Effect of Several Cellulosic Binders and Method of Their Addition on the Properties and Binder Distribution of Granules Prepared in an Agitating Fluidized Bed

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A model system consisting of lactose–cornstarch was used to examine the effect of five cellulosic binders [hydroxypropylcellulose (HPC) (6 cP), hydroxypropylmethylcellulose 2910 (HPMC) (3, 6, 15 cP) and methylcellulose (MC) (15 cP)] on the particle size distribution of granules prepared in an agitating fluidized bed under fixed operating conditions. The distribution of binder in different size fractions of granules was also determined by measuring the contents of methoxyl and hydroxypropoxyl groups. When the binders were added by the solution method, higher solution viscosity resulted in the granule size being increased, with almost equivalent binder distributions in different size fractions. The granules prepared by the dry mixing method with HPC (6 cP) or HPMC (3 cP) also showed a good correlation between median particle size and binder level, though the binders were concentrated in the coarse-sized particle fractions of the granules. The results are consistent with our previous findings on wet granulation with a fluidized bed.[1-4] When a trace amount of water-soluble dye was mixed with the granulating liquid or powder components to examine the granulation mechanism in both the solution and the dry mixing methods of binder addition, the dye distributions were more uniform than the binder distributions, especially in the dry mixing method. This suggests that the solubility of binders or dye in water is a critical factor determining their distribution in the different size fractions of the granules.

Key words cellulose ether; agitating fluidized bed granulation; binder distribution; dye distribution; granule size distribution; granulation mechanism

Water-soluble cellulose ethers are widely used as binders in various granulation methods for pharmaceutical preparations. Granule size and size distribution are critical determinants of the flowability of the granules and the hardness of tablets prepared from them. Thus, analysis of the effects of various water-soluble cellulose ethers on granule size distribution is very important in the field of pharmaceutical technology.

Agitating fluidized bed granulation, using a combination of a high-speed mixer and fluidized bed granulation, is a new method which is extremely versatile.[5] However, the outcome in granulation is highly dependent on the nature of the starting materials, the method of application of binders, and the processing devices employed.[6-9] It was therefore of interest to investigate how various cellulose binders and methods of binder addition influence the granule growth and size distribution in an agitating fluidized bed.

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.[1-4] In this study, we extended that work by employing an agitating fluidized bed as a model machine, and examined the mechanism of the granulation by measuring the distributions of the binder and a water-soluble dye in different size fractions of granules prepared by the solution method and by the dry mixing method of binder addition.

Experimental

Materials Powder materials used were lactose (Pharmatose 200M, DMV Co.) and cornstarch (Cornstarch W, Nihon Shokuhin Kako Co.). Binders used were hydroxypropylcellulose (HPC : HPC EF-P, JP, Shin-Etsu Chemical Co.), hydroxypropyl methylcellulose 2910 (HPMC: Pharmacoat 603, 606 and 615, USP, Shin-Etsu Chemical Co.) and methylcellulose (MC: Metolose SM-15, JP, Shin-Etsu Chemical Co.). Table 1 shows the viscosity of a 2% aqueous solution of each cellulose binder measured at 20 °C with an Ubbelohde-type viscometer and the median particle size measured by a sieving method. Brilliant blue food color (San-Ei Chemical Ind. Co.) was used for dye distribution analyses.

Mixture Composition As shown in Table 2, the basal material was prepared by mixing lactose and cornstarch at a ratio of 7 : 3 (350 g and 150 g) for both the solution and dry mixing methods. The amounts of each binder tested were 10, 17.5 and 25 g for the solution method, and 10, 25 and 40 g for the dry mixing method (Table 2).

Table 1. Cellulosic Binders Used

Type	Viscosity (cP)	Median particle size (μm)
Hydroxypropylcellulose (HPC)	5.56	104
Hydroxypropyl methylcellulose (HPMC) 2910		
HPMC (3 cP)	3.22	48
HPMC (6 cP)	5.74	52
HPMC (15 cP)	16.0	54
Methylcellulose (MC)	15.8	55

Table 2. Formulation of Powder Mixture

Component	Solution (g)	Dry mixing (g)
Lactose	350	350
Cornstarch	150	150
Total	500	500
Binder	10, 17.5, 25	10, 25, 40
Water	240, 232.5, 225	250

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Table 3. Operating Conditions

Item	Solution method	Dry mixing method
Supply air temperature	80 °C	80 °C
Exhaust air temperature	30—35 °C	28—33 °C
Supply air flow rate	$30\,m^3/h$	$16.5\,m^3/h$
Gun position	45 cm	45 cm
	from powder bed surface	
Spray air	$1.4\,kg/cm^2$, 30 ml/min	
Spray feed rate	12.5 g/min	15 g/min
Disk rotation	300 rpm	300 rpm
Maximum moisture content[a)]	14%	18%

a) Determined at the end of spraying.

