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RESEARCH PAPER

Particle Size Distributions in Mesh Cuts and Microscopically Estimated Volumetric Shape Factors

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ABSTRACT

When particle size distribution parameters are calculated from sieve analysis, it is generally assumed that the distribution within the particle cut is either linear, producing a mean particle size equal to the average of the mesh openings (1–3), or that a more proper number is the geometric mean of these two apertures. It is shown here that particles within a mesh cut are not linearly distributed, but rather may be normally, log-normally, or biphasic combinations of the two. Three compounds were examined in this fashion, and results are reported here.

INTRODUCTION

Most solid pharmaceuticals are polydisperse; most often, a particle size specification is included in drug substance specifications. The reason for this is that this number affects dissolution characteristics (4,5), bioavailability (6), and machinability (flow, compression) of the substance (7,8).

However, it should be possible by simple micromeritic means, in conjunction with particle dissolution, to obtain distribution parameters in a meaningful way that involves much larger samples than those employed for usual particle size distribution determinations. This paper confines itself to micromeritics by microscopy simply to establish the character of a drug substance in a mesh cut.

MATERIALS AND METHODS

Three substances were used as model compounds: oxalic acid hydrate, salicylic acid, and phthalimide. Each substance was thermally recrystallized from water by slow evaporation, and the crystals harvested were filtered, air dried, and subjected to sieve separation. The sieves used are discussed in tables below.

The particle size distribution of each mesh cut was determined by a microscope equipped with image analy-

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Table 1

Data Generated for 100/200 Mesh Salicylic Acid

Range (μm)	b_{avg} (μm)	Count	Frequency f	Cumulative f	Normal Z value[a]
202	215	14	0.056	0.056	−1.590
228	241	32	0.127	0.183	−0.905
254	267	43	0.171	0.354	−0.360
280	293	44	0.175	0.529	0.075
306	319	45	0.179	0.708	0.550
332	345	40	0.159	0.867	1.115
358	371	18	0.072	0.939	1.550
384	397	9	0.036	0.976	1.980
410	423	6	0.024		

[a] Obtained from a normal error table.

sis equipment to facilitate counting. From each sieve fraction, 300 particles were measured, and the breadths were grouped into $k = 9$ class intervals. This number of intervals is based on Sturge's rule (9):

$$k = 1 + 3.322[\log_{10}(N)]$$

where N is the number of particles.

The frequency distribution was then obtained. The dimensions measured were the breadth b and the length L of the particles. All distributions discussed below are number distributions.

RESULTS AND DISCUSSION

An example of the microscopic figures are represented in Table 1 to specify the method of data generation. The frequencies may be presented in histogram form (Fig. 1).

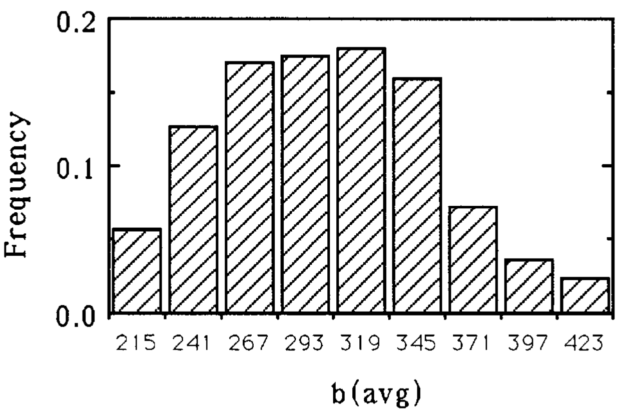

Figure 1. Histogram of the data in Table 1.

