# Effect of Process Variables on the Properties and Binder Distribution of Granules Prepared by a High-Speed Mixer

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**A model system consisting of lactose-cornstarch-microcrystalline cellulose with hydroxypropyl methylcellulose 2910 (HPMC 3 cP) as a binder was used to estimate the effects of process variables (granulation time, amount of granulating water and impeller speed) on the particle size distribution of granules prepared in a high-speed mixer using a dry mixing method of binder addition. The distribution of binder in different size fractions of granules was also determined by measuring the contents of methoxyl group. The binder content interpolated at the median particle size was close to the theoretical value calculated from the formulation. Longer granulation time, greater amount of granulating water and higher impeller speed increased the granule size and strength. An expanded binder distribution was seen at higher impeller speed. At extremely short granulation time (1 min), the granules were friable and the binder content in the larger size fraction of the granules changed during fluid-bed and tray drying because of insufficient binder dissolution or granular compaction. Binder behavior during wet granulation seems to be closely related to the observed differences in granule strength.**

**Key words** cellulose ether; high-speed mixer; binder distribution; granule size distribution; dry mixing; process variable

In wet granulation processes the binder not only affects the liquid bridging of particles, but also prevents agglomerated particles from separating during the drying process. Binder distribution in the different size fractions has profound effects on the properties of both the granules, as shown in our previous papers,[1,2] and the final products, as shown by others,[3] and thus control of the binder distribution is very important in the field of pharmaceutical technology.

High-speed mixer granulation is widely employed for the production of granules for tablets and fine granule preparations, and its many process variables have been extensively studied.[4-6] However, most studies have focused on the wet granulation process using binder solution, and little information is available regarding the dry mixing method of binder addition.[7]

In the dry mixing method of binder addition, dissolution of the binder particles is the key step in bond formation between particles through the formation of solid bridges after drying. In the solution method of binder addition using a yellow aluminum lake, distribution of the dye component in different size fractions of granules can be determined as the ratio of the amount of dye on the carrier surface to that between particles, and it was shown by this means that drying conditions had no influence on the distribution.[8-10]

In a previous study, we employed a high-speed mixer to analyze the granule size dependency of binder content in order to examine the role of binders in the dry mixing method.[1] The aim of the present study was to extend this approach and examine the effects of process variables (granulation time, amount of granulating water, impeller speed and drying conditions) on the properties and binder distribution of granules obtained with a fixed formulation using hydroxypropyl methylcellulose 2910 (HPMC 3 cP) as the binder. Based on the powder properties of the granules and the binder distribution in them, we discuss the behavior of binder particles during the wet granulation process.

## Experimental

**Materials** Powder materials used were lactose (Pharmatose 200M, DMV Co.) and cornstarch (Cornstarch W, Nihon Shokuhin Kako Co.). Hydroxypropyl methylcellulose 2910 (HPMC : Pharmacoat 603, JP, Shin-Etsu Chemical Co.) was used as a binder and its 2% aqueous solution showed a viscosity of 3.22 cP at 20 °C.

**Mixture Composition** As shown in Table 1, the basal material was prepared by mixing lactose and cornstarch at a ratio of 7 : 3 (3360 g and 1440 g, respectively) and adding microcrystalline cellulose to make 4% (200 g) of the total (5000 g). The binder level tested was fixed at 3% (150 g).

**Wet Granulation** In the standard condition, lactose (3360 g), cornstarch (1440 g), microcrystalline cellulose (200 g) and HPMC (150 g) were mixed for 1 min in a high-speed mixer (Vertical granulator, Model FM-VG-25, Powrex Co.) at an impeller speed of 300 rpm and a chopper speed of 3000 rpm. Water (1 l) was then added and granulation was conducted for 10 min. The obtained granules were dried in a fluidized bed apparatus (Glatt WSG-5, Ohkawara Manufacturing Co.) with a supply air temperature of 70 °C, until the exhaust air temperature reached 35 °C. Dried granules were sieved through a 12 mesh sieve and subjected to analyses.

