

# Dissolution Profile for Multisized Drug Particles: New Approximate Expression

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**Abstract** □ New approximate expressions for the weight fraction undissolved were obtained using the Taylor series expansion. These approximations were tested using simulated data for multisized drug particle populations. The resulting calculations show that: (a) the approximations are not dependent on a knowledge of the analytical form of the particle-size density function, (b) the distribution effects are accounted for, but only a knowledge of the sample mean and standard deviation is required, and (c) the approximations (especially on a weight basis) lead to values within the limits of error in dissolution studies, thus posing the question of whether published exact expressions have practical value.

**Keyphrases** □ Dissolution—multisized drug particles, approximate expressions for weight fraction undissolved □ Particles, multisized—dissolution profile, approximate expressions for weight fraction undissolved □ Weight fraction undissolved—multisized drug particles, approximate expressions

The effects of multisized particle distributions on dissolution kinetics were studied using either experimental or simulated data (1–7). One area of particular concern has been the acceptability of treating the kinetics of dissolution for a multisized particle population with an approximate mathematical treatment for the kinetic model of interest.

The importance of including the distribution effects was recognized in the mathematical treatment of a diffusional model proposed for the dissolution of micronized methylprednisolone (1, 2). The complexity of these equations led to simplified forms *via* an approximation for the particle-size density function.

Approximate expressions were discussed in connection with the cube root kinetic model (3–5). For example, an approximation to the cube root model was described for a log-normal particle-size population that relaxes to the exact cube root law when the standard deviation of the particle population approaches zero. However, such an approximation, requiring a knowledge of the mean and variance of the log normal population, has limited practical value (5). Certainly, the approximation could not be used intelligently unless the powder of interest was *confirmed* to obey the log-normal distribution and the parameters of the distribution could be estimated.

An interest in an approximation illustrating the effects of different particle sizes derives, in part, from difficulties in obtaining monosized powder cuts for dissolution studies. The mathematical treatment of dissolution data from actual drug powders, which may contain a range of sizes, has often been based on the assumption of monosized particles. Recent papers (8, 9) proposed treatments of dissolution data on powders without a calculation of the effect of a distribution of particle sizes. Because of such difficulties, the relationship between dissolution theory and its experimental justification remains fragile. The approximations reported here enable one to estimate the effect of varying particle sizes on dissolution data and may strengthen the relationship between theory and data.

Interest in an approximation can also be appreciated if

one considers the complex and cumbersome calculations involved. The use of a distribution function in connection with the dissolution model of interest, *i.e.*, cube root, Dankwert's, *etc.*, requires integration over the random variable of particle size as well as a consideration of time. Therefore, any reasonable approximation is inviting.

To date, no convenient treatment can be justified for any particular kinetic model with a particular distribution function. This report describes a simplified procedure that can be justified by a standard mathematical (and statistical) derivation. The procedure utilizes estimators of the dispersion of sizes in a powder, which are readily accessible from particle-size data (*e.g.*, automated counter and microscopic data). The limitations and uses of the procedure are tested using simulated data.

## THEORETICAL

Let there be a population of spherical particles of initial diameters  $A_0$  that are randomly distributed on a numbers basis according to the continuous density function  $f_n(A_0)$  or on a weight basis according to the density function  $f_w(A_0)$ . The dissolution profile of such a population of particles exposed to a dissolution medium is often analytically expressed in terms of the weight fraction undissolved. Let there be a function  $g(A_0, t)$  of the random variable  $A_0$  and the dissolution time  $t$  that reflects a suitable dissolution model. For example, let  $A_\tau$  be the diameter of a particle exposed to a dissolution medium for some function  $\tau$  of time so that:

$$g(A_0, t) = A_\tau^3 \quad (\text{Eq. 1})$$

If the dissolution is diffusion rate limited and takes place under sink conditions, then  $g(A_0, t)$  describes the well-known cube root law kinetic model:

$$g(A_0, t) = A_\tau^3 = (A_0 - \tau)^3 \quad (\text{Eq. 2})$$

For a numbers distribution, the weight fraction undissolved,  $W_{fn}$ , will be seen to be a ratio of expected values as follows:

$$W_{fn} = \frac{\int_{\text{all } A_0 \text{ undissolved}} g(A_0, t) f_n(A_0) d(A_0)}{\int_{\text{all } A_0} g(A_0, 0) f_n(A_0) d(A_0)} = \frac{E(A_\tau^3)}{E(A_0^3)} \quad (\text{Eq. 3})$$

If the initial population of particles is described on a weight basis, the weight fraction undissolved,  $W_{fw}$ , is the expected value of a ratio as follows:

$$\begin{aligned} W_{fw} &= \int_{\text{all } A_0 \text{ undissolved}} \frac{g(A_0, t)}{g(A_0, 0)} f_w(A_0) dA_0 \\ &= \int_{\text{all } A_0 \text{ undissolved}} h(A_0, t) f_w(A_0) dA_0 = E\left(\frac{A_\tau^3}{A_0^3}\right) \quad (\text{Eq. 4}) \end{aligned}$$

where  $h(A_0, t)$  is  $g(A_0, t)$  divided by  $g(A_0, 0)$ .

