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RESEARCH PAPER

Prospective Validation of High-Shear Wet Granulation Process by Wet Granule Sieving Method. II. Utility of Wet Granule Sieving Method

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ABSTRACT

The general utility of a method for determination of high-shear wet granulation end point by monitoring the wet granule particle size distribution was evaluated. 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). For each drug formulation, its wet granule particle size fraction and target range for granulation end point determination were selected based on the tablet characteristics that are known to be influenced by the wet granulation process. Granules manufactured under different conditions (i.e., different main and chopper blade speeds and binder supplying rate) but manufactured to the same granulation end point determined by the selected fraction and range showed very similar granule characteristics and subsequently very similar tablet characteristics. From the fact that there was a good correlation between the wet and dry-sized granule particle size distributions even if the drying method was changed from fluid-bed drying to vacuum drying, the general application of the end point determining method was verified. Further, the method was shown to be sensitive to the critical granulation parameters for granulation progression and to be very capable of determining the granulation extent. Thus, it was suggested that the method is applicable to various drugs and formulations for determination of wet granulation end point.

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INTRODUCTION

A high-shear wet granulation method is very useful for the production of granules for tablets in the pharmaceutical industry. The wet granulation process is well known to influence final tablet characteristics, such as content uniformity, dissolution rate, disintegration time, hardness, and friability (1). Therefore, it is very important to adequately control the granulation process to obtain final tablet quanlity.

The method that directly characterizes the wet granulation progression 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 (2,3). The in-process method is available on the spot, simple, fast, independent of operator evaluation, and requires a small sample amount. Since this method is also independent of mixer design and scale, it is very useful during scale-up. It is also expected that the WGSM is capable of validating the wet granulation process prospectively.

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. In a previous study (Part I), we selected and characterized a general sieving method to obtain wet granule particle size data reflecting the granulation progression of various drug formulations (4). The objective of the present study (Part II) was to evaluate the general utility of the WGSM for granulation end point determination, using the selected general sieving method.

As in the Part I of the study, we used the four model drugs of different solubilities and particle sizes, and the formulations contained high percentages of active ingredients in the granulation portion. 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. In the first experiment, the wet granule particle size fraction and the target range for determination of granulation end point were selected for each drug formulation. In the second experiment, the usefulness of the WGSM was evaluated using the selected fraction and target range.

MATERIALS AND METHODS

Materials

Ethenzamide, unmilled acetaminophen (acetaminophen), and milled acetaminophen (acetaminophen-milled) were purchased from Yoshitomi Pharmaceutical Co., Ltd. (Osaka, Japan); and antipyrine from Yashiro Pharmaceutical Co., Ltd. (Osaka, Japan). 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. Lactose (DMV 200M; DMV Japan, Tokyo, Japan), hydroxypropyl cellulose (HPC-LE-P; Shin-Etsu Chemical Co., Tokyo, Japan), cornstarch (Cornstarch W; Nihon Shokuhin Kakou Co., Ltd., Tokyo, Japan), microcrystalline cellulose (Avicel PH-101; Asahi Kasei Co., Ltd., Tokyo, Japan), low-substituted hydroxypropyl cellulose (L-HPC LH-11; Shin-Etsu Chemical), and magnesium stearate (Taihei Chemical Industrial Co., Ltd., Nara, Japan) were obtained commercially. All drugs and excipients were of JP grade except cornstarch, which was of food grade. Other reagents used were of analytical grade.

Manufacturing

Tablets were manufactured using the core formulation shown in Table 1 and the manufacturing process described below.

Wet Granulation

Wet granulation was conducted in a 25-liter high-shear mixer (Model FM-VG-25; Powrex Co., Osaka, Japan). The theoretical granulation batch size was 12,000 tablets. Drug and intragranular excipient powders were weighed and added to the bowl of the high-shear mixer. After premixing the powders, purified water was added to the powders using a peristaltic pump and a spray nozzle while both main and chopper 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

Table 1

Formulation Composition of Tablets

Component	Amount per Tablet (mg)
Intragranular phase	
Drug	250.0
Cornstarch	21.0
Lactose	49.0
Hydroxypropyl cellulose	10.0
Extragranular phase	
Microcrystalline cellulose	11.0
Low-substituted hydroxypropyl cellulose	7.5
Magnesium stearate	1.5
Total	350.0

additional time. The scheme of water addition and mixing was repeated several times.

