Effect of Several Cellulosic Binders on Particle Size Distribution in Fluidized Bed Granulation

Hiroyasu KOKUBO,*[,a] Shinichiro NAKAMURA,[a] and Hisakazu SUNADA[b]

Specialty Chemicals Research Center, Shin-Etsu Chemical Co., Ltd.,[a] 28–1, Nishifukushima, Kubiki, Nakakubiki-gun, Niigata 942, Japan and Faculty of Pharmacy, Meijo University,[b] 150, Yagotoyama, Tenpaku-ku, Nagoya 468, Japan. Received February 21, 1995; accepted April 10, 1995

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 a 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 without any increase in the percentage of coarse (>500 μm) particles generated. 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. The other binders did not show such a correlation, as higher concentrations of the binders were present in the medium-sized particle fractions of the granules at higher binder levels, and partly aggregated was the observed binder in these granules. The results support our previous conclusion, in a study of wet granulation with a high-speed mixer, that analysis of granule size dependency of binder content is useful for evaluating the effectiveness of binders added by dry mixing.

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

Water-soluble cellulose ethers are commonly employed as binders in various granulation methods for pharmaceutical preparations. Granule size distribution is a critical factor affecting the flowability of granules and the hardness of the 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.

Fluidized bed granulation is widely employed for the production of granules for tablets and fine granule preparations, and its many process variables have been extensively studied. The effects of sprayed droplet size, spray feed rate, moisture content during operation, conditions of drying and starting materials on the granule size and size distribution have all been investigated.[1–10] Uniformity of drug content in granules of different sizes is also an important consideration in minimizing the variation of drug content in tablets. In the fluidized bed granulation process, the binder affects not only the liquid distribution in the powders during agglomeration due to liquid bridging of particles, but also prevents agglomerated particles from separating during the drying process. However, little information is yet available regarding differences among various water-soluble cellulosic binders, although various species of binders have been compared and the effects of different methods of binder addition have been examined.[10–14]

In our previous study, we employed a high-speed mixer to analyze of the granule size dependency of binder content in order to examine the role of binders in the dry mixing method.[15] As a continuation of that work, the present study was designed to examine the role of cellulosic binders in fluidized bed granulation. A model system of lactose–cornstarch was used as the excipient in both the solution method and the dry mixing method under fixed granulating conditions, and the distribution of the binder in granules of various sizes was determined by measuring the contents of methoxyl and hydroxypropoxyl groups. Based on the powder properties of the granules and the binder contents in different size fractions of granules, we have discussed the role of the binder in fluidized bed granulation, especially the dry mixing method.

* To whom correspondence should be addressed.

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, JP, 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 using an Ubbelohde-type viscometer and the median particle size measured by a sieving method.

Mixture composition As shown in Table 2, the basal material was prepared by mixing lactose and cornstarch at a ratio of 7 : 3 (2800 g and

Table 1. Various Types of 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
MC	15.8	55

Table 2. Formulation of Powder Mixture

Component	Solution (g)	Dry mixing (g)
Lactose	2800	2800
Cornstarch	1200	1200
Total	4000	4000
Binder	80, 140, 200	80, 200, 320
Water	1920, 1860, 1800	1600

1200 g) for both the solution and dry mixing methods. The amounts of each binder tested were 80, 140 and 200 g for the solution method, and 80, 200 and 320 g for the dry mixing method (Table 2).

Fluidized Bed Granulation In the dry mixing method, lactose (2800 g), cornstarch (1200 g) and a test binder (80, 200 or 320 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 80 g/min. In the solution method, lactose (2800 g) and cornstarch (1200 g) were similarly mixed for 5 min under a 4.0 m^3/min drying air flow rate at 80 °C, then sprayed at 100 g/min. The process variables of the fluidized bed are shown in Table 3. 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 granule strength was expressed by 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 are the granules. 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.[15]

Table 3. Operating Conditions

Item	Conditions for Solution	Dry mixing
Supply air temp.	80 °C	80 °C
Exhaust air temp.	24—27 °C	24—27 °C
Supply air flow rate	4.0 m^3/min	2.2 m^3/min
Gun position	40 cm	25 cm
	from powder bed surface	
Spray air	3 kg/cm^2, 200 ml/min	
Spray feed rate	100 g/min	80 g/min
Maximum moisture content[a]	14%	18%

a) Determined at the end of spraying. temp. = temperature.

