APPENDIX

Sensitivity of the Best Fit Analysis to P—To relate the present results to their sensitivities to P, the parameters C_s and D must be considered. As already shown, there was good agreement between the solubilities obtained from the best fit analysis and those obtained from extrapolation of the partial saturation data. Diffusivities obtained from the best fit analysis were in fairly good agreement with those obtained experimentally. Diffusivity measurements were made at 37° in a small volume diaphragm diffusion cell employing a modified Keller's method (14). The D values determined experimentally in 0.0, 0.25, and 0.50% benzalkonium chloride solutions were 1.52, 1.40, and 1.28×10^{-6} cm^2/sec, respectively. These compare with the best fit D values of 1.25, 1.04, and 1.08×10^{-6} cm^2/sec.

Because of the good agreement between experimental and best fit parameters for C_s and D, an assessment of P can now be made. It must be remembered that as a system approaches total diffusion control, P becomes very large (surface equilibrium is fast) and therefore, $1/P$ becomes small. The smaller the $1/P$ ratio, the less sensitive the best fit results will be to small changes in P. Another look at the systems studied shows that the diffusion control/interfacial control ratios are small to moderate except for the melt pellets in 5% sodium cholate, 0.1 M phosphate buffer, and 0.50% benzalkonium chloride at pH 8.0 where the diffusion control/interfacial control ratio is ~90%. By making small changes in P, the sensitivity of the best fit results can be seen. It can be shown that if P is varied by ±10% there is little change in the best fit results. However, a change in P greater than 10% will result in marked deviation of the experimental results and the theoretical curves. For the case where the diffusion control/interfacial control ratio is ~90%, the uncertainty in P can be as high as 25%.

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ACKNOWLEDGMENTS

Supported by Grant AM 16694 from the National Institute of Arthritis, Metabolism, and Digestive Diseases.

Particle Size Reduction by a Hammer Mill I: Effect of Output Screen Size, Feed Particle Size, and Mill Speed

B. R. HAJRATWALA

Received May 15, 1981, from the *Pharmaceutics Department, Wayne State University, Detroit, MI 48202.* Accepted for publication June 30, 1981.

Abstract ☐ A hammer mill is an impact mill commonly used in pharmaceutical manufacturing for reducing particle size for a variety of drugs. Commercial grade ammonium sulfate was milled as a model powder. This salt was sieved to obtain particle size fractions with average diameters of 1.3, 0.9, and 0.72 mm which were used as feed particles. The milled material was analyzed for particle size distribution (PSD) using standard sieves. At a moderate speed (~2500 rpm), the feed size did not result in a significantly changed arithmetic mean diameter, $d_{\bar{x}}$ of milled particles. A new particle size reduction constant, k, is proposed as a result of a linear relationship between $d_{\bar{x}}$ and output screen size, d_{ss}. As d_{ss} decreases, the PSD range of milled particles narrows; as mill speed increases (~5000 rpm), $d_{\bar{x}}$ decreases. The decrease is of a greater magnitude for larger d_{ss} (2 mm) than for a smaller d_{ss} (1 mm). At low speeds (~1000 rpm), the PSD is wider compared to medium and high speeds.

Keyphrases ☐ Particle size—reduction by hammer mill, effect of output screen size, feed particle size, and mill speed ☐ Pharmaceutics—particle size reduction by a hammer mill ☐ Hammer mill—particle size reduction, pharmaceutics

The hammer mill is an impact mill commonly used in pharmaceutical manufacturing for reducing particle size for a variety of drugs (1–3). Milling is an essential unit operation in tablet and capsule manufacture, yet very little has been reported about factors that affect milling (4, 5).

The present report examines the effect of related parameters such as output screen size, feed particle size, and mill speed on particle size reduction by a hammer mill. Commercial grade ammonium sulfate was used as a model substance due to its low cost and large particle size distribution.

EXPERIMENTAL

Equipment—A laboratory bench-type hammer mill[1], USP standard testing sieves[2], and a laboratory sieve vibrator[3] were used. The sieve sizes used were: 2.0, 1.6, 1.0, 0.8, 0.63, 0.4, 0.315, and 0.1 mm for preparation and analysis.

Particle Size Reduction—Ammonium sulfate was sieved to obtain various particle size fractions with average diameters of 1.3, 0.9, and 0.72 mm. Sieve sizes used were 1.6, 1.0, 0.8, and 0.63 mm. The particles were stored at room temperature (25 ± 3°) and at a constant humidity (60 ± 2%, to prevent agglomeration of particles) until required for milling.

