,24):

$$b = b_0 - Kt \quad (12)$$

It is noted that the initial distribution function can be used to calculate the mass undissolved until the critical time, t^*. It is at the critical time that the smallest particle disappears from the dissolution medium, and up to this point in time (t^*) the total number of particles in the system remains the same (4,5,15). If the powder is allowed to dissolve at time $t < t^*$, the mass undissolved will be

$$M_0 = \int_{b_{min}}^{b_{max}} \{N\rho\ f(b_0)(\alpha_{v_0})(b_0 - Kt)^3\}db_0 \quad (13)$$

If the cubed term is expanded, then

$$M = A_1 - B_1t + C_1t^2 - D_1t^3 \quad (14)$$

where the coefficients A_1, B_1, C_1, and D_1 are elaborated below.

$$A_1 = N\rho\alpha_{v_0}\int_{b_{min}}^{b_{max}} f(b_0)b_0^3db_0 = N\rho\alpha_{v_0}\mu_3 \quad (15)$$

This term is obviously the original mass of the powder sample and μ_3 is the third moment of the probability distribution function (25).

The third coefficient in Eq. (14) is

$$C_1 = 3N\rho K^2\alpha_{v_0}\int_{b_{min}}^{b_{max}} f(b_0)b_0db_0 = 3K^2N\rho\alpha_{v_0}\mu_1 \quad (16)$$

where μ_1 is the first moment of the probability density function and also the mean of the distribution (25).

The second coefficient in the expansion is

$$B_1 = 3N\rho K\alpha_{v_0}\int_{b_{min}}^{b_{max}} f(b_0)b_0^2db_0 = 3KN\rho\alpha_{v_0}\mu_2 \quad (17)$$

where μ_2 is the second moment of the probability density function (25). The variance of the powder population is given by

$$\sigma^2 = \mu_2 - \mu_1^2 \quad (18)$$

The coefficient to the last term is given by

$$D_1 = N\rho K^3\alpha_{v_0}\int_{b_{min}}^{b_{max}} f(b_0)db_0 = K^3N\rho(\alpha_{v_0}) \quad (19)$$

where the probability density function as used is normalized [Eq. (8)].

Equation (14) may be divided through by $A_1 = M_0$, in which case it takes the form

$$M/M_0 = 1 - B_2t + C_2t^2 - D_2t^3 \quad (20)$$

and the coefficients with subscript "2" are then the coefficients with subscript "1" divided by M_0.

The coefficients of the terms in t, t^2, and t^3 in Eq. (20) are given by the following equations:

$$B_2 = {}^3K\mu_2/\mu_3 \quad (21)$$

$$C_2 = {}^3K^2\mu_1/\mu_3 \quad (22)$$

$$D_2 = K^3/\mu_3 \quad (23)$$

In a typical research and development setting, in the event that a new drug candidate is recognized by the drug discovery group, then the dissolution rate constant K, for that compound under specified hydrodynamic conditions, can be determined from powder dissolution data and particle size analysis by microscopy (15). This can be done via Eqs. (20) and (21). From the dissolution data, the coefficient B_2 is obtained and through the results from microscopy the moments μ_2 and μ_3 can be evaluated. Similarly, from Eqs. (14) and (17), by knowing N, the initial number of particles, and the density of the solid, the average initial volume shape factor for a polydisperse powder can be estimated (1). Dissolution

Table 2

α_{v_0} Values Obtained from Microscopy and Dissolution for Several Sieve Fractions of Oxalic Acid Dihydrate

Sieve Fraction	Mean of Breadth (μm)	α_{v_0} from Microscopy	α_{v_0} from Dissolution	Mean $h_0/b_0 = n$
–30/+40	410	4.8	2.7	0.56
–40/+50	299	8.0	3.8	0.47
–50/+60	240	8.8	4.2	0.47

studies and particle size analysis on three sieve fractions of oxalic acid dihydrate; –30/+40, –40/+50, and –50/+60, yielded a K value of $(1.42 \pm 0.19) \times 10^{-4}$ cm/sec when dissolution was carried out in 0.1 N HCl in a USP paddle apparatus at 25°C and 50 rpm. The K value should be independent of particle size.[1] The results for volume shape factor obtained by two methods are shown in Table 2. These results will be used in the interpretation of size distribution parameters obtained from powder dissolution in the next section.