In the first experiment, the premixing time, the main and chopper blade speeds, and the binder (water) supplying rate were 1 min, 250 and 3000 rpm, and 70 g/min, respectively. For each formulation, 4 to 5 lots were granulated by changing the amount of water and mixing time. The total amount of water added and the total mixing time for each lot are listed in Table 2. The wet granule particle size distributions of the individual lots were determined immediately after completing the granulation process. A 500-g sample of wet granules was then dried.

On the other hand, in the second experiment, the granulation parameters were 2-min premixing time, 150 rpm main and 1500 rpm chopper blade speeds, and 40 g/min water supplying rate. During the granulation process, the wet granule particle size distribution was determined at the appropriate time points. A 500-g sample of wet granules was taken from the mixer chamber at the granulation end point, which was determined by the selected fraction and target range, and further at the point of undergranulation and/or overgranulation.

Drying

Wet granules were hand-screened through a 2000-μm screen and then dried in a vacuum dryer (Kobayashi Rikakiki Co., Ltd., Tokyo, Japan) at 40°C for more than 12 hr. Loss on drying (LOD) 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.

Lubrication

The appropriate amount (1200 tablet lot size) of dry-sized granules and extragranular excipient powders were hand-mixed.

Compressing

Lubricated granules were compressed into tablets with a nominal weight of 350 mg using a single compressing machine (Model N-20E; Okada Seiko Co., Ltd., Tokyo, Japan) and round (9.5 mm in diameter), flat-face, and beveled-edge tooling. The target hardness was 14 to 16 Strong–Cobb Units (SCU; 1 SCU is equivalent to about 0.7 kg) for ethenzamide, 5–7 SCU for acetaminophen, 8–10 SCU for acetaminophen-milled, and 6–8 SCU for antipyrine. These targets were preliminarily selected using granules which were obtained at the granulation end point determined by operator's evaluation. The hardness achieved by 1000-kg compressing force was selected as the target, and when it was less than 5 SCU, the hardness by 1500-kg force.

Table 2

Amount of Water Added and Mixing Time for Wet Granulation

Drug	Lot No.	Total Water Amount (%)[a]	Total Mixing Time (min)
Ethenzamide	EA1-1	14.0	8.7
	EA1-2	16.3	10.2
	EA1-3	18.3	14.0
	EA1-4	19.9	16.0
	EA1-5	20.8	17.5
Acetaminophen	AA1-1	2.5	3.2
	AA1-2	4.2	5.3
	AA1-3	8.3	8.4
	AA1-4	13.4	15.7
Acetaminophen-milled	AAM1-1	10.0	10.0
	AAM1-2	11.8	12.3
	AAM1-3	15.2	17.3
	AAM1-4	17.7	19.8
	AAM1-5	20.7	22.4
Antipyrine	AP1-1	1.5	2.1
	AP1-2	3.2	4.1
	AP1-3	4.6	5.8
	AP1-4	7.1	8.4

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

Characterization

The following in-process and tablet characteristics were determined:

Wet Granulation Particle Size Analysis

The wet granule particle size determination was conducted according to the sieving method selected and characterized in the previous study (4). A sonic sifter (Model Gilsonic AutoSiever GA-1; Gilson Company, Inc., Ohio, USA) equipped with 7 screens (1700, 850, 425, 250, 180, 150, and 106 μm) and a latex fines collector were used. Further, a 2000-μm screen was used for presieving. A 10-g sample of wet granules was taken from the high-shear mixer bowl to determine particle size distribution in duplicate immediately after sampling. The mean value was used for data analysis. 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. The sieving parameters used were 80% intensity of full-scale amplitude, 3-min sieving time, bottom and side tapping on, 0.2-min ramp-up time, and 0.2-min ramp-down time. Duplicate measurements were completed within 15 min.

Dry 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.

Tapped Density

The tapped density of lubricated granules was determined using a Tapdenser KTY-3000 (Seishin Enterprise Co., Ltd., Tokyo, Japan) and a 100-ml graduated cylinder. The tapping stroke was 10 mm. Tapped density and compressibility index (*CI*) were calculated from Eqs. (1) and (2), respectively.

$$\text{Tapped density} = W/V_{2400} \quad (1)$$

where W is the weight of granules in the graduated cylinder and V_{2400} is the volume of granules after tapping 2400 times.

$$CI = (V_0 - V_{2400}) \times 100/V_0 \quad (2)$$

where V_0 is the initial volume of granules.

Tablet Weight and Hardness

Twenty tablets were weighed individually and then the hardness was measured with a hardness tester (Model PTB301; Pharma Test, Germany).

Tablet Friability

Tablet friability was determined using 20 tablets and a friabilator (Kayagai Co., Ltd., Tokyo, Japan) operated at 25 rpm for 4 min.