**Analyses of Granules** A 50 g sample was sieved for 5 min using combinations of standard sieves (20 cm in diameter) with a Ro-Tap Testing Sieve Shaker (The W. S. Tyler Co.). The weight of residual granules in each sieve was measured and used for calculation of the median particle size (D50). The granule strength was expressed as the percentage difference in the quantity of granules that passed through a 75 $\mu$m sieve between 20 min sieving and 5 min sieving. The smaller the percentage, the stronger the granules are. The binder contents in sieved fractions of granules were analyzed by gas chromatography according to the test method of the JP XII, as previously described.[1]

Table 1. Formulation of Powder Mixture

| Component | Weight (g) |
|---|---|
| Lactose | 3360 |
| Cornstarch | 1440 |
| Microcrystalline cellulose | 200 |
| Total | 5000 |
| Binder | 150 |
| Water | 1000 (900, 1100 ml) |

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## Results and Discussion

**Effect of Process Variables on Particle Size Distribution** The results obtained by granulation with various values of the process variables are summarized in Table 2.

Longer granulation time increased granule size and the particle size distribution, as shown in Fig. 1a. From the profiles of particle size distribution (Table 2), it appears that in the early stage of the granulation, coarse agglomerates ($>500\,\mu$m) were formed, then some breakdown occurred as the granules compacted. It is well known that the amount of granulating liquid used strongly affects the granule growth. A greater amount of granulating water resulted in granule growth and expansion of the particle size distribution (Fig. 1b). Higher impeller speed had similar effects, especially expansion of the particle size distribution (Fig. 1c). At 450 rpm, the granules were separated into two portions, a fine powder fraction ($<106\,\mu$m) and a coarse particle fraction ($>250\,\mu$m), by cutting of the agglomerates as a result of the excess mechanical agitation (Table 2).

The relationships between median particle size, geometric standard deviation and the operating conditions are illustrated in Fig. 2. As shown, a granulation time of 10 min in the present case, granulating water amount of 1000 ml, and impeller speed of 300 rpm were recognized as appropriate standard conditions giving the minimum values of geometric standard deviation ($\sigma g$).

**Effect of Process Variables on Binder Distribution** The binder content in each granule fraction is shown in Table 3, and the relationships between binder distribution and the operating conditions are illustrated in Fig. 3. For all conditions tested, the binder content interpolated at the median particle size was close to the theoretical value calculated from the formulation. This trend was consistent with that previously reported.[1,2]

Longer granulation time decreased the binder content in each fraction, especially under 75 $\mu$m, where a significant reduction of the binder content was observed, as shown in Fig. 3a. A greater amount of granulating water also decreased the binder content in each fraction (Fig. 3b), as did a higher impeller speed (Fig. 3c). With all three variables, as the granule size increased, more of the binder was concentrated in the coarse particle fraction. This suggests that the binder is dissolved and is located at the interstices of the carrier rather than on the surface, based on the study of the solution method of binder addition by Nishimura and his colleagues,[8-10] in which the amount of inter-carrier binder increased with localization of the binder in the coarse fraction.

**Effect of Drying Conditions on Binder Distribution and Granule Strength** The binder content of the granules

Table 2. Particle Size Distribution for Dry Mixed Batches Prepared by High-Speed Mixer with Drying until the Exhaust Air Temperature Reached 35 °C

| Batch | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| Granulation time (min) | 10 | 1 | 3 | 20 | 10 | 10 | 10 | 10 |
| Granulating water (ml) | 1000 | 1000 | 1000 | 1000 | 900 | 1100 | 1000 | 1000 |
| Impeller speed (rpm) | 300 | 300 | 300 | 300 | 300 | 300 | 150 | 450 |
| Particle size distribution (%) | | | | | | | | |
| 500 $\mu$m on | 8.6 | 11.0 | 9.4 | 10.7 | 6.6 | 17.3 | 14.0 | 8.0 |
| 355 $\mu$m on | 9.8 | 3.4 | 5.2 | 25.0 | 5.2 | 39.4 | 7.2 | 35.9 |
| 250 $\mu$m on | 17.3 | 7.0 | 10.2 | 30.7 | 9.2 | 21.1 | 9.2 | 15.5 |
| 180 $\mu$m on | 18.6 | 8.7 | 14.8 | 7.3 | 12.6 | 3.9 | 12.6 | 2.8 |
| 150 $\mu$m on | 12.4 | 8.6 | 11.7 | 2.2 | 11.2 | 2.6 | 11.8 | 2.0 |
| 106 $\mu$m on | 15.9 | 24.6 | 26.7 | 8.3 | 31.2 | 6.5 | 27.8 | 9.0 |
| 75 $\mu$m on | 10.6 | 23.9 | 14.8 | 8.7 | 16.2 | 4.5 | 12.6 | 12.9 |
| 75 $\mu$m pass | 6.8 | 12.8 | 7.2 | 7.1 | 7.8 | 4.7 | 4.8 | 13.9 |
| Median particle size ($\mu$m)[a)] | 194 | 128 | 153 | 302 | 142 | 376 | 162 | 309 |

*a)* Cumulative 50% by weight.

