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RESEARCH PAPER

Scale-up Feasibility in High-Shear Mixers: Determination Through Statistical Procedures

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ABSTRACT

The wet granulation scale-up of a formulation exhibiting plastic deformation behavior under compression was examined. Through experimental factorial design, the effect of solution level, mixing time, and mixer speed on granulation properties was investigated. Measurements of mean particle size, tapped density, bulk density, Carr's index, coarse-to-fine ratio, cumulative percentage, and flow rate were taken and compared among granulations. In addition, comparisons were done on the hardness of tablets made from the formulations. It was shown that the characteristics of the granulations made under different conditions were highly reproducible. The excipient system of microcrystalline cellulose and pregel starch was shown to be a very robust formulation that is resistant to changes in the scaling-up process in high-shear mixers.

INTRODUCTION

The technological process of wet granulating is extensively used in the pharmaceutical industry. This process of size enlargement of powdered materials to granules provides better flow during tableting and encapsulating processes. Although the wet granulating process is extensively used, there is a lack of systemic research concerning the relationship between process variables and the granule properties on different size high-shear mixers.

The need for such information has surfaced in the pharmaceutical industry for several reasons. Industry favors using high-shear mixers over planetary mixers in production for their contained system, densifying action, mixing efficiency, and faster operation. Historically, in the initial stages of formulation development, drug availability is limited, and mortar and pestle or small-scale planetary mixers were used. High-shear mixers were designed originally for production needs, and small-scale models were not available. Therefore, when formulation needs increased and larger batches were produced, the transition from planetary to high-shear process resulted in

changes in the behavior and characteristics of the granulation and, ultimately, in the characteristics of tablets. In addition, with larger size batches, there is a factor of increased mixing efficiency. This is why scale-up is not normally a linear relationship. Now that smaller size high-shear mixers are commercially available, it is necessary to examine how to scale up from small-size mixers to large-size mixers.

The techniques of optimization in pharmaceutical dosage from design are well documented (1–4). Schwartz et al. (5,6) developed a technique by which a formulation with optimum properties could be obtained through computer-assisted data analysis. They used the result of statistically designed series of experiments, based on five independent variables, as input into a computer. Down et al. (7) used a desktop computer for product optimization. Their method offered rapid access and versatility to large-scale computing facilities, which frequently are not readily accessible. Sequential prediction analysis (8) has been suggested for optimizing multiple potency systems with invariant tablet weight. In another study (9), key variables in dosage form design were determined by employing two interrelated statistical techniques, correlation analysis and principal component analysis.

A wet granulation with the excipient system of microcrystalline cellulose and pregel starch was scaled down from the production-size mixer of 400-L to 25-L, 10-L, and 2-L mixers, and the granule properties affected by the process variables were examined through factorial design. The objective of this study was to determine the scale-up feasibility in different size high-shear mixers for a system that displays plastic deformation.

EXPERIMENTAL

The granulating equipment used were the 400-L, 25-L, and 10-L T. K. Fielder (Niro-Fielder, Maryland) and the 2-L Fukae (Fukae Powtec, Kobe, Japan) high-shear mixers. Both the Fielder and the Fukae mixers are similar in geometric arrangement and mixing action. Both use compressed air while n-dxing to eliminate the static powder area and fluidize powder, which improves mixing efficiency. Both have an impeller at the base of the bowl, which is responsible for the shearing and densifying action, and a side-mounted chopper that breaks apart large agglomerates. The chopper and the impeller of the Fielder can only be set at either high speed or low speed. Tip speed is equal to revolutions per minute times the circumference of the mixing bowl. The tip speeds at the high and low settings are the same for any Fielder mixer. The Fukae mixer has adjustable speeds for its impeller and chopper. The impeller speed of the Fukae was adjusted to match the same tip speeds of the Fielder speed settings. The same measures were taken for the chopper speed.

A 2^3 factorial design was used with each granulator independently. In this design, the main and interactive effects of the process variables on the formulation characteristics can be identified and analyzed. The independent variables (process variables) are shown in Table 1; in this study, we used granulation solution level, mixing time, and impeller tip speed. The design matrix involved 10 experiments that were run in random order (Table 1). The experimental ranges varied from -1 to $+1$ experimental units. Table 2 shows the factorial design matrix used in this study.