Results and Discussion

The Solution Method The results obtained by fluidized bed granulation using aqueous solutions of various water-soluble cellulose ethers as binders are shown in Table 4. The relationship between binder content and median particle size is shown in Fig. 1, and the relationship between binder content and the percentage generation of coarse particles (greater than 500 μm) is illustrated in Fig. 2. The viscosity of the binder solutions is shown in Fig. 3.

The binder levels used in this study, 2, 3.5 and 5%, correspond to the concentrations of 4, 7 and 10%, as shown in Fig. 3, and there was no difference in the viscosity–concentration relationship among the same viscosity type of binders used (6 cP: HPMC, HPC; 15 cP: HPMC, MC). The median particle size of product granules increased as the binder content was raised, regardless of

Table 4. Particle Size Distribution and Granule Strength for Some Batches Prepared by the Solution Method in a Fluidized Bed

Batch	A	B	C	D	E	F	G	H	I	J	K
Binder		HPC		HPMC (3 cP)[a]		HPMC (6 cP)[a]		HPMC (15cP)[a]		MC	
Content (%)	2.0	3.5	5.0	3.5	2.0	3.5	5.0	2.0	3.5	2.0	3.5
Particle size distribution (%)											
500 μm on	4.0	2.8	1.0	0.0	5.0	3.6	6.4	2.0	1.2	0.2	0.2
355 μm on	3.4	8.3	6.7	1.2	4.6	12.5	25.9	7.3	13.8	3.5	5.9
250 μm on	5.4	15.3	17.6	5.6	7.4	22.2	28.8	16.8	26.6	13.0	21.8
180 μm on	12.7	29.0	31.6	23.3	17.8	29.7	21.9	30.4	26.7	27.8	31.7
150 μm on	12.9	16.3	16.0	19.9	15.2	12.9	6.6	15.8	10.3	18.5	14.5
106 μm on	34.4	20.7	18.2	31.0	29.8	13.1	6.0	19.4	12.0	23.4	15.8
75 μm on	18.7	5.6	5.7	12.2	13.2	3.6	2.4	5.9	5.1	8.4	5.7
75 μm pass	8.5	2.0	3.2	6.8	7.0	2.4	2.0	2.4	4.3	5.2	4.4
Median particle size (μm)[b]	133	191	193	150	150	220	286	193	225	171	199
Granule strength (%)[c]	0.4	0.4	0.4	0.6	1.7	1.4	0.6	0.6	0.3	0.1	0.4

a) Viscosity of 2% aqueous solutions measured by Ubbelohde-type viscometer at 20 °C. *b*) Cumulative 50% by weight. *c*) Difference of 75 μm pass between 5 and 20 min sieving time.

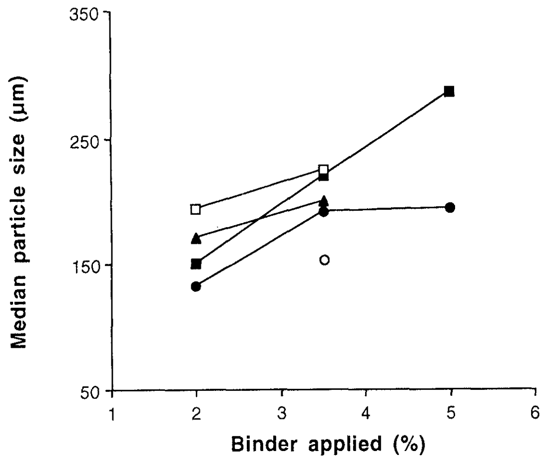

Fig. 1. Effect of Binder Applied on Median Particle Size of Granules Prepared by the Solution Method in a Fluidized Bed

