

## Sieve Cuts as Monodisperse Powders in Dissolution Studies

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**Abstract** □ Dissolution profiles are calculated for sieve cuts of varying width based on a derived equation, which assumes diffusion rate-limited dissolution under sink conditions from spherical particles. It is shown that even the narrowest of sieve cuts may vary from cube root law expectations by as much as 3%, depending on the distribution of particles across the cut. Much smaller deviations from the cube root law occur when the weight distribution of diameters is constant across a sieve cut. It is concluded that when experimental data are treated on the assumption that sieve cuts act like monosized powders, errors generally will be acceptable except in cases of critical tests of dissolution rate theory. In those cases, more information about the powder distribution should be given.

**Keyphrases** □ Sieve cuts—dissolution studies, assumption of monodisperse powders □ Dissolution—error introduced from assumption of monodisperse powders in sieve cuts □ Particle size—sieve cuts, monodisperse powders from sieve cuts, introduction of error □ Powder distribution—sieve cuts, assumption of monodisperse powders, introduction of error in dissolution testing

Sieve cuts from powders have often been used as substrates in dissolution experiments. The idea that a narrow distribution of particle sizes can be treated as a monodisperse distribution seems to be fairly well established (1). Some workers have staked quantitative treatments of experimental data on the correctness of the assumption that sieve cuts from powders can be treated like monosized powders.

For example, Niebergall and Goyan (2) calculated dissolution rate constants from data on 20–30-mesh salicylamide and 80–100-mesh benzoic acid by extension of the Hixson–Crowell (3) cube root law. In another paper, Niebergall *et al.* (4) suggested that particles under rapid agitation followed a square root law on the basis of the dissolution behaviors of sieve cuts from various powders. Later, Goyan (5) used some of their data (4) to support a Danckwerts' penetration model for dissolution of particles under rapid agitation. Recently, Pothisiri and Carstensen (6) tested an equation for the nonsink dissolution of monosized particles against experimental data. They used data from their own laboratory and from Hussain (7) on the dissolution of narrow cuts from powders.

Since dissolution rate theory is being proposed or tested on the basis of experimentation with sieve cuts from powders, it seemed worthwhile to examine the validity of the assumption that sieve cuts behave like monodisperse powders. This paper does not consider errors that might arise in dissolution studies from other popular assumptions; for example, when the hydrodynamics of the experimental system do not

conform to theory, when dissolution is anisotropic, when particles are not spherical, or when particles agglomerate. This paper seeks to define the limits on errors that might occur in the treatment of dissolution data solely because the particles within a sieve cut are not all the same size.

Dissolution profiles are calculated for narrow cuts of spherical particles wherein the probability frequency, on a weight basis, of diameters is some linear function of particle size. These profiles are compared with that expected for a monodisperse powder in which the diameter is an average of the largest and smallest diameters possible in the sieve cut. Diffusion rate-limited dissolution under sink conditions is assumed.

As will be seen, the assumption that a sieve cut behaves like a monosized distribution should lead to no more than about 3% error, as reflected in a cube root law slope, if the narrowest sieve cuts are used. Wider cuts lead to greater inherent errors. If the frequency of occurrence of diameters on a weight basis is fairly constant across the cut, errors will tend to be much smaller than if the frequency changes sharply, as