Tablet Disintegration

Tablet disintegration was tested using the JP XII disintegration test apparatus (Toyama Sangyo Co., Ltd., Osaka, Japan). Water kept at 37°C was used as disintegration medium, and the basket was raised and lowered at a constant frequency of 30 cycles per minute. Six tablets from each tablet lot were tested.

Dissolution

The dissolution test was performed according to the paddle method (JP XII). The apparatus employed consisted of a dissolution tester (Model NTR-VS6P; Toyama Sangyo), an autosampler (Model PAS-615; Toyama Sangyo), a ultraviolet (UV) spectrophotometer (Model UV-160A; Shimazu, Kyoto, Japan) with a cell positioner (Model CPS-240B; Shimazu), and a personal computer (NEC, Tokyo, Japan). Nine hundred milliliters of JP XII disintegration first medium (pH 1.2) was used at 37°C, and the paddle was rotated at 50 rpm. At the appropriate time points, the drug concentration was monitored automatically, at 234 nm for ethenzamide, 242 nm for acetaminophen, and 230 nm for antipyrine. One tablet was used in each dissolution test, and six replications of tests were done for each tablet lot. The dissolution rate of ethenzamide from the 425- to 850-μm fraction of dry-sized granules was also determined in triplicate according to the same method as tablets and using 330 mg of the fraction per test.

RESULTS AND DISCUSSION

Verification of General Sieving Method

It is very important that the wet granule particle size distribution determined reflects the granulation extent which is practically defined based on the dry or dry-sized granule characteristics. The general sieving method used in this study was selected in the previous study because of the good correlation between wet and dry-sized granule particle sizes (4). However, the

present study used a vacuum dryer while the previous study used a fluid-bed dryer. Therefore, the correlation between the wet and dry-sized granules was confirmed. The data from the first experiment was used. Figure 1 shows good correlations of geometric mean diameter (D_{50}) for individual drug formulations, demonstrating the usefulness of the general sieving method.

Selection of Wet Granule Fraction and Target Range for End Point Determination

The wet granule particle size fraction and the target range for determination of granulation end point were selected based on the tablet characteristics that are known to be influenced by the wet granulation process (1,5).

Ethenzamide

Table 3 summarizes the tablet characteristics and granule dissolution rates of ethenzamide lots. The relative standard deviation (RSD) of tablet weight for lot EA1-5 exceeded 3%, presumably due to the large particle size of dry-sized granules (D_{50} of 1400 μm) caused by excess water and longer kneading time (5).

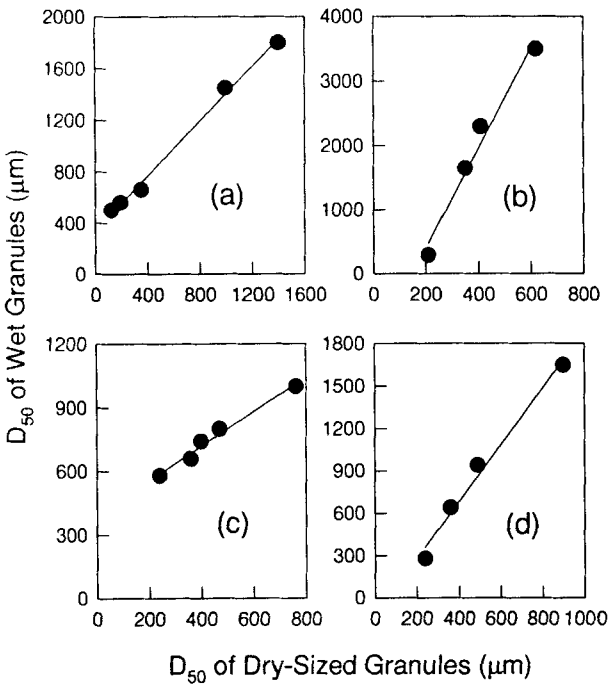

Figure 1. Correlations of D_{50} between wet granules and dry-sized granules: (a) ethenzamide (r = 0.997), (*b*) acetaminophen (r = 0.98), (c) acetaminophen-milled (r = 0.990), and (d) antipyrine (r = 0.992).

