

Influence of Granulation Liquid Flow Rate on Particle-Size Distribution in Spray-Granulated Products

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Abstract □ Granulations were made at various air speeds and various rates of addition of granulating liquid in a spray-granulating assembly. The ensuing particle sizes were log-normal, and the data substantiate that the process is of the nature previously described. The mean diameter obtained was approximately proportional to the liquid flow rate squared but was independent of air rate. The standard deviation was independent of both parameters.

Keyphrases □ Granulations, spray—effect of liquid flow rate on particle-size distribution □ Particle-size distribution—spray granulations, effect of liquid flow rate □ Flow rate, liquid—effect on particle-size distribution in spray granulations □ Dosage forms—spray granulations, effect of liquid flow rate on particle-size distribution

The advantage of producing tablets from wet granulations was demonstrated previously (1, 2). Wet granulations are traditionally batch processes (3), although some products are successfully produced by continuous processes (3–7). In general, batch processes lend themselves to better process control than do continuous processes, but this is not the case with wet granulations. The kneading action present in sigma-type mixers (and to some extent in V-type blenders) necessitates close time control, since overkneading produces granules that are denser (less porous) than optimum (8, 9). Granulations formed in a fluid-bed drier (4, 7, 10–12) are not subject to the kneading action, and dried granules are not particularly affected by attrition (13). Therefore, aside from the economic aspects of fluid-bed drying (whether batch or continuous), this process seems to be of great advantage.

Zoglio *et al.* (13) described the dynamics of the fluid-bed drier. The particle-size distributions obtained by wet granulation and subsequent milling also were described (14, 15). Some descriptions were published of distributions from a continuous drier (4, 7). Dimensional and air kinetic parameter effects on several qualities of the spray-granulated product were discussed (16, 17). The purpose of this study was to explain the phenomena leading to experimental particle distributions (18, 19) obtained in a batch fluid-bed granulator.

EXPERIMENTAL

Granulations were made of the following composition: 17.5% sucrose, 69.9% lactose USP, 12.2% starch USP, and 0.4% pregelatinized starch. The powders (500 g) were placed in the basket of a spray granulator¹ and mixed for 5 min by air flow. The granulating liquid (water) was added at various rates, and addition was continued for 5 min. The granulated material was then dried for 8 min.

The temperature of the inlet air was 70° and the temperature of the outlet air was 36–44° for the first 6 min of drying. Drying was continued for 8 min, and the outlet temperature at that point was 44–46°. The moisture content of the granulations was determined by Karl Fischer moisture test and was 6–8% at that point.

Sieve analysis of the granulations was performed, and the percent undersize was calculated. Several samples were discontinued after 2, 4, and 6 min of drying; their particle size was determined and did not differ from that at 8 min (Table I).

The water pressure and the nozzle setting can be changed to give different granulation liquid flow rates; three such flow rates were employed at an air velocity close to the minimum fluidization velocity (48 ft³/min) and close to the entrainment velocity (58 ft³/min).

Hardness of granules was tested as described previously (8, 9).

RESULTS AND DISCUSSION

An experiment was run in which the material was wet granulated and the semiwet granulation was dried by a method comparable to that of Bhutani and Bhatia (20). The material was in the first falling rate period, showing that an essential part of the drying (as expected) already was accomplished (3, 9).

Because the dilution of the binder solution has some effect when solutions are added (10–12, 21, 22), it was decided to add water to a mixture containing the binders (sucrose and pregelatinized starch) in the dry powder blend.

Since wrong conclusions could be drawn if the particle-size distributions were to change during the drying step, *i.e.*, after the water addition is complete, this point was checked by stopping the process after 2, 4, 6, and 8 min of drying. The results shown in Table I indicate that the particle-size distribution does not change during the drying step. The hardness (of a 14-mesh fraction) of granules made at a liquid flow rate of 23 ml/min after 2 min of drying was 80 ± 40 g/mg and increased to a plateau level of 230 ± 80 g/mg after 4, 6, and 8 min.

Figures 1 and 2 show the particle-size distributions achieved at the various granulation liquid flow rates at the two different fluidization air rates. All distributions can be characterized as being log-normal. The least-squares fit parameters are shown in Table II; the ordinate in this case is the normal standard deviate (t) corresponding to the cumulative percent over the diameter, and the abscissa (x) is the log of the diameter in micrometers.