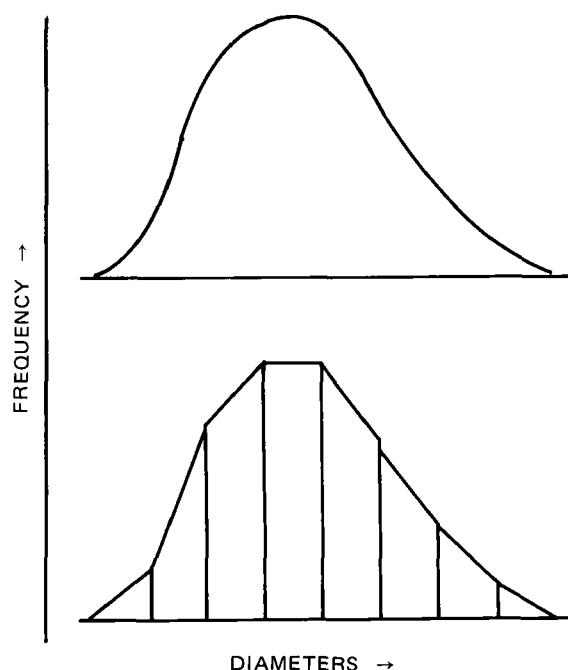
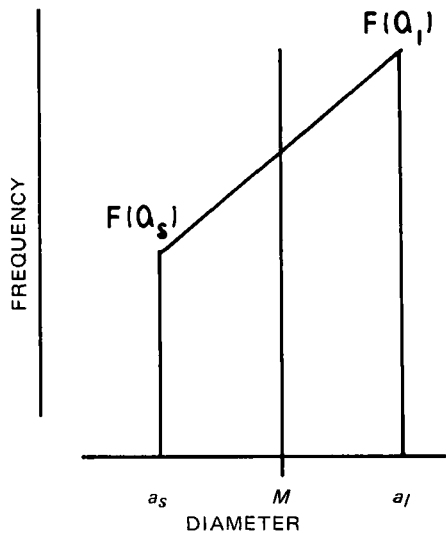


Figure 1—Approximation of a continuous powder distribution as a series of sieve cuts.



**Figure 2**—Representation of a sieve cut from a powder as a separate distribution in which the probability frequency is taken as a linear function of particle size. See text.

might be the case in a cut from near the tail of a powder.

### THEORY AND CALCULATIONS

Consider a powder containing spherical particles of diameters  $a_0$ , which are distributed, on a weight basis, according to a continuous probability frequency  $f(a_0)$ . Let there be a series of cuts approximating the distribution (Fig. 1), and assume that  $f(a_0)$  is a linear function of  $a_0$  in each cut (Fig. 2). Once a cut is segregated from the parent distribution, it must be considered a separate distribution with characteristics determined by the original powder.

If the cut is not too wide, it is not unreasonable to consider  $f(a_0)$  linear with  $a_0$ . However, the derivations of dissolution profiles do not depend on this simplification, since derivations based on considerably more complicated distributions are possible (8, 9). The assumption of linearity does allow a much more general treatment of dissolution profiles than might otherwise be possible.

In Fig. 2, the smallest and largest possible diameters ( $a_s$  and  $a_l$ , respectively) are averaged to gain a mean diameter  $M$ . It is convenient to express  $a_s$  as  $sM$  and  $a_l$  as  $lM$  where  $s + l = 2$ . The probability frequency  $f(a_l)$  of particles of diameter  $a_l$  is conveniently expressed in terms of  $f(a_s)$  by  $f(a_l) = Rf(a_s)$ . The probability frequency  $f(a_0)$  of diameters  $a_0$  can now be derived in terms of  $a_0$ ,  $R$ ,  $s$ ,  $l$ , and  $M$  based on the recognition that the slope of the linear function  $f(a_0)$  is:

$$\text{slope} = \frac{Rf(a_s) - f(a_s)}{lM - sM} \quad (\text{Eq. 1})$$

and that the area under the curve is unity so that:

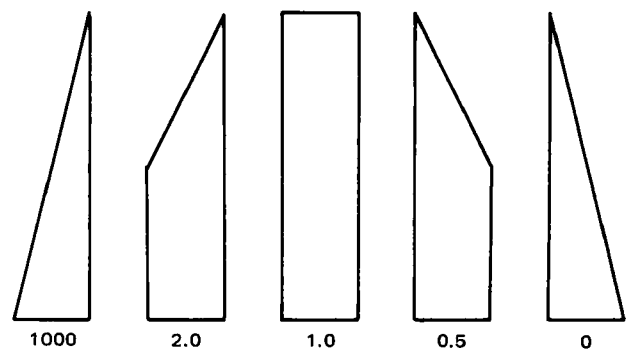
$$\text{area} = 1.0 = (lM - sM)f(a_s) + \frac{1}{2}(lM - sM)[Rf(a_s) - f(a_s)] \quad (\text{Eq. 2})$$