If the frequencies in Table 1 are divided by the interval length, then the frequency function y value is obtained. Figure 2 shows a graph of the frequency function of the average breadth measurements in Table 1. The shape of the figure implies a normal distribution, and when Z (in the last column of Table 1) is plotted versus the minimum value of the breadth interval values, then the trace in Fig. 3 results. The data seem to be normally distributed. The least-squares equation is

$$Z = -6.8862 + 0.031355b \quad (1)$$

so the mean ($Z = 0$) is at

$$b_{avg} = 6.8862/0.031355 = 220 \ \mu\text{m} \quad (2)$$

and the standard deviation is

$$1/0.031355 = 32 \ \mu\text{m} \quad (3)$$

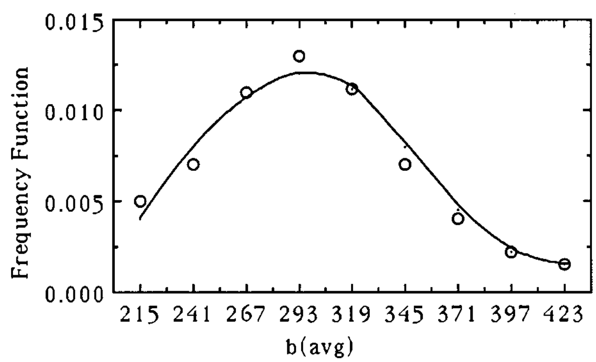

Figure 2. 40/50 mesh oxalic acid. b(avg) is the average small dimension found in an interval. The solid line represents a normal distribution.

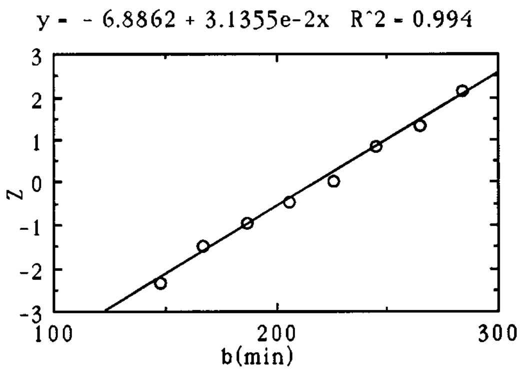

Figure 3. 40/50 mesh oxalic acid dihydrate. b(min) is the smallest dimension found in an interval.

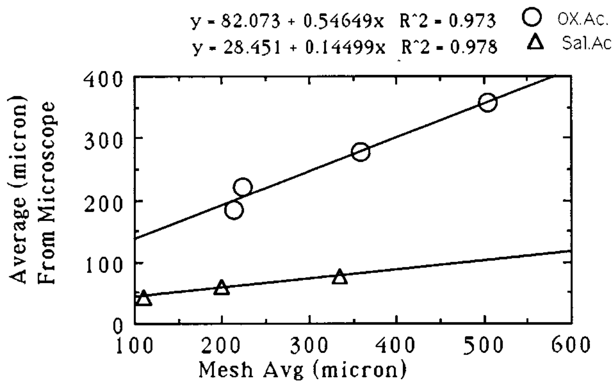

Figure 4. Correlation between mesh average and microscopic average.

However, most of the particle size distributions were not neatly normal. The data for the various sieve cuts of the substances tested are shown in Table 2. Strictly speaking, if the sieving were 100% effective, the distribution should be linear, but it is seen in Table 2 at times the distributions can be bimodal, and that a certain percentage of the sieved population seems to logically belong to a neighboring mesh cut and that a certain smaller fraction is either a part the screen one mesh above or of one mesh below the population. This may be due to the fact that either (*a*) smaller particles attach themselves to larger ones, or (b) there is an alignment problem with part of the separated population that does not accommodate passage of the smallest particle.

Figure 4 shows a one-to-one correspondence between mesh averages and microscopic average, but (as might be expected) not identity. Salicylic acid forms needles, and the microscopic average is considerably smaller than the average of mesh cuts; oxalic acid dihydrate is more regular in shape, and hence the two parameter values are closer.

