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Effect of Process Variables on the Properties and Binder Distribution of Granules Prepared in a Fluidized Bed

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A lactose-cornstarch model system with hydroxypropyl methylcellulose 2910 (HPMC 3 cP) as a binder was used to evaluate the effects of several process variables (moisture level, spray feed rate and drying air flow rate) on the particle size distribution of granules prepared in a fluidized bed using a dry mixing method of binder addition. Moisture levels were controlled *via* an infrared moisture sensor. The distribution of binder in different sized fractions of granules was also determined by measuring the contents of the methoxyl group. Moisture level was the most important factor for granule growth, and higher moisture levels increased the granule size. The time for which a given moisture level was maintained and the fluidizing air flow rate had little effect on granule size, size distribution, binder distribution or apparent density. This implies that mixing is efficient during fluidized bed granulation by the dry mixing method and that binder behavior is mainly determined by the moisture level of the wet mass. It was concluded that if a fixed moisture level is maintained during fluidized bed granulation with the dry mixing method of binder addition, variation of the other operational conditions should have little effect on the consistency of the product.

Key words cellulose ether; fluidized bed granulation; binder distribution; granule size distribution; dry mixing; process variable

Control of the binder distribution in wet granulation processes is critical because the binder not only affects the liquid bridging of particles, but also prevents separation of agglomerated particles during the drying process. Binder distribution in different sized fractions profoundly affects the properties of both the granules, as shown in our previous papers,[1−3] and the final products.[4]

Fluidized bed granulation is widely employed for the production of granules for tablets and fine granule preparations, and meets the requirements of good manufacturing practice (GMP) very well, since mixing, granulation and drying are combined in a single process. Much is known about the mechanism of granulation and the effects of process variables.[5−9] However, relatively little focus has been placed on the dry mixing method of binder addition.[10−13] In this method, dissolution of the binder is essential for the bonding of particles through the formation of solid bridges after drying. It is well known that the moisture content of the powder mixture is the most important factor for granule growth, and a practical method of measurement and control of the moisture content in fluidized bed granulation by using an infrared moisture sensor has been reported.[14,15] These studies, however, were focused on controlling the process, but little information is available concerning the binder behavior or mechanism of granulation. It was therefore of interest to investigate the process variables, at a fixed moisture level, that influence the granule growth and distribution.

In previous studies, we employed a high-speed mixer and a fluidized bed to analyze the granule size dependency of binder content in order to examine the role of the binder in the dry mixing method.[1−3] Here, we extend this approach to examine the effects of several process variables (moisture level, spray feed rate and drying air flow rate) on granule growth and binder distribution in the fluidized bed granulation of a fixed formulation with hydroxypropyl methylcellulose 2910 (HPMC 3 cP) as the binder.

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, USP, 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, and to this mixture, 5% binder was added.

Granulation For the standard procedure, lactose (2000 g), cornstarch (1200 g) and HPMC (200 g) were mixed for 5 min in a fluidized bed (Flow coater, Model FLO-5, Freund Industry Co.) under a 2.2 m^3/min drying air flow rate at 80 °C. Water (1600 g) was then sprayed at 100 g/min. The process variables of the fluidized bed are listed in Table 2. Drying was conducted continuously in the same vessel until the exhaust temperature reached 35 °C. Dried granules were sieved through a 12-mesh sieve and subjected to analyses.

Moisture Content Control The moisture content of the powder bed during operation was continuously monitored by an infrared moisture sensor (Wet Eye, Fuji Paudal Co.) fitted to the fluidized bed system at the container. The sensor was calibrated before use.

The moisture level was maintained by on–off switching of a roller pump at the desired value for each experiment, and overshoot of the moisture content was within 0.5% in all experiments.

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

Table 1. Formulation of Powder Mixture

Component	
Lactose	2800 g
Cornstarch	1200 g
Total	4000 g
Binder	200 g
Water	1600 g (2400 g)

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75 μm sieve between 20 min sieving and 5 min sieving; the smaller the percentage, the stronger the granules. The binder content in sieved fractions of granules was analyzed by gas chromatography according to the test method of the JP XIII, as previously described.[1]

Results and Discussion

Effect of Process Variables on the Particle Size Distribution The results obtained by granulation with various values of the process variables are summarized in Table 2. The moisture fluctuation patterns in these experiments are illustrated in Fig 1. We used a slightly higher spray feed rate than the moderate spray feed rate in a previous study[2] in order to control the moisture level as required. The patterns of change in moisture (%) for various values of target moisture level, maintain time and drying air flow rate are shown in Figs. 1a), 1b) and 1c), respectively.