The tablet disintegration time was prolonged as the granulation proceeded, and lots EA1-4 and EA1-5 showed considerably longer times than the other lots. Similarly, the tablet dissolution rates of lots EA1-4 and EA1-5 were significantly delayed. Since the dissolution from the 425- to 850-μm fraction of dry-sized granules was also suppressed remarkably for lots EA1-4 and EA1-5, the delay of tablet dissolution rate for the two lots appeared to be caused by the suppression of granule dissolution, decrease in granule surface area, and prolongation of tablet disintegration. The reason for suppressed granule dissolution seems to be that the insoluble drug was granulated into very tight particles with excess water and longer kneading time. With regard to tablet hardness, the target (14 to 16 SCU) was achieved within the limit pressure of the compressing equipment used (below 2000 kg), although the hardness for lots EA1-1 and EA1-2 was slightly low. The tablet friability was quite good for all lots (0.13% to 0.20%). From the above results, lots EA1-4 and EA1-5 were defined as overgranulated.

The individual wet granule particle size fractions for ethenzamide lots are given in Fig. 2. Since the wet granulation progression involves a decrease in small particle size fraction and an increase in large fraction (5), the wet granule particle size fraction for determination of the end point was selected from the decreasing small fractions and the increasing large fractions. The wet granule fraction is required to discriminate lots EA1-4 and EA1-5 from the other lots and to detect the change from EA1-3 to EA1-4 in advance. The fraction smaller than 250 μm de-escalated as the granulation proceeded—i.e., 10.7%, 10.0%, 1.8%, 0.3%, and 0.3% for EA1-1, EA1-2, EA1-3, EA1-4, and EA1-5, respectively—while the fraction larger than 1700 μm slightly de-escalated and then increased suddenly. Therefore, the fraction smaller than 250 μm was selected for the end point determination, and 2–10% was selected as the target range.

Acetaminophen

As shown in Table 4, tablet disintegration and dissolution rate were fast for all lots. Also, RSDs of weight were less than 3% for all lots although the value escalated with granulation progression. However, lot AA1-1 showed a remarkably high friability, and the target hardness (5 to 7 SCU) was not achieved within the limit pressure for lots AA1-1 and AA1-2, i.e., 2.5 SCU for lot AA1-1 by 2050-kg force and 7.0 SCU for lot AA1-2 by force considerably more than 2000 kg. Therefore, lots AA1-1 and AA1-2 were defined as undergranulated. The fraction smaller than 425 μm decreased and the

Table 3

Tablet Characteristics and Granule Dissolution Rates for Ethenzamide

Characteristics	EA1-1	EA1-2	EA1-3	EA1-4	EA1-5
		Tablets			
Weight (mg)					
Mean	351.50	351.83	357.93	359.29	365.12
%RSD	0.38	0.33	0.34	2.05	3.12
Hardness (SCU)					
Mean	13.4	13.4	14.0	15.5	14.9
SD	1.0	0.8	0.7	0.7	1.5
Friability (%)	0.20	0.13	0.17	0.18	0.19
Disintegration time (sec)					
Mean	86.3	116.5	308.8	839.2	942.2
SD	19.1	68.3	24.5	150.6	72.2
Max	114	304	341	980	1034
Dissolution[a]					
D5 (%)					
Mean	54.8	60.0	49.5	15.1	19.2
SD	12.7	10.3	16.2	1.8	2.6
D10 (%)					
Mean	78.1	83.3	80.1	39.3	47.9
SD	9.8	4.2	6.8	4.6	8.6
D15 (%)					
Mean	87.4	91.6	90.3	70.0	76.6
SD	7.3	1.9	1.9	9.6	7.3
D30 (%)					
Mean	97.6	97.1	97.9	97.0	96.5
SD	1.2	1.0	0.8	2.0	2.4
		Granules[b]			
Dissolution[a]					
D2 (%)					
Mean	89.1	82.5	72.8	37.4	41.0
SD	1.4	1.1	2.5	2.2	3.3
D10 (%)					
Mean	96.9	95.4	91.7	57.1	56.1
SD	1.1	0.4	1.1	2.8	3.5

[a]D*x*: dissolution at *x* min.
[b]425–850 μm fraction.

fraction larger than 1700 μm increased as the granulation extent increased. Thus, the fraction smaller than 425 μm (less than 1%) and the fraction larger than 1700 μm (65 to 75%) were selected as the targets.

Acetaminophen-Milled

Table 5 shows that there were no problems in tablet weight variation, hardness, friability, disintegration, and dissolution for all lots. However, lot AAM1-5 showed a relatively higher RSD of weight, longer disintegration time, and slower dissolution rate than the other lots. Only for convenience' sake, in order to select the fraction and range for end point determination, AAM1-5 was defined as overgranulated. The fraction smaller than 425 μm that showed a continuous decrease during the granulation progression was selected for determination of end point. The target range selected was 5% to 15%.