Granulation The standard procedure for the solution method was as follows: lactose (350 g), and cornstarch (150 g) were mixed for 5 min in an agitating fluidized bed (Multi-plex, Model MP-01, Powrex Co.) with a disk rotation rate of 300 rpm under a $30\,m^3/h$ drying air flow at 80 °C. The binder solution (250 g) was then sprayed at 12.5 g/min. In the dry mixing method, lactose (350 g) and cornstarch (150 g) were similarly mixed for 5 min with a disk rotation rate of 300 rpm under a $16.5\,m^3/h$ drying air flow at 80 °C, then water (250 g) was sprayed at 15 g/min. The process variables of the agitating fluidized bed are listed in Table 3. 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.

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 (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 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)]

Granule Hardness Each of 30 granules from the sieved size fraction of 355—425 μm was vertically pressed using a granule hardness tester (Grano, Okada Seiko Co.) at a fixed displacement to measure the crushing load, and the mean value was taken as the granule hardness.

Tackiness of the Binder Solution Tackiness of HPC and HPMC (3 cP) aqueous solutions was measured using a rheological measuring instrument (Rheo Meter, Model NRM-2010J-CW, Fudoh Ind. Co.) under the following conditions: clearance between the glass plate (lower plate) and the circular metal plate (upper) 30 mm in diameter was set at 1 mm, press and remove stroke was controlled at 5 times/min at 5 mm/sec stroke speed. One ml of aqueous solution (approx. 28%; dry basis) was placed on the glass plate, and the instrument was run continuously under a gentle drying air flow at room temperature. The change of tackiness was measured in terms of the separating force between the two plates, and the change of moisture content of the test solution was determined by weighing.

Dye Distribution In the solution method, 100 mg of dye (Brilliant blue food color) was added to the solution or to the powder mixture. In the dry mixing method, 100 mg of dye was similarly added to the water or the powder mixture. To measure the dye content, 500 mg of the obtained granules was dissolved in 50 ml of purified water and the absorbance of the solution was measured at 628 nm.

Results and Discussion

The Solution Method Granulations were carried out by an agitating fluidized bed using aqueous solutions of various water-soluble cellulose ethers. The relationship between binder content and median particle size is shown in Fig. 1, and the relationships between binder content and granule strength and granule hardness are shown in Figs. 2 and 3, respectively. The maximum moisture content of 14% (Table 3) was consistent with that we previously found in fluidized bed granulation.[2)]

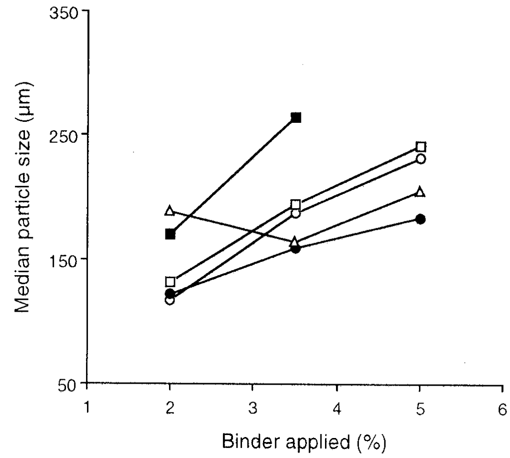

Fig. 1. Effect of Binder on the Median Particle Size of Granules Prepared by the Solution Method in an Agitating Fluidized Bed

○, HPC; ●, HPMC (3 cP); □, HPMC (6 cP); ■, HPMC (15 cP); △, MC.