Thus, the probability frequency of particle sizes on a weight basis is:

$$f(a_0) = \frac{2[l - Rs + (R - 1)a_0/M]}{(R + 1)(l - s)^2M} \quad (\text{Eq. 3})$$

The contribution  $dw_0$  of particles of size  $a_0$  to the total initial

<sup>1</sup> It should be obvious that  $2 \geq l > s \geq 0$  and that Eq. 1 and others in these derivations are undefined for  $s = l$ . It further should be recognized that since  $2 - l = s$ , it is not strictly necessary to use both parameters in all equations.



**Figure 3**—Representation of various narrow powder distributions for which dissolution profiles are calculated. The plots are similar to the one in Fig. 2, and values for  $R$  are indicated. See text for additional details.

weight  $w_0$  can be expressed as:

$$dw_0 = w_0 f(a_0) da_0 \quad (\text{Eq. 4})$$

The number  $dn$  of particles of size  $a_0$  can be calculated by dividing  $dw_0$  by the weight of a single particle  $\pi p a_0^3/6$ , where  $p$  is particle density:

$$dn = \frac{w_0 f(a_0) da_0}{\pi p a_0^3/6} \quad (\text{Eq. 5})$$

Dissolution profiles for sieve cuts can now be derived using the same philosophical approach used in deriving an expression for the dissolution of powders that follow a log-normal distribution (9, 10).

The diameter  $a_\tau$  of a particle exposed to a medium for some function  $\tau$  of time can be expressed by:

$$a_\tau = a_0 - \tau \quad (\text{Eq. 6})$$

where  $\tau$  is  $2kC_s t/p$  and  $k$  is a dissolution rate constant,  $C_s$  is solubility, and  $t$  is time. This notation is essentially that of Carstensen and Musa (11). The equation is based on assumptions of diffusion rate-limited dissolution under sink conditions, isotropic behavior, and a particle-size-independent solubility.

As long as particles that were initially of size  $a_0$  exist (that is, if  $\tau < a_0$ ), the particles will grow smaller but the number of those particles  $dn$  will not change. Therefore, the contribution  $dw_\tau$  to the weight undissolved of particles of size  $a_\tau$  can be calculated by:

$$dw_\tau = \frac{\pi p a_0^3}{6} dn = \frac{\pi p}{6} (a_0 - \tau)^3 dn \quad (\text{Eq. 7})$$

Substitution for  $dn$  using Eq. 5 and for  $f(a_0)$  using Eq. 3 completes the derivation, except for an integration, to achieve  $w_\tau$ . As far as the integration is concerned,  $\tau$  is a constant. The integration is over all of the initial particle sizes  $a_0$  of particles remaining because  $dn$  is based on initial sizes  $a_0$ . Thus, for  $\tau \leq a_s = sM$ , the integration is from  $a_s = sM$  to  $a_l = lM$ . After the smallest particles begin to disappear, the integration is from  $\tau$  to  $a_l$ . That is, after  $\tau > a_s$ , the smallest nonzero particle remaining at  $\tau$  was initially of size  $a_0$  such that  $a_0 - \tau \rightarrow 0$ . Thus, it can be shown that the weight fraction undissolved ( $w_\tau/w_0$ ) after some  $\tau$  is:

$$w_\tau/w_0 = [2/(1 + R)(l - s)^2] \times \left[ \begin{aligned} &(l - Rs)(l - t) + (R - 1)(l^2 - t^2)/2 \\ &- 3[(R - 1)(l - t) + (l - Rs)\ln(l/t)]\tau/M \\ &+ 3[(R - 1)\ln(l/t) + (l - Rs)(l - t)/t]\tau^2/M^2 \\ &- [(R - 1)(l - t)/t + (l - Rs)(l^2 - t^2)/2l^2t^2]\tau^3/M^3 \end{aligned} \right] \quad (\text{Eq. 8})$$

where  $t = s$  when  $\tau \leq sM$  and  $t = \tau/M$  when  $\tau > sM$ .

