Micromeritics of Granular Pharmaceutical Solids II

Factors Involved in the Sieving of Pharmaceutical Granules

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This report deals with basic studies concerned with the use of sieving as an accurate means of classifying granular pharmaceutical solids. Attention was focused on the effects of *sieve shaker speed, initial load and particle size distribution of the granulation* on the rate of particle size reduction and the cumulative per cent of material passing a sieve. The size and concentration of the smaller-than-mesh particles were shown to exert a profound influence on the equilibrium time of a sieve. Using a nest of sieves, an equilibrium time technique was developed to obtain the particle size distribution and permit calculation of various statistical parameters dependent on the observance of the log-normal law. An equilibrium time procedure such as developed here permits the quantitative classification of granular pharmaceutical solids by sieving, with a better assurance that separation has been achieved with the minimum of attrition.

THERE ARE few reports in the literature concerning the sieving of granular pharmaceutical solids for the purposes of classification or size analysis. It would appear that, in the past, such important considerations as size of the initial load, the sieve shaker speed, time of sieving, and the hardness, particle size distribution, and shape of the material being sieved have either been left to chance or substantially neglected. Such fundamental parameters as the type of particle size distribution and the magnitude of various statistical diameters on a weight or count basis have also not been applied to pharmaceutical granulations.

Since sieving is the easiest technique available for classifying particles in the size range of granular pharmaceutical solids, it finds wide industrial application. However, sieving errors can arise from a number of different variables. According to Herdan (1), the most predominant are variations in sieve loading, duration of sieving, random orientation of particles, fluctuation through sampling, errors of observation and experiment, and the effect of different equipment and operations. Consequently, if sieving is to be applied as an accurate, quantitative technique for classification, it is necessary to obtain more information as to the effect of the parameters previously enumerated on both the sieving process and the particle size distributions obtained.

Whitby (2) has carried out an extensive study of the physical laws which govern the sieving of fine particles. It was shown that the sieving curve under nonsteady-state conditions can be divided into two distinctly different regions, with a transition region between. The sieving curve was obtained by plotting the cumulative per cent by weight passing the sieve against time on either log-log or log-probability paper. A typical example of the former case is shown in Fig. 1. Whitby found that the rate at which the material passes a sieve in region 1 is a constant closely following the relationship:

$$\%\text{ material passing} = at^b \qquad \text{(Eq. 1)}$$

where t is the sieving time, b is a constant very nearly equal to 1, and a is a sieving rate constant. Region 2 was found to follow the log-normal law. In this region all the particles much smaller-than-mesh size have already passed the sieve; consequently, the particles now passing the sieve are of a constant mesh size. For all practical purposes the sieve is considered to be at equilibrium at that time when the second linear portion (region 2) begins, since the slight positive slope of the line is due mostly to the attrition of larger-than-mesh size particles (Fig. 1).

The purpose of this report is to (*a*) present useful techniques and theories developed in other fields of study for the computation of various statistical diameters, (*b*) investigate the magnitude of particle size reduction which occurs on a vibrating sieve, (*c*) investigate the effects of load, shaker speed, and particle size distribution on the cumulative per cent of material passing a sieve, and (*d*) suggest a method for determining the sieving time for a nest of sieves.

EXPERIMENTAL

Preliminary Controls.—Brass screens[1] constructed to A.S.T.M. specifications were used in all cases. A Cenco-Meinzer[2] sieve shaker was employed with the speed setting at position 5, except for those studies concerned with the effect of varying the sieve

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[1] Fisher Scientific Co., New York, N. Y.
[2] Central Scientific Co., Chicago, Ill.

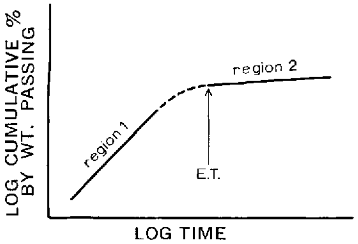

Fig. 1.—Typical plot of the cumulative per cent by weight of material passing a sieve as a function of time.

shaker speed. A nylon brush was used to clean the sieves. Each granulation batch was gently mixed prior to sampling by placing the granulation on a sheet of paper and lifting the corners in sequence toward the center of the sheet. The preparation and properties of all granules used have been described elsewhere (3).

Particle Size Reduction on a Single Sieve.—Granules prepared using a hand screen and an oscillating granulator were examined (3). No sieve cuts were used and the initial load for sieve analysis was 100 Gm. The cumulative per cent by weight passing a No. 16 sieve was plotted against time on log-probability paper over an extended shaking period.

