Drug Development and Industrial Pharmacy, 23(2), 193-202 (1997)

RESEARCH PAPER

Prospective Validation of High-Shear Wet Granulation Process by Wet Granule Sieving Method. I. Selection and Characterization of Sieving Parameters for Wet Granules

Hisatoshi Emori,[1,]* Teruhisa Yoshizawa,[1]
Toshiaki Nishihata,[1] and Tadanori Mayumi[2]

[1]*Pharmacy Research, Upjohn Tsukuba Research Labs, Upjohn Pharmaceuticals Ltd., 23 Wadai, Tsukuba, Ibaraki 300-42, Japan*
[2]*Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565, Japan*

ABSTRACT

To characterize the progression of high-shear wet granulation for various drugs and formulations based on the particle size distribution of wet granules during granulation, a general sieving method for wet granules was investigated. Wet granulation was conducted in a 25-liter high-shear mixer using four model drugs with different solubilities and particle sizes (ethenzamide, unmilled and milled acetaminophen, and antipyrine). Because of its small size and efficient sifting mechanism, a sonic sifter was used to determine the wet granulation particle size distribution. From the good correlation of particle size distribution between wet granules and dry-sized granules, an intensity of 80% of full-scale amplitude and a sieving time of 3 min were selected as wet granule sieving parameters. This general sieving method showed good measurement precision as long as the determination was completed within 20 min after sampling. Further, the method was independent of sampling position within the mixer chamber.

*To whom correspondence should be addressed.

INTRODUCTION

A wet granulation method with a high-shear mixer is widely used to produce granules for tablets in the pharmaceutical industry. The primary purposes of wet granulation are to improve the properties of powders, i.e., material handling, flowability, dissolution, and compression characteristics (1). Because the wet granulation process is known to influence final tablet characteristics, such as content uniformity, dissolution rate, disintegration time, hardness, and friability (2), this process is often defined as a critical process for the final tablet characteristics. The end point determination method in this process influences the tablet performance.

The wet granulation process, especially granulation end point, is often controlled by subjective operator evaluation, by power consumption of the mixer motor (3–12), or by torque of the mixer shaft (13–19). However, the operator evaluation technique has the inherent intra- and interoperator variability. The power consumption and torque techniques are dependent on formulation, process, and equipment variables. Thus, these techniques are not always adequate during formulation development and scale-up, while they are very convenient methods to determine granulation end point in production site.

The method that directly characterizes the progression of wet granulation by monitoring the wet granule particle size distribution (wet granule sieving method; WGSM) has been briefly developed for a proprietary formulation containing over 70% insoluble micronized drug in the granulation phase, in order to control the granulation process and to determine the end point (20,21). The in-process method is available on the spot, simple, fast, independent of operator evaluation, and requires a small sample amount. A sonic sifter has been employed as wet granule particle sizing equipment because of its small size and efficient sifting mechanism. Since this method is also independent of mixer design and scale, it is very useful during scale-up. A correlation between the amount of wet granules larger than 2 mm and the degree of homogeneity of liquid distribution was reported by Holm et al. (22). However, they did not focus this work on a granulation end point method.

If the WGSM can be shown to be applicable to other drugs and formulations, it will provide very useful information on in-process parameters in the high shear wet granulation process. Also, the wet granule particle size distribution should be determined by a characterized sieving method, since it is expected that the WGSM is capable of validating the wet granulation process prospectively. A general sieving method to determine the wet granule particle size distributions of various drug formulations was selected and then characterized in the present study (Part I).

Four model drugs with different solubilities and particle sizes were used, and formulations containing high percentages of active ingredients in the granulation portions were employed so that the drug properties were well reflected in the wet granulation. The following experiments were carried out:

1. First experiment to select sieving parameters (sieving time and intensity) for wet granules
2. Second experiment to determine the measurement precision for wet granule sieving using the selected parameters and the effect of granule standing time (time between sampling and analysis)
3. Third experiment to determine the effect of sampling position of wet granules within the high-shear mixer bowl

MATERIALS

Ethenzamide (low solubility), acetaminophen (medium solubility), and antipyrine (high solubility) were used. Further, two bulk drug lots with different particle sizes were used for acetaminophen, i.e., unmilled (acetaminophen) and milled (acetaminophen-milled) lots. Mean particle sizes were 1.1 μm for ethenzamide, 192.7 μm for acetaminophen, 36.1 μm for acetaminophen-milled, and 251.8 μm for antipyrine. Ethenzamide, acetaminophen, and acetaminophen-milled were of JP grade and purchased from Yoshitomi Pharmaceutical Co., Ltd. (Osaka, Japan); antipyrine JP was from Yashiro Pharmaceutical Co., Ltd. (Osaka, Japan). Lactose JP (DMV 200M; DMV Japan, Tokyo, Japan) and hydroxypropyl cellulose JP (HPC-LE-P; Shin-Etsu Chemical Co., Tokyo, Japan) were obtained commercially. Cornstarch (Cornstarch W; Nihon Shokuhin Kakou Co., Ltd., Tokyo, Japan) was of food grade.