A higher moisture level increased the granule size and expanded the particle size distribution, as shown in Fig.

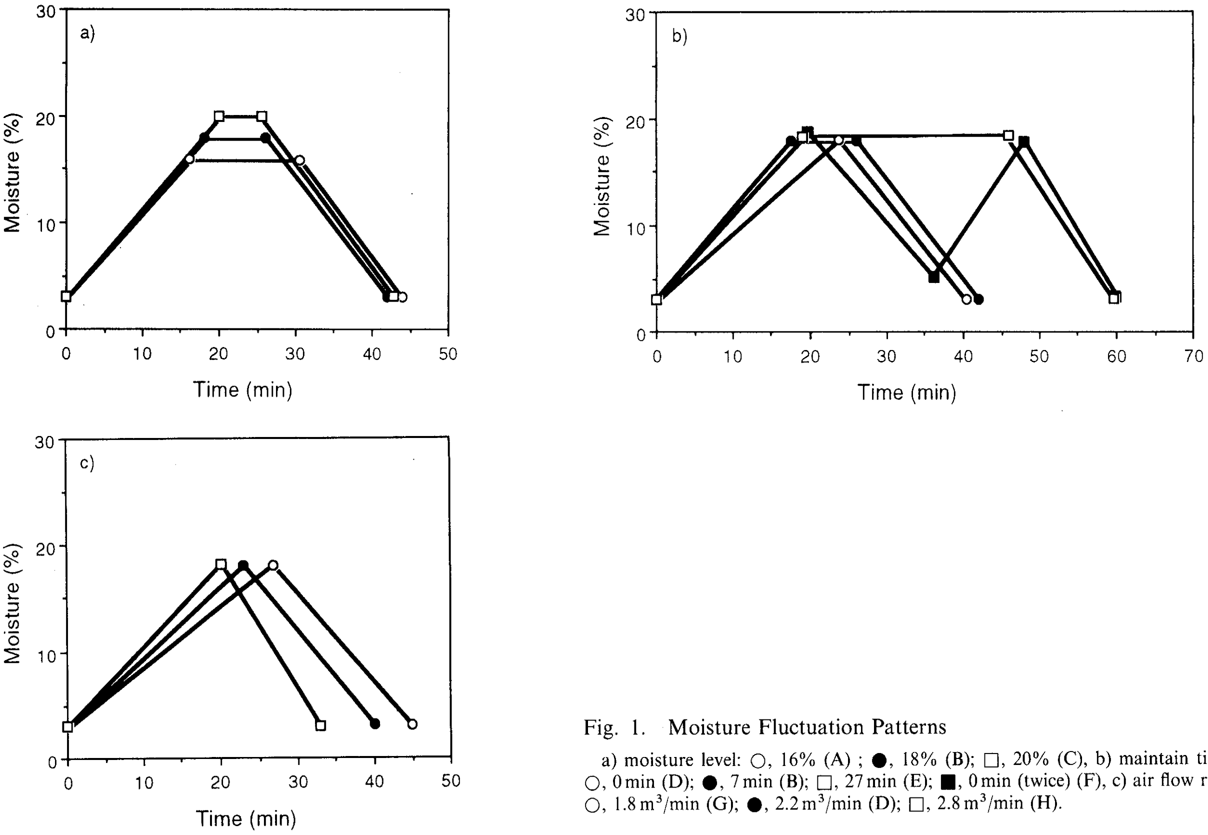

Fig. 1. Moisture Fluctuation Patterns

a) moisture level: ○, 16% (A) ; ●, 18% (B); □, 20% (C), b) maintain time: ○, 0 min (D); ●, 7 min (B); □, 27 min (E); ■, 0 min (twice) (F), c) air flow rate: ○, 1.8 m³/min (G); ●, 2.2 m³/min (D); □, 2.8 m³/min (H).