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[1] Model C580, micro hammer mill, Glen Creston, Stanmore, England.
[2] W. S. Tyler Inc., Mentor, OH 44060.
[3] Model 150, Derrick Inc., Buffalo, N.Y.

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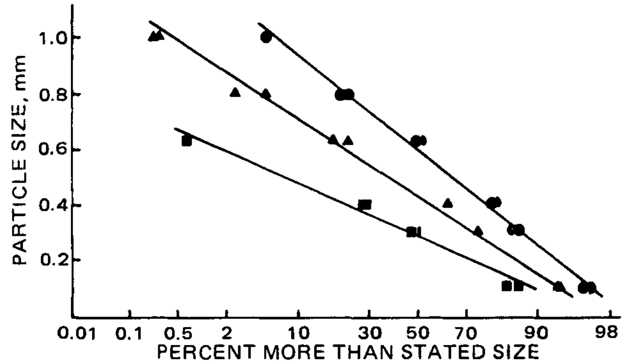

Figure 1—*Effect of varying* d_{ss} *on the particle size distribution. Feed particle size range, 1.6–1.0 mm. Speed setting 4. Key* (d_{ss}): ●, *2.0;* ▲, *1.5; and* ■, *1.0 mm.*

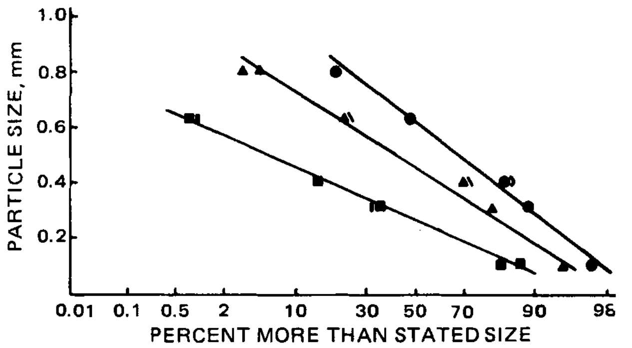

Figure 2—*Effect of varying* d_{ss} *on the particle size distribution. Feed particle size range, 1.0–0.8 mm. Speed setting 4. Key* (d_{ss}): ●, *2.0;* ▲, *1.5; and* ■, *1.0 mm.*

The mill was equipped with three free-swinging hammers with impact edges and variable rotational speed control. The material was fed as 5 g portions.

The total amount milled for each experiment was 50 g. The mill was fitted with round-hole design output screens with 2.0-, 1.5-, or 1.0-mm sizes. They were 3.03-, 3.06-, and 1.23-mm thick, respectively. The milled material was collected in a closed plastic bag and analyzed for particle size distribution using the standard vibrating nested sieve method.

All data were obtained in duplicate and were virtually identical in all cases.

Evaluation of $d_{\bar{x}}$**, and** σ—The mean diameter, $d_{\bar{x}}$, was obtained from arithmetic probability plots. The particle size at 50% was taken as $d_{\bar{x}}$.

The standard deviation, σ, was also obtained from the arithmetic probability plots. The difference in particle sizes at 84.13 and 50% size was taken as σ.

RESULTS AND DISCUSSION

The rate at which a mill is fed is an important variable. Various amounts of feed material were milled to determine the optimum feed rate. This was determined experimentally by noting the discharge rate (grams per second) of milled material. Five grams was the optimum amount, giving the maximum discharge rate for this mill with ammonium sulfate as the feed material.

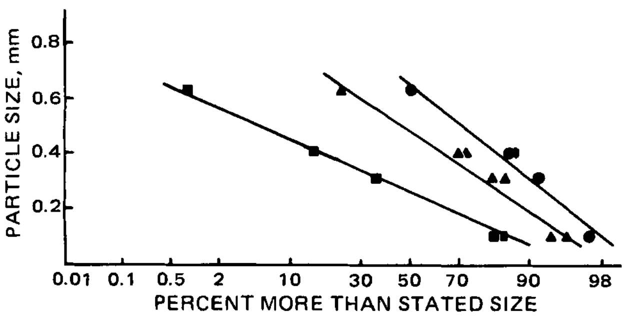

Figure 3—*Effect of varying* d_{ss} *on the particle size distribution. Feed particle size range, 0.8–0.63 mm. Speed setting 4. Key* (d_{ss}): ●, *2.0;* ▲, *1.5; and* ■, *1.0 mm.*

Table I—Effect of Output Screen Size on the Arithmetic Mean and Standard Deviation of the Milled Particles for Various Sizes of Feed Particles at Setting 4 (~2500 rpm)