The mean diameter, as expected, increased with increasing fluid addition rate; since the liquid was added over a certain time (5 min), a higher fluid rate essentially implies a larger total addition of water. Furthermore, although larger amounts of granulating liquid increased the diameter, the standard deviation of the population (the slopes of the plots in Figs. 1 and 2) remained the same regardless of liquid and air velocities.

These distributions may be explained by the model proposed by Irani and Callis (18); the growth is assumed to be such that the particle size, M , starts as a minimum close to zero, M_0 , and grows to a maximum, M_∞ . At the end of the process, any agglomerate is characterized by the fact that it has been exposed to growth for a length of time, t , at a unit spray rate, R . There is an average time of growth, \bar{t} , and the times are normally distributed around this average; defining the time:

$$\tau = t - \bar{t} \quad (\text{Eq. 1})$$

allows expression of time by:

$$f(\tau) = (1/\sqrt{2\pi}) \exp(-\tau^2/2) \quad (\text{Eq. 2})$$

where f is the Gaussian frequency function, with unit variance (see Appendix).

The conditions of growth are such that (see Appendix):

$$dM/dt = \Phi(M) = M/b \quad (\text{Eq. 3})$$

or:

$$t = a + b \ln(M/\bar{M}) \quad (\text{Eq. 4})$$

Equations 4 and 1 may be combined to read:

$$\tau = b \ln(M/\bar{M}) \quad (\text{Eq. 5})$$

¹ Aeromatic spray granulator model STREA-1, Aeromatic AG, Farnsburgerstrasse 6, CH-4132 Muttenz, Switzerland.

Table I—Sieve Analysis of a Granulation at 23 ml/min of Liquid Addition as a Function of Drying Time

Minutes	Percent on Mesh						Pan
	14	20	40	60	80	100	
2	4	15	49	27	4	1	0
4	5	14	48	27	5	1	0
6	4	14	49	28	4	1	0
8	3	14	50	28	4	1	0

where the condition that $\tau = 0$ when $M = \bar{M}$ dictates that:

$$\bar{t} = a \quad (\text{Eq. 6})$$

Inserting Eq. 5 into Eq. 2 then yields:

$$f[b \ln (M/\bar{M})] = (1/\sqrt{2\pi}) \exp\{-[b \ln (M/\bar{M})]^2/2\} \quad (\text{Eq. 7})$$

which shows² that $b(\ln M - \ln \bar{M})$ is normally distributed with mean zero and unit standard deviation; i.e., $\ln M - \ln \bar{M}$ is normally distributed with mean zero and a standard deviation of $\ln \sigma = 1/b$ or $\ln M$ is normally distributed with mean $\ln \bar{M}$ and a standard deviation of $\ln \sigma = 1/b$.

From the development of Eq. 1, increasing the spray rate, R , increases the time elements t and \bar{t} by an (added) constant but leaves τ unaltered. This result is compatible with the fact that b (e.g., in Eqs. 3-5) is a constant. Hence, the standard deviation of the distributions should be independent of the spray rate; examination of Table II shows this to be the case.

The value of \bar{M} must increase with increasing R , and M and \bar{M} must increase in the same fashion (so that M/\bar{M} is rate independent); otherwise, $t - a$ could not remain constant as described. The only way this can be accomplished is by M (and \bar{M}) being proportional to R or to a power of R , i.e.:

$$\ln \bar{M} = q(\ln R) + p \quad (\text{Eq. 8})$$

The data are plotted in this fashion in Fig. 3; the exponent is close to 2 ($2.221 = q$). The correlation is good ($r = 0.96$). Therefore, the spray granulation follows Irani-Callis kinetics in producing log-normal particle distributions, the standard deviation is spray rate independent, and the mean particle diameter is approximately proportional to the square of the spray rate. The mean diameter is not a function of the fluidization air rate (since both sets of data fit the same line).

Some stochastic models are attractive at first sight; their development and the reasons for their rejection are shown in the Appendix. This de-

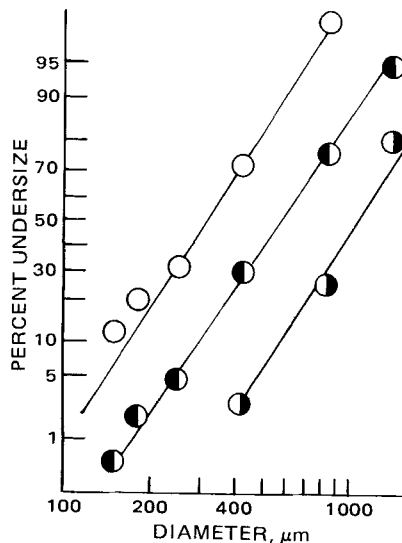


Figure 1—Particle-size distributions (cumulative undersize) of granulations made at low fluidization air rate. Liquid flow rates are: ○, 23 ml/min; ●, 26 ml/min; and ◐, 30 ml/min. Least-squares parameters are shown in Table II.