METHODS

Wet Granulation

Wet granulation was conducted in a 25-liter high-shear mixer (Model FM-VG-25; Powrex Co., Osaka, Japan) using the core formulation shown in Table 1. Powders were weighed and added to the bowl of the

Table 1

Formulation Composition for Wet Granulation

Component	Amount per Batch (g)
Drug	3000
Cornstarch	252
Lactose	588
Hydroxypropyl cellulose	120
Total	3960

high-shear mixer. After premixing the powders for 1 min, purified water was added to the powders using a peristaltic pump and a spray nozzle while both main (250 rpm) and chopper (3000 rpm) blades were activated. The powders were then mixed for a suitable time. Further, the powders were kneaded longer or additional purified water was added and mixed for an additional time. The scheme of water addition and mixing was repeated several times. In each experiment, one batch per drug was wet granulated.

Wet Granule Particle Size Analysis

A sonic sifter (Model Gilsonic AutoSiever GA-1; Gilson Company, Inc., Ohio, USA) was used as the wet granule particle sizing equipment. A wide range (106 to 1700 μm) of screens were selected to cover wet granulations of various drugs—i.e., 7 screens (1700, 850, 425, 250, 180, 150, and 106 μm)—and a latex fines collector to serve as a conventional pan screen. It was found through experience that routinely, wet granule samples contain a few unrepresentative lumps which presumably are granule agglomerates formed by aggregating, and the large agglomerates cause variances in the wet granule particle size determination. Thus, a presieving step was employed before the sieving step. A 2000-μm screen was used for presieving because it was observed in a preliminary study that most of the granules except lumps passed through the screen easily. At several time points during the granulation process, wet granules were sampled from the high-shear mixer chamber. The cumulative amount of water added and the cumulative mixing time at each sampling time point in the first experiment are listed in Table 2. In the first and second experiments, about 30 g of wet granules were taken from the middle granulation bed of position B within the high-shear mixer bowl (diagramed in Fig. 1). In the third experiment, about 5 g of wet granules were individually sampled from the middle granulation bed of positions A, B, and C (positions AM, BM, and CM, respectively) for ethenzamide and acetaminophen; and

Table 2

Amount of Water Added and Mixing Time for Wet Granulation

Drug	Sampling Time Point	Cumulative Water Amount (%)[a]	Cumulative Mixing Time (min)
Ethenzamide	1st	15.0	8.8
	2nd	17.1	11.0
	3rd	18.2	12.7
	4th	19.3	14.3
	5th	19.3	15.3
Acetaminophen	1st	8.0	4.0
	2nd	9.1	5.4
	3rd	10.2	6.8
	4th	12.4	11.0
Acetaminophen-milled	1st	10.0	6.5
	2nd	12.1	8.7
	3rd	14.3	10.8
	4th	16.6	13.1
Antipyrine	1st	5.0	3.8
	2nd	5.0	6.8
	3rd	6.1	9.3
	4th	8.4	13.4

[a]Based on the total solid weight in the wet granulation.

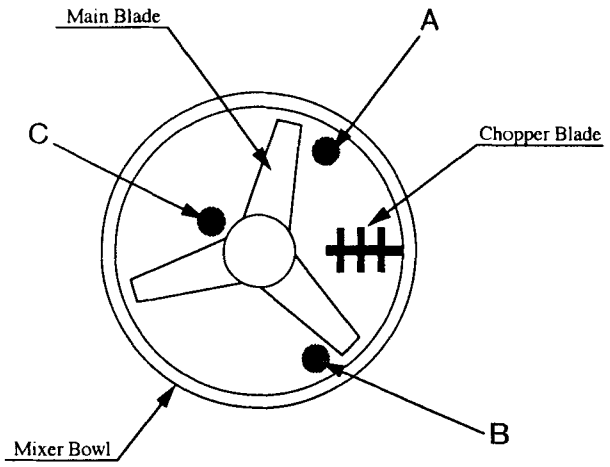

Figure 1. Sampling positions of wet granules within high-shear mixer bowl.

from the upper, middle, and lower beds of position B (positions BU, BM, and BL, respectively) for acetaminophen-milled and antipyrine. The wet granule sample was placed in a sealed container immediately after sampling.

Three grams of wet granules were placed on the top of a nest screens (2000-μm screen, 7 screens, and latex fines collector), and passed through the 2000-μm screen mildly and quickly by loosening the granule agglomerates with a spatula. The 2000-μm screen was replaced with the top screen holder and the assembly's diaphragm, and the whole assembly immediately placed in the sifter unit. The sieving test was then run. In the first experiment the sieving parameters were selected; i.e., sieving times of 0.5, 1, and 3 min and intensities of 20%, 40%, and 80% of full-scale amplitude were compared. For the other two experiments, the selected sieving time and intensity were used. Bottom and side tapping, 0.2-min ramp-up time, and 0.2-min ramp-down time were employed for all experiments.