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

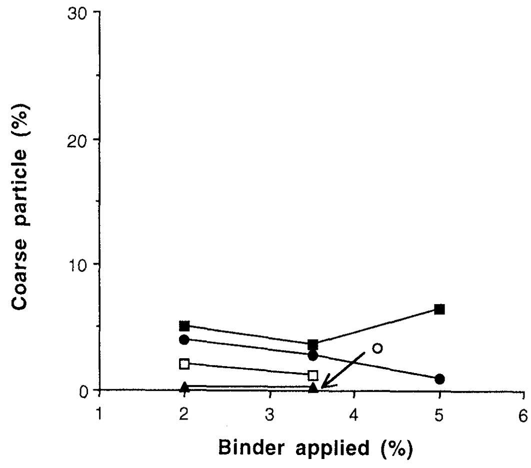

Fig. 2. Effect of Binder Applied on Coarse Particle Generation of Granules Prepared by the Solution Method in a Fluidized Bed

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

the species of binders. In general, the median particle size is strongly related to the size of the sprayed droplets, which is regulated by the viscosity of the solution and the atomizing conditions.[4,6,9] The percentage of coarse particles generated and that of particles passing through a 75 μm sieve were not increased in comparison with the case of the dry mixing method, described later, or the case of wet granulation as previously described.[15] These results suggest that the particle size distribution of the granules prepared by a fluidized bed with the solution method of binder addition was narrow and homogeneous. All size fractions, including that less than 75 μm, showed good agglomeration of lactose with cornstarch according to microphotographs. This indicates that the granulated products had not broken up during the drying process.[5] In this experiment there were no differences in granule strength among the binders used.

The binder content in each granule fraction is shown in Table 5. For all binders tested, the greater the particle size, the higher the binder content. The binder content interpolated at the median particle size was close to the theoretical value calculated from the formulation.

The Dry Mixing Method The results obtained by adding various binders (water-soluble cellulose ethers) in the form of powder are shown in Table 6. The relationship between binder content and median particle size is illustrated in Fig. 4, and that between binder content and the percentage generation of coarse particles (greater than 500 μm) is shown in Fig. 5.

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 use of other binders led to slight decreases in the median particle size when 5 or 8% binder was applied. This reduction in median particle size is considered to be due to insufficient dissolution of the binders in the dry mixing method, *i.e.*, the quantity of dissolved binder particles was not sufficient for granulation. At 5 or 8% binder applied, the water per binder applied was decreased. HPC did not lose its adhesive power even at a low water content, while that HPMC which has a low degree of polymerization, such as HPMC (3 cP), was as soluble and as adhesive as HPC at a low water content. These water-soluble cellulose ethers have characteristic thermal gelation properties (MC undergoes gel-formation at about 35 °C[16]), and the temperature during granulation was around 28°C in the recent experiments. Thus, the dissolution of the MC particles was significantly reduced compared with the other binders.

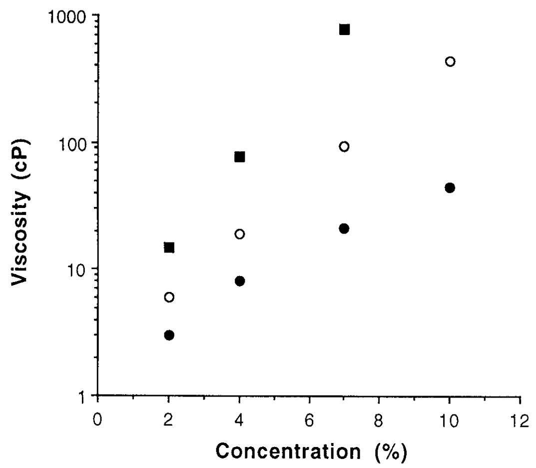

Fig. 3. Relationship between Concentration and Viscosity of the Solution

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

Table 5. Binder Content Distribution According to Particle Size for Batches Prepared by the Solution Method in a Fluidized Bed

