Investigation of High Shear Wet Granulation Processes Using Different Parameters and Formulations

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This study compared the granulation processes for different formulations using a laboratory-scale high shear mixer. The effects of critical process parameters (impeller speed, chopper speed and kneading time) on granule characteristics were evaluated. The characteristics of the granules studied included the size distribution, friability and morphological properties. The flow profiles of the wet mass and material deposition during the process were also studied. The results obtained showed that the effect of the impeller speed was determined by the starting material system. On the other hand, chopper speeds from 1200 to 3600 rpm and kneading times from 120 to 240 s had a consistent influence on all formulations. Moreover, it was found that the toroidal flow pattern of the wet mass could be maintained for a longer period and granules with a good spherical shape were obtained by removing the chopper during the last 120 s of the granulation process. In addition, the use of the pregelatinized starch in the formulation also led to a reduction in the wall adhesion of the material. It was concluded that the effectiveness of high shear wet granulation could be improved by choosing a proper combination of starting material and process parameters and by monitoring the mass motion during the process.

Key words high shear granulation; process parameter; granule characteristics; flow pattern

High shear mixers have been widely used in the pharmaceutical industry. There are several advantages of granulation in a high shear mixer: a shorter processing time; a need for less liquid binders compared with fluid bed granulators and, thus, a shorter drying process is obtained; voluminous materials can be densified. Moreover, granulation is performed in a closed system, which can include drying (microwave or vacuum); the porosity of the product can be influenced by the massing time and impact of the impeller; cleaning operations can be carried out easily either manually or by a clean-in-place system.[1)] Different phases of growth were identified for high shear granulation: nucleation, fragmentation, densification, exponential growth due to coalescence, and break up.[2)]

Scale-up of the wet granulation processes from laboratory scale to pilot and production scale is problematic. Even within the same manufacture of machine, liquid requirement and granule properties in terms of granule size distribution and granule porosity might change by scaling-up due to the difference space and impact force between large-scale and small-scale machines. However, in many situations, pharmaceutical researchers have to deal with a shortage of active substances and granulation materials. In order to develop a formulation and study the process effectively, laboratory-scale equipment is used during the early stages of research.[3)] Because of the similar structure design to the pilot and production equipments, lab-scale machines are supposed to provide useful information for subsequent granulation in large scale machines of the same type and it is believed that this information will facilitate subsequent large-scale processing.[4,5)]

High shear granulation is a multivariate process and the product properties are sensitive to changes in the process variables such as impeller speed, chopper speed and kneading time hence it is important to work out the effects of these critical parameters.[2,4,6—8)] The microcrystalline cellulose-based (MCC-based) system and starch-based system are two main material systems used for high shear granulation; however, researchers usually chose one of the two systems for their investigations.[5,9)] Because of the popularity of these two systems and the difficulty in scaling up the process, comparison of the high shear granulating process with the two systems mentioned using lab-scale equipment that is representative of large-scale circumstances is necessary for the application of this technique. In addition, it has been found that the toroidal motion of the wet mass during the granulating process could have marked impact on the product properties and the reproducibility of the manufacturing process.[10)] However, few studies report the possibility of maintaining this flow pattern of wet mass by adjusting the process parameters and the raw material.

The aims of present study are to compare the manufacturing process for the two main material systems used for high shear granulation and to try to obtain information about preventing material adhesion and maintaining toroidal motion of the wet mass for the high shear granulation process using a lab-scale high shear mixer. It is expected that this information will be valuable for future manufacturing processes using both lab-scale and large-scale high shear mixers.

Experimental

Materials All the chemicals used in this research were of standard pharmaceutical grade. Microcrystalline cellulose (MCC, Avicel PH 101) was purchased from Asahi Kasei (Japan), α-lactose (Pharmatose 200M) from DMV (Vaghel, The Netherlands) and corn starch and pregelatinized starch from Huzhou Zhanwang Pharmaceutical Co. Ltd. (Zhejiang province, China). Purified water was used as the binder liquid.