For each granule sample in the first experiment, nine measurements at different sieving conditions were completed within 60 min after sampling. To determine the measurement precision, the particle size distribution was measured in triplicate within 20 min after sampling. An additional determination was conducted 60 min after sampling in order to investigate the granule standing time effect. Three granule samples taken from different positions at each time point were also measured within 20 min after sampling.

Drying

In the first experiment, about 100 g of wet granules were additionally sampled at the same time points for the wet granule particle size determination. The wet granules were immediately dried in a fluid-bed dryer (Model Pulvis Mini-Bed GA22; Yamato Scientific Co., Ltd., Tokyo, Japan) using an inlet temperature of 80°C. Drying proceeded until a product temperature of 45°C was reached. Loss on drying (LOD) of the dry granules was measured using an infrared moisture meter (Model Kett FD-220; Kett Kagaku, Tokyo, Japan) at 80°C. All LOD results were less than 3%. Dry granules were then hand-screened through a 2000-μm screen.

Dry-Sized Granule Particle Size Analysis

The particle size distribution of dry-sized granules was determined using the same method as the wet granule particle size analysis except that only 50% of full-scale amplitude was used for the sieving intensity. This sieving condition was selected in a preliminary study from the result that there was no difference in the particle size distribution of dry-sized granules among the sieving intensities of 20%, 50%, and 80% of full-scale amplitude.

RESULTS AND DISCUSSION

Selection of Sieving Parameters for Wet Granules

The extent of wet granulation is defined practically on the basis of characteristics of the dry or dry-sized granules. For selection of sieving conditions (sieving time and intensity of a sonic sifter), the particle size distribution of wet granules was compared with that of dry-sized granules. In all cases, the wet granules were larger than the dry-sized granules, due to breaking down of granule agglomerate and/or granule itself in the fluid-bed dryer and during the dry-sizing process. Since it has been reported that the wet granulation progression involves a decrease in small particle size fraction and an increase in large particle size fraction (1), the correlation between the wet and dry-sized granules was determined for the increasing fraction (up-fraction) and decreasing fraction (down-fraction), instead of comparing wet and dry-sized granules for each individual particle size fraction.

Figure 2(a) shows the changes in individual dry-sized granule particle size fractions of ethenzamide with the

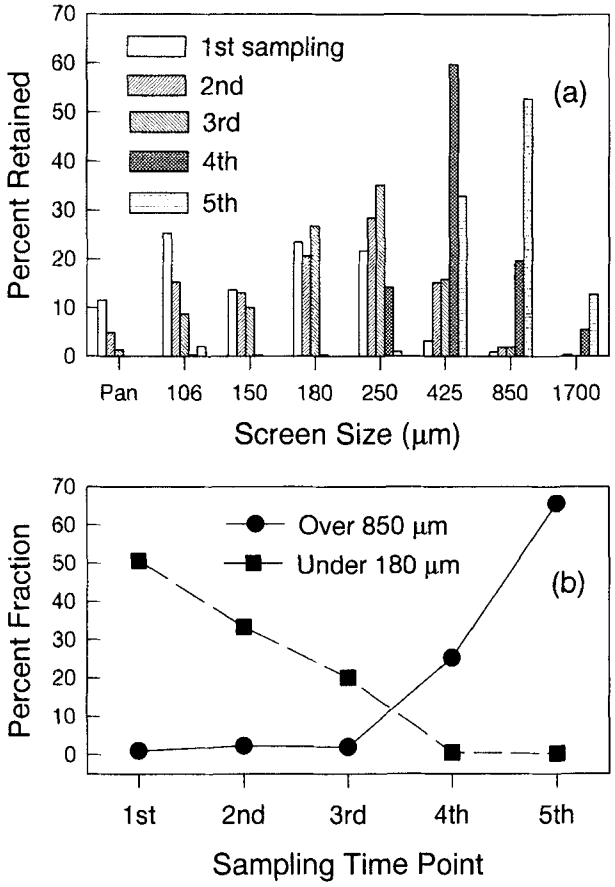

Figure 2. Changes in particle size distributions of dry-sized granules of ethenzamide with wet granulation progression: (a) changes in individual particle size fractions; (b) changes in up-fraction and down-fraction.