Table II—Least-Squares Fit Parameters of t^a versus $\ln d$ for Six Granulations

Air Flow	Liquid Flow, ml/min	Slope	Intercept	Mean, μm
Low	23	-1.98 ± 0.02	12.52 ± 0.02	557
Low	26	-2.01 ± 0.02	13.22 ± 0.03	718
Low	30	-1.99 ± 0.02	13.24 ± 0.02	775
High	20	-1.90 ± 0.04	10.82 ± 0.06	297
High	26	-1.86 ± 0.10	11.81 ± 0.08	634
High	33	-2.60 ± 0.10	18.02 ± 0.02	1023

^a Normal standard deviate.

velopment implies the necessity of employing a kinetic rather than a stochastic model.

APPENDIX

Distribution of Time of Exposure—To show that the times of exposure of particles to liquid, t , are normally distributed, consider the situation where N particles are exposed to a flow of liquid.

In a time element, δt , a fraction, f , of the solid mass will be wetted and there will be $N(1 - f)$ unwetted particles and Nf wetted particles. After $2\delta t$, there will be $N(1 - f)^2$ unwetted particles and Nf^2 particles that have been wetted twice (i.e., a fraction, f , of the Nf once wetted particles will be wetted again). The amount of once wetted particles will be the original Nf less the Nf^2 that became wetted twice plus the $N(1 - f)f$ particles that were wetted during the second (but not the first) interval. The total is:

$$Nf - Nf^2 + N(1 - f)f = 2N(1 - f)f \quad (\text{Eq. A1})$$

A combination of this argument will show that after $n\delta t$ the number of particles that have received i application of liquid will be:

$$N_i = \binom{n}{i} f^i (1 - f)^{n-i} N \quad (\text{Eq. A2})$$

Equation A2 is obviously a binomial distribution which, for large n , approaches a normal distribution. The "number of applications" in the discrete sense, δt , is equivalent to the time, t , of exposure on a continuous sense so that the time of exposure is normally distributed.

Growth Rate of Agglomerate—The growth rate of an agglomerate is related to its size, M , in the sense that the larger it is the higher the collisional cross-section, i.e., the higher the probability of growth. If one assumes that:

$$dM/dt = (1/b)M \quad (\text{Eq. A3})$$

then:

$$\ln M = (1/b)(t - \bar{t}) + q \quad (\text{Eq. A4})$$

where $(1/b)$ is a constant and $q = (\bar{t}/b)$ is an integration constant.

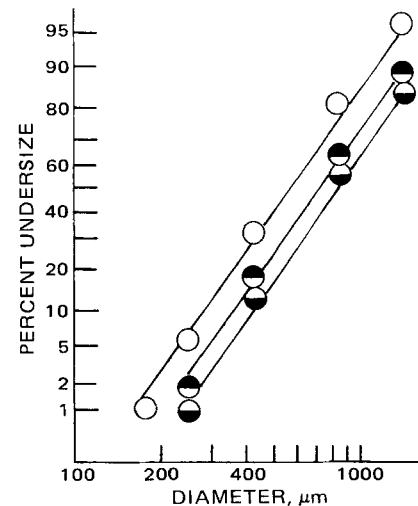


Figure 2—Particle-size distributions (cumulative undersize) of granulations made at high fluidization air rate. Liquid flow rates are: ○, 20 ml/min; ●, 26 ml/min; and ◐, 33 ml/min.

² If d is normally distributed with standard deviation σ' and mean x , then $(d - x)$ is normally distributed with standard deviation σ' and mean zero and $b(d - x)$ is normally distributed with standard deviation $b\sigma'$ and mean zero. In the above, $d = \ln M$ and $x = \ln \bar{M}$, so $b\sigma' = 1$; i.e., $\sigma' = 1/b$. Traditionally, the standard deviation for a log-normal distribution is denoted $\sigma' = \ln \sigma$; i.e., $\ln \sigma = 1/b$.