It is often of importance to have values of the surface-volume mean diameter d_{sv}, which is defined by

$$d_{sv} = \Sigma f d_i^3 / \Sigma f_i d_i^2 \tag{4}$$

where f denotes fraction. The parameters were obtained from the microscopic count by the program in BASIC listed in the appendix, and the moments and the surface-volume mean diameter are shown in Table 3.

Crystals are not spheres, and a parallelepiped is a better approximation of a crystalline substance. In microscopy, only the breadth b and length L can be measured, whereas the height h cannot be measured directly (Fig. 5). Microscopy, however, may be employed to assess the average value of h in a mesh cut by the following procedure.

If a certain number N (e.g., 300–1000) particles are sampled randomly from a mesh cut and their weight W

Table 2

Types of Distribution Within Sieve Cuts

Substance	Mesh Cut	Distribution Type	b_{avg} or ln b_g	σ or ln σ
Oxalic acid dihydrate	30/40	Log *n*	369	0.02282
Oxalic acid dihydrate	40/50	Normal	277	52
Oxalic acid dihydrate	50/60	Normal	220	32
Oxalic acid dihydrate	60/80	Log *n*	142	0.2306
Salicylic acid	100/200	Log *n*	42.7	0.4123
Salicylic acid	60/100	Normal	60.2	25.3
Phthalimide	40/60	Log *n*	39.7	0.4337
Phthalimide	60/100	Bimodal	43	26.8

Table 3

Distribution Parameters of Substances Tested

Substance	Mesh Cut	$\Sigma f_i d_i = b_{avg}$	$\Sigma f_i d_i^2$	$\Sigma f_i d_i^3 \times 10^{-6}$	d_{sv}	Standard Deviation b_{avg}
Oxalic acid didydrate	30/40	422.8	186584	85.7966	459	88
Oxalic acid didydrate	40/50	303.0	94256	30.0880	319	50
Oxalic acid didydrate	50/60	240.5	58968	14.7110	249	38
Oxalic acid didydrate	60/80	162.7	27606	0.48780	177	33
Salicylic acid	40/60	104.0	12045	0.15342	130	35
Salicylic acid	60/100	81.2	7392.4	0.74269	100	28
Salicylic acid	100/200	57.0	3726.4	0.27318	73.3	22
Phthalimide	40/60	52.0	3172	0.22235	70.1	22
Phthalimide	60/100	60.3	4179	0.32821	78.5	23

is determined, then the average volume v of a particle is given by

$$v = W/(N\rho) \tag{5}$$

where ρ is density. If, for instance, 300 particles weighed 0.0375 g and their density was $\rho = 1.25$ g/cm^3, then the average volume of the particle in the mesh cut would be

$$v = 0.0375/(1.25 \cdot 300) = 10^{-4} \text{ cm}^3$$

In general, if a microscopic count consists of N particles, then the total volume V of the examined (cumulative) samples would be

$$V = Nv = \sigma hbL \tag{6}$$

where the nomenclature of Fig. 5 has been used.

It is conventional to report the smaller dimension and the ratio of the two observable dimensions b/L or its inverse, and this ratio is denoted ε here, that is,

$$L = \varepsilon b \tag{7}$$

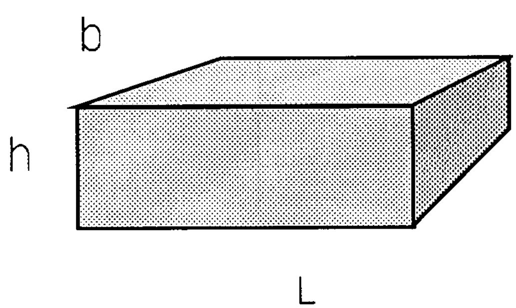

Figure 5. Nomenclature used for a parallelepiped. Note that the volume v is hbl.