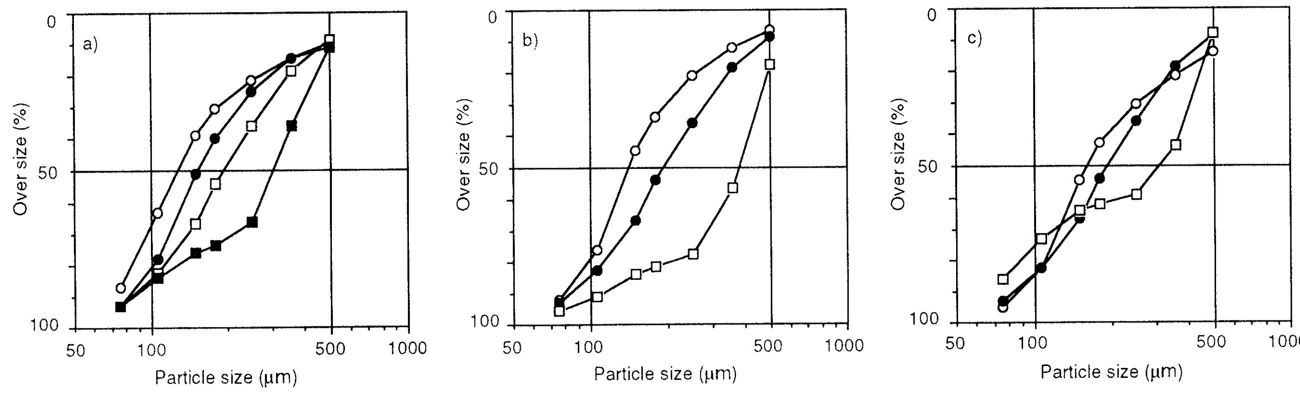


Fig. 1. Effect of Operating Conditions on the Particle Size Distribution

a) Granulation time: ○, 1 min; ●, 3 min; □, 10 min; ■, 20 min; b) granulating water: ○, 900 ml; ●, 1000 ml; □, 1100 ml; c) impeller speed: ○, 150 rpm; ●, 300 rpm; □, 450 rpm.