Determination of Particle Size Distribution Parameters from Powder Dissolution Data

The same problem can be considered in the opposite direction. With the knowledge of K value for oxalic acid dihydrate under specified hydrodynamic conditions, from the fraction undissolved as a function of time, the moments of the distribution function of a "dimension of significance" can be obtained. Only the dissolution data up to the critical time are utilized in this manner. At the critical time, there is a change in slope in the cube root law plot (4,26). The fraction undissolved data until the critical time can be least-squares-fit to a third-degree polynomial in time as dictated by Eq. (20). The moments of distribution, μ_1, μ_2, and μ_3, can be evaluated from Eqs. (21), (22), and (23), with three equations to solve for three unknowns. Earlier, to get an estimate of K value for oxalic acid dihydrate, the moments of the distribution function had to be known. Thus the restriction of breadth being the defining dimension was imposed on the integrals before they could be evaluated numerically. In the process of working backward, to get the distribution parameters from powder dissolution data, the integrals that define the moments of distribution function are allowed to "float." In other words, no restriction regarding the kind of dimension is imposed at this point. Thus, it is of interest to determine which of the three dimensions of the particle is perceived by this approach.

To exemplify these ideas, dissolution of three sieve fractions of oxalic acid dihydrate were carried out. For these sieve fractions the distribution parameters for the lengths and breadths of the particles were known. This was necessary in order to have assurance about the validity of the approach. Fig. 2 shows the dissolution curve for a –40/+50 mesh fraction of oxalic acid dihydrate. The cube root law plot for the same event is shown in Fig. 3 from which an estimate of the critical time was obtained. The plot for fraction undissolved until the criti-

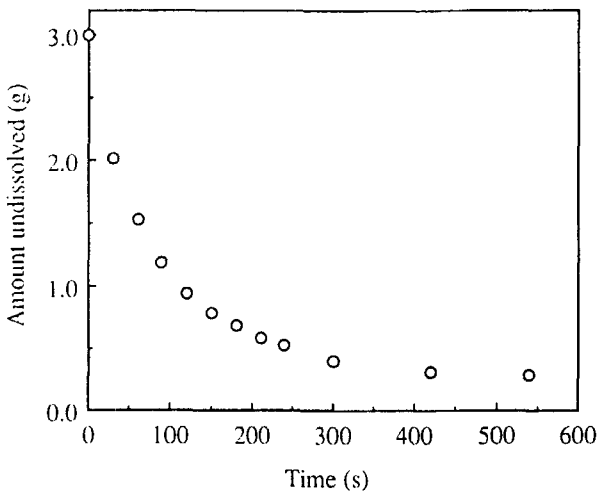

Figure 2. Amount undissolved for the dissolution of a –40/+50 sieve fraction of oxalic acid dihydrate in 0.1 N HCl at 25°C and 50 rpm.

[1]It is assumed, at this point in the presentation, that b is the significant dimension (i.e., the one which disappears first). If indeed it is h, then the moments of h may be obtained by means of the shape factor and Eq. (3), and K can be iterated.

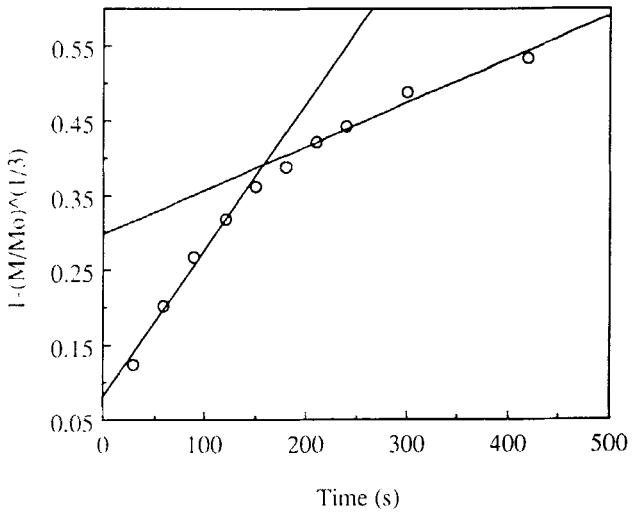

Figure 3. Cube root law plot for the dissolution of a –40/+50 mesh fraction of oxalic acid dihydrate showing the critical time.

cal time is shown in Fig. 4. From the least-squares-fit to the data, the coefficients of terms in t as per Eq. (20) can be obtained.