Effect of Load and Shaker Speed on Granule Breakdown.—Granules produced from an oscillating granulator (3) were employed. A 16-mesh sieve was used and no sieve cuts were taken. The effect of varying the initial load was studied between the limits of 50 and 150 Gm. The effect of altering the speed setting was studied using a standard load of 100 Gm. and varying the speed between the limits of positions 2 and 8 on the shaker speed control.

Particle Size Reduction on a Nest of Sieves.—The effect of shaking time on the estimation of the geometric mean diameter on a weight basis, $\bar{M}$, was determined using 16, 20, 40, and 60 screens in a nest. An initial 100-Gm. load of granules prepared using the hand screen was used and no sieve cuts were taken. The particle size distributions obtained at various shaking time intervals were plotted on log-probability paper. The values for $\bar{M}$ were then plotted against time on log-log paper.

Influence of Particle Size on the Equilibrium Time of a Sieve.—This investigation was carried out using a No. 20 mesh sieve and a commercially prepared calcium sulfate base granulation.[3] Three systems of granulations were studied. System *1* consisted of 12/16 mesh particles together with various concentrations of 40/60 mesh particles over the range from 12.5–100% by weight. System *2* contained 12/16 mesh particles and 30/40 mesh particles in concentrations ranging from 25–100% by weight. System *3* was composed of 12/20 mesh particles plus various concentrations of 20/40 mesh particles ranging from 12.5–100% by weight. The equilibrium times were obtained, from log-log plots of the cumulative per cent passing the sieve as a function of time, as that time at which the second linear portion of the plot began. This is shown as E.T. in Fig. 1. (See also Fig. 6.)

Characterization of Particle Size Distribution.—Various statistics were computed from the distribution of particle sizes obtained using two techniques.

Standard Procedure.—The standard procedure consisted of sieving a 200-Gm. sample of the lactose granulation (3), prepared using the hand screen, for 10 min. on a nest composed of a No. 16, 20, 30, 40, 60, and 80 mesh sieve. The cumulative per cent less-than-stated size was plotted against stated size on log-probability paper.

Equilibrium Time Procedure.—The equilibrium time procedure was based upon a sequential analysis developed from the equilibrium time values of the individual sieves in the nest. This approach was necessary because the upper sieves in a nest will unload their smaller-than-mesh particles before those sieves near the bottom of the nest. Consequently, the equilibrium time for a sieve in a nest can only be computed when the smaller mesh screens are at nonsteady-state conditions. Therefore, the sieve immediately below the sieve whose equilibrium time was being determined was covered with a sheet of paper. The material collected after the upper sieve had come to equilibrium was then used as the sample for the previously covered sieve; the next lower sieve in the nest was covered in this case. The equilibrium times for the individual sieves, obtained from log-log plots of the cumulative per cent passing the sieve as a function of time, are presented in Table I.

On the basis of these results, the following procedure was used to obtain the particle size distribution of 200 Gm. of the lactose granulation (3). The same nest of sieves was employed but no sieves were covered. The No. 16 sieve was removed after 90 sec. of shaking and its contents weighed. It was then emptied and returned to the nest. After 150 sec. of shaking, the 20- and 30-mesh sieves were removed and their contents weighed. The screens were emptied and then returned to the nest. Finally, the last three screens were removed and weighed after a total of 200 sec. of shaking (this time was obtained by adding the individual equilibrium times together). Selection of the times for removal of the sieves is not highly critical, although the selected time must *not* be less than the computed equilibrium time for the sieve being removed.

RESULTS AND DISCUSSION

Particle Size Reduction on a Sieve.—The data from extended shaking time studies performed on particles from the oscillating granulator were found to follow the log-normal law as predicted by Whitby (2), for sieving times beyond the equilibrium time value previously defined. Figure 2 represents a plot of cumulative per cent passing *versus* time on log-probability paper. It is evident that a considerable number of particles are still passing the sieve after 140 min. of shaking. Since it is not likely that undersize particles would take this long to reach the classification area, it must be assumed that particle size reduction is occurring.

Table I.—Equilibrium Times for the Individual Sieves in a Nest[a]

Mesh size	16	20	30	40	60	80
Equilibrium time, sec.	45	30	25	20	36	44

[a] 200 Gm. of the lactose granulation prepared by the hand screen method (3) was used.

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[3] Miles Laboratories Elkhart, Ind.

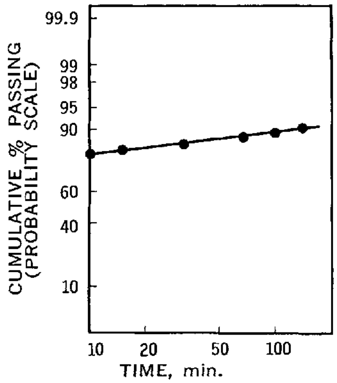

Fig. 2.—Log-probability plot of the rate of attrition of particles from the oscillating granulator. Load: 100 Gm.; speed setting: 5; sieve size: 16 mesh.