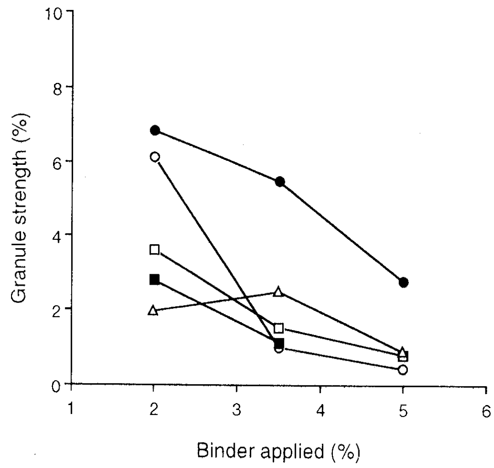

Fig. 2. Effect of Binder on the Strength of Granules Prepared by the Solution Method in an Agitating Fluidized Bed

○, HPC; ●, HPMC (3 cP); □, HPMC (6 cP); ■, HPMC (15 cP); △, MC.

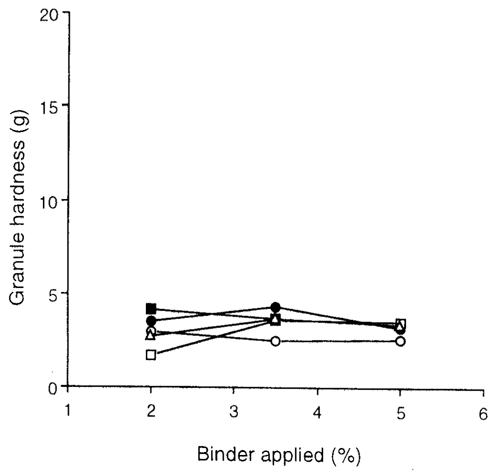

Fig. 3. Effect of Binder on the Hardness of Granules Prepared by the Solution Method in an Agitating Fluidized Bed

○, HPC; ●, HPMC (3 cP); □, HPMC (6 cP); ■, HPMC (15 cP); △, MC.

The median particle size of product granules increased as the binder content and binder viscosity grade were raised, except in the case of MC. Similar patterns of granule strength were observed for all binders. The anomalous

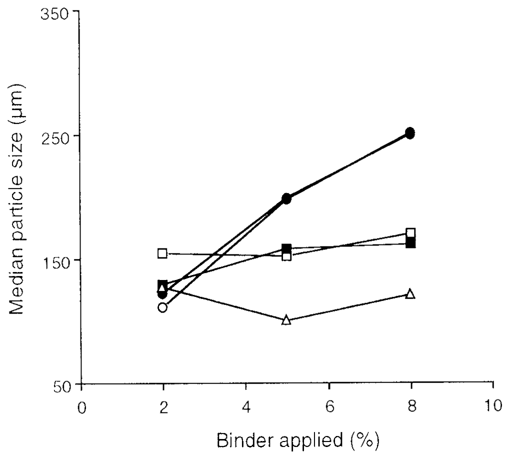

Fig. 4. Effect of Binder on the Median Particle Size of Granules Prepared by the Dry Mixing Method in an Agitating Fluidized Bed

○, HPC; ●, HPMC (3 cP); □, HPMC (6 cP); ■, HPMC (15 cP); △, MC.

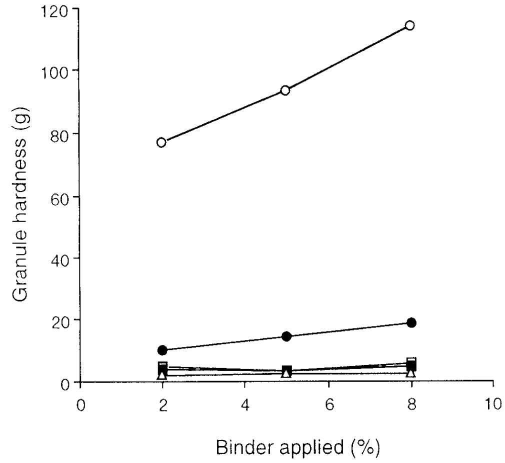

Fig. 6. Effect of Binder on the Hardness of Granules Prepared by the Dry Mixing Method in an Agitating Fluidized Bed

○, HPC; ●, HPMC (3 cP); □, HPMC (6 cP); ■, HPMC (15 cP); △, MC.