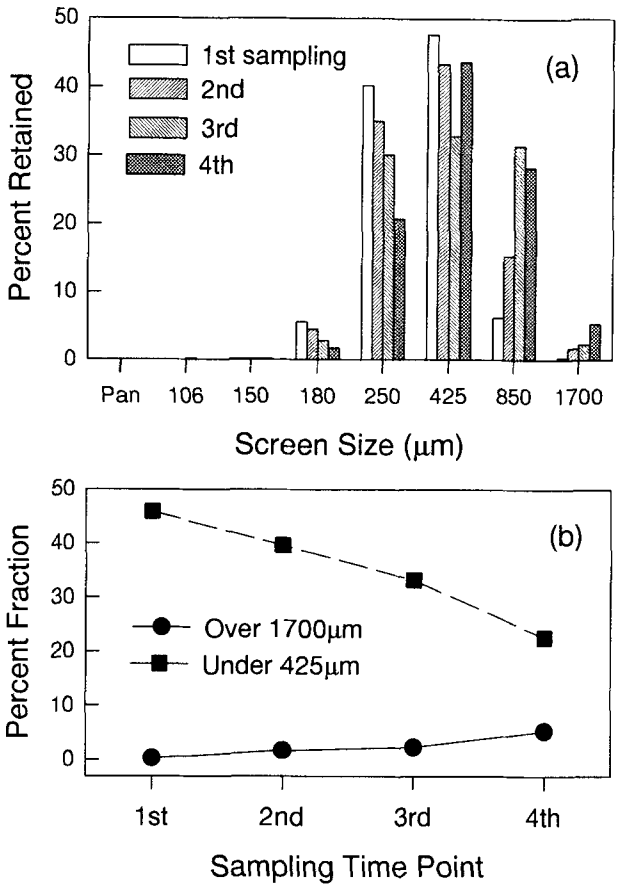

Figure 3. Changes in particle size distributions of dry-sized granules of acetaminophen with wet granulation progression: (a) changes in individual particle size fractions; (b) changes in up-fraction and down-fraction.

wet granulation progression. Fractions larger than 850 μm increased and fractions smaller than 180 μm decreased continuously as the sampling time point of wet granules went. Therefore, fractions over 850 μm and under 180 μm were defined as up-fraction and down-fraction for the ethenzamide formulation, respectively. Changes in the up-fraction and down-fraction are illustrated in Fig. 2(b), showing the granulation progression that the small particle size fraction decreased continuously and disappeared by the fourth sampling, and that the large fraction increased drastically after the third sampling.

Results for dry-sized granules for the acetaminophen, acetaminophen-milled, and antipyrine formulations are shown in Figs. 3 to 5. Fractions over 1700 μm and under 425 μm, fractions over 425 μm and under 250 μm, and fractions over 850 μm and under 425 μm were defined as up-fraction and down-fraction for acetaminophen, acetaminophen-milled, and antipyrine, respectively, because of their continuous increase and decrease with the wet granulation progression [Figs. 3(a), 4(a), and 5(a)]. Because the bulk drug particle sizes of acetaminophen (192.7 μm) and antipyrine (251.8 μm) were large, there was little fraction smaller than 180 μm in the dry-sized granule particle size distribution. Figures 3(b), 4(b), and 5(b) indicate that the granulation process involved a continuous granule growth.

Similarly, the wet granule particle size data obtained under various sieving conditions were analyzed. Next, percent changes in up-fraction and down-fraction of dry-sized granules were compared with those of wet granules for the various sieving conditions. Correlations

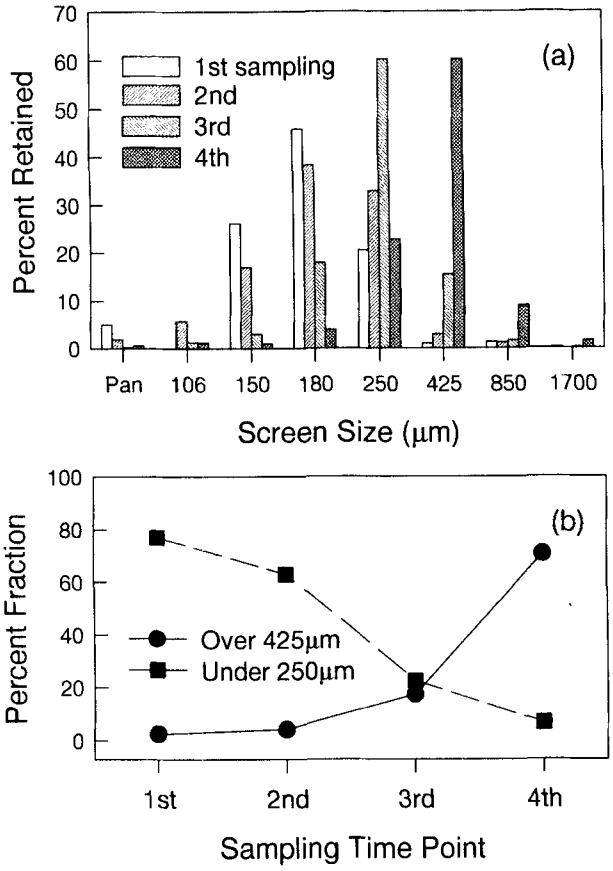

Figure 4. Changes in particle size distributions of dry-sized granules of acetaminophen-milled with wet granulation progression: (a) changes in individual particle size fractions; (b) changes in up-fraction and down-fraction.