The physical units that correspond to the factorial units are shown in Table 3. For granulation solution level, the amount of solution used at 0 conditions was scaled down from the formulation used in production. For mixing time, conditions at -1 of 30 s were used in production. A mixing time of less than 30 s would be impractical; therefore, there are only two experimental units for mixing time. Because the Fielder mixers had only two speed settings, there were only two experimental units for tip speed. The conditions at 0 for solution level, -1 for mixing time and -1 for speed of mixer (0, 1, -1), were identical to conditions used in production for this formulation. Only experimental conditions represented by runs 9 and 10 were used for the 400-L mixer.

FIXED PARAMETERS/ASSUMPTIONS

Ratio of batch size to granulator volume was kept constant.

Table 1

Independent Variables

X_1	Granulation solution level
X_2	Mixing time
X_3	Impeller tip speed

Table 2

Factorial Design Matrix

Run No.	X_1	X_2	X_3
1	+1	+1	+1
2	+1	+1	−1
3	+1	−1	+1
4	+1	−1	−1
5	−1	+1	+1
6	−1	+1	−1
7	−1	−1	+1
8	−1	−1	−1
9	0	+1	−1
10	0	+1	−1

Table 3

Physical Unit Assignment to Experimental Unit

Factor	−1 e.u.	0	+1 e.u.
X_1, solution level, 1 e.u. = 25%			
2 L	97 ml	129 ml	161 ml
10 L	483 ml	644 ml	805 ml
25 L	1208 ml	1610 ml	2012 ml
X_2, mixing time	30 s	—	90 s
X_3, impeller tip speed	670 ft/min	—	8124 ft/min

Ratio of granulating solution to batch size was kept constant.

The amount of solution for any granulation was added over the same period (e.g., the rate of solution addition per granulation mass was constant).

All formulations were tray dried to the same loss on drying (LOD) and nulled (1B screen) using the same procedure.

Equal amounts from each granulation were lubricated in I quart V blender for 5 min.

The responses (dependent variables) that were measured are shown in Table 4. Average particle size was measured by sieve analysis, and the screen size combination used was 16, 35, 50, 100, 200, 325, base. Tablet hardness, tapped density, and bulk density were measured on standard equipment in the laboratory. The coarse-to-fine ratio was the ratio of material retained on the 100-mesh screen and above to the material that passed through the 100-mesh screen. Carr's index is defined as the tapped density minus the bulk density divided by the tapped density multiplied times 100. Flow rate was tested on the powder characteristic tester.

Table 4

Dependent Variables

Y_1	Average particle size (μ)
Y_2	Percentage of fine particles that passes through 100-mesh screen (%)
Y_3	Bulk density (gm/cc)
Y_4	Tapped density (gm/cc)
Y_5	Powder flow rate (gn/min)

Table 5

Formulation

	Percentage Composition Milligrams/Tablet	
Drug	5.0	10.00
Microcrystalline cellulose	47.35	94.7
Pregel starch	47.35	94.7
Magnesium stearate	0.30	0.6

Ratio of 95% ethanol: water was 1:45.

The formulation chosen for the study is shown in Table 5. The small percentage of drug in the formulations indicates that the behavior of the formulation will rely heavily on the behavior of the excipient system.

Before each experiment, the microcrystalline cellulose, pregel starch, and drug were dry mixed for 5 min with the impeller and chopper on low speed. Then, with only the impeller on low speed, the solution was added to the powder over a period of 2 min. The spraying action of the granulation solution available in production mixers was simulated in laboratory-scale mixers, which do not have this feature, using a pressure pot. After solution delivery, the material was mixed for the specified granulation time and then dried in a forced air dryer to an LOD of 4%. Each sample was milled with a 1B screen. To eliminate lubrication variation, 200 g of each batch was lubricated with 0.6 g of magnesium stearate for 5 min in a V blender. Tablets were compressed on the Carver Press (Carver, Inc., WI) at 2000, 3000, and 4000 pounds of applied force using 11/32-inch tooling.

