Effects of Milling on Granulation Particle-Size Distribution

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Abstract □ A series of lactose granulations made with various amounts of starch paste and water was subjected to milling through different screens and the particle sizes were determined. The distributions were log-normal when the size of the coarse material was determined by sieve analysis and the size of the fine material was determined microscopically. An equation was developed to describe the increase in surface area, ΔO, when material is milled through a screen with n holes of diameter d; this equation takes the form: $\log[n(\Delta O)] = -q(\log d) + p$, where q and p are constants.

Keyphrases □ Milling—effects on granulation particle-size distribution, equations □ Particle-size distribution—effects of milling on granulations, equations □ Granulations, lactose, starch, and water—used to determine effects of milling on granulation particle-size distribution, equations

Although milling is an essential step in tablet and capsule manufacture, the basic concepts of pharmaceutical comminution have received only a small degree of attention in the literature. The treatise by Parrott (1) is the only theoretical approach reported on milling of *granulations*. Milled granulations are usually considered to be log-normally distributed (2), although frequent deviations seem to occur.

Pharmaceutical granulations are, of course, heterogeneous, porous substances. In contrast, milling of pure and compact substances has been treated extensively, *e.g.*, in the literature of the mining and engineering sciences. Log-normal size distributions have frequently been reported (3–12), as have other distributions (13–15). The usual distribution functions in these latter instances are the Rosin–Rammler (16) and Alyavdin (17) equations. Harris (18) employed these and the Weibull (15) distribution in construction of special grids with a wide range of utility in powder description.

THEORETICAL

The Weibull (15) distribution has gained wide use, primarily due to its universal character; it is strictly phenomenological and based on a fractional undersize function, $f(x)$, which may be described by:

$$f(x) = 1 - e^{-\psi(x)} \qquad \text{(Eq. 1)}$$

According to Weibull (15), the function $\psi(x)$ is subject only to the general condition that it be a positive, nondecreasing function that vanishes at a value x_u. The value of x_u is not necessarily zero, and the simplest general function meeting these requirements is:

$$\psi(x) = [x - x_u]^{\lambda}/k \qquad \text{(Eq. 2)}$$

Harris (18) applied this to particle-size distributions. In this case, x is a dimension of the particle, *e.g.*, diameter, largest dimension, or cube root of volume. It is assumed that x_u is zero, so Eq. 2 then takes the form:

$$\psi(x) = [x/k]^{\lambda} \qquad \text{(Eq. 3)}$$

Table I—Composition of Granulating Fluid in the Granulations and Loss on Drying

Designation	Starch, g	Water, g	Loss on Drying[a], %
B-2	50	450	0.83
B-3	50	495	1.10
B-4	50	540	1.18
C-2	60	540	0.79
C-3	60	594	1.34
C-4	60	648	2.20
D-2	55	495	0.79
D-3	55	545	0.90
D-4	55	594	1.40

[a] One hundred grams of dried granulation was dried further until constant weight (w g) was recorded. The difference ($100 - w$ g) is assumedly moisture, so the percent loss on drying is $100 - w$.

where $f(x) = 1 - e^{-\psi(x)}$ is the fraction oversize in the particle-size analysis. The fraction undersize, y, is then given by:

$$y = 1 - f(x) = e^{-\psi(x)} = \exp[-(x/k)^{\lambda}] \qquad \text{(Eq. 4)}$$

or:

$$1/y = \exp[(x/k)^{\lambda}] \qquad \text{(Eq. 5)}$$

The logarithmic transformation of this is:

$$\ln (1/y) = [x/k]^{\lambda} \qquad \text{(Eq. 6)}$$

$$\log[\ln (1/y)] = \lambda[\log (x/k)] \qquad \text{(Eq. 7)}$$

Normal and log-normal distributions, as will be shown, "almost" fit this type of presentation; indeed, Eq. 5 is a function of wide applicability.

As opposed to the statistical empirical approach leading to Eq. 5, some model approaches for pure substances lead to log-normal distributions. For instance, Irani and Callis (12) showed that crystal growth leads to a log-normal distribution truncated from above. Fines destruction in crystallizers accomplish truncation from below, so, indeed, many crystalline substances are log-normally distributed. One purpose of this study was to show that pharmaceutical comminution results in a log-normal distribution rather than a Weibull distribution. It was also the aim to advance a rational method for treating sieve analysis data. Finally, a study of the energetics of milling was a logical outcome of the investigation.