Table 2. Particle Size Distribution, Binder Distribution, Bulk Density and Granule Strength for Dry Mixed Batches Prepared in a Fluidized Bed

Batch	A	B	C	D	E	F	G	H
Moisture level (%)	16	18	20	18	18	18	18	18
Maintain time (min)	13.7	6.9	5.7	0	27.4	0	0	0
Granulating water (g)	1600	1600	1600	1600	2400	2400	1600	1600
Spray speed (g/min)	100	100	100	85	100	100	70	110
Air flow rate (m³/min)	2.2	2.2	2.2	2.2	2.2	2.2	1.8	2.8
Particle size distribution (%)								
500 μm on	6.8	9.0	15.9	7.1	11.4	9.0	10.4	21.3
355 μm on	3.8	6.6	14.7	6.3	7.6	6.6	6.2	10.7
250 μm on	5.8	12.4	19.8	11.9	12.4	12.4	9.4	14.9
180 μm on	14.5	25.0	23.4	26.5	24.5	23.9	22.4	23.5
150 μm on	15.3	16.0	11.1	12.8	15.6	14.1	11.4	8.2
106 μm on	28.2	20.8	11.1	21.7	18.7	20.8	23.0	14.0
75 μm on	14.1	7.4	2.6	8.5	6.8	8.8	10.0	4.4
75 μm pass	11.5	2.8	1.4	5.2	3.0	4.4	7.2	3.0
Median particle size (μm)[a]	143	187	252	184	195	185	175	239
Binder content (%)								
250—355 μm	5.17	5.55	5.66	5.27	5.45	5.45	5.07	5.21
106—150 μm	5.72	4.59	4.66	4.93	4.59	4.86	5.24	4.86
75 μm pass	2.03	2.52	2.62	2.79	2.86	2.52	2.66	2.55
Theoretical value (%)	4.76							
Bulk density tapped (g/ml)	0.608	0.589	0.598	0.590	0.595	0.598	0.597	0.604
Granule strength (%)[b]	0.6	0.2	0.1	0.6	0.0	0.2	0.2	0.0

a) Cumulative 50% by weight. *b)* Difference of 75 μm pass between 5 and 20 min sieving time.

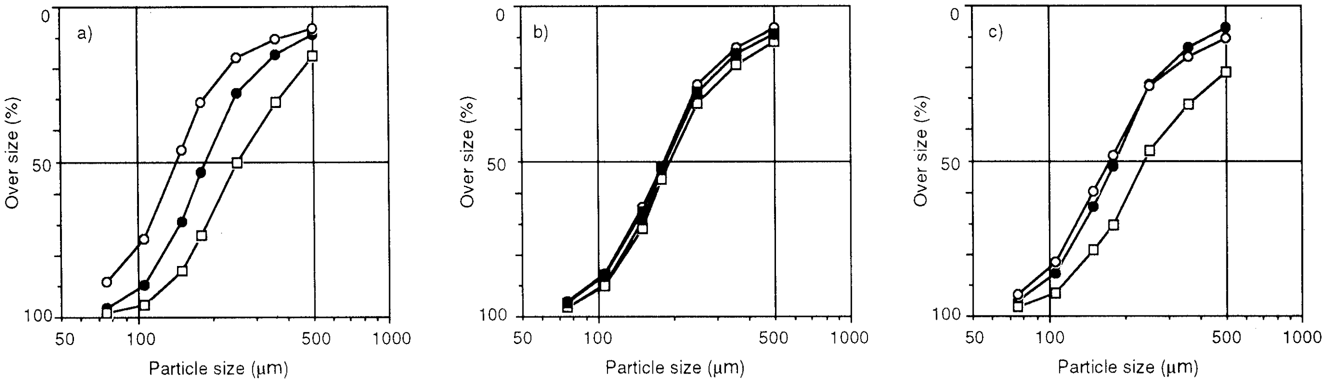

Fig. 2. Effect of Operating Conditions on the Particle Size Distribution

a) moisture level: ○, 16% (A); ●, 18% (B); □, 20% (C), b) maintain time: ○, 0 min (D); ●, 7 min (B); □, 27 min (E); ■, 0 min (twice) (F), c) air flow rate: ○, 1.8 m^3/min (G); ●, 2.2 m^3/min (D); □, 2.8 m^3/min (H).