Equipment A laboratory-scale vertical high shear mixer (MicroGral®, Collette, Belgium) equipped with 1000 and 4000 ml transparent glass bowls which makes the entire process visible, two three-blade impellers with curved blade tips and choppers were used for granulation in this study. In this design of mixer-granulator, both the impeller blades and chopper are mounted on a vertical shaft fixed through the lip, so that the vessel is easily locked in place and removed when required. The rotational speed of the impeller and chopper can be varied between 0—1800 rpm and 0—4000 rpm, respectively. The product temperature, impeller torque, impeller speed and chopper speed were measured and recorded throughout the granulation process.

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Manufacturing Process In order to compare the characteristics of granules manufactured using different granulation conditions, three formulations and three process parameters were investigated. The compositions of each formulation are shown in Table 1. The process parameters subjected to study were the kneading time, which was defined as the processing time after the addition of binder liquid, the impeller speed and the chopper speed. To examine the basic independent effects of these factors separately for the formulations and the granulator being used, a one-factor experimental approach was applied. Table 2 gives an overview of the settings of the three studied process variables. The effect investigations of the three process parameters were performed for each formulation. Furthermore, in order to fully investigate the basic effects of the above process parameters and to obtain a granulation process without lots of fines and big lumps, we chose a fixed amount of liquid binder for each formulation according to the results of preliminary trials. The amount of liquid was 110 ml, 90 ml and 90 ml for formulations A, B and C, respectively. Liquid was added at a constant rate of 10 ml/min and each experiment was performed in triplicate.

The total mass of each run was 150 g. All the compositions were filled into the vessel and initially blended for 3 min at an impeller speed of 300 rpm and the chopper was turned off during this stage. Binder liquid was then added to the powder bed using a titration device (Universal Titronic, Schott, Germany) while the impeller and chopper speeds were set to the experimental level, and the mass was kneaded for a preset period after addition of the liquid. Prior to standard analysis, the granules produced were dried in a tray dryer at 50 °C for 24 h and then stored in sealed bags.

Granule Characterization. Size Distribution The granule size distribution was estimated by sieve analysis. Samples of about 100 g were sieved using a set of standard sieves (2000, 1600, 1250, 1000, 800, 560, 355, 280 μm), vibrating at an amplitude of 1 mm for 10 min on a Retsch VE1000 shaker (Germany). The fraction remaining on each screen was weighed and expressed as a percentage of the total weight. Meanwhile the medium diameter of granules, which was defined as the particle size corresponding to the 50th weight percentile (X_{50}) of the cumulative particle size distribution was obtained from the cumulative size distribution. All results presented are the mean of 3 determinations. Analysis of variance (ANOVA) of the granule size was performed to evaluate the influence of different process parameters.

Granule Friability A Roche friabilator (Erweka TA20, Heusenstamm, Germany) was used for determination of the granule friability. Samples of 10 g (>250 μm) were placed in the friabilator with 25 6-mm steel balls followed by rotation for 5 min at a speed of 200 rpm. After rotating, granules were sieved using a 160 μm screen. The friability value was calculated as the percentage of the undersize weight after sieving relative to the initial weight of the granules (10 g).

Particle Image Analysis Particle image analysis of the granules produced was carried out using a computer-assisted image analysis system. The samples were magnified by a Sony color video camera and the output signals were captured and analyzed by Olympus Micro Image-Image analysis software, in an MS Windows operating system. Therefore, useful morphological information about the granules was obtained by computing the digitization of the particle images. The assays were performed on 8 granules each time and a total of 120 granules were tested for each batch. Some important shape descriptors of the granules, such as the aspect ratio, perimeter, area and roundness, were taken into account. In our study, the roundness value of granules was calculated as $4\pi\times[\text{area}/(\text{perimeter})^2]$.

Scanning Electron Microscopy (SEM) Photomicrographs of the granules were obtained using a scanning electron microscope (JSM-5200, Jeol, Japan). Samples were mounted on a plate using carbon paint and coated with gold before the examination.