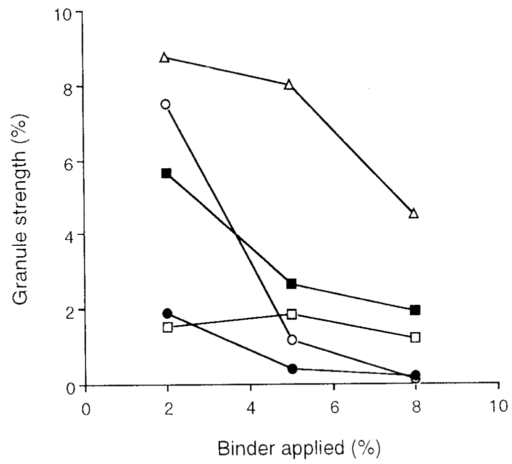

Fig. 5. Effect of Binder on the Strength of Granules Prepared by the Dry Mixing Method in an Agitating Fluidized Bed

○, HPC; ●, HPMC (3 cP); □, HPMC (6 cP); ■, HPMC (15 cP); △, MC.

behavior of MC might be explained by the fact that MC has the lowest thermal gelation temperature,[2] and thus MC solutions lose their adhesiveness earlier than the other binder solutions (Fig. 9). Granule hardness was almost the same, regardless of the species of binder and the binder content employed (Fig. 3).

The Dry Mixing Method Granulations were carried out by adding various binders (water-soluble cellulose ethers) in the form of powder using water as a granulating liquid. The relationship between binder content and median particle size is shown in Fig. 4, and that between binder content and granule strength and granule hardness in Figs. 5 and 6, respectively. The maximum moisture content of 18% (Table 3) was consistent with the value we had previously obtained using using fluidized bed granulation.[2]

As shown in Fig. 4, when HPC or HPMC (3 cP) was used, the median particle size increased as the binder content was raised, while the other binders gave almost the same median particle size at every content level. The granule strength increased as the binder content was raised (Fig. 5). The low granule strength in the case of MC is believed to be due to insufficient dissolution of MC particles in the dry mixing method. These results were consistent with those in our former report.[2] As shown in Fig. 6, when HPC was used, the granule hardness became extremely high, and HPMC (3 cP) gave a slightly higher hardness than the others. These results seem to be closely related to the granulation efficiency, as will be discussed later.

Comparison between the Solution Method and the Dry Mixing Method Using 5% HPC and HPMC (3 cP) in the solution method and 8% HPC and HPMC (3 cP) in the dry mixing method, the effect of the manner of binder addition on the granulation was investigated. The relationships between particle size and granule hardness and binder content are shown in Figs. 7 and 8, respectively. With the solution method, the two binders gave very similar results. In our previous study[2] on fluidized bed granulation, the binders had been concentrated in the larger particle size fractions, but the granules prepared by the agitating fluidized bed showed a more uniform binder distribution, presumably due to the mechanical agitation effect. These results suggested that the granule structure was highly homogeneous, regardless of the particle size.

The difference between HPC and HPMC (3 cP) in the dry mixing method might be explained by differences in the flexibility of the film and the adhesiveness of the dissolved binder solution. HPC film is more flexible than HPMC film.[10] The tackiness of HPC and HPMC solutions is shown in Fig. 9. Below 45% moisture (wet basis; 31%, dry basis), the solutions change to the gel state, but HPC maintained its adhesiveness in the gel state until it reached 16.2% moisture (wet basis; 13.9%, dry basis), whereas HPMC lost its adhesiveness. Therefore, granulation using HPC proceeds through compaction at a low moisture content, so the granules obtained using HPC show greater hardness than those prepared with HPMC even at the same particle size.

Mechanism of Granulation by the Solution Method and the Dry Mixing Method To compare those two methods, a water-soluble dye was added to the granulating liquid or powder components. The median particle size and the size distributions of granules were consistent with those in the experiments without dye addition.