If the mean  $E(A_0) = \mu$  and variance  $V(A_0) = \sigma^2$  of the population of particles are known, the important expected value terms in Eqs. 3 and 4 can be approximated, provided that  $f(A_0)$  takes significant values in an interval near  $A_0 = \mu$  of the order of  $\sigma$  and that  $g(A_0, t)$  is "smooth" in this interval. The approximation given in Eqs. 5 and 6 in the terminology of this derivation is found in standard texts on probability and statistics (10, 11) and can be proved using a Taylor series expansion<sup>1</sup>. The ap-

<sup>1</sup> See Appendix for additional information on this technique.

**Table I—Dissolution Profiles for Simulated Log-Normal Powders with Narrow Distribution Using the Cube Root Law**

Summary of Population Parameters				
Numbers Basis		Weight Basis		
$E(\ln A_0) = 3.68888$		$E(\ln A_0) = 3.71888$		
$V(\ln A_0) = 0.01$		$V(\ln A_0) = 0.01$		
$E(A_0) = 40.20$		$E(A_0) = 41.43$		
$V(A_0) = 16.24$		$V(A_0) = 17.25$		

  

$\tau$	$W_f(\text{exact})$	$W_{fn}(\text{approx})$	$W_{fw}(\text{approx})$	$\left(\frac{\bar{A}_0 - \tau}{A_0}\right)_w^3$
10	0.4337	0.4336	0.4337	0.4366
20	0.1381	0.1379	0.1381	0.1384
29.63	0.0255	0.02534	0.02575	0.0231
30	0.0234	0.02328	0.02370	0.0210
35	0.0063	0.00589	0.00646	0.0037

proximations of interest are:

$$E(A, \tau^3) = g(\mu, t) + \frac{\sigma^2}{2} g''(\mu, t) \quad (\text{Eq. 5})$$

and:

$$E\left(\frac{A - \tau^3}{A_0^3}\right) = h(\mu, t) + \frac{\sigma^2}{2} h''(\mu, t) \quad (\text{Eq. 6})$$

Thus, approximations for the weight fraction undissolved on a numbers basis or a weight basis are:

$$W_{fn}(\text{approx}) = \frac{g(\mu, t) + \frac{\sigma^2}{2} g''(\mu, t)}{g(\mu, 0) + \frac{\sigma^2}{2} g''(\mu, 0)} \quad (\text{Eq. 7})$$

and:

$$W_{fw}(\text{approx}) = h(\mu, t) + \frac{\sigma^2}{2} h''(\mu, t) \quad (\text{Eq. 8})$$

Generally, the sample mean,  $\mu$ , of a population will be understood to be the numbers or weight average,  $\bar{A}_0$ , and the variances,  $\sigma^2$ , will be the square of the sample standard deviations<sup>2</sup>. Thus, for the cube root dissolution model, the weight fraction undissolved of a multisized particle distribution will be:

$$W_{fn}(\text{approx}) = \frac{(\bar{A}_0 - \tau)^3 + 3\sigma^2(\bar{A}_0 - \tau)}{\bar{A}_0^3 + 3\sigma^2\bar{A}_0} \quad (\text{Eq. 9})$$

or:

$$W_{fw}(\text{approx}) = \left(\frac{\bar{A}_0 - \tau}{A_0}\right)^3 - \frac{\sigma^2}{2} \left(\frac{6\tau}{A_0^3} - \frac{18\tau^2}{A_0^4} + \frac{12\tau^3}{A_0^5}\right) \quad (\text{Eq. 10})$$

For another popular dissolution model, the Higuchi-Hiestand model (1):

$$g(A_0, t) = A, \tau^3 = (A_0^2 - \tau)^{3/2} \quad (\text{Eq. 11})$$

and the weight fractions become:

$$W_{fn}(\text{approx}) = \frac{(\bar{A}_0^2 - \tau)^{3/2} + \frac{3\sigma^2}{2} \left[ \frac{\bar{A}_0^2}{(\bar{A}_0^2 - \tau)^{1/2}} + (\bar{A}_0^2 - \tau)^{1/2} \right]}{\bar{A}_0^3 + 3\sigma^2\bar{A}_0} \quad (\text{Eq. 12})$$

or:

$$W_{fw}(\text{approx}) = \left(\frac{\bar{A}_0^2 - \tau}{A_0^2}\right)^{3/2} + \frac{\sigma^2}{2} \left[ \frac{3\tau}{\bar{A}_0^5} \right] \left[ \frac{\tau}{(\bar{A}_0^2 - \tau)^{1/2}} - 3(\bar{A}_0^2 - \tau)^{1/2} \right] \quad (\text{Eq. 13})$$