EXPERIMENTAL AND RESULTS

Granulations were made by mixing 2325 g of lactose USP[1] and 175 g of starch[2] for 8 min in a 10-liter mixer[3]. Starch pastes of the compositions shown in Table I were made in a steam-heated vessel by adding cold distilled water to the starch and heating it under stirring until it became translucent. After cooling to 30°, it was added to the powder mix and kneaded for 17 min at low speed (50 rpm). The wet mix was passed through a No. 4A perforated round hole screen [opening 7.92 mm (0.312 in.)] in a comminuting machine[4] at 957 rpm.

The granulations were dried on trays in an oven at 54° for 4 hr. One hundred-gram samples were left in the oven until constant weight had been reached and then the loss on drying was calculated (Table I). As expected, the loss on drying values were di-

[1] Lot 08915, Ruger Chemical Co., Irvington, NJ 07111
[2] Pure corn starch ARGO, Best Foods Division, CPC International Inc., Englewood Cliffs, NJ 07632
[3] Hobart mixer, Hobart Manufacturing Co., Troy, Ohio.
[4] Fitzpatrick model M55, Fitzpatrick Co., Elmhurst, IL 60126

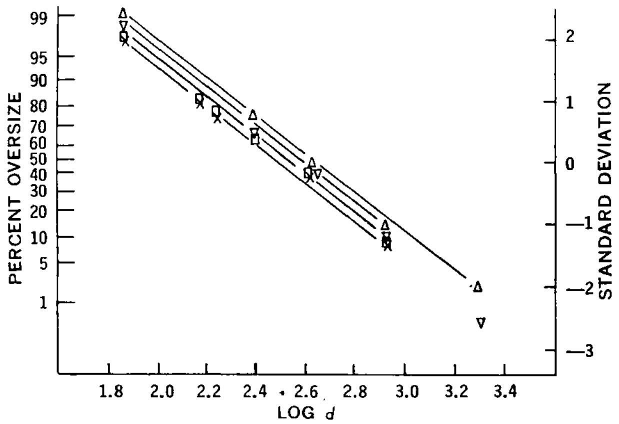

Figure 1—*Log-normal distribution of experimental Sample B-2. Key:* △, *screened through a 2B screen;* ▽, *screened through a 2A screen;* □, *screened through a 2AA screen; and* ×, *screened through a 0065 screen.*

rectly proportional to the amounts of water added in each group. The dried granulations were milled through a comminuting machine[4] at 1610 rpm using the following screens: 2A, 2AA, 2B, and 0065 with knives forward. The characteristics of these screens are listed in Table II.

Sieving tests were performed through series of screens of U.S. Standard sizes as follows: 10, 20, 40, 60, 80, 100, and pan or 20, 40, 60, 80, 100, 200, and pan. In general, a 5-min mimimum is required for good sieving operations; the shaker[5] used in these experiments was tested by the method of Fahrenwald and Stockdale (19) and it was found that 200 sec sufficed for 100% efficiency. Therefore, the general procedure for the sieving tests was to shake a sample of 100 g for 200 sec on the shaker[5] and to determine the weights of powder retained by the screens used. Specific gravity of the granulations was determined by a pycnometer, using toluene as the liquid. Particle-size distributions are shown graphically as percent oversize either on a log-probability grid when the distribution is log-normal or according to Eq. 7. The notation d is used to denote the largest dimension of the screen opening in the sieving tests; d is an estimate of x as described under *Theoretical*. Examples of data fitting a log-normal distribution are shown in Fig. 1, and examples of data presented according to Eq. 7 are shown in Fig. 2; least-squares fit values of λ and log k are shown in Table III.

Knowing the specific gravity and the mesh analysis allows calculation of the geometric surface areas (Table IV). The material

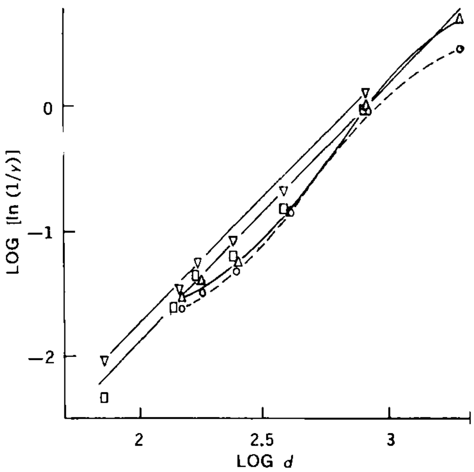

Figure 2—*Weibull plotting of data from experimental Sample C-2. Key:* ○, *screened through a 2B screen;* △, *screened through a 2A screen;* □, *screened through a 2AA screen; and* ▽, *screened through a 0065 screen.*

[5] Ro-Tap testing sieve shaker, W. S. Tyler Co., Cleveland, Ohio.