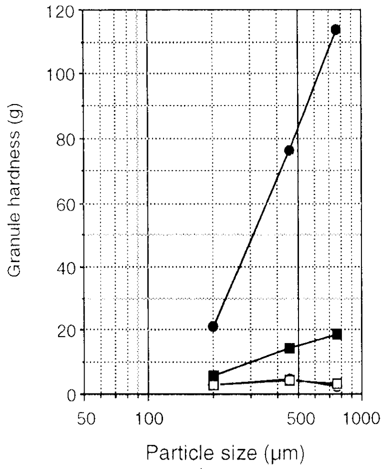

Fig. 7. Relationship between Granule Hardness and Particle Size

○, HPC solution (5%); ●, HPC dry mixing (8%); □, HPMC (3 cP) solution (5%); ■, HPMC (3 cP) dry mixing (8%).

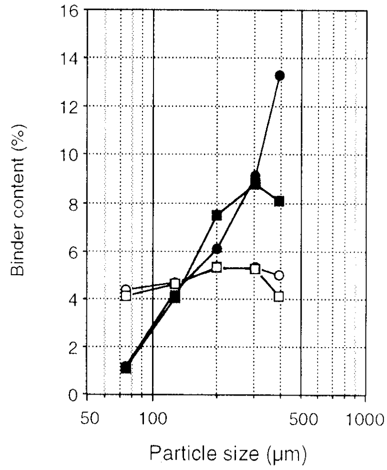

Fig. 8. Relationship between Binder Content and Particle Size

○, HPC solution (5%); ●, HPC dry mixing (8%); □, HPMC (3 cP) solution (5%); ■, HPMC (3 cP) dry mixing (8%).

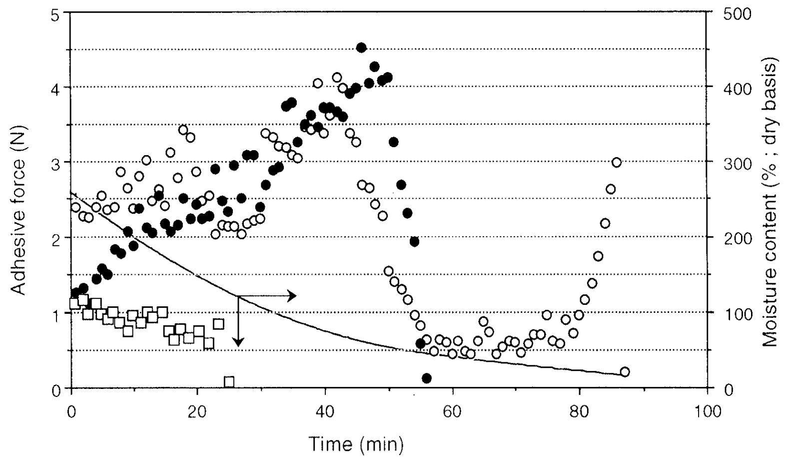

Fig. 9. Tackiness and Moisture Fluctuation Patterns of Binder Solution

○, HPC solution; ●, HPMC (3 cP) solution; □, MC (15 cP); ——, moisture.

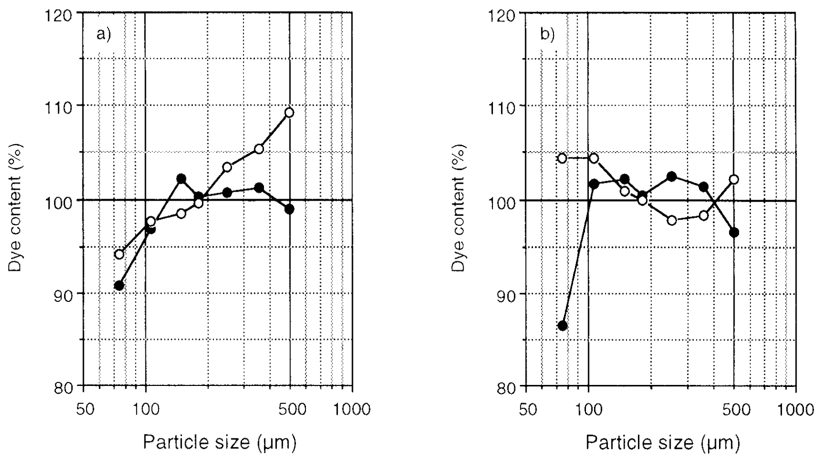

Fig. 10. Effect of Binder Application Method on the Distribution of Water-Soluble Dye

a) solution method: ○, dye in the solution; ●, dye in powder; b) dry mixing method: ○, dye in water; ●, dye in powder.