	Output Screen Size, d_{ss}		
	2.0 mm	1.5 mm	1.0 mm
Feed Size Range, mm	$d_{\bar{x}} \pm \sigma$	$d_{\bar{x}} \pm \sigma$	$d_{\bar{x}} \pm \sigma$
1.6–1.0	0.59 ± 0.26	0.43 ± 0.22	0.28 ± 0.15
1.0–0.8	0.61 ± 0.25	0.45 ± 0.21	0.27 ± 0.15
0.8–0.63	0.65 ± 0.26	0.48 ± 0.24	0.26 ± 0.15

Table II—Effect of Milling Speed on Arithmetic Mean and Standard Deviation of the Milled Particles at Varying Output Screen Size [a]

	Milling Speed Setting		
	2	4	8
d_{ss}, mm	$d_{\bar{x}} \pm \sigma$	$d_{\bar{x}} \pm \sigma$	$d_{\bar{x}} \pm \sigma$
2.0	0.88 ± 0.40	0.59 ± 0.26	0.31 ± 0.27
1.0	0.34 ± 0.24	0.28 ± 0.15	0.22 ± 0.15

[a] Feed particle size range, 1.6–1.0 mm.

This mill had a maximum speed of 6000 rpm. (Any reference to a constant speed implies that the speed setting on the mill was not changed during the experiment). Milling was done at three preselected settings. A low speed (setting 2, ~1000 rpm), a medium speed (setting 4, ~2500 rpm), and a high speed (setting 8, ~5000 rpm) were arbitrary selections.

Effect of Output Screen Size at Moderate Milling Speed—The evaluation of particle size data utilizing histograms has limited use. It is convenient to express data as arithmetic probability or normal probability plots (1).

Figures 1–3 show the effect of output screen size (d_{ss} represents diameter of screen openings) on the particle size distribution of milled product for various sizes of feed material. Although milled material may show a log-normal distribution (4), the particle size distributions for milled particles in this study show a linear relationship on arithmetic probability plots indicating near normal distribution. Some plots show departure from linearity at extremes indicating nonasymptotic distribution; however, the usefulness of the data is not reduced.

Table I shows that the output screen size, d_{ss}, has a significant effect on the arithmetic mean size, $d_{\bar{x}}$, of the milled particles. Since the average feed particle size does not show a significant effect at setting 4, the data can be pooled.

It is expected that decreasing d_{ss} would decrease the particle size of the milled particles, as was confirmed in this study. However, no relationship between d_{ss} and milled particle size has been reported. It is also not known how decreasing d_{ss} would affect the magnitude of σ for the particle size distribution of the milled particles.

A simple relationship may be hypothesized between d_{ss} and $d_{\bar{x}}$ of the milled particles and may be expressed as:

$$d_{\bar{x}} = k/d_{ss} \qquad \text{(Eq. 1)}$$

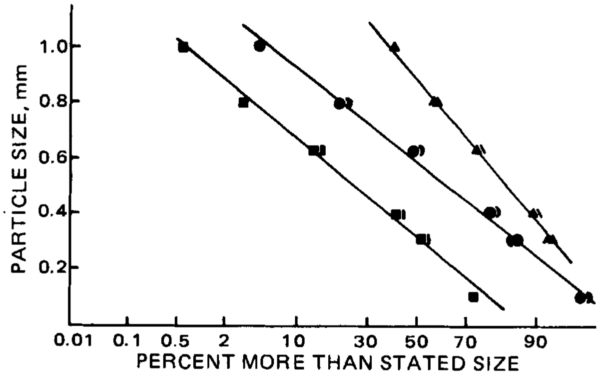

Figure 4—*Effect of varying milling speed on the particle size distribution,* d_{ss} *= 2.0 mm. Feed particle size range, 1.6–1.0 mm. Key (speed):* ▲, *setting 2 (~1000 rpm);* ●, *setting 4 (~2500 rpm); and* ■, *setting 8 (~5000 rpm).*

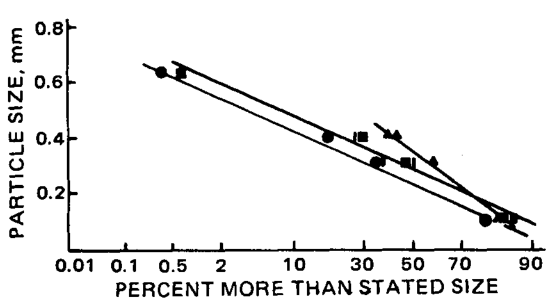

Figure 5—*Effect of varying milling speed on the particle size distribution,* d_{ss} = *1.0 mm. Feed particle size range, 1.6–1.0 mm. Key (speed):* ▲, *setting 2 (~1000 rpm);* ■, *setting 4 (~2500 rpm); and* ●, *setting 8 (~5000 rpm).*

based on data in Table I where k is a particle size reduction factor. The value of k for Table I data is 0.294 (n = 9, SD = 0.022). This means that $d_{\bar{x}}$ is about one-third less in size than the output screen size, regardless of the feed particle size range used in this experiment, at a moderate milling speed setting of 4 on this mill.