Table II—Screen Specifications

Screen Number	Number of Holes	Diameter[a] Inches	Diameter[a] Millimeters	Log of Diameter, mm
2B	2784	0.109	2.77	0.442
2A	2632	0.093	2.36	0.37
2AA	4200	0.079	2.01	0.303
0065	4165	0.065	1.65	0.21

[a] From: "Operating Instructions and Parts Manual, Model D Comminuting Machines," Fitzpatrick Co., Elmhurst, Ill.

passing the finest screen onto the pan was subjected to a microscopic count as described previously (20). A total of 10,000 particles was counted in each case. This is taken into account in Tables IV and V and Figs. 5 and 6 but not in Tables III and VI and Figs. 1-4; this will be subject to discussion.

DISCUSSION

The first point of discussion is the particle-size distributions. Only three samples (B-2, C-4, and D-2) appeared to be distributed log-normally on a weight basis. The remaining distributions, when plotted in log-normal fashion, yielded curves with downward curvature (Fig. 3). All of the curves, when plotted as Weibull functions (Eq. 7), give fairly good linearity (Fig. 2). One interesting aspect, as shown in Table III, is that the intercepts are fairly constant; that is, log k is, within an order of magnitude, the same for all of the granulations. More important, however, is the general tendency for slight S-shapes. On the surface, this might not seem significant; however, a normal or log-normal distribution will show exactly such an almost linear, but slightly S-shaped, relation when plotted according to Eq. 7 (Fig. 4). The original Weibull function was not purported to have a theoretical basis but was justified by the fact that the lack of theoretical basis is true for "other distribution functions applied to real populations from natural and biological fields" (15). The Harris grid

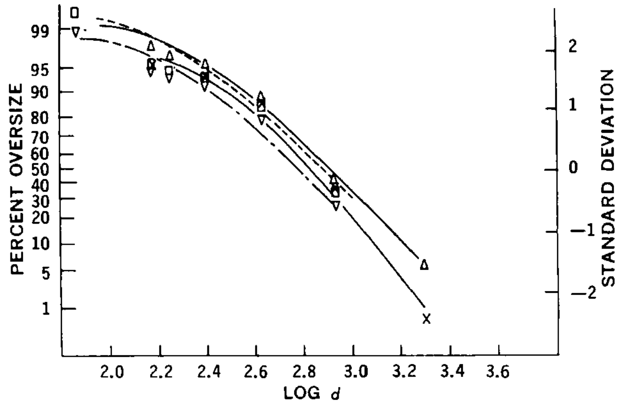

Figure 3—*Data from experimental Sample C-2 plotted in log-normal fashion. Key:* △—, *screened through a 2B screen;* □- - -, *screened through a 2A screen;* × ——, *screened through a 2AA screen; and* ▽— - —, *screened through a 0065 screen.*

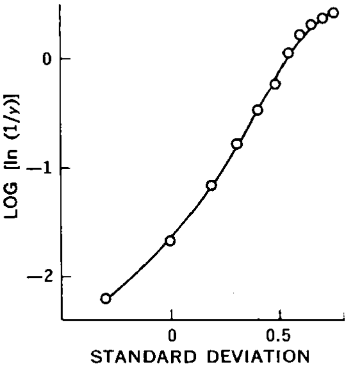

Figure 4—*Normal distribution plotted as a Weibull function.*

Table III—Weibull Parameters of Milled Granulations (Eq. 7)

Experiment Number	2B Screen		2A Screen		2AA Screen		0065 Screen	
	λ	log k	λ	log k	λ	log k	λ	log k
B-2	2.51	−3.1240	1.61	−2.7292	1.79	−2.6705	1.75	−2.6284
B-3	1.44	−2.9898	1.52	−2.8895	1.64	−2.8631	1.47	−2.8500
B-4	2.34	−3.0313	2.15	−3.0958	1.54	−3.3736	1.55	−3.1743
C-2	1.94	−3.0989	1.99	−2.9769	2.08	−2.9398	1.93	−2.9090
C-3	2.44	−2.848	2.08	−3.1477	1.04	−3.7728	1.13	−3.2810
C-4	1.34	−3.4113	1.35	−3.0350	0.90	−3.2127	0.88	−3.0937
D-2	1.73	−2.9367	1.82	−2.8744	2.03	−2.8014	1.89	−2.7893
D-3	2.51	−3.0411	2.28	−2.9994	1.75	−3.0901	1.80	−3.0544