Results and Discussion

Effect of the Impeller First of all, the effects of the impeller were studied. From the statistical analysis results reported in Table 3 and the size distribution information shown in Fig. 1, it can be seen that the effect of the impeller speed on the granule size distribution observed in the case of formulation A was quite different from that observed in the case of formulations B and C. However, in the case of formulations B and C, the impeller speed affected the granule size distribution in a similar way. As can be seen, increasing the impeller speed resulted in the formation of large granules in formulation A ($p<0.01$). The larger medium particle diameter obtained from the cumulative size distribution curve could be probably caused by the increased chance of colliding resulting from the impeller rotation at a high speed, which is necessary for granule growth. This is in accordance with the results reported by other researchers.[7,11] In contrast with the effect observed in formulation A, the results obtained from formulations B and C showed a reduction in granule size when high impeller speeds were used ($p<0.05$). The impeller of a high shear mixer in general imparts shearing and compaction forces to the wet mass and promotes material agglomeration and a size increase. However, a destructive force is also produced by the impeller, and its power is especially significant at a high rotation speed. Therefore, the smaller granule size values attained for formulations B and C may be explained by the destructive force exerted by the high speed rotation. When the destructive force resulting from the

Table 1. Composition of the Formulations Investigated

Formulation	MCC (g)	Lactose (g)	Corn starch (g)	Pregelatinized starch (g)
A	100	50	—	—
B	—	50	100	—
C	—	50	80	20

Table 2. Granulation Conditions Chosen for Investigations of the Process Parameters

Parameter being investigated	Trial No.	Level of parameter	Other process parameters used in the experiments		
			Impeller speed (rpm)	Chopper speed (rpm)	Kneading time (s)
Impeller speed (rpm)	1 2 3	300 500 700	—	1500	180
Chopper speed (rpm)	4 5	1200 3600	500	—	180
Kneading time (s)	6 7 8	120 s 180 s 240 s	600	1500	—
Additional test on the existence of the chopper	9	—	500	1500 (chopper was removed during the last 120 s)	180

Table 3. Analysis of Variance (ANOVA) of the Mean Size of Granules Produced Using Different Process Parameters

	Statistical parameter	Impeller speed		Chopper speed		Kneading time	
		Between groups	Within groups	Between groups	Within groups	Between groups	Within groups
Form. A	Sum of squares	99432.850	7703.851	8706.537	3693.231	155230.609	21318.053
	Mean square	49716.425	1283.975	4354.769	615.539	77615.304	3553.009
	F-value	38.721		7.075		21.845	
	Significance (p)	0.000		0.026		0.002	
Form. B	Sum of squares	57156.989	7755.151	8944.154	1486.767	99558.589	10361.061
	Mean square	28578.494	1292.525	4472.077	247.794	49779.295	1726.844
	F-value	22.111		18.048		28.827	
	Significance (p)	0.002		0.003		0.001	
Form. C	Sum of squares	41036.513	11757.512	3820.167	2120.318	71718.202	6944.400
	Mean square	20518.257	1959.585	1910.084	353.386	35859.101	1157.400
	F-value	10.741		5.405		30.982	
	Significance (p)	0.011		0.045		0.001	

Process parameters being studied: Impeller speed, Chopper speed, Kneading time.