## RESULTS AND DISCUSSION

An examination of the adequacy of the approximations derived for the cube root model (Eqs. 9 and 10) or for the Higuchi-Hiestand model (Eqs. 12 and 13) is limited to cases where drug particle sizes follow the log-

**Table II—Dissolution Profiles for Simulated Log-Normal Powders with Moderate Distribution Using the Cube Root Law**

Summary of Population Parameters				
Numbers Basis		Weight Basis		
$E(\ln A_0) = 3.68888$		$E(\ln A_0) = 3.95888$		
$V(\ln A_0) = 0.09$		$V(\ln A_0) = 0.09$		
$E(A_0) = 41.84$		$E(A_0) = 54.81$		
$V(A_0) = 164.87$		$V(A_0) = 282.92$		

  

$\tau$	$W_f(\text{exact})$	$W_{fn}(\text{approx})$	$W_{fw}(\text{approx})$	$\left(\frac{\bar{A}_0 - \tau}{A_0}\right)_w^3$
5	0.7320	0.7262	0.7314	0.7505
10	0.5215	0.5113	0.5197	0.5464
16.26	0.3273	0.3129	0.3240	0.3479
25	0.1575	0.1395	0.1547	0.1609
40	0.0372	0.00975	0.04533	0.0197

normal distribution as given by:

$$f(\ln A_0) = \frac{1}{s\sqrt{2\pi}} e^{-(\ln A_0 - m)^2/2s^2} \quad (\text{Eq. 14})$$

where  $m$  and  $s^2$  refer to the (numbers basis) population mean  $E(\ln A_0)$  and variance  $V(\ln A_0)$ , respectively. The approximations, however, require a knowledge of the arithmetic mean  $E(A_0)$  and the corresponding variance  $V(A_0)$ . These may be calculated from:

$$E(A_0) = e^{m+s^2/2} \quad (\text{Eq. 15})$$

and:

$$V(A_0) = E(A_0^2) - [E(A_0)]^2 = (e^{s^2} - 1)e^{2m+s^2} \quad (\text{Eq. 16})$$

These transformations arise from the appropriate use of Eq. 9 of Ref. 4. Since approximations are given for populations where particle-size parameters are evaluated on a numbers basis or a weight basis, it is also necessary to use the Hatch and Choate relationships for log-normal distributions (12), which state:

$$m_{\text{weight}} = m_{\text{numbers}} + 3s_{\text{numbers}}^2 \quad (\text{Eq. 17})$$

$$s_{\text{weight}}^2 = s_{\text{numbers}}^2 \quad (\text{Eq. 18})$$

**Cube Root Model**—The exact and approximate weight fraction undissolved quantities for the cube root kinetic model are presented in Tables I-III. The exact weight fraction undissolved is taken from published data (4). The data in Table I are for a log-normal population with a relatively narrow distribution, as evidenced by the near equality between  $E[A_0]_{\text{numbers}}$  and  $E[A_0]_{\text{weight}}$ . The approximate  $W_f$  values are reasonably close to  $W_f(\text{exact})$  throughout the dissolution profile, although  $W_{fw}(\text{approx})$  from Eq. 10 appears to give slightly better results.

The populations shown in Tables II and III stress the approximations by increasing the magnitude of the standard deviation. The approximation values given in Table II are adequate throughout most of the dissolution time frame. Only at  $\tau = 40$  do the approximate values for  $W_{fw}(\text{approx})$  begin to diverge from the exact values. The  $W_{fn}(\text{approx})$  values begin to diverge from the exact values at  $\tau = 25$ , but this approx-

**Table III—Dissolution Profiles for Simulated Log-Normal Powders with Wide Distribution Using the Cube Root Law**

Summary of Population Parameters				
Numbers Basis		Weight Basis		
$E(\ln A_0) = 3.68888$		$E(\ln A_0) = 4.43888$		
$V(\ln A_0) = 0.25$		$V(\ln A_0) = 0.25$		
$E(A_0) = 45.33$		$E(A_0) = 95.96$		
$V(A_0) = 583.51$		$V(A_0) = 2615$		