Table IV—Geometric Surface Areas[a] of Test Granulations

Experiment Number	Unprocessed Granule	2.77-mm[b] Screen	2.36-mm[b] Screen	2.01-mm[b] Screen	1.65-mm[b] Screen
B-2	1.210	1.494	1.591	1.592	1.819
B-3	0.805	0.955	1.099	1.109	1.295
B-4	0.450	0.507	0.536	0.585	0.725
C-2	0.601	0.686	0.727	0.745	0.865
C-3	0.300	0.427	0.461	0.564	0.892
C-4	0.268	0.461	0.894	1.281	1.461
D-2	0.617	0.936	1.106	1.067	1.168
D-3	0.291	0.610	0.650	0.726	0.760
D-4	0.172	0.464	0.511	0.802	0.865

[a] Surface areas are in $m^2/100$ g. [b] Fitzpatrick round perforated plate size 2B, 2A, 2AA, and 0065 (see Table II).

was constructed to avoid "the kind of congestion frequently observed" (18) with other modes of plotting. An example is the conventional plotting of data in Figs. 1 and 3. Expanded scaling is necessary to show details in the graphs.

The distributions are not normal, so one is left with the choice of either an approximate fit to log-linear or a Weibull-type presentation. All curves are, however, only partially complete in the sense that the pan material from the sieve analysis is not broken down further. Therefore, samples were subjected to a microscopic count to estimate the particle-size distribution of the fine fraction (Table V and Fig. 5); the 2.36% by weight retained was broken down into subgroups (100–150, 50–100, 25–50, 10–25, and 5–10 μm, no particle being finer than 5 μm). It is noted from Fig. 5 that when the subdivision of the pan material is included, the distributions become log-normal. The distributions are shown as weight and number frequencies in Table V and as number distributions in Fig. 5; it is apparent from the Hatch-Choate (4) equation that there is no loss in generality in this conversion. In converting to the number distribution, more emphasis is placed on the finer fraction; the microscopic examination revealed that particles 50 μm and above in general were still agglomerates. Between 25 and 50 μm, some were prime particles (single crystals), and the 10–25-μm fraction appeared to be single crystals only. Therefore, it is logical to combine screen analysis data with a microscopic (or other suitable) count of the material retained on the pan and to treat the data as a number distribution in a log-normal fashion.

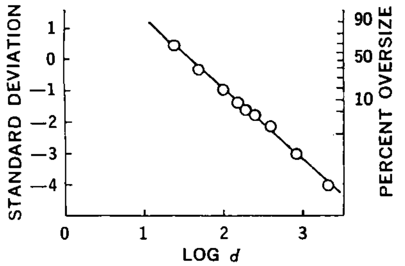

Figure 5—*Data from Table V plotted in log-normal fashion.*

The milling experiments reported here give information relative to the energy actually imparted on the granulation during milling. To measure this directly is difficult; motor current can be used as an estimate of the amount of energy leaving the mill, but some (unknown) fraction of this is dissipated as heat, so that this (and other similar) measures are not indicative of the amount of energy transferred to the powder mass. There is evidence of long standing [as reported by Martin (21) and Gross and Zimmerley (22)] that the area of new surface (ΔO) produced in milling is proportional to the work input (E). This, essentially, is a direct