The effect of d_{ss} on the particle size range distribution of milled particles can be seen by comparing its standard deviation. As d_{ss} decreased, σ decreased, *i.e.*, the particle size distribution became narrower. The distributions were unaffected by the feed particle size due to a narrowing of the angle of particle discharge range as output screen size became smaller.

It should be noted that the thickness of the 1-mm output sieve is approximately half of the 2- and 1.5-mm sieves. Decreasing the thickness of the output screen should increase the range of particle discharge angles (6). Thus, the observed data for the 1-mm size should be viewed with caution.

Effect of Milling Speed—The speed at which a mill operates is an important factor in particle reduction. At any given speed, as the material is fed, a mill slows down due to attrition of particles by the hammers until most of the material is discharged and the speed returns to the unloaded speed.

Figures 4 and 5 show the effect of milling speed on the milled product at varying output screen sizes. The arithmetic mean, $d_{\bar{x}}$, and standard deviation (σ) of the milled particles are shown in Table II.

It was expected that milling at higher speeds would further reduce the average particle size of the milled product due to the decreased angle of particle discharge (6). However, the extent of reduction or its effect on the range of particle size distribution of the milled particles has not been reported.

At settings 2, 4, and 8, the mill speeds are ~1000, 2500, and 5000 rpm, respectively. Table II shows that as the mill speed increases, the arithmetic mean of the milled particle decreases. This decrease is of a greater magnitude for the larger output screen size (2 mm) than for the smaller output screen size (1 mm).

At low speeds, the standard deviation of the milled particles is larger compared to medium and high speeds. This is reasonable because at lower speeds the particles are not expected to be discharged at a steeper angle. As the rotational speed increases, the angle of discharge reaches some optimum value, *i.e.*, the particles cannot be discharged at an angle lower than the optimum, and a leveling off of the standard deviation is observed.

Figure 6 shows the effect of output screen size and speed on the average particle size of the milled particles. The feed particle size range was 1.6–1.0 mm.

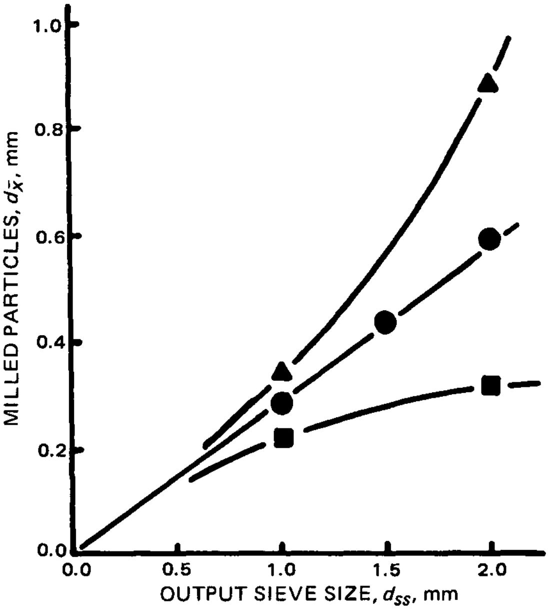

Figure 6—*Effect of* d_{ss} *on* $d_{\bar{x}}$ *of the milled particles at varying milling speeds. Key (speed):* ▲, *setting 2 (~1000 rpm);* ●, *setting 4 (~2500 rpm); and* ■, *setting 8 (~5000 rpm).*

The plot shows that Eq. 1 holds true at a moderate speed in this experimental series, the slope of the line being particle size reduction factor k. Equation 1 does not hold true at a low milling speed (setting 2) or at a high milling speed (setting 8). The equation plot passes through the origin as it would be expected; if the output screen size were zero, then no milled particles would be obtained.

Further work is in progress to determine the mathematical relationship of a change in k and to study milling characteristics of other selected pharmaceuticals.

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ACKNOWLEDGMENTS

The technical assistance of Ms. Margaret Sturtevant is gratefully acknowledged. This work was done in part at the Pharmacy Department, University of Otago, Dunedin, New Zealand. The author thanks Dr. W. E. Moore of Pharmaceutics Department, Wayne State University, for helpful suggestions and his astute review of this manuscript.