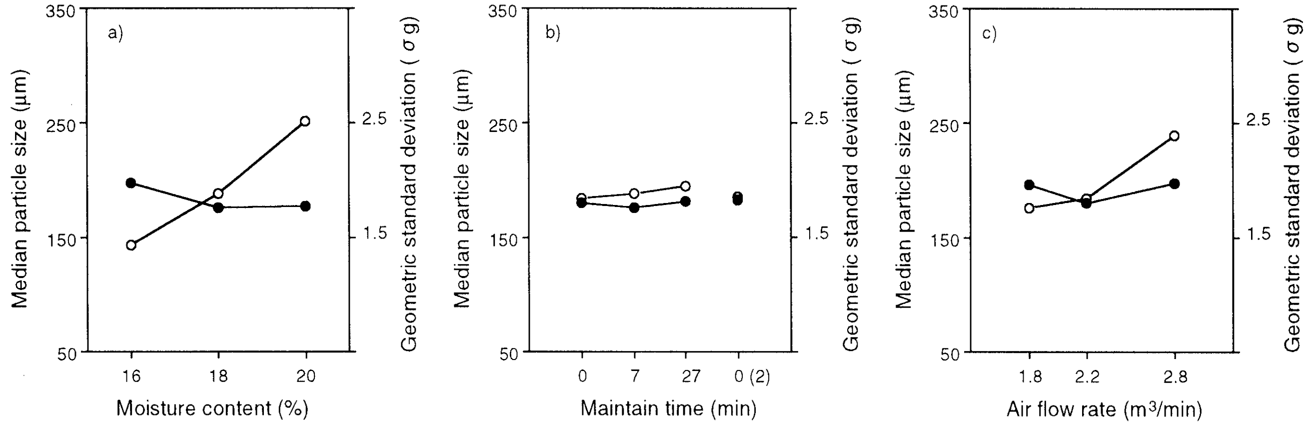

Fig. 3. Relationship between Median Particle Size, Geometric Standard Deviation and Operating Conditions

a) moisture level, b) maintain time, c) air flow rate. Key; ○, median particle size (μm); ●, geometric standard deviation (σg).

2a) (batches A, B, C). It is well known that the content of granulating liquid used greatly affects granule growth. Using the constant spray feed technique, a larger amount of granulating water, that is, a higher moisture level, resulted in granule growth and expansion of the particle size distribution. At a given moisture level, 18%, the moisture maintain time or interval drying had almost no influence on granule size or size distribution (Fig. 2b), (batches D, B, E, F). This suggested that sprayed water was efficiently distributed throughout the powder mixture, leading to the formation of stable agglomerates which did not grow further during fluidization under these operating conditions. A higher drying air flow rate with a higher spray feed rate increased the granule size (Fig. 2c), (batches G, D, H). At a higher drying air flow rate, the powder bed rose, and local over-wetting might have occurred due to the small separation between the spray gun and the bed compared with the other experiments. Based on moisture control experiments using water of low viscosity, the effect of droplet size of the sprayed mist on granule growth is believed to be quite small.[6)]

The relationships among median particle size, geometric standard deviation and the operating conditions are illustrated in Fig. 3. At a drying flow rate of 2.2 m^3/min, the moisture level of 18% gave minimum values of geometric standard deviation (σg).

Effect of Process Variables on Binder Distribution, Bulk Density and Granule Strength The binder content in each granule fraction is shown in Table 2, and the relationships between binder distribution and the operating conditions are illustrated in Fig. 4. For all conditions tested, except for batch A with the lower moisture level, the binder content interpolated at the median particle size was close to the theoretical value calculated from the formulation.[1-3)]

Schæfer *et al.* proposed that the granulation process in a fluidized bed is composed of three stages, nucleation, transition and ball growth regions.[9)] At the start of the nucleation stage, nuclei are formed from two or more primary particles linked by liquid bridges, which are primarily pendular. In the transition region, the liquid bridges change gradually from a pendular to a funicular state, and most of the primary particles are agglomerated. In the ball growth region, most of the liquid bridges change to a capillary state, resulting in uncontrolled granule growth. In our experiments, most of the fine particles were granulated, indicating that the granulation proceeded through the nucleation region to the transition region.[9)] From the viewpoint of binder distribution, similar binder levels were observed in the medium and in coarse particle size fractions, and the binder content was markedly lower in the fine particle size fraction. This finding suggested