Dissolution profiles for sieve cuts like those shown in Fig. 3 ( $R =$

Table I—Dissolution Profiles<sup>a</sup> for a Monodisperse Powder and for Powders from Sieve Cuts

$\tau/M$	Mono-disperse Powder	$s = 0.91$					$s = 0.83$					$s = 0.75$									
		$R = 0$					$R = 1000$					$R = 0$					$R = 1000$				
		0.5	1.0	2.0	1000	100.00	0.5	1.0	2.0	1000	100.00	0.5	1.0	2.0	1000	100.00	0.5	1.0	2.0	1000	
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
0.05	85.74	85.70	85.84	86.11	84.83	85.35	85.61	85.87	86.39	84.29	85.07	85.46	85.74	86.33	84.29	85.07	85.46	85.74	86.33	84.29	85.07
0.10	72.90	72.84	73.09	73.57	71.29	72.22	72.69	73.15	74.08	70.35	71.74	72.44	73.15	74.08	70.35	71.74	72.44	73.15	74.08	70.35	71.74
0.15	61.41	61.34	61.67	62.32	59.29	60.53	61.15	61.77	63.01	58.06	59.92	60.84	61.77	63.01	58.06	59.92	60.84	61.77	63.01	58.06	59.92
0.20	51.20	51.12	51.51	52.27	48.72	50.19	50.92	51.65	53.11	47.33	49.50	50.59	51.65	53.11	47.33	49.50	50.59	51.65	53.11	47.33	49.50
0.25	42.19	41.69	42.11	43.38	39.51	41.11	41.92	42.72	44.32	38.03	40.41	41.60	42.72	44.32	38.03	40.41	41.60	42.72	44.32	38.03	40.41
0.30	34.30	34.23	34.67	35.55	31.55	33.22	34.06	34.89	36.56	30.08	32.55	33.78	34.89	36.56	30.08	32.55	33.78	34.89	36.56	30.08	32.55
0.40	21.60	21.56	21.99	22.85	19.03	20.65	21.47	22.28	23.90	17.75	19.75	21.32	22.28	23.90	17.75	19.75	21.32	22.28	23.90	17.75	19.75
0.50	12.50	12.13	12.87	13.62	10.41	11.81	12.51	13.21	14.60	9.49	11.52	12.53	13.21	14.60	9.49	11.52	12.53	13.21	14.60	9.49	11.52
0.60	6.40	6.15	6.73	7.30	4.95	6.01	6.54	7.08	8.14	4.44	5.96	6.73	7.08	8.14	4.44	5.96	6.73	7.08	8.14	4.44	5.96
0.70	2.70	2.77	2.96	3.33	1.91	2.60	2.94	3.29	3.98	1.75	2.74	3.23	3.29	3.98	1.75	2.74	3.23	3.29	3.98	1.75	2.74
0.80	0.80	0.78	0.97	1.16	0.54	0.89	1.07	1.25	1.60	0.57	1.09	1.35	1.60	0.57	1.09	1.35	1.60	1.61	2.12	0.57	1.09
$\beta$	1.0000	1.0328	1.0126	0.9925	1.0671	1.0285	1.0093	0.9901	0.9519	1.1073	1.0493	1.0204	0.9917	0.9346	1.1073	1.0493	1.0204	0.9917	0.9346	1.1073	1.0493

<sup>a</sup>The values in the body of the table were calculated from Eq. 8 or 9 and are  $(w_\tau/w_0) \times 100$ .