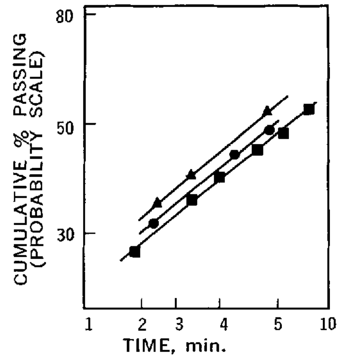

Fig. 3.—Effect of initial load upon the rate of attrition of particles from the oscillating granulator. Speed setting: 5; sieve size: 16 mesh. Key: ▲, 50 Gm.; ●, 100 Gm.; ■, 150 Gm.

Effect of Load on Granule Breakdown.—Figure 3 illustrates the results obtained for the three different initial loads studied. Since the curves for each initial load are virtually parallel, the attrition rate constant is apparently unaffected by the initial load over the range of values studied. However, it is evident from Fig. 3 that the cumulative per cent passed at any one time increases as the initial load decreases over the range of values studied. This means that the smaller loads have passed a greater percentage of their particles at equilibrium time than have the higher loads, *i.e.*, the smaller the load, the more efficient is the sieving process. This phenomenon is probably due to less "blinding" on the sieve and greater maneuverability of the particles at these smaller loads.

Effect of Shaker Speed on Granule Breakdown.—The results obtained from this portion of the study are plotted in Fig. 4. Since the actual vibration rates of the shaker at the various speed settings could not be determined, it was not possible to plot attrition rate as a function of vibration rate. Nevertheless, it is apparent from Fig. 4 that higher speeds of shaking may markedly influence the reduction in size of particles on a sieve.

Effect of Sieving Time on the Geometrical Mean Diameter by Weight.—Plots of the geometrical mean diameter by weight, $\bar{M}$, for particles from the oscillating granulator, at various sieving times are shown in Fig. 5. These data were obtained from studies on the particle size reduction on a nest of sieves.

It is apparent from Fig. 5 that much care must be exercised when selecting a sieving time, especially if the ultimate objective is to characterize the distribution of particle sizes. The mean particle size by weight obtained from sieve analysis will continually decrease as the sieving time increases. Similar data were obtained for particles prepared from the hand screen; however, the slopes of the two lines were different. Thus, the slope of the sieving curve for particles from the oscillating granulator was 0.096 μ/sec. and the slope for particles from the hand screen was 0.174 μ/sec. This implies that the particles prepared from the oscillating granulator are harder than those from the hand screen, a finding which is in agreement with the hardness index values determined for these granulations in earlier work (3).

Influence of Particle Size on the Equilibrium Time of a Sieve.—The effects of different proportions by weight of three sieve fractions of smaller-than-mesh size calcium sulfate granules on the equilibrium time of a 20-mesh sieve are shown in Fig. 6. Each point on the curve represents the mean of two equilibrium

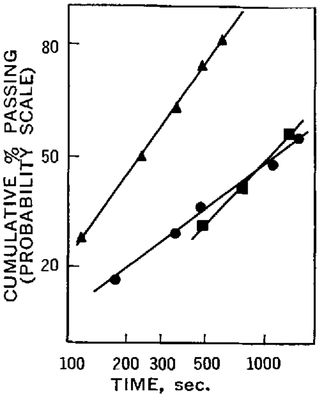

Fig. 4.—The effect of the speed setting of the sieve shaker upon the rate of attrition of particles from the oscillating granulator. Load: 100 Gm.; sieve size: 16 mesh. Key: ■, speed setting 2; ●, speed setting 5; ▲, speed setting 8.

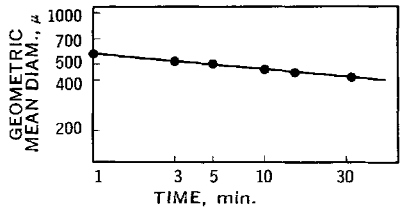

Fig. 5.—Plot of the geometric mean diameter by weight against sieving time for particles from the oscillating granulator. Load: 100 Gm.; speed setting: 5; sieve sizes: 16, 20, 40, and 60 mesh.