Batch	A	B	C	D	E	F	G	H	I	J	K
Binder		HPC		HPMC (3 cP)		HPMC (6 cP)		HPMC (15 cP)		MC	
Content (%)	2.0	3.5	5.0	3.5	2.0	3.5	5.0	2.0	3.5	2.0	3.5
Binder content (%)											
250—355 μm	2.03	3.64	5.25	3.65	2.09	3.65	5.15	2.45	3.81	2.12	3.65
106—150 μm	1.94	3.58	4.65	3.65	1.96	3.51	4.92	1.81	3.49	1.97	3.40
75 μm pass	1.35	2.22	3.11	2.98	1.46	2.18	3.07	1.43	2.01	1.50	2.25
Theoretical value (%)	1.96	3.38	4.76	3.38	1.96	3.38	4.76	1.96	3.38	1.96	3.38

Table 6. Particle Size Distribution and Granule Strength for Some Batches Prepared by the Dry Mixing Method in a Fluidized Bed

Batch	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
Binder		HPC			HPMC (3 cP)			HPMC (6 cP)			HPMC (15 cP)		MC	
Content (%)	2.0	5.0	8.0	2.0	5.0	8.0	2.0	5.0	8.0	2.0	5.0	8.0	2.0	5.0
Particle size distribution (%)														
500 μm on	3.4	14.2	72.2	4.2	12.3	68.0	8.0	15.0	6.7	14.0	15.2	7.1	9.9	3.6
355 μm on	5.2	22.7	14.9	5.2	14.6	16.9	5.4	10.1	6.0	7.5	11.6	6.8	6.5	2.2
250 μm on	12.4	29.2	6.9	7.0	22.1	7.3	12.6	13.8	9.9	11.6	13.4	7.5	6.1	2.8
180 μm on	16.8	21.1	3.6	15.8	27.8	3.8	28.6	21.2	17.9	19.8	18.6	11.9	9.1	7.0
150 μm on	14.8	5.5	0.6	14.2	10.7	1.2	17.0	12.6	13.1	12.4	11.4	11.3	7.3	10.4
106 μm on	33.8	4.5	1.0	33.7	8.5	1.7	18.2	17.6	26.0	19.1	18.0	29.0	22.1	35.0
75 μm on	10.6	1.6	0.6	15.6	2.2	0.8	5.4	6.1	12.5	9.3	7.2	17.3	20.1	23.1
75 μm pass	3.0	1.2	0.2	4.3	1.8	0.3	4.8	3.6	7.9	6.3	4.6	9.1	18.9	15.9
Median particle size (μm)	155	303	>500	145	247	>500	187	211	158	189	210	145	126	118
Granule strength (%)	2.8	0.2	0.4	0.5	0.0	0.1	1.0	1.0	1.2	0.8	0.6	1.0	3.1	2.2

As shown in Fig. 5, changes in the percentage generation of coarse granules were similar to the changes in median particle size. MC showed a lower generation of coarse granules at higher levels of binder applied due to the presence of insufficient water for the dissolution of MC particles. Except in the case of MC and 2% HPC, the granule strength was adequate (Table 6).

The binder content in each granule fraction is shown in Table 7. In the cases of HPC and HPMC at 2 or 5% binder level, the granule size increased with increasing amounts of binder applied, and the binder content interpolated at median particle size was close to the theoretical value. These results are analogous to those previously reported[15] for wet granulation with dry mixing. On the other hand, in the cases of HPC and HPMC at 8% binder level and MC at 2 and 5%, where the granule size did not increase with increasing amount of binder applied, a higher amount of binder was found in the medium-sized fractions in comparison with the former cases. These medium-sized fractions contained partly aggregated binder in the granules. Thus, the irregular binder distribution was due to aggregation of the binder itself. Such aggregation of the binder was not observed previously in wet granulation with a mixer,[15] presumably because high-speed mixer granulation involves a much greater degree of mechanical agitation in comparison with fluidized bed granulation.