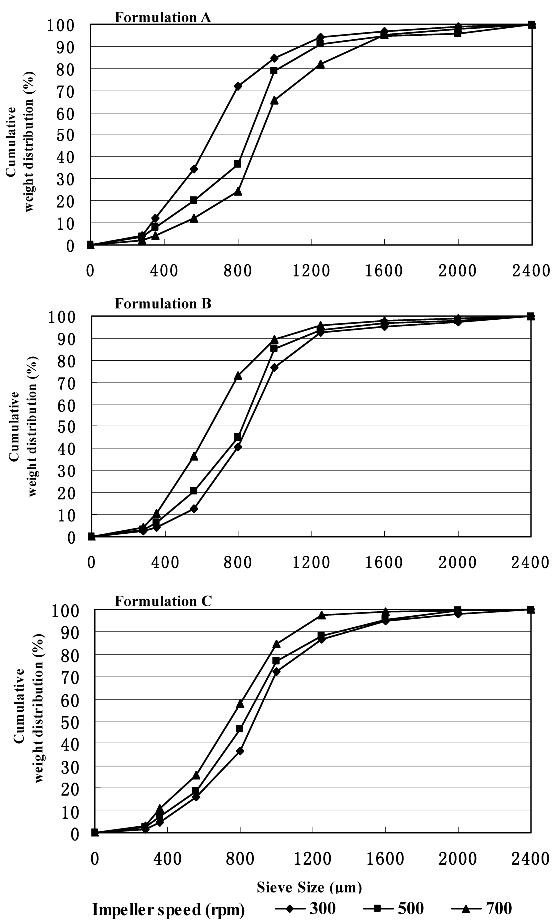

Fig. 1. Granule Size Distributions for the Experiments Carried Out with Different Impeller Speeds and Formulations

intensive agitation exceeds the bonding force, the equilibrium between granule growth and break-up is disrupted and the latter is preferred.[10] This means that further growth is retarded and the proportion of fines is increased. This equilibrium point is also determined by the properties of the starting material. In this study, it is assumed that the strength of the granules obtained using the starch-based system (formulations B and C) is weaker than that obtained from the microcrystalline cellulose-based system (formulation A). The results of the friability test (Table 4) showed a difference in granule strength between the starch-based and microcrystalline cellulose-based granules, which confirms that the granulation process using starch as dominant starting material produced granules with a relatively weaker strength under the same production conditions.

Effect of the Chopper The primary function of the chopper in a high shear mixer is to cut lumps into smaller pieces and help the distribution of the binder. The observed effects of the chopper speed on the granule properties in this study can be seen in Fig. 2. The fact that increasing the chopper speed from 1200 to 3600 rpm slightly reduced the granule size expressed by the X_{50} value may be due to the scale of the chopper. It appeared that the small chopper in this lab-scale high shear mixer failed to provide an adequate destructive force even at a high rotation speed. As a result, the power of the chopper to prevent the granule from increasing in size is limited compared with the dramatic effect provided by the routine large-scale chopper.

Another interesting and important effect of the chopper on the granulation process must be paid attention to is that the particle moving direction changed after the particle–chopper interaction during the kneading stage, resulting in a fluctuation in the flow profile of the wet mass. At the early stage of the granulation process, big lumps were formed by nucleation owing to topical overwetting of the dry powder bed and the poor distribution of the liquid binder. The big lumps then disappeared because of the improved binder distribution which was attributed to the presence of the impeller and chopper. At this stage, as described in the literature, the powder bed was wet enough and granule growth occurred.[2] In our study, a torus flow pattern was observed at this stage, demonstrating that the homogeneity of the wet mass was improved. To ensure efficient granule growth and make the process more reproducible, it is important that high shear granulation maintains the wet mass motion in this kind of flow pattern. Unfortunately, in the case of formulations A and B, the toroidal motion of the wet mass failed to be maintained for a long enough period. It was observed that the toroidal motion was disturbed as the granules changed their direction after the granule–chopper collision and the propor-

Table 4. Overview of the Granule Friability and Material Deposition in All Runs[a,b]

Parameter being investigated	Trial No.	Friability (%)			Material deposited (%)		
		Form. A	Form. B	Form. C	Form. A	Form. B	Form. C
Impeller speed	1	10.7	30.2	28.8	18.6	24.1	7.2
	2	7.2	26.6	27.1	21.9	27.8	8.0
	3	5.5	19.4	23.7	28.8	29.1	8.7
Chopper speed	4	8.9	28.6	23.1	24.6	30.7	9.4
	5	9.4	26.1	20.9	20.5	27.7	9.0
Kneading time	6	11.8	34.1	31.4	20.6	26.5	6.1
	7	6.0	24.4	25.0	27.9	30.3	7.7
	8	2.6	19.3	16.7	30.8	36.9	10.8
Additional test	9	4.7	20.2	14.7	12.6	17.3	6.9

a) Observed values are the mean of 3 determinations. *b*) Settings of the process parameters in each trial are in accordance with those given in Table 2.