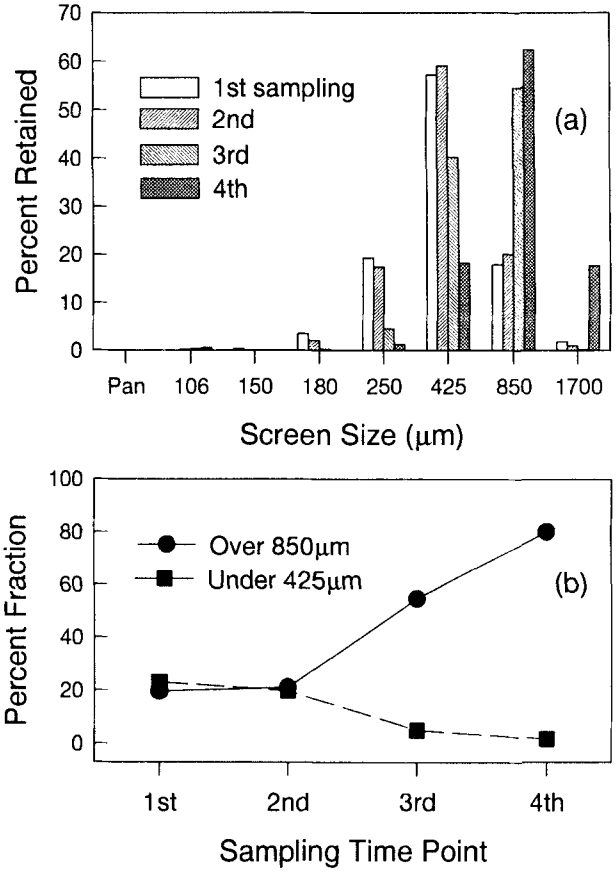

Figure 5. Changes in particle size distributions of dry-sized granules of antipyrine with wet granulation progression: (a) changes in individual particle size fractions; (b) changes in up-fraction and down-fraction.

between the dry-sized and the wet granules of ethenzamide are shown in Fig. 6. All results of the four granulations are also listed in Table 3. For the up-fraction of ethenzamide, stronger sieving conditions (40% for 1 and 3 min; and 80% for 0.5, 1, and 3 min) provided very high correlation coefficients (r = 0.9953–0.9991), and also for the down-fraction all conditions showed a good correlation (r = 0.9019–0.9616).

Regarding acetaminophen-milled, only three stronger sieving conditions (intensities of 20%, 40%, and 80% of full-scale amplitude for 3 min) produced up- and down-fractions of wet granules, whereas the clear changes in up- and down-fractions of the dry-sized granules were observed. Continuous decrease in small particle size fraction and increase in large particle size fraction of wet granules with the wet granulation progression were not observed when sieving times of 0.5 and 1 min were used. This suggests that the granulation of acetaminophen-milled proceeded to formation of strong granules and strong granule agglomerates. Two (20% and 80% of full-scale amplitude for 3 min) of the three conditions gave good correlations between the dry-sized and wet granules (r = 0.9035–0.9899) for both up- and down-fractions, although the reason for the low correlation coefficient obtained at 40% intensity for 3 min is not known.

The up- and down-fractions of acetaminophen dry-sized granules were well correlated with those of wet granules under all sieving conditions except the weakest condition evaluated (20% for 0.5 min), i.e., r = 0.9187–0.9902 for the up-fraction and r = 0.9205–0.9999 for the down-fraction. From these results, the

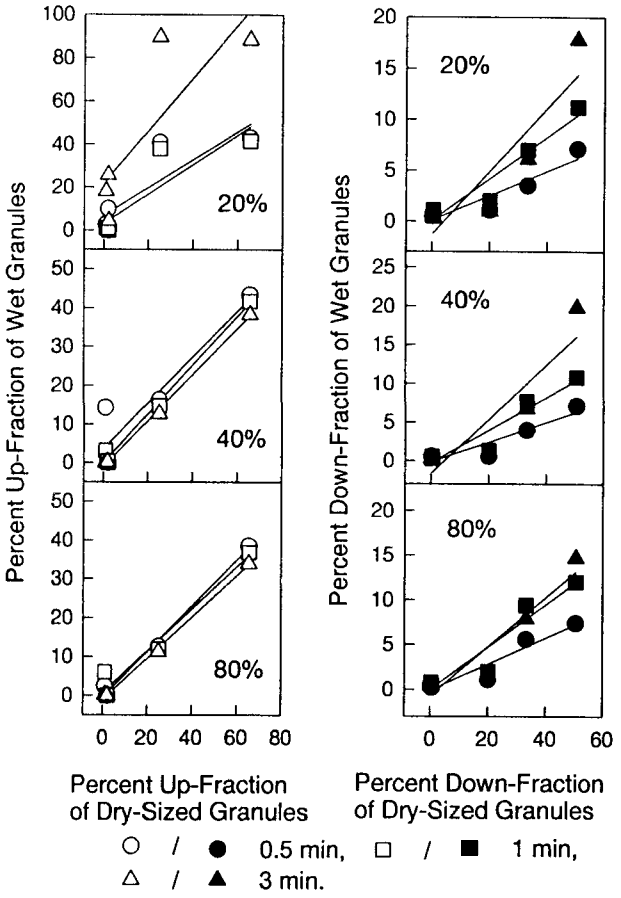

Figure 6. Correlations between dry-sized granules and wet granules of ethenzamide.

granule formation of acetaminophen appeared to be weak, contrary to the granulation of acetaminophen-milled.