In the solution method with the dye in the solution, the dye was concentrated in the coarse particle size fraction, while with the dye in the powder mixture, the dye content was uniform except for the fine particle size fraction, as shown in Fig. 10a. This suggests that, in the former case, larger particles received more of the sprayed solution, while in the case of the dye in the powder mixture, the dye was dissolved and fixed in the initial stage of granulation. However, the dye distribution in both cases was within the range of 90% to 110%, so that the dye distributions can be considered as rather uniform and similar.

In the dry mixing method with the dye in the solution

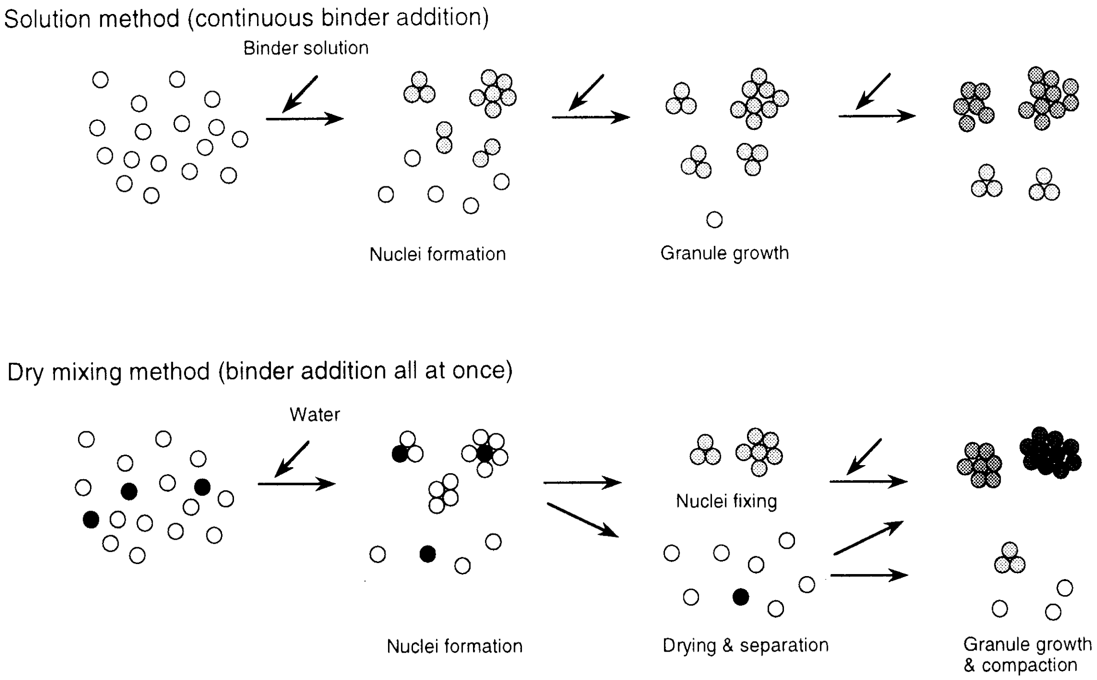

Fig. 11. Proposed Mechanisms of Granulation in an Agitating Fluidized Bed Using the Solution and Dry Mixing Methods
○, primary particles (lactose and cornstarch); ●, binder particles.

and with the dye in the powder mixture, similar levels of dye contents were observed except for the fine particle size fraction with the dye in the powder mixture (Fig. 10b). These results suggest that, for the dye in the water, the solution was well distributed throughout the whole agglomerate due to its almost total lack of viscosity, while in the powder mixture, the dye dissolved and was fixed at the initial stage of the granulation due to its comparatively high solubility in water. The dye distribution was different from the binder distribution (Fig. 8): the binders were concentrated in the coarse particle size fraction, presumably due to their comparatively low solubility in water and the difficulty of uniformly distributing the resultant viscous solutions through the powder mixture. These observations also support our previous findings on binder localization due to mechanical agitation promoting binder separation.[1-4]