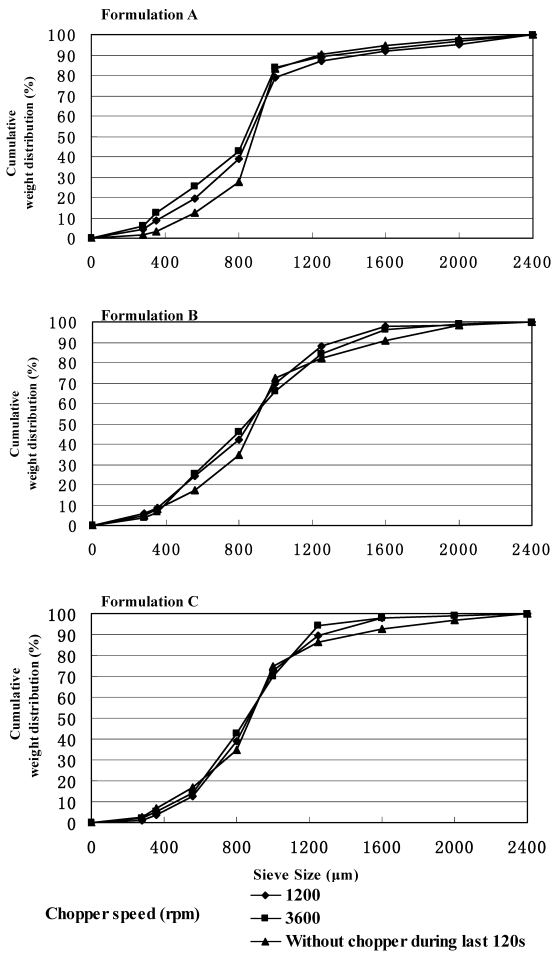

Fig. 2. Granule Size Distributions for the Experiments Carried Out with Different Chopper Speeds and Formulations

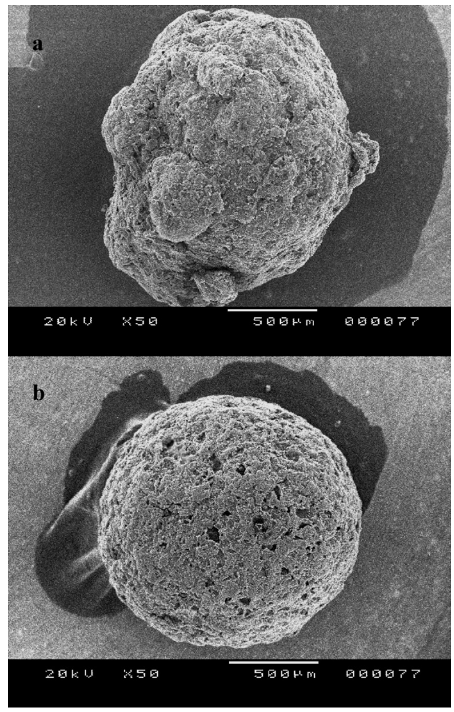

Fig. 3. SEM Photographs of Granules Prepared Using Formulation A with Chopper (a) and without Chopper (b) during the Last 120 s of the Kneading Phase

tion of the material that adhered to the inner surface of the bowl was increased. As a consequence, the granulation process was invisible and the amount of motive granules was reduced leading to excessive powder agglomeration at a later stage of the process. This phenomenon may be due to the narrow space between the chopper and the wall. After colliding with the chopper, the granules changed their direction of movement. However, the granules failed to pass through the narrow channel and can not return to their previous trajectory, resulting in the adhesion of material and the loss of toroidal motion. This phenomenon was not observed in a 600-L vessel[12] and this is consistent with our assumption.