The mean and standard deviation for a particular sieve fraction can be calculated using the following equations:

$$\text{Mean} = \mu_1 \tag{24}$$

$$\sigma = \sqrt{\mu_2 - (\mu_1)^2} \tag{25}$$

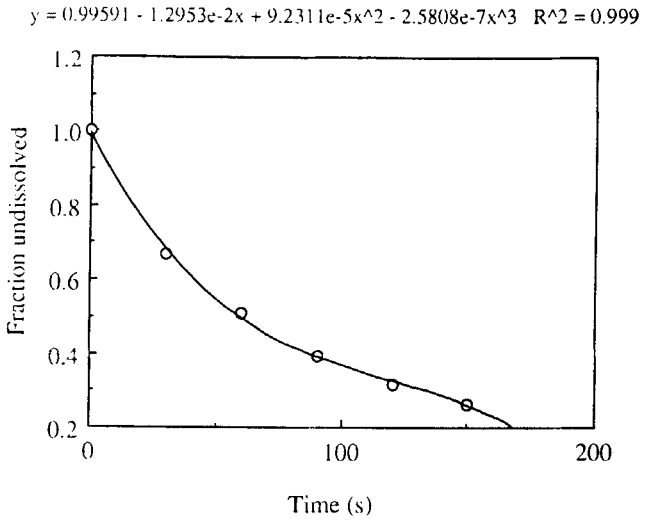

Figure 4. Fraction undissolved for the dissolution of a –40/+50 mesh fraction of oxalic acid dihydrate.

The results for the three sieve fractions are shown in Table 3. The mean and standard deviation obtained by such means can now be compared with those for the breadth of the particles from respective sieve fractions obtained from microscopy. Note that in all of the three sieve fractions, the mean obtained directly from dissolution data is less than the mean from microscopy. In the wake of this observation, the following question arises: Is it possible, by not imposing any restrictions about the dimension of the particles on the integrals comprising the moments of distribution, that the smallest dimension (height) of the particles is recognized? To answer this query, we decided to resort to the volume shape factor data for these sieve fractions that were obtained earlier and are shown in Table 2. As mentioned before, the ratio of mean height to the mean breadth can be calculated via Eq. (6) from the volume shape factors obtained from microscopy and dissolution. Thus, the mean of height ($M_{h_0} = M_{b_0} \cdot n$) for particles belonging to a particular sieve fraction can be predicted using Eq. (6). These values can be compared with the means obtained directly from dissolution data. Table 3 shows that these two sets of values are in excellent agreement. The standard deviations of the breadth of particles are also comparable with those obtained from dissolution.

It is obvious that the longer the precritical time is, the better the assessment of the coefficients. It is natural to carry out the dissolution in water, but just for the purpose of determination of distribution parameters, other solvents and apparatuses may be used. If a solvent exerting less solubilizing power on the substance is used, or an apparatus allowing slower dissolution is employed, then longer time intervals prior to t^* may be used, thereby improving precision. If, however, the value of (aqueous) K is sought under USP-type dissolution apparatus conditions, then this apparatus should be used, and water, N/10 hydrochloric acid, or simulated gastric fluids could be used as the dissolution media.

CONCLUSIONS

For any compound, a drug substance or a pharmaceutical excipient, particle size specifications form an important aspect of routine quality control. Particle size is also important from a dissolution standpoint. If the dissolution rate constant K for such a substance under specified hydrodnamic conditions is known, or can be determined as indicated in this article, then it is possible to get useful information about the particle size distribution parameters directly from powder dissolution data, with-

Table 3

Distribution Parameters for Sieve Fractions of Oxalic Acid Dihydrate Determined from Dissolution Data and Comparison with those Obtained from Microscopy

Sieve Fraction	M_{b_0} from Microscopy (μm)	σ_b from Microscopy (μm)	Mean from Dissolution (μm)	Standard Deviation from Dissolution (μm)	n = Mean (h_0/b_0)	Predicted M_{h_0} (μm)
–30/+40	410	85	222	84	0.56	230
–40/+50	299	55	167	70	0.47	140
–50/+60	240	32	120	33	0.47	113

out having to rely on microscopy or any other method of particle size analysis. As shown in the studies with the sieve fractions of oxalic acid dihydrate, distribution parameters for the thickness (height) of the particle can be obtained. This is most desirable because in most pharmaceutically encountered, crystalline substances are needle-shaped or have a prismatic crystal habit. Also, in such cases where aggregation of solids is not a problem, this dimension invariably corresponds to the size of a sieve opening. The salient features of this particle size determination method from dissolution data are (*a*) it is less time consuming and less tedious than microscopy; (*b*) it affords a larger sample size than what microscopy would allow, and, hence, can make the sample more representative of the population; and (*c*) the method serves the end purpose in the most appropriate manner, i.e., conforming with dissolution requirements. Thus, this methodology has the potential for serving as a time-efficient quality control test for particle size distributions.

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