There were no remarkable differences in correlation coefficient for the up-fraction of antipyrine among the sieving conditions (r = 0.8082–0.8962), and all except weaker conditions (20% and 40% for 0.5 min) showed good correlation coefficients for the down-fraction (r = 0.9252–0.9747).

The evaluation results of wet sieving conditions are summarized in Table 4. Each formulation had its own ideal sieving conditions. In all of the four different wet granulations, however, the strongest sieving condition evaluated in this study (intensity of 80% of full-scale amplitude and sieving time of 3 min) showed good correlations between wet and dry-sized granules for both up- and down-fractions.

It is also hypothesized that wet granulation involves an increase in mean particle size of component particles. Therefore, correlations of geometric mean diameter (D_{50}) of wet granules obtained at 20%, 40% or 80% of full-scale amplitude for 3 min to D_{50} of dry-sized granules were determined. The correlation coefficients for 20%, 40% and 80% intensities for 3 min were 0.9710, 0.9977, and 0.9941 for ethenzamide; 0.9464, 0.9383, and 0.9859 for acetaminophen; 0.7894, 0.9016, and 0.9586 for acetaminophen-milled; and 0.9918, 0.9911, and 0.9852 for antipyrine, respectively. For all of the four granulations, the three wet sieving conditions, especially 80% intensity for 3 min, resulted in good correlations.

From the above results, an intensity of 80% of full-scale amplitude and a sieving time of 3 min were selected as general sieving parameters for the Gilsonic AutoSiever to obtain wet granule particle size data reflecting the granulation progression of various drugs and formulations. A sieving time as short as possible is desirable to minimize the time the granulation process is interrupted. For this purpose, the 0.5-min sieving time is more useful than 3 min. However, it is more important for the sieving time to reflect granulation progression than to minimize interruption time. Further, the 3.4-min total sieving time (0.2-min ramp-up, 3-min sieving, and 0.2-min ramp-down) is not long enough from the practical standpoint during formulation development and scale-up.

Characterization of Sieving Parameters for Wet Granules

To characterize the sieving method consisting of the selected parameters (intensity of 80% of full-scale amplitude and sieving time of 3 min), the measurement precision was determined. Since there was a possibility that the wet granule particle size distribution changed as the granules were drying, the influence of granule standing time between sampling and sieving was also investigated. Further, the effect of sampling position of wet granules within the mixer bowl was investigated.

Figures 7(a) to 7(d) show the reproducibility of wet granule sieving using 80% intensity and 3-min sieving time for ethenzamide, acetaminophen, acetaminophen-milled, and antipyrine, respectively. For each of two wet granule samples at an early time point and at a late time point in each granulation, triplicate measurements were completed within 20 min after sampling. The particle size distribution was very reproducible for all samples. Standard deviations of individual particle size fractions were less than 5%. Therefore, it was verified that the measurement precision of wet granule sieving

Table 3

Correlations Between Dry-Sized and Wet Granules for Up- and Down-Fractions

Wet Sieving Intensity and Time		Up			Down		
		Wet Fraction (Over)	Slope	Correlation Coefficient (r)	Wet Fraction (Under)	Slope	Correlation Coefficient (r)
Ethenzamide[a]							
20%	0.5 min	1700 μm	0.6493	0.8628	250 μm	0.1193	0.9343
	1 min	1700 μm	0.6850	0.8867	250 μm	0.2045	0.9616
	3 min	850 μm	1.2192	0.8352	180 μm	0.3098	0.9019
40%	0.5 min	1700 μm	0.5922	0.9382	250 μm	0.1272	0.9309
	1 min	1700 μm	0.6309	0.9956	250 μm	0.2107	0.9524
	3 min	1700 μm	0.5961	0.9991	180 μm	0.3502	0.9090
80%	0.5 min	1700 μm	0.5848	0.9953	250 μm	0.1455	0.9522
	1 min	1700 μm	0.5380	0.9982	250 μm	0.2361	0.9529
	3 min	1700 μm	0.5275	0.9990	180 μm	0.2735	0.9482
Acetaminophen[b]							
20%	0.5 min	1700 μm	2.1314	0.7005	1700 μm	0.4500	0.6985
	1 min	1700 μm	4.0278	0.9187	1700 μm	0.8835	0.9506
	3 min	1700 μm	4.3581	0.9706	1700 μm	0.9276	0.9704
40%	0.5 min	1700 μm	5.4895	0.9796	1700 μm	1.1860	0.9985
	1 min	1700 μm	5.7928	0.9864	1700 μm	1.2445	0.9999
	3 min	1700 μm	6.2327	0.9902	1700 μm	1.3325	0.9990
80%	0.5 min	1700 μm	4.7072	0.9642	1700 μm	0.9507	0.9205
	1 min	1700 μm	5.4842	0.9593	1700 μm	1.1234	0.9285
	3 min	1700 μm	5.7838	0.9795	1700 μm	1.1858	0.9488
Acetaminophen-milled[c]							
20%	3 min	850 μm	0.4522	0.9899	425 μm	0.4719	0.9600
40%	3 min	850 μm	0.0785	0.7210	425 μm	0.2085	0.5719
80%	3 min	425 μm	0.3455	0.9035	425 μm	0.3634	0.9828
Antipyrine[d]							
20%	0.5 min	1700 μm	0.5369	0.8950	850 μm	0.2193	0.8212
	1 min	1700 μm	0.5094	0.8927	850 μm	0.3032	0.9400
	3 min	1700 μm	0.5098	0.8962	850 μm	0.5934	0.9747
40%	0.5 min	1700 μm	0.4734	0.8172	850 μm	0.1191	0.8279
	1 min	1700 μm	0.4614	0.8174	850 μm	0.2684	0.9264
	3 min	1700 μm	0.4432	0.8243	850 μm	0.4239	0.9400
80%	0.5 min	1700 μm	0.3930	0.8082	850 μm	0.1896	0.9371
	1 min	1700 μm	0.3941	0.8193	850 μm	0.3192	0.9294
	3 min	1700 μm	0.3798	0.8189	850 μm	0.4155	0.9252