In agitating fluidized bed operation using the solution method, the granulation appears to proceed step by step to form homogeneously structured granules, as in the growth mechanism proposed by Schæfer and Woerts.[7] (see Fig. 11). In the dry mixing method, nuclei are thought to be formed from two or more primary particles linked by liquid bridges in the initial stage of the granulation, and this is followed by the formation of stable agglomerates together with reversible separation of other agglomerates during drying under mechanical agitation due to lack of binder or insufficient dissolution of binder (Fig. 11). This granulation mechanism is similar to the mechanisms of wet granulation in a high-speed mixer or a rotating drum[6,11]; these experiments were carried out with all liquid being added at once, in contrast to the solution method of agitating fluidized bed or fluidized bed granulation, where granules are formed by continuous addition of binder solution. In high-speed mixer granulation,[1] there was no significant difference between the solution method and the dry mixing method of binder addition, because in both cases the localization of the binder was fixed at an early stage. In both wet granulation in a high-speed mixer and agitating fluidized bed granulation with the dry mixing method of binder addition, the binder localization becomes fixed at the beginning of the granulation, so the dry mixing method can be regarded as analogous to conventional wet granulation. The difference lies in the effect of mechanical agitation on the binder distribution and the granule density. It was concluded that the granulation mechanisms can be divided into two categories, corresponding to continuous binder addition (the solution method in a fluidized bed) and binder addition as a bolus (the dry mixing method in a fluidized bed and both the solution method and the dry mixing method in a high-speed mixer), at least in the case of the lactose–cornstarch model system used in this study.

These proposed models for granulation in an agitating fluid bed using the solution method and the dry mixing method can well explain both the binders and the dye distributions observed here. The agitating fluidized bed is conducted to be very similar to a conventional fluidized bed, *i.e.*, the agitation mainly improves the mixing efficiency and has little effect on binder distribution, at least under the operating conditions employed in this study.

Conclusion

We have examined the effects of changes in the amounts of various water-soluble cellulose ethers used as binders, and in the method of binder addition on the distribution of the binders in different size fractions as well as on the physical properties of the granulated products obtained by agitating fluidized bed granulation. The granulation mechanism was investigated by analyzing the distributions of the binders and a water-soluble dye. The results were as follows: 1) In the solution method, the difference among the cellulosic binders tested was small. Higher viscosity of the binder solution resulted in a larger granule size. In the dry mixing method, HPC and HPMC (3 cP) were effective as binders because they were soluble and adhesive at a low water content in the powder bed mixture. 2) In the solution method, the granule structure was more homogeneous, regardless of the particle size. In the dry mixing method, the granules tended to be more compacted and the binders were concentrated in the coarse particle size fraction by the mechanical agitation during the agitating fluidized bed operation, especially when HPC was used as the binder. 3) Dye distribution analysis showed that the water-soluble dye is fixed at the initial stage of the granulation, resulting in a uniform distribution of the dye in the granules in the different size fractions.

Based on these results, we propose that agitating fluidized bed granulation by the solution method proceeds through continuous growth as the binder solution is sprayed, affording homogeneous granules. In the dry mixing method, however, cutting and compaction of granules by mechanical agitation, results in heterogeneous granules with wide distributions of particle size and binder content.

References

1) Kokubo H., Nakamura S., Sunada H., *Chem. Pharm. Bull.*, **41**, 2151—2155 (1993).
2) Kokubo H., Nakamura S., Sunada H., *Chem. Pharm. Bull.*, **43**, 1402—1406 (1995).
3) Kokubo H., Sunada H., *Chem. Pharm. Bull.*, **44**, 1546—1549 (1996).
4) Kokubo H., Sunada H., *Chem. Pharm. Bull.*, **45**, 1069—1072 (1997).
5) Myo N., Takei N., *J. Soc. Powder Technol., Japan*, **26**, 103—107 (1989).
6) Kapur P. C., *Chem. Engng. Sci.*, **27**, 1863—1869 (1972).
7) Schæfer T., Woerts O., *Arch. Pharm. Chem. Sci.*, **6**, 69—82 (1978).
8) Nishimura K., Kakizawa H., Fukazawa T., Kishitani S., Kasahara K., Asai T., *Yakuzaigaku*, **38**, 196—204 (1978).
9) Wan L. S. C., Lim K. S., *S. T. P. Pharm.*, **5**, 244—250 (1989).
10) Park H. J., Testin R. F., Vergano P. J., Weller C. L., *J. Food Sci.*, **58**, 1361—1370 (1993).
11) Kristensen H. G., Schæfer T., *Drug Dev. Ind. Pharm.*, **13**, 803—872 (1987).