  

$\tau$	$W_f(\text{exact})$	$W_{fn}(\text{approx})$	$W_{fw}(\text{approx})$	$\left(\frac{\bar{A}_0 - \tau}{A_0}\right)_w^3$
8.93	0.6929	0.6469	0.6875	0.7460
10	0.6625	0.6142	0.6559	0.7188
20	0.4326	0.3513	0.4140	0.4960
40	0.1831	0.0549	0.1639	0.1983

<sup>2</sup> The authors use  $\bar{A}_0$  to represent the numbers average diameter in those approximations derived for distributions evaluated on a numbers basis. The same character,  $A_0$ , represents a weight mean diameter in those approximations offered for distributions stated on a weight basis.

**Table IV—Dissolution Profiles for Simulated Log-Normal Powders with Narrow Distribution Using the Higuchi–Hiestand Model**

Summary of Population Parameters				
Numbers Basis		Weight Basis		
$E(\ln A_0) = 2.99573$		$E(\ln A_0) = 3.02573$		
$V(\ln A_0) = 0.01$		$V(\ln A_0) = 0.01$		
$E(A_0) = 20.10$		$E(A_0) = 20.712$		
$V(A_0) = 4.061$		$V(A_0) = 4.3116$		
$\tau$	$W_f(\text{numerical integration})$	$W_{fn}(\text{approx})$	$W_{fw}(\text{approx})$	$\left(\frac{\bar{A}_0^2 - \tau}{\bar{A}_0^2}\right)_w^{1.5}$
30.77	0.8911	0.8913	0.8913	0.8944
92.31	0.6873	0.6874	0.6874	0.6953
153.85	0.5032	0.5031	0.5031	0.5136
246.15	0.2702	0.2697	0.2689	0.2783
307.69	0.1519	0.1501	0.1477	0.1504
369.23	0.07189	0.07870	0.06739	0.0520
400.00	0.04596	—	0.05706	0.0176

imation is satisfactory over at least 80% of the total dissolution profile.

A log-normal population, where  $E[\ln A_0]_{\text{numbers}} = 3.68888$  and  $V[\ln A_0]_{\text{numbers}} = 0.25$ , represents a rigorous test for the approximate expressions for the weight fraction undissolved. This population stresses the approximations by virtue of the large standard deviation and the skewed shape of the density function. The approximate and exact  $W_f$  values for this population are presented in Table III. Both the  $W_{fn}$  and  $W_{fw}$  values are consistently lower than the exact values. Again, the weight fractions undissolved calculated using Eq. 10 are more satisfactory than those calculated using Eq. 9.

Also presented in Tables I–III are  $(\bar{A}_0 - \tau)^3/\bar{A}_0^3$  values, which reflect the dissolution profile for a monosized powder that obeys the cube root law. This term obtains from either approximation in Eq. 9 or 10 when  $\sigma^2$  becomes zero. For a monosized population, the average diameter on a numbers basis is equal to the average diameter on a weight basis so that  $(\bar{A}_0 - \tau)^3/\bar{A}_0^3$  calculated on either basis leads to the same estimate of weight fraction undissolved. However, for powders where particles have a wide range of sizes, the calculation on a *weight basis* generally provides a better estimate of the undissolved weight fraction. The calculation provided in Tables I–III employs the average diameters on a weight basis as signified by a subscript  $w$ .

The first term of Eq. 10 is actually  $[(\bar{A}_0 - \tau)^3/\bar{A}_0^3]_w$ . The remaining term in Eq. 10 indicates the effect of the particle-size distribution on the dissolution profile. Thus, this approximation provides a means of quantitating the errors that may occur when data on a polydisperse powder are treated as having come from a monosized powder. Although the simple  $[(\bar{A}_0 - \tau)^3/\bar{A}_0^3]_w$  is useful for narrow distributions, the data of Tables I–III indicate that the weight basis approximation, which includes consideration of size distribution, provides better estimates of the weight fraction undissolved.

**Table V—Dissolution Profiles for Simulated Log-Normal Powders with Moderate Distribution Using the Higuchi–Hiestand Model**

Summary of Population Parameters				
Numbers Basis		Weight Basis		
$E(\ln A_0) = 2.99573$		$E(\ln A_0) = 3.11573$		
$V(\ln A_0) = 0.04$		$V(\ln A_0) = 0.04$		
$E(A_0) = 20.40$		$E(A_0) = 23.01$		
$V(A_0) = 16.99$		$V(A_0) = 21.60$		
$\tau$	$W_f(\text{numerical integration})$	$W_{fn}(\text{approx})$	$W_{fw}(\text{approx})$	$\left(\frac{\bar{A}_0^2 - \tau}{\bar{A}_0^2}\right)_w^{1.5}$
30.77	0.9036	0.9031	0.9040	0.9141
92.31	0.7229	0.7215	0.7232	0.7502
153.85	0.5603	0.5579	0.5587	0.5975
246.15	0.3580	0.3529	0.3471	0.3914
307.69	0.2554	0.2533	0.2340	0.2711
369.23	0.1774	0.2145	0.1502	0.1665
461.54	0.09972	—	0.1185	0.0046