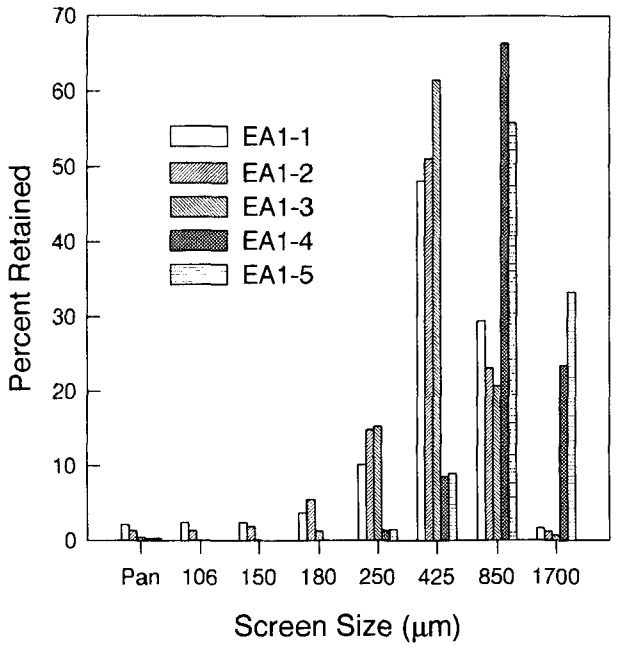

Figure 2. Particle size distributions of wet granules for ethenzamide.

Antipyrine

The hardness of lot AP1-1 was low and out of the target (6–8 SCU) although it was compressed using the limit force, and subsequently the friability was high (Table 6). Thus, AP1-1 was defined as undergranulated. Further, AP1-4 was defined as overgranulated for convenience' sake because of its higher RSD of weight than the other lots, although the value (2.49%) was not a problem from the practical standpoint. The fraction smaller than 425 μm de-escalated and the fraction larger than 1700 μm escalated as the granulation progressed. These were considered the fractions capable of detecting the changes from AP1-1 to AP1-2 and from AP1-3 to AP1-4. Thus, 1–3% (larger than 1700 μm) and 1–10% (smaller than 425 μm) were selected as the targets.

Evaluation of General Utility of WGSM

The utility of WGSM was evaluated by comparing characteristics of tablet lots which were manufactured under different granulation conditions but to the same granulation end point determined by the selected wet

Table 4

Tablet Characteristics for Acetaminophen

Characteristics	AA1-1	AA1-2	AA1-3	AA1-4
Weight (mg)				
Mean	348.78	354.54	362.27	342.76
%RSD	0.33	0.66	1.37	2.94
Hardness (SCU)				
Mean	2.5	7.0	7.7	6.9
SD	0.1	0.3	0.4	0.7
Friability (%)	8.34	0.41	0.25	0.26
Disintegration time (sec)				
Mean	18.3	41.3	35.8	34.0
SD	1.4	1.5	3.0	4.8
Max	20	44	40	42
Dissolution[a]				
D5 (%)				
Mean	66.2	72.9	50.5	68.9
SD	4.5	7.4	4.6	5.2
D10 (%)				
Mean	84.8	93.2	76.8	92.4
SD	3.6	4.3	4.7	3.4
D15 (%)				
Mean	92.6	96.2	87.8	98.5
SD	2.2	2.5	3.5	2.5

[a]D*x*: dissolution at *x* min.

Table 5

Tablet Characteristics for Acetaminophen-Milled

Characteristics	AAM1-1	AAM1-2	AAM1-3	AAM1-4	AAM1-5
Weight (mg)					
Mean	357.29	354.56	355.81	358.71	357.09
%RSD	0.37	0.58	0.74	0.72	1.55
Hardness (SCU)					
Mean	10.4	11.5	11.2	10.4	10.5
SD	0.3	0.3	0.3	0.3	0.9
Friability (%)	0.27	0.20	0.15	0.15	0.24
Disintegration time (sec)					
Mean	35.0	33.5	44.0	47.2	58.3
SD	3.9	6.4	3.9	3.9	4.3
Max	40	42	47	51	65
Dissolution[a]: D5 (%)					
Mean	92.2	92.1	92.5	79.3	73.1
SD	5.8	6.7	1.4	5.6	6.6

[a]D5: dissolution at 5 min.