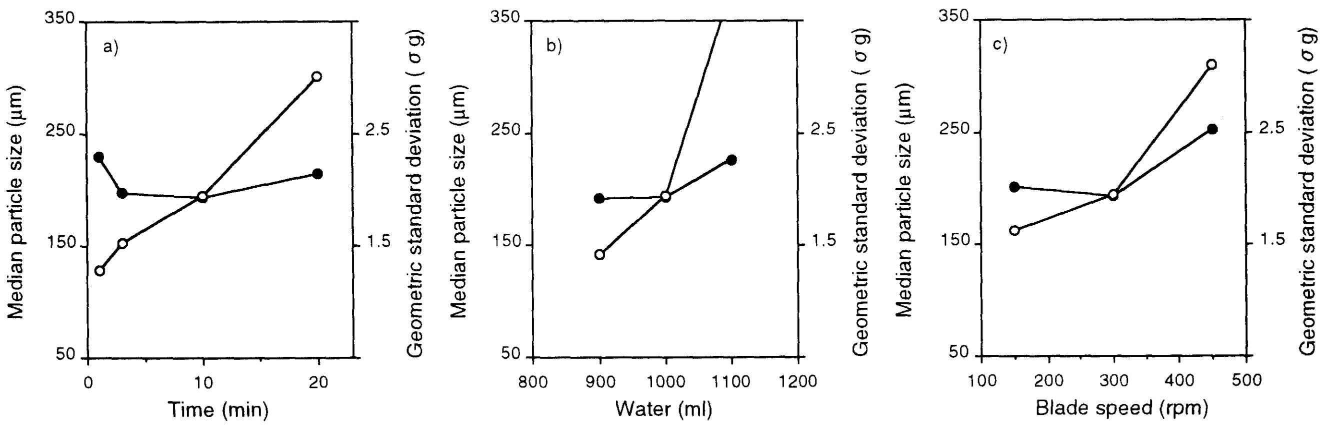


Fig. 2. Relationship between Median Particle Size, Geometric Standard Deviation and Operating Conditions
a) Granulation time, b) granulating water, c) impeller speed. Key: ○, median particle size (μm); ●, geometric standard deviation (σg).

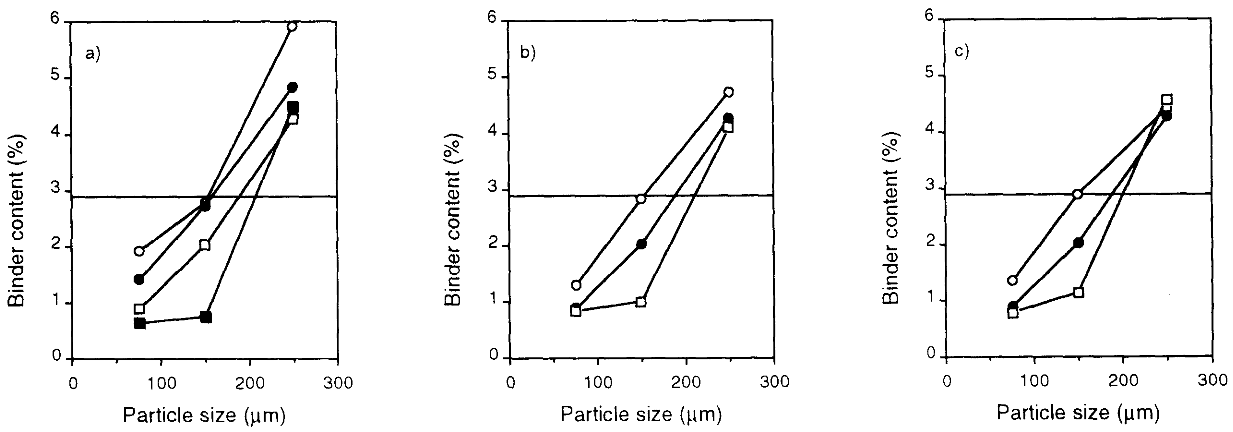


Fig. 3. Effect of Operating Conditions on the Binder Distribution
a) Granulation time: ○, 1 min; ●, 3 min; □, 10 min; ■, 20 min; b) granulating water: ○, 900 ml; ●, 1000 ml; □, 1100 ml; c) impeller speed: ○, 150 rpm; ●, 300 rpm; □, 450 rpm.

Table 3. Binder Content Distribution According to Particle Size for Dry Mixed Batches Prepared by High-Speed Mixer with Drying until the Exhaust Air Temperature Reached 35 °C

| Batch | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| Granulation time (min) | 10 | 1 | 3 | 20 | 10 | 10 | 10 | 10 |
| Granulating water (ml) | 1000 | 1000 | 1000 | 1000 | 900 | 1100 | 1000 | 1000 |
| Impeller speed (rpm) | 300 | 300 | 300 | 300 | 300 | 300 | 150 | 450 |
| Binder content (%) | | | | | | | | |
| 250—355 μm | 4.28 | 5.93 | 4.83 | 4.48 | 4.72 | 4.10 | 4.41 | 4.59 |
| 106—150 μm | 2.03 | 2.79 | 2.72 | 0.76 | 2.83 | 1.00 | 2.90 | 1.14 |
| 75 μm pass | 0.90 | 1.93 | 1.41 | 0.66 | 1.31 | 0.83 | 1.34 | 0.79 |
| Theoretical value (%) | 2.91 | | | | | | | |