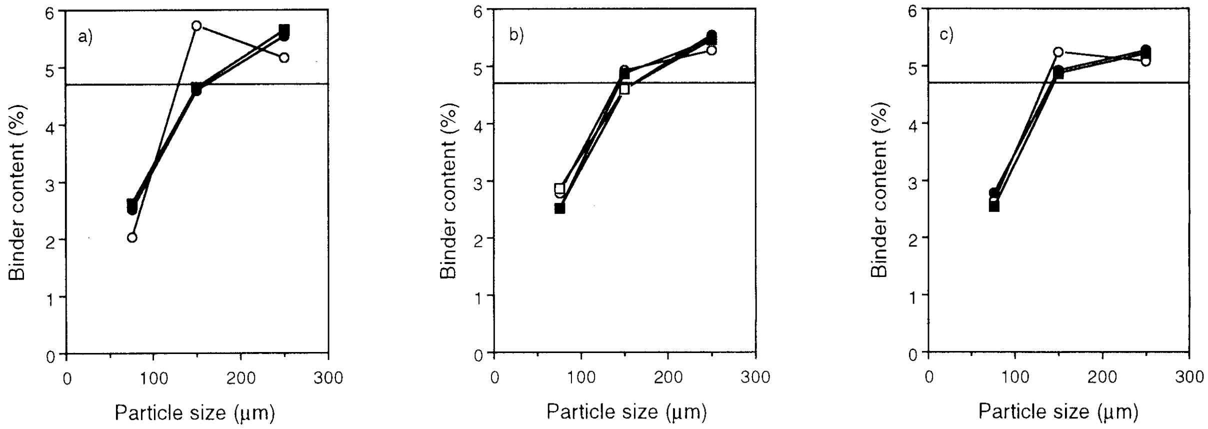

Fig. 4. Effect of Operating Conditions on the Binder Distribution

a) moisture level: ○, 16% (A); ●, 18% (B); □, 20% (C), b) maintain time: ○, 0 min (D); ●, 7 min (B); □, 27 min (E); ■, 0 min (twice) (F), c) air flow rate: ○, 1.8 m^3/min (G); ●, 2.2 m^3/min (D); □, 2.8 m^3/min (H).

that most of the binder particles were fixed in the primary nuclei, and this was followed by the formation of stable agglomerates without cutting or compaction during fluidized bed operation with the dry mixing method of binder addition. On the other hand, in the case of high-speed mixer granulation, the agglomerates tended to grow further as a consequence of mechanical agitation, thus promoting binder separation, *i.e.*, the binder was concentrated in the coarse particles. At the lower moisture level, 16%, higher binder content was observed in the medium sized fraction. This trend was consistent with that previously reported[3] in the case of high-speed mixer granulation. This also supports the primary formation of nuclei with binder particles.

The effects of process variables on granule strength and bulk density are shown in Table 2. No significant difference in bulk density was observed among the batches. In our previous study on high-speed mixer granulation using almost the same formulation as in the present study,[3] the granules showed a higher bulk density of around 0.8 g/ml than that of around 0.6 g/ml obtained in these experiments. This suggests that for fluidized bed granulation with the dry mixing method of binder addition, mechanical compaction or densification does not occur during the operation. Granule growth seems to occur by nuclei formation and successive coalescence of the nuclei.

Conclusion

Here, we have investigated the effects of process variables on the relationship between the distribution of the binder in different sized fractions and the physical properties of the granulated products obtained by fluidized bed granulation using the dry mixing method. The results were as follows: 1) In the dry mixing method of binder addition, moisture level was the most important factor for granule growth, while the other maintain time and drying air flow rate had little influence on the granule properties. At a fixed moisture level, experiments with various values of the latter process variables showed very similar results, in terms of particle size and size distribution, binder distribution and bulk density. This suggests that the agglomerates formed are comparatively stable due to the lack of mechanical agitation in the fluidized bed. 2) Similar binder levels were observed in the medium and coarse particle size fractions. This implies that most of the binder particles were fixed in the primary nuclei, and that further granulation might occur by coalescence of the nuclei. In the case of a solution spray system, granule growth by coalescence of nuclei and powders is dependent on the particle size of the sprayed mist,[16] whereas in the case of the dry mixing method of binder addition with a fluidized bed, moisture level controls the coalescence of nuclei, while other factors have a negligible effect. Thus, control of moisture is critical for optimum reproducibility. Further analysis of binder distribution in the product granules would be useful to confirm the proposed granulation mechanism.

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