**Table VI—Dissolution Profiles for Simulated Log-Normal Powders with Moderately Wide Distribution Using the Higuchi–Hiestand Model**

Summary of Population Parameters				
Numbers Basis		Weight Basis		
$E(\ln A_0) = 2.99573$		$E(\ln A_0) = 3.26573$		
$V(\ln A_0) = 0.09$		$V(\ln A_0) = 0.09$		
$E(A_0) = 20.92$		$E(A_0) = 27.41$		
$V(A_0) = 41.22$		$V(A_0) = 70.73$		
$\tau$	$W_f(\text{numerical integration})$	$W_{fn}(\text{approx})$	$W_{fw}(\text{approx})$	$\left(\frac{\bar{A}_0^2 - \tau}{\bar{A}_0^2}\right)_w^{1.5}$
30.77	0.9203	0.9194	0.9225	0.9392
92.31	0.7710	0.7684	0.7750	0.8215
153.85	0.6373	0.6326	0.6384	0.7091
246.15	0.4710	0.4651	0.4560	0.5513
307.69	0.3819	0.3883	0.3512	0.4537
369.23	0.3112	—	0.2620	0.3627
461.54	0.2279	—	0.1637	0.2395
500.00	0.2007	—	0.1385	0.1935

Equation 10 can be written in expanded form and expressed as:

$$W_{fw}(\text{approx}) = 1 - 3 \left(\frac{\tau}{\bar{A}_0}\right) \left(1 + \frac{\sigma^2}{\bar{A}_0^2}\right) + 3 \left(\frac{\tau}{\bar{A}_0}\right)^2 \left(1 + 3 \frac{\sigma^2}{\bar{A}_0^2}\right) - \left(\frac{\tau}{\bar{A}_0}\right)^3 \left(1 + 6 \frac{\sigma^2}{\bar{A}_0^2}\right) \quad (\text{Eq. 19})$$

If  $\bar{A}_0$  and  $\sigma^2$  are known, Eq. 19 can be solved by using a one-parameter model. Furthermore, as  $\sigma^2 \rightarrow 0$ , Eq. 19 assumes a perfect cube form:

$$W_f = 1 - 3 \frac{\tau}{\bar{A}_0} + 3 \left(\frac{\tau}{\bar{A}_0}\right)^2 - \left(\frac{\tau}{\bar{A}_0}\right)^3 \quad (\text{Eq. 20})$$

Recently, dissolution data for 20–40-mesh salicylic acid particles were reported (9). These data were treated using the cubic form of the expression to fit the experimental weight fraction undissolved values. For a sieve cut of this width, a considerable bias can be introduced if the terms accounting for the distribution effects are neglected. In fact, the curve fitting of data to a cubic form without regard for particle-size effects would lead to a parameter that would be in error by a factor having a value between  $[1 + (\sigma^2/\bar{A}_0^2)]$  and  $[1 + 6(\sigma^2/\bar{A}_0^2)]^{1/3}$ . For a powder uniformly distributed over a size range of 20–40 mesh, the factor would be between 1.037 and 1.069<sup>3</sup>. This point is significant in cases where critical model testing is the objective.

**Higuchi–Hiestand Model**—The approximate expressions for the Higuchi–Hiestand kinetic model (Eqs. 12 and 13) were tested (Tables IV–VI). The exact weight fraction undissolved was calculated from Eq. 4 using standard numerical integration techniques.

The weight fraction undissolved values shown in Table IV are for a log-normal population where  $E[\ln A_0]_{\text{numbers}} = 2.99573$  and  $V[\ln A_0]_{\text{numbers}} = 0.01$ . The approximate expressions yield values that are less than 3% in error when compared with those calculated using numerical integration over almost the total dissolution profile. At  $\tau = 369.23$ , the approximate expressions give values that are more than 5% in error when compared with the “exact” values. However, at this point, more than 90% of the initial population weight has dissolved.