Table 6

Tablet Characteristics for Antipyrine

Characteristics	AP1-1	AP1-2	AP1-3	AP1-4
Weight (mg)				
Mean	352.60	353.88	351.51	363.39
%RSD	0.58	0.73	1.25	2.49
Hardness (SCU)				
Mean	4.7	7.3	6.7	8.0
SD	0.3	0.4	0.3	0.7
Friability (%)	3.28	0.87	0.65	0.66
Disintegration time (sec)				
Mean	318.0	487.8	453.7	407.2
SD	44.3	62.6	25.9	78.3
Max	394	596	488	487
Dissolution[a]: D5 (%)				
Mean	43.4	33.9	33.0	32.7
SD	3.2	3.6	1.6	0.7
D10 (%)				
Mean	84.1	59.6	58.8	58.5
SD	6.3	4.8	2.1	1.1
D15 (%)				
Mean	97.4	78.3	77.2	77.4
SD	1.1	4.5	1.7	1.7

[a]D*x*: dissolution at *x* min.

granule fraction and target range. Granulation parameters that are known to influence the granulation progression were changed, i.e., main and chopper blade speeds and binder supplying rate (6–8). The tablet characteristics of the second experiment were compared with those of the lots defined as good granulation manufactured in the first experiment (target tablet characteristics).

Table 7 summarizes the percent fractions of wet granules at end point. The changes in percent fraction as a function of mixing time in the second experiment are illustrated in Figs. 3(a) to 3(d), as compared with those in the first experiment. Changing the main and chopper blade speeds and the water supplying rate from 250 and 3000 rpm and 70 g/min to 150 and 1500 rpm and 40 g/min, respectively, resulted in decreases in granulation rate for ethenzamide, acetaminophen, and antipyrine while there was no difference in the rate of acetaminophen-milled. With regard to the change in percent fraction as a function of amount of water added, however, the lots in the first experiment showed the same profiles as those in the second experiment [Figs. 4(a) to 4(d)]. From these results, it is suggested that the granulation extent depends on the amount of water added and the rate depends on the water distribution rate, i.e., the water distributing parameters (mixing speed and water supplying rate). This is in accordance with results in the pharmaceutical literature (5–8). Further, the WGSM is shown to be the method sensitive to the critical granulation parameters for granulation rate and very capable of determining the granulation extent.

The tablet characteristics of the lots in the second experiment of ethenzamide are listed in Table 8 with the target values. Lot EA2-1 (good granulation) met all targets while the overgranulation lot (EA2-2) showed a high RSD of weight and suppressed disintegration and dissolution. The hardness of lot EA2-2 being a little higher than the target was not a problem, because the hardness target could be achieved using the compressing force within the machine limit if the process was controlled more carefully. Regarding the granule dissolution rate, EA2-1 met the target based on the first experiment lots but EA2-2 was suppressed. As summarized in Table 9, the good granulation lot of acetaminophen (AA2-2) satisfied the targets. On the contrary, the overgranulation lot (AA2-1) was not compressed into tablets with the target hardness even at the upper limit of pressure, and the subsequent tablet friability was considerably high, as expected. The good granulation lot of acetaminophen-milled (AAM2-1) met all

Table 7

Percent Fraction of Wet Granules at End Point

Drug	Lot No.	Percent Fraction	
Ethenzamide		Under 250 μm	
	Target	2–10	
	EA2-1 (good granulation)	7.9	
	EA2-2 (overgranulation)	0.8	
Acetaminophen		Over 1700 μm	Under 425 μm
	Target	65–75	< 1
	AA2-1 (undergranulation)	0.02	86.5
	AA2-2 (good granulation)	68.8	0.5
Acetaminophen-milled		Under 425 μm	
	Target	5–15	
	AAM2-1 (good granulation)	9.5	
	AAM2-2 (overgranulation)	1.0	
Antipyrine		Over 1700 μm	Under 425 μm
	Target	1–3	1–10
	AP2-1 (undergranulation)	0.1	67.8
	AP2-2 (good granulation)	2.1	1.7
	AP2-3 (overgranulation)	35.1	0.3