Table 4. Binder Content Distribution According to Particle Size for Dry Mixed Batches Prepared in a High-Speed Mixer with Tray Drying at 40 °C

| Batch | A | B | C | D |
|---|---|---|---|---|
| Granulation time (min) | 10 | 1 | 3 | 20 |
| Granulating water (ml) | 1000 | 1000 | 1000 | 1000 |
| Impeller speed (rpm) | 300 | 300 | 300 | 300 |
| Binder content (%) | | | | |
| 250—355 μm | 4.14 | 4.48 | — | 4.34 |
| 106—150 μm | 2.03 | 2.79 | — | 0.76 |
| 75 μm pass | 0.86 | 2.03 | — | 0.62 |
| Theoretical value (%) | 2.91 | | | |

subjected to tray drying is shown in Table 4. At extremely short granulation time (1 min) even distribution of granulating water throughout the wet mass is difficult, and this may influence dissolution of the binder. Insufficient dissolution of the binder particles would result in a decrease of the binder content in the larger size fraction, producing weakly bonded particles which would tend to be broken during the drying process.

The effects of drying conditions on median particle size and granule strength are shown in Table 5. For all values of the process variables, granules prepared by tray drying showed great granule strength. Binder dissolution might

Table 5. Median Particle Size and Granule Strength for Dry Mixed Batches Prepared in a High-Speed Mixer under Different Drying Conditions

| Batch | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| Granulation time (min) | 10 | 1 | 3 | 20 | 10 | 10 | 10 | 10 |
| Granulating water (ml) | 1000 | 1000 | 1000 | 1000 | 900 | 1100 | 1000 | 1000 |
| Impeller speed (rpm) | 300 | 300 | 300 | 300 | 300 | 300 | 150 | 450 |
| Fluid-bed drying at 35 °C[c] | | | | | | | | |
| Median particle size ($\mu$m)[a] | 194 | 128 | 153 | 302 | 142 | 376 | 162 | 309 |
| Granule strength (%)[b] | 2.2 | 7.6 | 3.0 | 1.7 | 3.0 | 0.4 | 0.5 | 1.1 |
| Tray drying at 40 °C[d] | | | | | | | | |
| Median particle size ($\mu$m) | 221 | 142 | 176 | 295 | 163 | 380 | 170 | 335 |
| Granule strength (%) | 0.5 | 0.1 | 0.4 | 0.2 | 0.0 | 0.6 | 0.6 | 0.4 |

*a*) Cumulative 50% by weight. *b*) Difference of 75 $\mu$m pass between 5 and 20 min sieving time. *c*) Until the exhaust air temperature reached 35 °C. *d*) Drying in an oven at 40 °C for 16 h.

be promoted during the tray drying due to the slow evaporation of water. However, insufficient granulation time and amount of granulating water resulted in a significant reduction of the granule strength.

## Conclusion

The effects of process variables on the relationship between the distribution of the binders in different size fractions and the physical properties of the granulated products obtained by high-speed mixer granulation using the dry mixing method were investigated. The results were as follows: 1) Among the three variables, granulation time, amount of granulating water and impeller speed, changes that caused granule growth led to the binder being concentrated in the coarse particle fraction. These changes were believed to favor dissolution of the binder particles, and the binder solution was taken up mainly by the coarse particles. The binder content interpolated at the median particle size was close to the theoretical value calculated from the formulation. 2) Longer granulation time, higher amount of granulating liquid and higher impeller speed resulted in expansion of the binder distribution. Generally, in the wet granulation process, agglomeration of the particles by liquid bridging occurs initially, then further growth results from cutting, compaction and adhesion of the agglomerates.[11] This might be explained in terms of cleavage of bonded particles by the impeller at regions of the particles where the binder concentration is low, thus promoting binder separation, *i.e.*, the cutting occurs selectively, not at random, in the high-speed mixer granulation process. This mechanism of binder separation is consistent with the finding that the granules prepared at 450 rpm contained a larger amount of fine powder fraction with low binder concentration than those prepared under the standard condition, (300 rpm) (Fig. 1c). 3) At extremely short granulation time (1 min), weakly bonded particles were formed due to insufficient dissolution of the binder, and these particles were broken during the drying process.

In most cases of production by a wet granulation process, after high-speed mixer granulation, the wet mass is forced through oscillating screens or various kinds of mills.[12] Our study has shown that most of the binder is located in the coarse fraction of the granules after granulation, so the subsequent screening or milling process may improve its distribution. Analysis of the binder distribution in the product granules appears to be a useful approach to optimizing the process variables.


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