The data in Table V are for a log-normal population where  $E[\ln A_0]_{\text{numbers}} = 2.99573$  and  $V[\ln A_0]_{\text{numbers}} = 0.04$ . This population was designed to provide a more exacting test of the approximations by virtue of a large population variance. In this case, the coefficient of variation, *i.e.*,  $(V[A_0])^{1/2}/E[A_0]$ , is about 20%; the coefficient of variation for the data in Table IV is about 10%. The  $W_{fw}(\text{approx})$  values for this example follow the exact values closely over about 75% of the total dissolution profile. At  $\tau = 369.23$  and 461.54, the approximations begin to drift away from the exact values; at  $\tau = 470$ , the approximation fails. The failure at the latter end of the dissolution profile is closely related to the magnitude of the variance and the form of the approximate expression. It can be seen from Eq. 13 that as  $(\bar{A}_0^2 - \tau) \rightarrow 0$ ,  $\tau/(\bar{A}_0^2 - \tau)^{1/2}$  approaches infinity and becomes the dominating term.

Analysis of the  $W_{fn}(\text{approx})$  values shown in Table II shows that the approximation is useful over about 75% of the total dissolution profile.

<sup>3</sup> The terms  $E(A_0)$  and  $V(A_0)$  for a uniform distribution are calculable from Eq. 3 of Ref. 13 where  $R = 1$ .

Again, however, the magnitude of the variance and the form of the approximation contribute to the failure. According to Eq. 12, the term  $\bar{A}_0^2/(\bar{A}_0^2 - \tau)^{1/2}$  approaches infinity as  $\bar{A}_0^2 - \tau$  approaches zero. This is even more critical for a population based on numbers because  $E[A_0]_{\text{numbers}} < E[A_0]_{\text{weight}}$  for the log-normal populations under study.

The data in Table VI are for a log-normal drug population where  $E[\ln A_0]_{\text{numbers}} = 2.99573$  and  $V[\ln A_0]_{\text{numbers}} = 0.09$ . The coefficient of variation for this population is about 30%. Therefore, this population represents a severe test of the approximation. The data in Table VI show that the approximations are useful over about 60% of the total dissolution even for this population. Again, the failure of the approximations is related to the magnitude of the standard deviation and the form of the approximate expression.

The first term in Eq. 13,  $[(\bar{A}_0^2 - \tau)/\bar{A}_0^2]^{1.5}$ , was also tested as an approximation for the weight fraction undissolved. The data presented in Tables IV-VI show that this approximation is only useful for narrow distributions. Therefore, experimental dissolution data for many multisized drug populations will be incorrectly interpreted if the term for the distribution effects is not included.

When testing the approximate expressions for different kinetic models, some consideration must be given to the mathematical form of the kinetic equation. For the cube root model, each particle, independent of size, dissolves at the same rate with regard to diameter. On the other hand, small particles dissolving according to the Higuchi-Hiestand model dissolve much more rapidly than larger particles. The approximate expressions for the cube root model are only concerned with a population of particles all dissolving at a uniform rate. Approximate expressions for the Higuchi-Hiestand kinetic model, however, must deal with a population where the temporal characteristics of the sample mean and variance at time  $\tau$  are more complex. With this in mind, it is interesting to compare the data in Table II with the data in Table VI. The approximate weight fraction undissolved values in Table II are for the cube root model, and those in Table VI are for the Higuchi-Hiestand model. The coefficient of variation in both cases is about 30%. Comparison of the data in Tables II and VI shows that the approximations for the cube root model are better than those for the Higuchi-Hiestand model.

## SUMMARY

Approximate expressions for the weight fraction undissolved were tested using multisized (log-normal) distributions in connection with the cube root and Higuchi-Hiestand kinetic models. These simulated data show several important features:

1. The approximations are based on a recognized mathematical treatment and *not* on empirical relationships.
2. The distribution effects are accounted for, but only a knowledge of the arithmetic mean and standard deviation of the sample is required.
3. The approximations are not dependent upon a knowledge of the exact analytical form of the particle-size density function, *i.e.*, whether gamma, normal, log normal, *etc.*
4. The approximations lend themselves to usefulness with real laboratory data such as might be acquired by an automated counter (number or weight data), microscopic examination (numbers data), or sieve fractions (weight data).
5. The approximations are general and are potentially useful with any kinetic model that is at least twice differentiable at  $A_0 = \mu$ .
6. The approximations may find usefulness in a modeling technique to determine dissolution rate constants from dissolution data.

## APPENDIX

The approximation of an expected value of a function of a random variable, as set forth in various texts on statistics (10, 11), first requires approximating that function through a Taylor series expansion and then taking the expected value of the approximation to the function. In this case, the function of the random variable  $A_0$  (the initial particle diameter) is the dissolution model, *e.g.*,  $g(A_0, t)$ . It must be appreciated that the expected value of this function:

$$E[g(A_0, t)] = \int_{\text{all } A_0 \text{ remaining}} g(A_0, t)f(A_0)dA_0 \quad (\text{Eq. A1})$$

must be evaluated considering  $t$  as a constant whose value can be supplied after the integration. This consideration is important in derivations of dissolution equations by Brooke (4, 5, 13) and Pedersen and Brown (7).