RESULTS AND DISCUSSION

The experimental data are given in Table 6. The data from each granulator were fitted independently into a linear three-factor interaction mathematical model. This model describes the main effect of each factor and the interaction effects between factors on a measured response. The model has the following form:

$$y = \mu + a_1x_1 + a_2x_2 + a_3x_3 + a_{12}x_1x_2 + a_{13}x_1x_3 + a_{23}x_2x_3 + a_{123}x_1x_2x_3$$

where y is the measured response, μ is the overall mean average, and the coefficients a describe the change in response caused by change of process parameter and were estimated by least squares. This would allow us either to see the same relationship regardless of granulator size or to detect a scale-up effect.

In principle, the coefficients that have large magnitude relative to their standard errors indicate that the corresponding effect is important. Taking the response of average particle size as an example, it can be seen that, from the estimated coefficients given in Table 7 for average particle size for each granulator, no consistent conclusions can be drawn concerning the effect of the three process factors if their estimated least squares coefficients for the statistical model were compared to their standard errors. However, when the data for all three granu-

Table 6

Combined Data

Solvent X_1	Mixing, Time X_2	Mixing Speed X_3	Mixer Size X_4	Particle Size Before Milling	Bulk Density	Percentage Fines	Flow Rate
−1	−1	−1	2	347.63	0.406	61	200
−1	−1	1	2	217.17	0.440	64	227
−1	1	−1	2	331.00	0.454	63	221
−1	1	1	2	152.20	0.515	72	258
1	−1	−1	2	471.00	0.396	48	217
1	−1	1	2	380.36	0.456	51	225
1	1	−1	2	390.00	0.445	55	233
1	1	1	2	249.46	0.453	61	264
0	1	−1	2	415.00	0.420	52	199
0	1	−1	2	408.00	0.407	53	195
−1	−1	−1	10	407.00	0.448	64	196
−1	−1	1	10	225.00	0.476	65	247
−1	1	−1	10	462.00	0.406	52	198
−1	1	1	10	142.00	0.510	67	241
1	−1	−1	10	339.00	0.446	60	237
1	−1	1	10	384.00	0.422	54	219
1	1	−1	10	361.00	0.447	53	221
1	1	1	10	242.00	0.465	66	252
0	1	−1	10	421.00	0.401	54	199
0	1	−1	10	418.00	0.418	54	202
1	1	−1	25	449.30	0.425	68	210
1	1	1	25	237.11	0.454	66	238
1	1	1	25	444.00	0.436	55	219
1	1	1	25	163.53	0.505	73	273
1	1	1	25	366.00	0.458	66	229
1	1	1	25	395.05	0.445	55	229
1	1	1	25	370.98	0.449	57	243
1	1	1	25	256.00	0.476	68	303
0	1	−1	25	461.00	0.417	54	188
0	1	−1	25	469.00	0.420	54	185

Table 7

Coefficients for the Three Mixer Sizes: Particle Size Before Milling

Term	Coefficients, 2 L	SE, 2 L	Coefficients, 10 L	SE, 10 L	Coefficients, 25 L	SE, 25 L
Mean (μ)	336.18	21.76	340.10	22.99	361.20	30.38
Solvent (a_1)	55.35	24.33	11.25	25.70	11.76	33.97
Mixing time (a_2)	−36.69	24.33	−18.50	25.70	−26.62	33.97
Speed (a_3)	−67.56	24.33	−72.00	25.70	−72.32	33.97
Speed × Mixing time (a_{12})	−16.29	24.33	−11.50	25.70	−6.90	33.97
Solvent × Speed (a_{13})	9.76	24.33	53.50	25.70	50.84	33.97
Mixing time × Speed (a_{23})	−12.28	24.33	−37.75	25.70	−26.54	33.97

lators are plotted versus experimental settings as in Fig. 1 for the average particle size, the results follow the same general pattern, implying relatively consistent effects of the changes from one experimental combination to the next regardless of granulator size.

To confirm statistically the negligible granulator size effect, the data from all granulators were combined, and a coefficient for granulator size x_4 was added and fitted into the following model:

$$y(x_1, x_2, x_3, x_4) = \mu + a_1x_1 + a_2x_2 + a_3x_3 + a_4x_4 + a_{12}x_1x_2 + a_{13}x_1x_3 + a_{14}x_1x_4 + a_{23}x_2x_3 + a_{24}x_2x_4 + a_{34}x_3x_4$$

This demonstrated that the coefficients associated with granulator effects, a_4, a_{14}, a_{24}, and a_{34}, were not significant. Thus, it can be concluded that there was no granulator size effect.