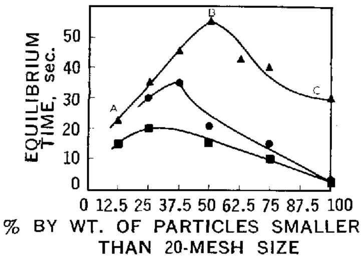

Fig. 6.—Effect of various particle size fractions upon the equilibrium time of a 20-mesh sieve using a commercial calcium sulfate granulation. Load: 200 Gm.; speed setting: 5. Key: ■, system *1* (12/16 and 40/60-mesh fractions); ●, system *2* (12/16 and 30/40-mesh fractions); ▲, system *3* (12/20 and 20/40-mesh fractions).

times. These were obtained graphically and, in most cases, were identical. System *3* was chosen because it contained many particles at, or near, mesh size.

From Fig. 6, it can be seen that the equilibrium times go through a maximum which is displaced to a lower percentage of smaller-than-mesh size particles as these smaller particles decrease in size. At the same time, the height of the peak decreases. In this particular study, all the variables were held constant with the exception of the per cent by weight of particles smaller-than-mesh size. The time taken for all the smaller-than-mesh size particles to pass the sieve is obviously a function of the number of these particles as well as the number of particles too large to pass which will hinder the passage of the smaller particles. Thus,

$$\text{E.T.} = f(n_u, n_0) \qquad \text{(Eq. 2)}$$

where E.T. is the equilibrium time in seconds, n_u is the number or weight of particles which can pass the screen, and n_0 is the number or weight of the greater-than-mesh size particles.

Increasing n_u while keeping n_0 constant would be expected to increase E.T. because of the increased number of particles which must now pass through the larger-than-mesh size particles and the sieve. On the other hand, holding n_u constant and decreasing n_0 would permit the smaller-than-mesh size particles to pass more rapidly through the sieve because the hindrance effect of the larger-than-mesh size particles is being progressively reduced.

In the system under discussion, we are increasing the weight concentration of the smaller-than-mesh size particles at the expense of the larger-than-mesh size particles, *i.e.*, n_u is increasing and n_0 is decreasing simultaneously. This reasoning may now be applied to the results shown in Fig. 6. Thus, it is postulated that over the region AB, the E.T. is increasing because the increase in n_u is of more significance than the decrease in n_0. However, at B, the effect of increasing n_u (tending to increase E.T.), and the effect of decreasing n_0 (tending to decrease E.T.), are equal and a maximum point is obtained. Over the region BC, the value for E.T. falls because the decreasing n_0 is now the controlling factor. We would expect, furthermore, the point at which the equilibrium time begins to decrease, after reaching the maximum B, to occur at lower concentrations of the smaller sized component, as the size of the latter decreases. This is because the hindrance of the smaller-than-mesh size particles by the larger particles decreases as the size of the former decrease. This is shown to occur in Fig. 6.

It is also evident from Fig. 6 that the maximum equilibrium time increases as the smaller-than-20-mesh particles increase in size. This is presumably due to the fact that the movement of the smaller sized particles through the void spaces in the granular bed becomes more difficult as the size of the smaller particle fraction increases. The large increase in equilibrium time for system *3* (12/20 mesh and 20/40 mesh particles), is most likely due to "blinding," since this system contained many particles at, or near, mesh size. Particles in this size range will reduce the effective open area of the sieve. Therefore, when selecting a sieving time, much thought should be given not only to the size of the smaller-than-mesh particles, but also to the *concentration* of such particles.

It is interesting to note the 100% point on the curves for the three systems shown in Fig. 6. At this point, there are no particles larger than mesh size present on the sieve. Therefore, an equilibrium time near zero is to be expected. This was not the case for system *3*, containing 20/40 mesh particles, where 6.7% of the granules by weight were still on the sieve after 15 min. of shaking. This phenomenon was checked by resieving the bulk sample of 20/40 mesh particles and running the determination again. The moisture content of the granules was checked before resieving and immediately following the 15 min. shaking period; it was constant at 1.6%. The same result was obtained, *i.e.*, approximately 7% by weight of the initial load of 200 Gm. did not pass. It is postulated that reduction in the

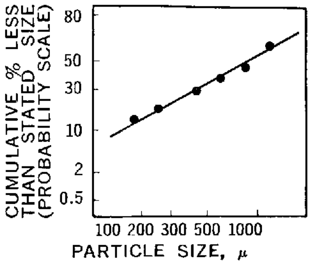

Fig. 7.—Plot of cumulative per cent less-than-stated size against stated size using the equilibrium time procedure for hand-granulated material. Load: 200 Gm.; speed setting: 5.