Therefore, it is imperative that all operations prior to the actual calculation of  $W_f$  consider  $t$  a constant.

The Taylor series approximation to a function of the random variable  $A_0$ , *e.g.*,  $g(A_0, t)$ , is most accurate in a region where values of  $A_0$  are within 1 *SD*,  $\sigma$ , of the initial population mean,  $\mu$ . Both  $\mu$  and  $\sigma$  are parameters of the initial (time zero) particle-size distribution. The expansion about  $\mu$  is written:

$$g(A_0, t) \simeq g(\mu, t) + (A_0 - \mu)g'(\mu, t) + \frac{1}{2}(A_0 - \mu)^2g''(\mu, t) + \dots \quad (\text{Eq. A2})$$

For  $t$  as a constant,  $g(\mu, t)$ ,  $g'(\mu, t)$ , *etc.*, are constants and the expected value  $E[g(A_0, t)]$  is approximated by:

$$g(\mu, t) + g'(\mu, t)E(A_0 - \mu) + \frac{1}{2}g''(\mu, t)E(A_0 - \mu)^2 + \dots \quad (\text{Eq. A3})$$

By neglecting higher order terms in the expansion and by recognizing that  $E(A_0 - \mu)$  is zero and  $E(A_0 - \mu)^2$  is  $\sigma^2$ , the approximation for  $E[g(A_0, t)]$  is written:

$$E[g(A_0, t)] \simeq g(\mu, t) + \frac{1}{2}g''(\mu, t)\sigma^2 \quad (\text{Eq. A4})$$

The use of Eq. A4 is illustrated by deriving the approximate weight fraction undissolved when the particle distribution is expressed on a numbers basis and the particles dissolve according to the Higuchi-Hiestand model. Here:

$$g(A_0, t) = (A_0^2 - \tau)^{3/2} = A_\tau^3 \quad (\text{Eq. A5})$$

which is twice differentiated in respect to the initial particle size,  $A_0$ , while  $t$  is considered a constant. That is:

$$g'(A_0, t) = 3(A_0^2 - \tau)^{1/2}A_0 \quad (\text{Eq. A6})$$

and:

$$g''(A_0, t) = 3(A_0^2 - \tau)^{1/2} + 3A_0^2/(A_0^2 - \tau)^{1/2} \quad (\text{Eq. A7})$$

In using Eq. A4, it is necessary to evaluate  $g(A_0, t)$  and  $g''(A_0, t)$  at the population mean  $\mu$ . For this purpose, the arithmetic mean of the initial diameters,  $\bar{A}_0$ , is considered an appropriate estimator. Furthermore, it is experimentally available. Therefore:

$$E[g(A_0, t)] = E(A_\tau^3) \simeq (\bar{A}_0^2 - \tau)^{3/2} + \frac{3\sigma^2}{2} \left[ \frac{\bar{A}_0^2}{(\bar{A}_0^2 - \tau)^{1/2}} + (\bar{A}_0^2 - \tau)^{1/2} \right] \quad (\text{Eq. A8})$$

and:

$$E[g(A_0, t)_{t=0}] = E(A_0^3) \simeq \bar{A}_0^3 + 3\sigma^2\bar{A}_0 \quad (\text{Eq. A9})$$

and  $W_{fn}(\text{approx})$  for the Higuchi-Hiestand model becomes Eq. 12 of the text by dividing Eq. A8 by Eq. A9.

The use of the approximate equations for weight undissolved is illustrated by considering  $W_{fn}(\text{approx})$  for the Higuchi-Hiestand model. Here, data are taken from Table V where the average particle size,  $\bar{A}_0$ , for the numbers distribution is 20.40  $\mu\text{m}$  and the squared standard deviation,  $V(A_0)$ , is 16.99  $\mu\text{m}^2$ . By using Eq. 12 of the text,  $W_{fn}(\text{approx})$  for  $\tau = 153.85 \mu\text{m}^2$  is:

$$W_{fn}(\text{approx}) = \frac{[(20.40)^2 - 153.85]^{3/2} + \frac{3}{2}(16.99) \left[ \frac{(20.40)^2}{[(20.40)^2 - 153.85]^{1/2}} - [(20.40)^2 - 153.85]^{1/2} \right]}{(20.40)^3 + 3(16.99)(20.40)} = 0.5587 \quad (\text{Eq. A10})$$

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# Dissolution Profiles for Multisized Prednisolone Acetate Suspensions

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**Abstract** □ Particle-size measurements and *in vitro* dissolution characteristics of commercial and formulated suspensions of prednisolone acetate were determined using a resistance particle counter and a spinning filter apparatus, respectively. Significant differences in dissolution rates were noted for the commercial suspensions. Particle size affected dissolution but did not account for all observed variations in the dissolution rate. Formulation differences, specifically the presence of hydroxypropyl methylcellulose, in suspensions seemed to be important in dissolution.