Table II—Sieve Cuts Using Standard Sieves Listed as a Function of  $s$

$s = 0.75$	$s = 0.83$	$s = 0.91$
40/60	20/30	50/60
50/80	30/40	60/70
60/100	40/50	70/80
70/120	50/70	80/100
120/200	60/80	100/120
200/325	70/100	200/230
230/400	80/120	230/270
	200/270	270/325
	230/325	325/400
	270/400	

0, 0.5, 1.0, 2.0, and 1000) were calculated using a computer<sup>2</sup>. Weight fractions undissolved ( $w_\tau/w_0$ ) are given in Table I as a function of  $\tau/M$ . The choice of a relative time value ( $\tau/M$ ) allows direct comparisons of all dissolution profiles. Also presented in Table I is a dissolution profile for a monosized powder of diameter  $M$ , i.e., a powder that exactly follows the cube root law. This profile was calculated using Eq. 9, where the slope  $\beta$  is chosen to be unity (10):

$$(w_\tau/w_0)^{1/3} = 1 - \beta(\tau/M) \quad (\text{Eq. 9})$$

The initial slope  $\beta$  for each calculated profile is also given in Table I based on Eq. 9.

The values for  $s$  were chosen to be 0.75, 0.83, and 0.91 because these values represent the three narrowest sieve cuts possible when using standard sieves as described in USP XVIII (12). Table II relates these values of  $s$  to certain possible sieve cuts.

## DISCUSSION

A brief comparison of the dissolution profile for a powder that follows the cube root law, with profiles calculated for various sieve cuts (Table I), will indicate that it is probably acceptable to treat sieve cuts as monosized powders for all but the most critical work. The data also show that the approximation is better for narrower sieve cuts.

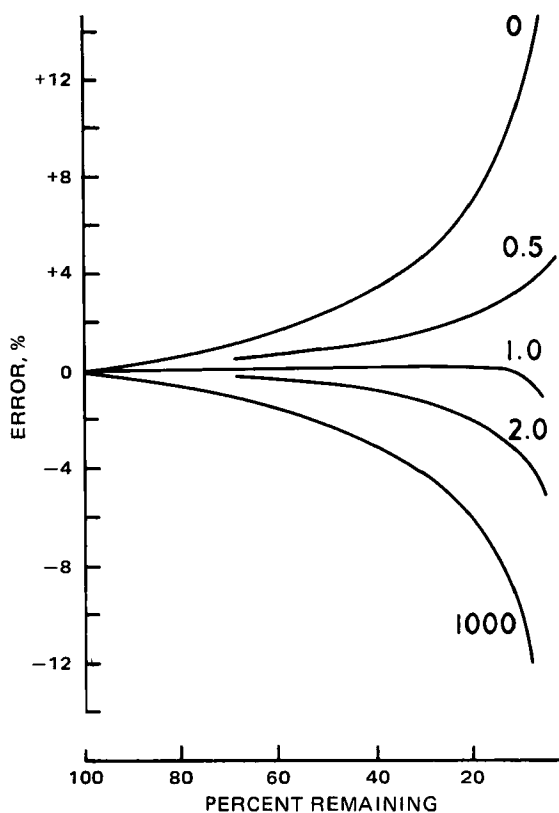
The errors that might occur when the approximation is applied to sieve cuts where  $s = 0.91$  are shown graphically in Fig. 4. For distributions that might come from the large or small particle tail of a powder ( $R = 0$  or 1000), the errors are greatest and exceed 10% as the weight fraction remaining falls below 10%. The characteristics of the sieve cut, as reflected by  $R$ , influence both the size of the errors expected and their direction (sign). It is clear from Fig. 4 that when the probability frequency is constant ( $R = 1.0$ ), the dissolution profile for a sieve cut approximates that of a monosized powder excellently. When  $R = 1.0$ , the error through 90% dissolution is generally less than 0.2% for the narrowest sieve cut ( $s = 0.91$ ). A graph of errors when sieve cuts with  $s = 0.83$  are compared to a monodisperse powder would look identical to Fig. 4, except that all errors would be twice as large as those in Fig. 4.