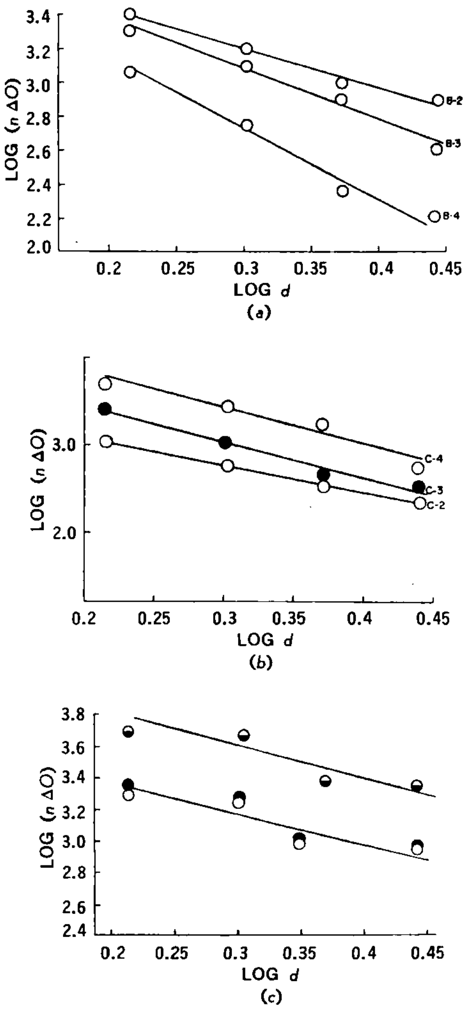

Figure 6—*Data from* (a) *B series,* (b) *C series, and* (c) *D series plotted according to Eq. 12. Key (for 6c):* ○, *Experiment D-2;* ●, *Experiment D-3; and* ◒, *Experiment D-4.*

Table V—Distribution of Sample C-2 Milled through a 2B Screen, with Inclusion of Distribution of Pan-Retained Material

Midsize Diameter, μm	Weight/100 g	10^{-3} × Number of Particles/100 g	Fraction by Number	Cumulative Fraction	Oversize Diameter, μm, *d*	Log *d*	Standard Deviation (*t*)
2680[a]	5.55	0.55	0.00003	0.00003	2000	3.301	−4.02
1420	35.15	23.45	0.001	0.001	840	2.924	−3.02
630	46.20	353	0.019	0.020	420	2.623	−2.05
335	8.55	435	0.023	0.043	250	2.398	−1.72
214	1.30	253	0.013	0.056	177	2.248	−1.58
163	0.80	353	0.019	0.075	149	2.173	−1.44
Pan:	2.45			0.075			
125	1.372	1342	0.071	0.146	100	2.00	−1.06
75	0.894	4049	0.213	0.359	50	1.699	−0.36
37.5	0.168	6087	0.321	0.679	25	1.398	+0.47
17.5	0.016	5705	0.300	0.979	10	1.00	+2.04
7.5	0.000086	390	0.021	1.000	5		

[a] Passes 6 mesh (3360 μm) and is retained by 10 mesh (2000 μm).

Table VI—Least-Squares Fit Statistics (Slope and Intercept) of Data in Table IV Fitted to Eq. 12

Experiment	Slope ($= -q$)	Intercept [$=\log(\beta/\gamma)$]	Moisture
B-2	−2.30	3.90	0.83
B-3	−3.04	4.00	1.10
B-4	−3.98	3.92	1.18
C-2	−3.03	3.69	0.79
C-3	−3.97	4.22	1.34
C-4	−4.15	4.66	2.20
D-2	−1.98	3.81	0.79
D-3	−1.74	3.70	0.90
D-4	−2.80	4.12	1.40

consequence of data originally published by Rittinger (23) and Dallavalle (24) and, when using these symbols, it takes the form:

$$E = \gamma(\Delta O) \qquad \text{(Eq. 8)}$$

where γ is a proportionality constant. It is noted in this study that there is a trend (Tables II and IV) that granule area increases as the screen plate hole area decreases.

In the screen, each hole offers a resistance associated with an energy expenditure, so that the energy is proportional to d^{-q}, where d is the diameter of the screen opening. The proportionality constant would have a dimension of erg cm^{+q}. The energy expenditure is inversely proportional to the number, n, of holes so that in all:

$$E = \beta(d^{-q}/n) \qquad \text{(Eq. 9)}$$

where β is an (unknown) proportionality constant. Combining this assumption with Eq. 8 then gives:

$$E = \beta(d^{-q}/n) = \gamma(\Delta O) \qquad \text{(Eq. 10)}$$

Rearranging gives:

$$\frac{\beta}{\gamma}(d^{-q}) = n(\Delta O) \qquad \text{(Eq. 11)}$$

The logarithmic form of Eq. 11 is:

$$-q(\log d) + \log(\beta/\gamma) = \log\,[n(\Delta O)] \qquad \text{(Eq. 12)}$$

Plotting of $\log[n(\Delta O)]$ *versus* log d is shown in Fig. 6. The least-squares fit parameters are shown in Table VI. It is noted that increasing water content increases q, *i.e.*, increases the resistance exponent. The term β/γ is (to the extent of order of magnitude comparisons) fairly constant as should be expected; *i.e.*, γ, the surface energy per square centimeter, is not a function of the size of the granulated particle or of the formulation. Thus, Eq. 12 appears to hold for the range of screens employed in the experiments.

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