**Keyphrases** □ Prednisolone acetate—multisized suspensions, dissolution profiles and particle-size measurements □ Suspensions, multisized—prednisolone acetate, dissolution profiles and particle-size measurements □ Dissolution—multisized suspensions of prednisolone acetate, effect of particle size □ Particle size—effect on dissolution of prednisolone acetate suspensions □ Glucocorticoids—prednisolone acetate, multisized suspensions, dissolution profiles and particle-size measurements

The dissolution rate and *in vivo* physiological availability of drugs are important research areas (1–5). The dissolution rate of a solid dosage form such as a tablet or a capsule can be the rate-limiting step in availability for the *in vivo* absorption of the active ingredient (6–8), particularly for poorly soluble or poorly wetted drugs (9).

At present, almost all dissolution rate research efforts are directed toward tablets and capsules. Although suspensions share many physical-chemical characteristics of tablets and capsules with respect to the dissolution process, they are almost completely ignored. Since tablets and capsules disintegrate into powder suspensions, pharmaceutical suspensions share the dissolution process as a rate-limiting step for absorption and bioavailability.

Bates *et al.* (10) studied the dissolution rates of nitrofurantoin tablets and suspensions and commented that it was inconsistent to provide a USP dissolution test for nitrofurantoin tablets without including a dissolution rate test for the suspension. They concluded that: "the rationale underlying the official dissolution rate specification for nitrofurantoin tablets appears quite arbitrary and inconsistent with the dissolution profile and potential toxicity of the official suspension dosage form."

These comments substantiate a need to pursue dissolution rate testing of suspension dosage forms. In the

current study, the dissolution and particle-size profiles of several commercially available suspensions were determined to obtain information about brand-to-brand variation and formulation characteristics directly related to dissolution.

Commercially available steroid ophthalmic/otic suspensions were studied. They represent a dosage form that requires dissolution as a prerequisite to therapeutic availability. These products contain a poorly soluble micronized steroid in a suitable vehicle. The solubility and particle-size characteristics of these products make them desirable prototype suspensions to study.

## EXPERIMENTAL

**Dissolution Testing**—All reported dissolution data were obtained using a device<sup>1</sup> described by Shah *et al.* (11). The basic features of the apparatus are a large volume fluid container, a rotating filter assembly, and an external variable-speed magnetic stirrer. The sample basket was removed.

The rotating filter assembly provides variable intensity of mild laminar liquid agitation and also functions as an *in situ* nonclogging filter to permit efficient intermittent or continuous filtration of dissolution fluid samples during the dissolution process. The assembly is suspended and freely rotates in the center of the flask on the flared end of a glass capillary pilot tube. The assembly rotates by means of a controlled, variable-speed, external magnetic stirrer coupled with a magnetic bar embedded in the bottom part of the assembly. A 0.5- $\mu$ m porosity sintered stainless steel filter also was employed.

One liter of distilled water was transferred into the flask, and the fluid was allowed to equilibrate at 25°. The stirring speed of the filter assembly was 960 rpm. A strobe lamp<sup>2</sup> was used to standardize the stirring speed.

Filtered fluid samples were continuously withdrawn through the capillary pilot tube at the rate of 100 ml/min and were circulated through the spectrophotometer and back to the flask. Air bubbles were periodically released from an air trap. The system was allowed to run for at least 15 min to ensure the consistency of the flow and stirring rate. The spectrophotometer<sup>3</sup> was then calibrated for zero absorbance at 246 nm with the dissolution medium in the reference cell. The baseline on the strip-chart<sup>4</sup> paper also was adjusted corresponding to zero absorbance.

<sup>1</sup> The dissolution apparatus was made available through the courtesy of The Upjohn Co., Kalamazoo, Mich.

<sup>2</sup> Glass Instrument Co., Quincy, Mass.

<sup>3</sup> Perkin-Elmer double-beam spectrophotometer, Coleman 124, Hitachi, Ltd., Tokyo, Japan.

<sup>4</sup> Chart recorder model SRG, Sargent-Welch Scientific Co., Cleveland, Ohio.