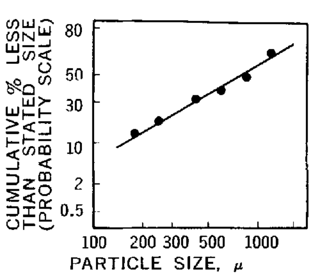

Fig. 8.—Plot of cumulative per cent less-than-stated size against stated size using a 10-min. sieving time for hand granulated material. Load: 200 Gm.; speed setting: 5.

Table II.—Statistical Parameters Calculated from Seiving Studies[a]

Parameter	Eq. Used (4)	Sieving Procedure	
		Std., 10 min.	Equilibrium Time
Geometric mean diam. by wt., $\bar{M}$	50% of stated size from plot on log-probability paper	840 μ	900 μ
Geometric S.D., σ_g	$\frac{84.13\% \text{ stated size}}{50\% \text{ stated size}}$ from plot on log-probability paper	3.67	4.12
Geometric mean diam. by count, d_g	$\log d_g = \log \bar{M} - 6.908 \log^2 \sigma_g$	5.13 μ	2.19 μ
Mean surface diam. by count, d_s	$\log d_s = \log \bar{M} - 4.605 \log^2 \sigma_g$	28.73 μ	16.29 μ
Mean vol. diam. by count, d_v	$\log d_v = \log \bar{M} - 3.454 \log^2 \sigma_g$	66.81 μ	44.40 μ
Arithmetic mean diam. by count, d_{av}	$\log d_{av} = \log \bar{M} - 5.757 \log^2 \sigma_g$	12.36 μ	5.97 μ
No. of particles/Gm., N	$\log N = \log \frac{1}{\rho \alpha_v} - \log d_g^3 - 10.362 \log^2 \sigma_g$	1.369×10^7	4.661×10^8

[a] 200 Gm. of the lactose granulation prepared by the hand screen method was used.

effective open sieve area, due to the large number of near-mesh-size particles present, was probably the major cause of this unexpected result.

Comparison of Various Statistical Diameters.—Using the standard and equilibrium time procedures for sieve analysis, it was possible to make a comparison of various statistical diameters. These were computed from the respective plots of size distribution by weight on log-probability paper shown in Figs. 7 and 8. In both cases, the distributions closely follow the log-normal law. Table II summarizes the results obtained from Figs. 7 and 8.

Owing to the increased duration of sieving, it was expected that those statistical diameters obtained by sieving for 10 min. would be smaller than those using the equilibrium time procedure. However, this was only true for the diameter calculated on a weight basis, $\bar{M}$. The expected order of statistical diameters by count was reversed because of the high value for σ_g in the equilibrium time analysis. (See Table II.) From this portion of the study, it can be concluded that although diameters on a weight basis will always decrease with increasing sieving times, those calculated diameters by count cannot always be assumed to decrease with increasing sieving times. In actuality, these parameters do decrease, but the computed values are arrived at from a consideration of the entire range of particle sizes. Since sampling of particle sizes was possible only over a finite range, the error in σ_g arising from lack of data at the very small sizes was probably responsible for the results shown in Table II.

Particle size reduction has been shown to occur when sieving is continued well beyond the equilibrium time, and this probably accounts for the widely varying values of $\bar{M}$ and σ_g shown in Table II. Therefore, to lessen the error introduced by particle breakdown, the equilibrium time procedure is suggested for the characterization of size distribution of pharmaceutical granular solids. Such an approach automatically takes account of the variable equilibrium times observed for the separate sieves. (See Table I.)

CONCLUSIONS

Basic studies on the sieving mechanism were carried out. It was found that particle size reduction occurred during sieving and was markedly influenced by the sieve shaker speed setting. The rate of particle size reduction was apparently independent of the initial load; however, the efficiency of the sieving operation is influenced by the initial load, as evidenced by Fig. 3. The equilibrium time of a sieve was found to be markedly dependent on the particle size of the sample used. This was particularly so when the size of the particles approach the mesh size of the sieve. Also shorter equilibrium times were observed when the concentration of smaller-than-mesh size particles was either fairly high or low in comparison to the greater-than-mesh size particles. At intermediate concentrations of the smaller-than-mesh particles, the equilibrium times can be expected to increase.

Comparative studies, using two different techniques to obtain particle size distribution curves, showed that the computed statistical diameters were influenced by the time of sieving. It is recommended that the equilibrium time procedure be used for the characterization of granular pharmaceutical solids by sieving. This in turn must entail prior knowledge of the equilibrium times of each individual sieve since, as is seen in Table I, these vary with screen mesh size. Only by the use of the equilibrium time method can the operator be confident that particle breakdown has been kept to a minimum and that equilibrium conditions on each sieve in the nest have been attained.

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