Table 8 shows that several coefficients of the fitted model using the data from the three granulators are substantially larger than their standard errors. While the effect of granulating speed is again obvious as it was when the coefficients were estimated for each granulator size, now the effect of granulating time is also important. This can be seen in Fig. 1, in which the responses for each granulator size rise and fall together as the granulating time increases from −1 (short mixing time) to +1 (long mixing time).

From Table 8, it can be seen that there is a large coefficient for the granulating solution by granulating speed interaction. This effect can be seen in Fig. 2, in which there is little effect of reducing the granulating solution level if granulating speed is low regardless of granulator size. However, the effect of solution reduction at high speed is a significant decrease in average particle size.

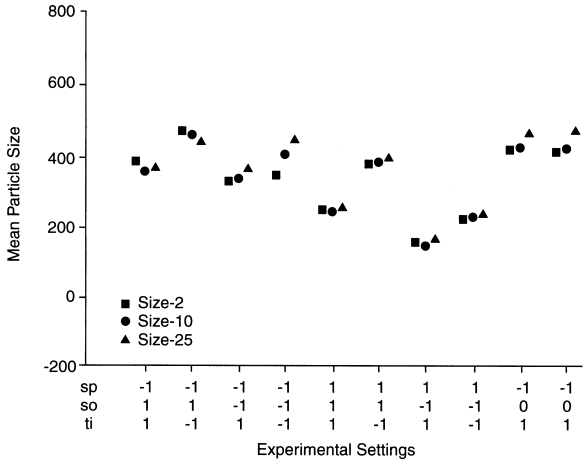

Figure 1. Average particle size before milling.

Table 8

Fitted Model Coefficients for Particle Size Before Milling

Term	Coefficient	SE	*T* Value	Significance
Mean	345.83	11.14		
Solvent	26.12	12.46		
Mixing time	−27.27	12.46		
Mixing speed	−70.63	12.46		
Solvent × Time	−11.56	12.46	−0.93	0.04
Solvent × *S*	38.03	12.46	3.05	0.01
Time × Speed	−25.52	12.46	−2.05	0.05

No. cases = 30; $R^2 = 0.7078$; RMS error = 61.02; residual $df = 23$; R^2 adjusted = 0.6316; Condition No. = I.

Figures 3–6 show contour plots of some interactive effects generated in this study.

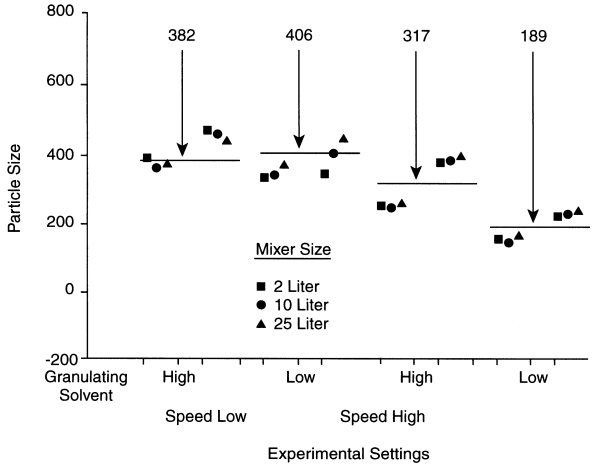

Figure 2. Particle size before milling.

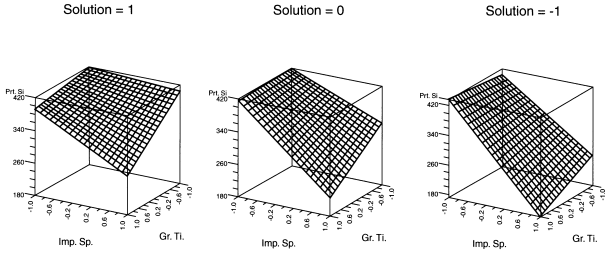

Figure 3. Average particle size: the effect of granulating time and impeller speed at three levels of granulating solvent.