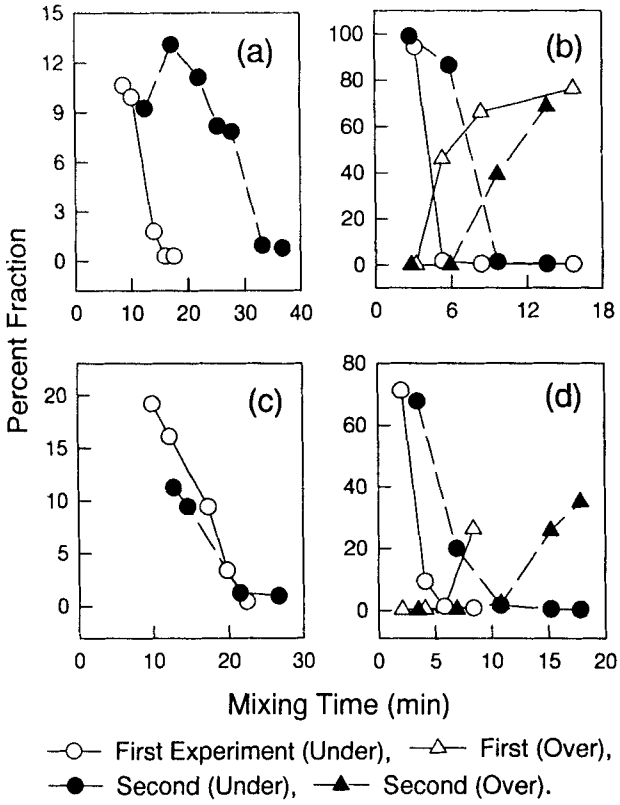

Figure 3. Percent fraction changes of wet granules as function of mixing time: (a) ethenzamide (under 250 μm), (b) acetaminophen (under 425 μm and over 1700 μm), (c) acetaminophen-milled (under 425 μm), and (d) antipyrine (under 425 μm and over 1700 μm).

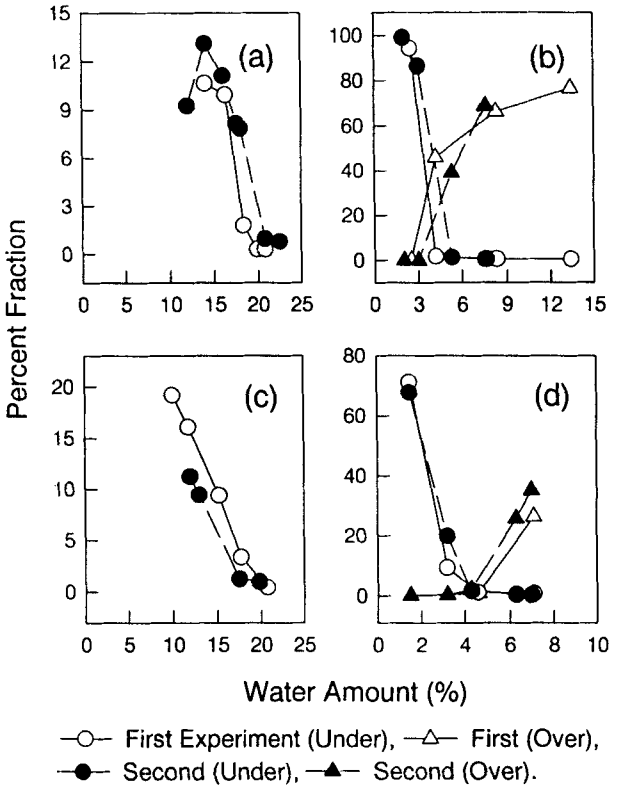

Figure 4. Percent fraction changes of wet granules as function of water amount: (a) ethenzamide (under 250 μm), (b) acetaminophen (under 425 μm and over 1700 μm), (c) acetaminophen-milled (under 425 μm), and (d) antipyrine (under 425 μm and over 1700 μm).

targets except weight RSD, which slightly exceeded the quite narrow target (Table 10). For the overgranulation lot (AAM2-2), a high RSD of weight and slow disintegration and dissolution were observed, similar to the results of ethenzamide. The good granulation lot of antipyrine (AP2-2) almost satisfied the targets while the friability and disintegration time slightly exceeded the targets as shown in Table 11. The undergranulation lot (AP2-1) and overgranulation lot (AP2-3) showed high friability and slightly slow dissolution rates at 10 and 15 min, respectively. For all four drug formulations, the good granulation lots manufactured according to the WGSM met the target tablet characteristics. Also, the undergranulation and overgranulation lots showed the expected tablet characteristics.

It is helpful, in generalizing the WGSM, to know if granules manufactured at the same granulation end point according to the WGSM possess the same granule characteristics. The D_{50} of dry-sized granules of the good granulation lot in the second experiment was within the range of the good lots in the first experiment, and different from those of the undergranulation and/or overgranulation lots in the first experiment. The values of the good lot in the second experiment and the good, undergranulation, and/or overgranulation lots in the first experiment were 210, 125–350, and 1000–1400 μm (over) for ethenzamide; 530, 410–620, and 210–350 μm (under) for acetaminophen; 280, 240–470, and 760 μm (over) for acetaminophen-milled; and 490, 360–490, 240 (under), and 900 μm (over) for antipyrine, respec-