[a]Up-fraction and down-fraction of dry-sized granules are over 850 μm and under 180 μm, respectively.
[b]Up-fraction and down-fraction of dry-sized granules are over 1700 μm and under 425 μm, respectively.
[c]Up-fraction and down-fraction of dry-sized granules are over 425 μm and under 250 μm, respectively.
[d]Up-fraction and down-fraction of dry-sized granules are over 850 μm and under 425 μm, respectively.

Table 4

Evaluation of Wet Sieving Conditions

Wet Sieving Intensity and Time		Evaluation[a]			
		Ethenzamide	Acetaminophen	Acetaminophen-Milled	Antipyrine
20%	0.5 min	B	D	E	C
	1 min	B	A	E	B
	3 min	B	A	A	B
40%	0.5 min	A	A	E	C
	1 min	A	A	E	B
	3 min	A	A	C	B
80%	0.5 min	A	A	E	B
	1 min	A	A	E	B
	3 min	A	A	A	B

[a]A: both correlation coefficients between dry-sized and wet granules for up- and down-fractions are more than 0.9; B: one coefficient is more than 0.9 and another 0.8 to 0.9; C: both coefficients are 0.8 to 0.9; D: one or both coefficients are less than 0.8; E: Up- and/or down-fraction is not produced.

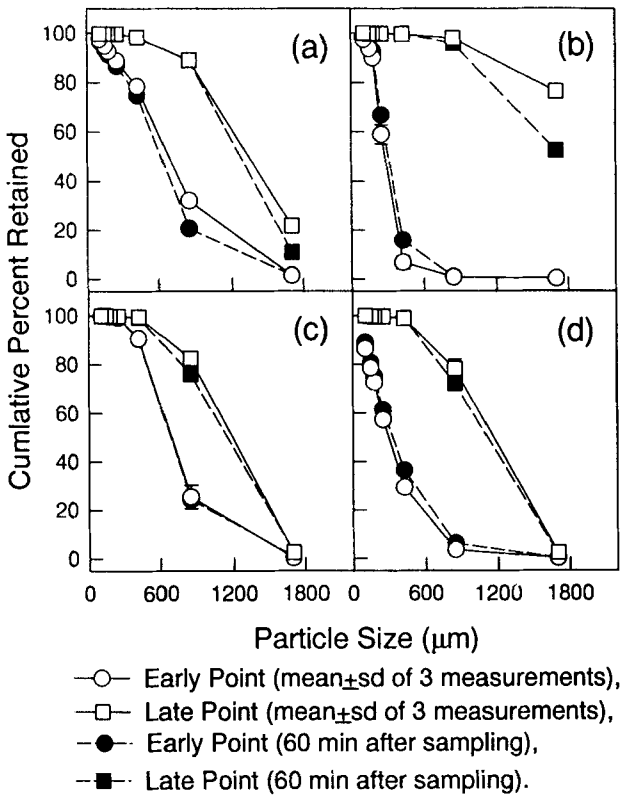

Figure 7. Effect of granule standing time on wet granule particle size distribution: (a) ethenzamide, (b) acetaminophen, (c) acetaminophen-milled, and (d) antipyrine.