In order to evaluate the effect of the chopper on the flow profile and the properties of the granules, an additional standard granulation process, with the removal of the chopper during the last 120 s of the kneading phase, was performed using the same formulations and process parameters. As shown in Table 3 and Fig. 2, granules prepared without using the chopper during the last 2 min were larger than those prepared with the chopper ($p<0.05$). Moreover, a narrower size distribution and reduced material deposition were obtained under this circumstance, revealing that granule homogeneity was improved and uncontrolled granule growth was prevented effectively (Table 4). Scanning electron micrographs of the granules prepared with and without the chopper using formulation A are shown in Fig. 3. As can be seen, granules prepared without the chopper were more spherical and had a smoother surface which was resulted from the longer period of toroidal motion. The results obtained with formulations B

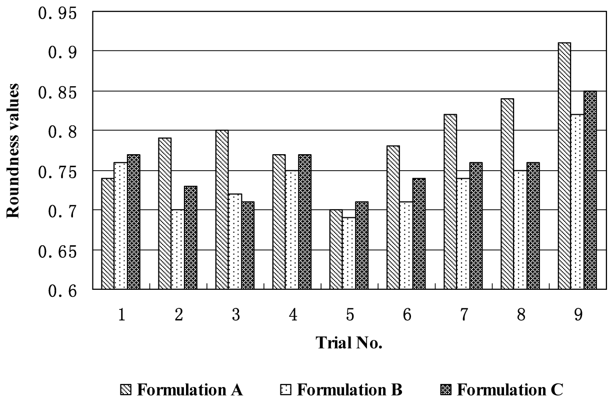

Fig. 4. Roundness Values of the Granules Prepared Using Different Granulation Conditions

and C were similar (pictures not shown). Moreover, image analysis was carried out to examine the morphological characteristics of the granules (only roundness values are presented). The result shows that, after removing the chopper, the extent of the increased granule roundness value was 0.21 (formulation A), 0.13 (formulation B) and 0.14 (formulation C), respectively (Fig. 4). Together with the SEM results, this shows that the granulation process and granule characteristics can be improved effectively by removal of the chopper during the later stage of the process.

Effect of the Kneading Time It is unsurprising that the effects of the kneading time on the medium size of granules prepared in all runs were thoroughly positive (Table 3, Fig. 5). This is in accordance with the results provided by other authors.[5] High X_{50} values were obtained when long kneading times were used. This can be explained by the improved wet status of the mass and the fact that a long kneading period offers more chances of colliding which is necessary for granule growth.

Material Deposition The material deposition is another important phenomenon which must be emphasized during the high shear granulation process since it leads to substantial material adhesion to the wall and an uncontrollable granule preparation. In our study, the percentage of material adhered to the wall was calculated as:

$$\text{adhesion (\%)} = \frac{W_i - W_f}{W_i} \times 100\%$$

Where W_i is the initial total weight of the powder and W_f is the final weight of granules collected.

As shown in Table 4, increasing the impeller speed in general led to a worsening of wall adhesion in all runs. The increasing centrifugal force exerted by the high rotation speed of the impeller may contribute to this problem. The observed influences of the kneading time on wall adhesion, as gradually increasing the amount of material adhered to the wall in all runs, may be explained by the fact that a long period of kneading increased the amount of liquid binder squeezed out from the interior of the granules to the surface. Consequently, the wet mass was more adhesive and the adhesion to the wall was worsened. In addition, this fact could be a reason for the granule size growth when a longer kneading time was used. Therefore, the kneading time is a critical process parameter which should be taken into account during the high shear granulation process.