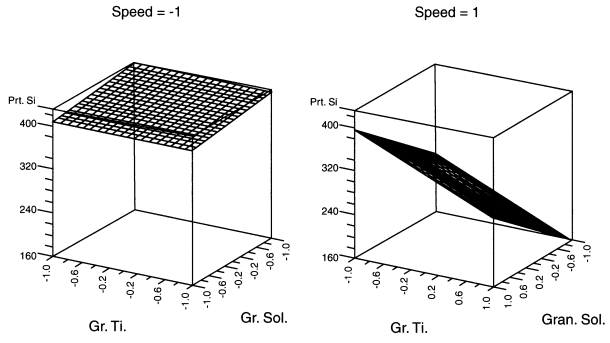

Figure 4. Average particle size: the effect of granulating time and solution at two levels of impeller speed.

CONCLUSIONS

Experimental Design

For the experimental design, it can be concluded that the experimental error can be substantially larger than the effect of a factor and thus obscure process factor effects if detection depends on the comparison of the magnitude of coefficients with their estimated standard errors. However, a close examination of the data will reveal consistent patterns of change in responses corresponding to the effect of the important factors.

Characterization Study

The individual and interactive process factors could be estimated using statistical factorial design. This will assist in controlling granulation characteristics and in process scale-up. For the particular formulation used in this evaluation, it can be concluded that there was no granulator size effect or granulator size by other process factor interaction. The results obtained in the small granulator can be generalized to larger granulators, as evidenced in Fig. 7.

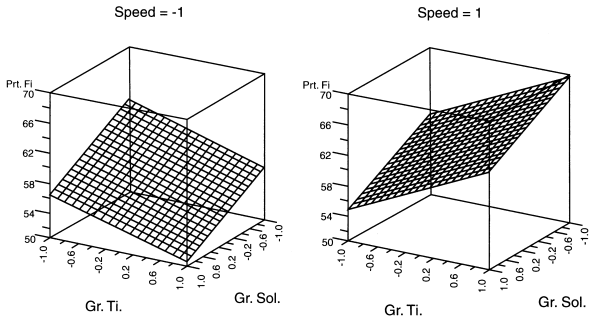

Figure 5. Proportion of fines: the effect of granulating time and solution at two levels of impeller speed.

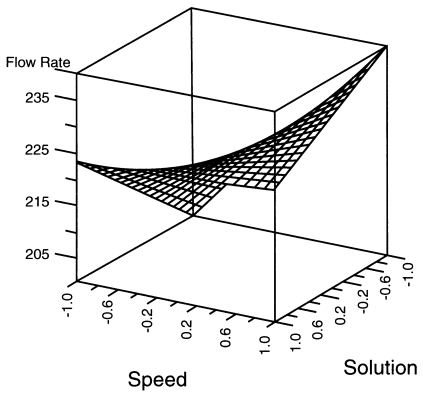

Figure 6. The effect of granulating solution and speed on flow rate (granulation time has insignificant effect).

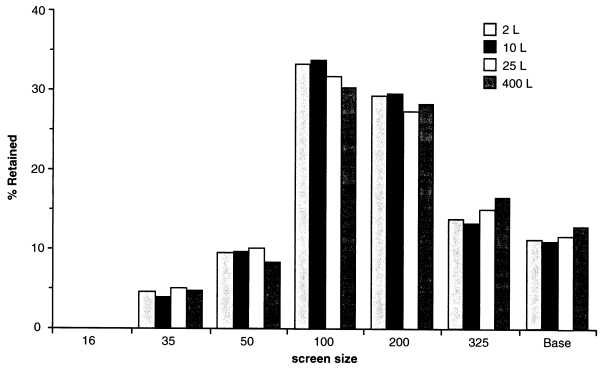

Figure 7. Mesh analysis comparison of granulations made in 2-L, 10-L, 25-L, and 400-L granulators using $x_1 = 0$, $x_2 = +1$, and $x_3 = -1$.

This study showed a significant impeller speed effect on granulation properties. Many large-size granulators are equipped only with two settings for speed control. The results of this study suggest that variable speed will result in better control of the granulating process.

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