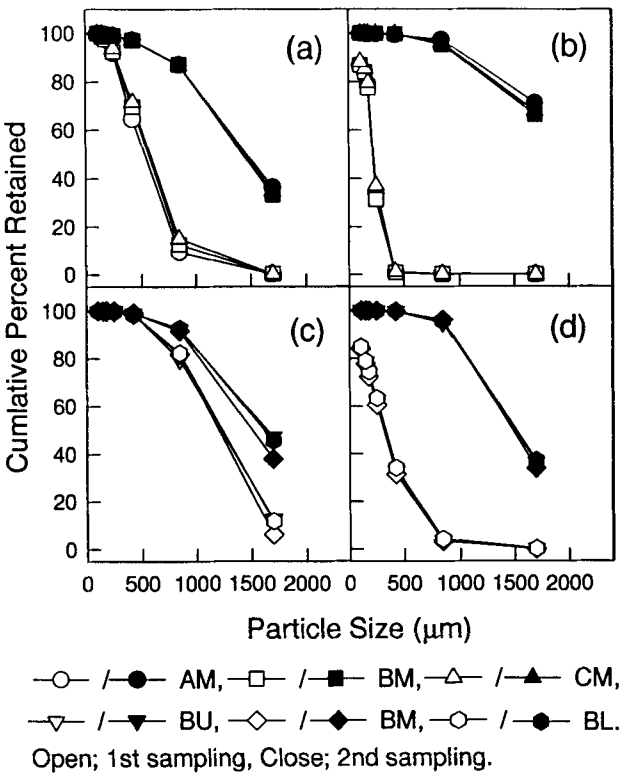

Figure 8. Effect of sampling position on wet granule particle size distribution: (a) ethenzamide; (b) acetaminophen, (c) acetaminophen-milled, and (d) antipyrine.

using the 80%–3 min condition is good as long as the determination is completed within 20 min.

Additionally, samples taken for determination of measurement precision were measured 60 min after sampling. For all of the wet granule samples, the wet granule particle size distribution determined 60 min from sampling was similar to those determined within 20 min after sampling (Fig. 7). It thus appears that the granule standing time effect is not a problem for the wet granule sieving as long as the sieving is completed within 60 min after sampling.

In each granulation, wet granules were sampled at two time points and from three different positions within the mixer chamber at each time point. As shown in Fig. 8, in all cases there was no difference in particle size distribution among three sampling positions. Standard deviations of individual particle size fractions were less than 5% and were similar to those for the reproducibility of wet granule sieving described above. Thus, it is believed that the wet granule particle size distribution is homogeneous within the mixer bowl, and that the sampling position does not influence the particle size determination.

REFERENCES

1. H. G. Kristensen and T. Schaefer, Drug Dev. Ind. Pharm., 13, 803 (1987).
2. D. E. Fonner, N. R. Anderson, and G. S. Banker, in *Pharmaceutical Dosage Forms: Tablets*, Vol. 2 (H. A. Lieberman and L. Lachman, eds.), Dekker, New York, 1981, Chap. 5.
3. B. M. Hunter and D. Ganderton, J. Pharm. Pharmacol., 25S, 71P (1973).
4. C. J. Flesch, Pharm. Ind., 40, 757 (1978).
5. H. Leuenberger, H. P. Bier, and H. Sucker, Pharm. Tech., 3, 60 (1979).
6. H. P. Bier, H. Leuenberger, and H. Sucker, Pharm. Ind., 41, 375 (1979).
7. H. Leuenberger, Pharm. Acta Helv., 57, 72 (1982).
8. H. Leuenberger and M. Durrenberger, Chem. Rundschau, 35, 1 (1982).
9. H. Leuenberger, Acta Pharm. Techn., 29, 274 (1983).
10. H. Leuenberger, Manuf. Chemist, 5, 67 (1984); 6, 53 (1984).
11. H. Leuenberger and G. Imanidis, Pharm. Tech., 10, 56 (1986).
12. J. Werani, Acta Pharm. Suec., 25, 247 (1988).
13. N. O. Lindberg, L. Leander, H. Helgesen, B. Reenstierna, and L. Wenngren, Acta Pharm. Suec., 11, 603 (1974).
14. D. N. Travers, A. G. Rogerson, and T. M. Jones, J. Pharm. Pharmacol., 27S, 3P (1975).
15. N. O. Lindberg, P. G. Nilsson, B. Reenstierna, and L. Leander, Acta Pharm. Seuc., 14, 191 (1977).
16. N. O. Lindberg, L. Leander, and B. Reenstierna, Drug Dev. Ind. Pharm., 8, 775 (1982).
17. N. O. Lindberg, Drug Dev. Ind. Pharm., 10, 45 (1984).
18. S. R. Ghanta, R. Srinivas, and C. T. Rhodes, Drug Dev. Ind. Pharm., 10, 305 (1984).
19. M. Kopcha, E. Roland, G. Bubb, and W. A. Vadino, Drug Dev. Ind. Pharm., 18, 1945 (1992).
20. K. Yamamoto, R. J. Wald, H. Emori, S. Narita, T. Yoshizawa, T. Nishihata, and G. E. Amidon, Pharm. Res., 12, S159 (1995).
21. R. J. Wald, G. E. Amidon, D. J. Reits, F. J. McGill, K. Yamamoto, H. Emori, and T. Nishihata, Pharm. Res., 12, S160 (1995).
22. P. Holm, O. Jungersen, T. Schaefer, and H. G. Kristensen, Pharm. Ind., 45, 806 (1983).