Another way of judging the degree to which a sieve cut approximates the cube root law would be to examine the values for the slope ( $\beta$ ) when the data are fitted to Eq. 9. In the ideal case,  $\beta$  will be unity. When the slopes were calculated on the initial portion of the profiles for cuts where  $s = 0.91$ , the calculated values ranged from 0.9725 to 1.0328. When all points in the profiles were subjected to least-squares regression, the values for  $\beta$  ranged from 0.9680 to 1.0252.

The exact value calculated for the slope depends on the number of data points and the extent to which dissolution is followed, because all cube root plots based on dissolution of sieve cuts will show some curvature. In some cases the curvature may be too small to identify because of random experimental errors. Nevertheless, it is clear that cuts from the large particle tail of a powder ( $R = 0$ ) will tend to dissolve faster than might be expected while a cut from the small particle end ( $R = 1000$ ) will dissolve more slowly than expected.

It can be said that dissolution data based on the narrowest pos-

<sup>2</sup> IBM 1800.



**Figure 4**—Deviations between dissolution profiles for an ideal (monodisperse) powder and sieve cuts of  $R = 0, 0.5, 1.0, 2.0,$  or  $1000$  as a percent of powder undissolved plotted against percent undissolved for sieve cuts having  $s = 0.91$ .

sible sieve cut ( $s = 0.91$ ) might contain up to 3.0% error if the treatment of results included the assumption that sieve cuts are equivalent to monosized powders. If, however, sufficient particle-size data are presented with the dissolution data to show that  $R$  is close to or equal to 1.0, then the errors could be considered much less than 1.0%. For the next widest sieve cut ( $s = 0.83$ ), the errors in a cube root law slope could be as great as 6.0%. Errors of 7–10%

would be possible if wider sieve cuts ( $s = 0.75$ ) were treated according to the cube root law. If, on the other hand, the particle sizes within a sieve cut could be described, then an exact equation like Eq. 8 might be useful.

It is concluded that when dissolution data are based on sieve cuts with no further definition of powder sizes and the assumption of a monosized powder is used in the data treatment, then the results may be in error by as much as 3% even for the narrowest sieve cuts. For wider sieve cuts, errors of 6 or even 10% should not be ruled out. These errors would occur solely from the assumption that sieve cuts behave like monosized powders.

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#### ACKNOWLEDGMENTS AND ADDRESSES

Received July 22, 1974, from the *Division of Pharmaceutical Sciences, Mead Johnson Research Center, Mead Johnson and Company, Evansville, IN 47721*

Accepted for publication December 26, 1974.

The author thanks Mr. E. G. McBride of Technical Information Services, Mead Johnson Research Center, for programming the calculations of dissolution profiles for this report. The comments of Dr. S. T. David, Division of Pharmaceutical Sciences, were appreciated.

## Comparison of Analytical Methods for Residual Ethylene Oxide Analysis

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**Abstract** □ A round-robin study compared four methods of residual ethylene oxide analysis. Results from the six participating laboratories, along with a statistical treatment of the data, are presented.

**Keyphrases** □ Ethylene oxide—residual analysis, comparison of four analytical methods by six laboratories □ Sterilants—residual-ethylene oxide analysis, comparison of four analytical methods by six laboratories □ Plastics—analysis of residual ethylene oxide, comparison of four analytical methods by six laboratories

Ethylene oxide gas has had wide use as a sterilant in the health field. Since many sterilized items are used in such a way that they contact sensitive human tissue, the residual ethylene oxide should be at a safe

level since ethylene oxide is in itself toxic. The Z79 Subcommittee on Ethylene Oxide Sterilization (an Association for the Advancement of Medical Instrumentation group) is concerned with the safe use of