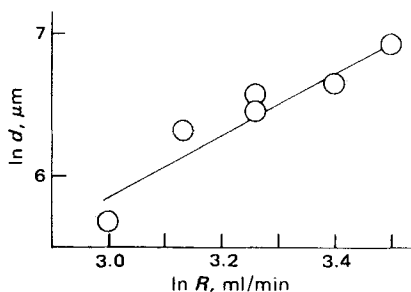


Figure 3—Plot of the mean diameters from Figs. 1 and 2 plotted versus the spray rate in log-log fashion. The least-squares fit equation is $\ln \bar{d} = 2.221 \ln R - 0.8$.

Agglomerates characterized by the average time exposure, \bar{t} , will have a size \bar{M} so that:

$$\ln \bar{M} = 0 + q \quad (\text{Eq. A5})$$

Inserting Eq. A5 into Eq. A4 gives:

$$\ln (\bar{M}/M_0) = (1/b)(t - \bar{t}) = \tau/b \quad (\text{Eq. A6})$$

which is equivalent to Eq. 5.

It is recalled that $t - \bar{t} = \tau$ is normally distributed with mean zero, so that as $t \rightarrow -\infty$, $\ln (\bar{M}/M_0) \rightarrow -\infty$, i.e., $\bar{M} \rightarrow 0$, which is compatible with the process. As $t \rightarrow \infty$, $\bar{M} \rightarrow \infty$; but, because of truncation, \bar{M} will reach a maximal size.

The limit sizes can be introduced formally by expressing Eq. A3 as $dM/dt = (1/b)(M - M_0)$ and imposing boundary conditions if desired.

Other Models—There are other hypothetically feasible models, but they fail to adhere to the experimental data. These models are all based on collision and "sticking" probabilities; the most encompassing of these is exemplified here. If it is assumed that there are ζ collisions per second and a sticking probability of ϵ , then the overall probability of forming a j -mer from a $(j - m)$ -mer and an m -mer at time t is:

$$Pr = \gamma C_{j-m}(t) C_m(t) \quad (\text{Eq. A7})$$

where $\gamma = \epsilon \zeta$ is the overall reaction probability.

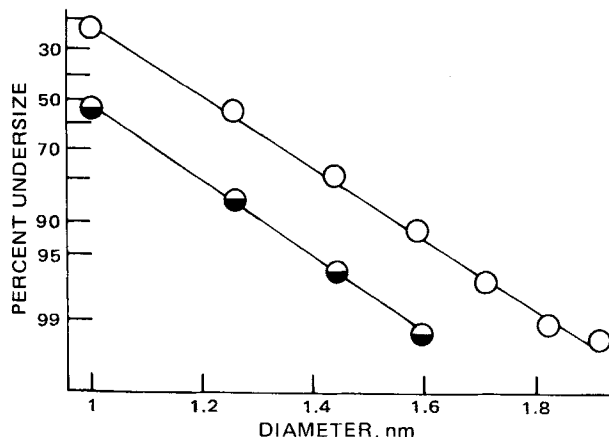


Figure 4—Distribution of sizes in a particle population initially consisting of 10,000 particles of the same size, calculated according to Eq. A8 with $\gamma = 0.3$ after $\delta t = 3$ (●) and $\delta t = 4$ (○) time intervals. The diameter is the cube root of the number of particles. Points are calculated, not experimental. Although $2^4 = 16$ -mers exist after time 4, only 7-mers and lower have significant concentrations.

If the largest particle is an l -mer, then j 's are formed by Eq. A7 in summation of all m 's smaller than j , and j -mers are lost in forming $(j + 1)$ -mers, $(j + 2)$ -mers, and so on up to and including l -mers; i.e., the j -mer population between time t and $t + \delta t$ increases by:

$$\delta C_j(t) = \sum_{m=1}^{j-1} \gamma C_{j-m}(t) C_m(t) - \sum_{q=1}^{l-j} \gamma C_j(t) C_q(t) \quad (\text{Eq. A8})$$

Simulated data by this model with a value of $\gamma = 0.3$ and an initial population of $N = 10,000$ particles after $\delta t = 3$ and $\delta t = 4$ are shown in Fig. 4; the distribution is normal (i.e., not log-normal). The failure of this model to adhere to the data probably lies in assuming that γ is independent of the size of j , q , m , and l . If the probability is a function of the size of the agglomerate, then the best approach is the kinetic one discussed in the body of the paper.

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