Table 8

Tablet Characteristics and Granule Dissolution Rates for Ethenzamide

Characteristics	Target	EA2-1	EA2-2
	Tablets		
Weight (mg)			
Mean	—	352.77	363.94
%RSD	Not more than 0.5	0.33	1.71
Hardness (SCU)			
Mean	14–16	15.2	17.5
SD	—	0.9	1.5
Friability (%)	Not more than 0.3	0.04	0.11
Disintegration time (sec)			
Mean	—	297.3	505.8
SD	—	30.6	68.1
Max	Not more than 400	350	615
Dissolution[a]			
D5 (%)			
Mean	Not less than 40	45.5	24.7
SD	—	9.2	4.1
D10 (%)			
Mean	Not less than 70	82.4	66.1
SD	—	5.8	8.3
D15 (%)			
Mean	Not less than 80	90.8	83.5
SD	—	3.4	5.1
D30 (%)			
Mean	Not less than 95	97.2	96.8
SD	—	0.6	1.4
	Granules[b]		
Dissolution[a]			
D2 (%)			
Mean	Not less than 70	84.3	63.1
SD	—	4.5	2.0
D10 (%)			
Mean	Not less than 90	95.6	77.7
SD	—	0.5	3.4

[a]D*x*: dissolution at *x* min.
[b]425–850 μm fraction.

tively. In each formulation, tapped densities of lubricated granules of the good lots in the first and second experiments were quite similar. Also, in CI of lubricated granules, the good lots in the first and second experiments were nearly similar, i.e., 19.0–23.0 and 17.5% for ethenzamide, 11.5–12.0 and 8.8% for acetaminophen, 15.5–21.0 and 16.0% for acetaminophen-milled, and 8.8–17.0 and 10.0% for antipyrine, respectively. Thus, it was found that the granules manufactured at the same end point showed very similar granule characteristics and then very similar tablet characteristics.

As described above, it was demonstrated that the WGSM was useful for controlling the high-shear wet granulation process in the formulations of the four model drugs with considerably different solubilities and particle sizes. Therefore, it is believed that the WGSM is applicable to various drugs and formulations for de-

Table 9

Tablet Characteristics for Acetminophen

Characteristics	Target	AA2-1	AA2-2
Weight (mg)			
Mean	—	352.04	360.55
%RSD	Not more than 3	0.36	1.49
Hardness (SCU)			
Mean	5–7	3.1	7.5
SD	—	0.1	0.4
Friability (%)	Not more than 0.3	9.44	0.29
Disintegration time (sec)			
Mean	—	41.3	18.8
SD	—	1.6	0.4
Max	Not more than 60	44	19
Dissolution[a]			
D5 (%)			
Mean	Not less than 50	64.7	69.3
SD	—	8.4	7.5
D10 (%)			
Mean	Not less than 75	84.5	93.2
SD	—	6.9	4.0
D15 (%)			
Mean	Not less than 85	91.6	96.8
SD	—	4.7	2.3

[a]Dx: dissolution at *x* min.

Table 10

Tablet Characteristics for Acetminophen-Milled

Characteristics	Target	AAM2-1	AAM2-2
Weight (mg)			
Mean	—	357.92	332.94
%RSD	Not more than 1	1.59	2.76
Hardness (SCU)			
Mean	8–10	11.1	8.8
SD	—	0.6	1.2
Friability (%)	Not more than 0.3	0.17	0.18
Disintegration time (sec)			
Mean	—	34.7	88.7
SD	—	2.0	17.3
Max	Not more than 60	37	120
Dissolution[a]: D5 (%)			
Mean	Not less than 80	90.1	56.7
SD	—	6.5	5.4

[a]D5: dissolution at 5 min.

Table 11

Tablet Characteristics for Antipyrine

Characteristics	Target	AP2-1	AP2-2	AP2-3
Weight (mg)				
Mean	—	350.60	356.92	364.80
%RSD	Not more than 2	0.47	0.63	1.42
Hardness (SCU)				
Mean	6–8	4.6	6.4	7.2
SD	—	0.3	0.3	0.6
Friability (%)	Not more than 1	3.64	1.36	0.70
Disintegration time (sec)				
Mean	—	282.2	535.5	475.5
SD	—	33.4	114.2	40.5
Max	Not more than 600	337	763	553
Dissolution[a]				
D5 (%)				
Mean	Not less than 30	46.6	33.5	30.1
SD	—	4.9	1.1	2.3
D10 (%)				
Mean	Not less than 55	85.6	59.0	54.4
SD	—	3.6	1.1	2.6
D15 (%)				
Mean	Not less than 75	98.1	77.4	73.2
SD	—	1.0	1.6	2.8

[a]Dx: dissolution at *x* min.

termination of wet granulation end point, and further that the WGSM is capable of validating the wet granulation process, prospectively.

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