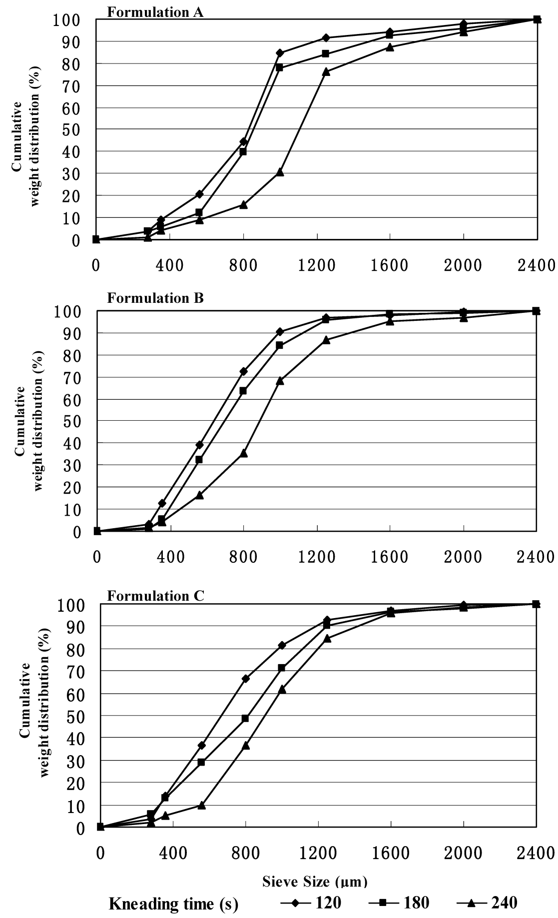

Fig. 5. Granule Size Distributions for the Experiments Carried Out with Different Kneading Times and Formulations

In the case of formulations A and B, the amount of wall adhesion ranged from 18.6 to 36.9%, hence it reduced the product yield. However, interestingly, the granulation process using formulation C, gave rise to a significantly decreased wall adhesion of 6.1%, implying that material deposition onto the wall could be lessened in presence of pregelatinized starch. Moreover, it was observed that the toroidal motion of the wet mass in the case of formulation C could be maintained for a longer period in comparison with the granulation process using formulations A and B. The observed anti-adherent effect of the pregelatinized starch may be due to its good flowability and self-lubrication which reduced the adhering interaction between the wet mass and the wall.

Conclusion

In summary, this research has enabled us to conclude that the manufacturing processes with both MCC-based and starch-based system are strongly affected by the process parameters. On the other hand, due to the difference between these two systems, product properties might be reversed even though the same manufacturing conditions were applied. Accordingly, choosing a good combination of process parameters and starting material is essential for high shear granulation. Moreover, by removing the chopper during the last stage of the process and using pregelatinized starch as the anti-adherent, the toroidal motion of the wet mass can be maintained for a longer period and wall adhesion can be lessened thereby increasing the effectiveness of the granulation process.

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References

1) Parikh D. M., "Handbook of Pharmaceutical Granulation Technology," Marcel Dekker, Inc., New York, 1997, pp. 152—204.
2) Vonk P., Guillaume C. P. F., Ramaker J. S., Vromans H., Kossen N. W. F., *Int. J. Pharm.*, **157**, 93—102 (1997).
3) Franke G., Steffens K. J., *Pharm. Ind.*, **61**, 861—865 (1999).
4) Ameye D., Keleb E., Vervaet C., Remon J. P., Adams E., Massart D. L., *Eur. J. Pharm. Sci.*, **17**, 247—251 (2002).
5) Bock T. K., Krass U., *Eur. J. Pharm. Biopharm.*, **52**, 297—303 (2001).
6) Fekete R., Marton S., Farkas E., Racz I., *Die Pharmazie*, **54**, 200—202 (1999).
7) Hamdani J., Moes A. J., Amighi K., *Int. J. Pharm.*, **245**, 167—177 (2002).
8) Voinovich D., Moneghini M., Perissutti B., Franceschinis E., *Eur. J. Pharm. Biopharm.*, **52**, 305—313 (2001).
9) Vojnovic D., Selenati P., Rubessa F., Moneghini M., Zanchetta A., *Drug Dev. Ind. Pharm.*, **18**, 961—972 (1992).
10) Ramaker J. S., Jelgersma M. A., Vonk V., Kossen N. W. F., *Int. J. Pharm.*, **166**, 89—97 (1998).
11) Zhou F., Veraet C., Remon J. P., *Int. J. Pharm.*, **147**, 23—30 (1997).
12) Faure A., Grimsey I. M., Rowe R. C., York P., Cliff M. J., *Eur. J. Pharm. Sci.*, **8**, 85—93 (1999).