These quantities can be determined experimentally by microscopy, and the obtained ε-values are shown in Table 4. If the ratio between h and b is denoted β, then

$$h = \beta b \tag{8}$$

Inserting Eqs. 7 and 8 into Eq. 6 yields

$$V = Nv = \beta\varepsilon\Sigma b^3 \tag{9}$$

The factor $\beta\varepsilon$ is frequently denoted the volumetric shape factor (10) α_v in relation to the dimension b, that is,

$$\alpha_v = \beta\varepsilon \tag{10}$$

Shape factors are not easily determined, and only a few publications (6,11) have appeared on the subject.

A similar set of equations could, of course, be developed for the two other dimensions as well, but it would have less or no practical utility. A better way to obtain V than the method described above is by electronic counting. In this manner, the volume (which is directly measured) of N particles (which are directly counted) will emerge, and can be used in Eq. 6. In Eq. 9, all quantities except β are known, and this quantity can hence be calculated. V may also be obtained by old-fashioned techniques such as the Andreasen apparatus (sedimentation).

However, the very best way of arriving at values of β is by using the volumetric shape factor α_v if an independent assessment of it is available (12). Equation 10 gives the value of $\beta = \alpha_v/\varepsilon$; such calculations of β are shown in Table 4. This may be important because, if crystal dissolution is followed microscopically, it may be essential to know the value of the smallest dimension since it is that dimension that is often likely to dissolve first.

Table 4

Shape Factors, β-Values and Calculated ε-Values of Sieve Fractions of Four Compounds

Compound	Sieve Fraction	α_v	ε from Microscopy	β (Mean *h*/*b*)
Oxalic acid dihydrate	−30/+40	2.7	4.8	0.56
	−40/+50	3.8	8.0	0.47
	−50/+60	4.2	8.8	0.47
	−60/+80	7.6	12.5	0.61
Salicylic acid	−40/+60	9.5	11.1	0.86
	−60/+100	13.4	14.6	0.92
	−100/+200	15.5	15.7	0.99
Phthalimide	−40/+60	10.3	11.0	0.94
	−60/+100	12.9	13.1	0.98

CONCLUSIONS

1. Particles in a mesh cut are rarely linearly distributed, yet the mean particle size of a mesh cut is related to the average of the openings of the confining screens.
2. Particle size distributions in a mesh cut are often bimodal.
3. If investigations that are not routine are carried out, it is worthwhile to carry out microscopic particle size distributions to obtain both the mean and the moments of the distribution.
4. Methods for obtaining the size of the smallest dimension (which is not visible microscopically) have been presented.

APPENDIX

The program for generating the data in Table 3 in BASIC is listed below:

```
100 INPUT ''No of Intervals=''; Q1
110 INPUT ''Total Number of Particles Counted='';
    Q2
180 PRINT ''a'', ''fa'', ''fa^2'', ''fa^3''
190 PRINT ''________________________________''
200 READ N1,D1
210 N2 = N2 + 1
215 N3 = N1/Q2
218 N4 = N4 + N3
220 X1 = (N3 * D1)
230 X2 = X2 + X1
240 X3 =(N3 * (D1^2))
250 X4 = X4 + X3
260 X5 =(N3 * (D1^3))
270 X6 = X6 + X5
280 PRINT D1, X1, X3, X5
280 IF N2 = Q1 GOTO 950
290 GOTO 200
400 DATA 3, 157.7
410 DATA 17, 177.16
420 DATA 31, 196.6
430 DATA 47, 216.04
440 DATA 54, 235.48
450 DATA 79, 254.92
460 DATA 41, 274.36
470 DATA 23, 293.80
480 DATA 5, 313.26
900 PRINT D1,X1,X2
950 PRINT ''sum fa=Mean='';X2
960 PRINT ''sum fa^2='';X4
970 PRINT ''sum fa^3='';X6
980 PRINT ''Surf/Vol D=''; X6/X4
980 PRINT ''Sum of f=1='';N4
990 S1 = X4–(X2^2)
1000 PRINT ''Std. Dev.=''; S1^(.5)
```

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