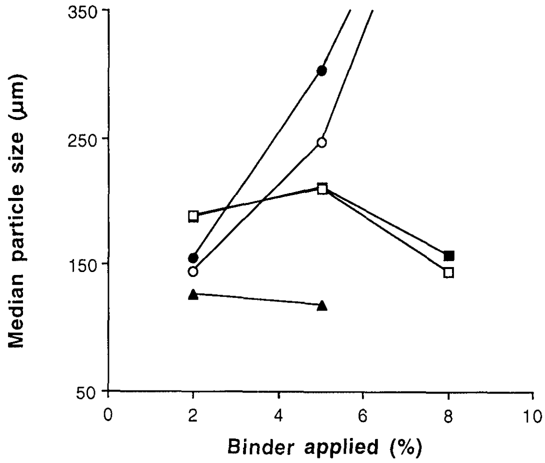

Fig. 4. Effect of Binder Applied on Median Particle Size of Granules Prepared by the Dry Mixing Method in a Fluicized Bed

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

Differences between the Solution Method and the Dry Mixing Method Granules were prepared using 2 and 5% HPC, and the relationship between particle size and binder content was compared between the solution method and the dry mixing method. As shown in Fig. 6 (data plotted from Tables 6 and 7), at fixed amounts of HPC, the solution method gave a more uniform distribution of binder for different size fractions than the dry mixing method. This was also the case for the other cellulose binders tested (Tables 6 and 7). Generally, in the solution method, granule growth is initiated by the formation of small nuclei consisting of particles held together by pendular or funicular bridging by the binder solution, then further growth results from coalescence of the nuclei. In the dry mixing method, agglomeration of the particles by

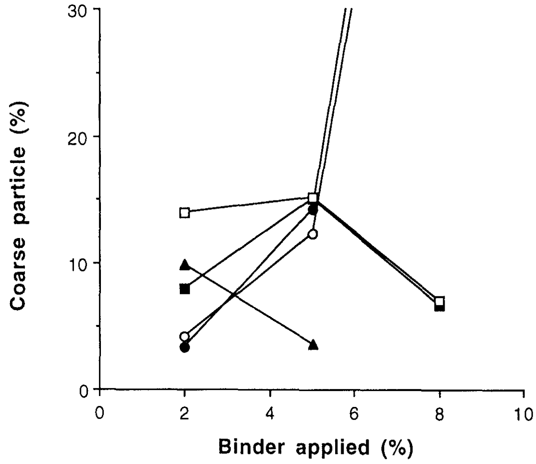

Fig. 5. Effect of Binder Applied on Coarse Particle Generation of Granules Prepared by the Dry Mixing Method in a Fluidized Bed

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

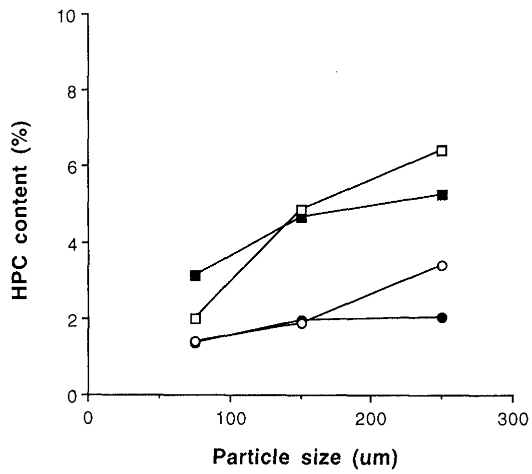

Fig. 6. Effect of the Method of Binder Addition on the Distribution of Binder in Different Size Fractions of Granules

●, HPC 2% solution method; ○, HPC 2% dry mixing method; ■, HPC 5% solution method; □, HPC 5% dry mixing method.

Table 7. Binder Content Distribution according to Particle Size for Batches Prepared by the Dry Mixing Method in a Fluidized Bed

Batch	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
Binder		HPC			HPMC (3 cP)			HPMC (6 cP)			HPMC (15 cP)		MC	
Content (%)	2.0	5.0	8.0	2.0	5.0	8.0	2.0	5.0	8.0	2.0	5.0	8.0	2.0	5.0
Binder content (%)														
250—355 µm	3.38	6.41	7.98	3.40	6.35	8.82	3.50	5.65	7.30	3.51	5.41	7.30	2.25	4.62
106—150 µm	1.86	4.86	9.15	1.79	4.81	8.30	1.77	5.30	9.47	1.75	5.61	9.47	3.72	6.86
75 µm pass	1.40	2.01	3.30	1.47	2.33	2.98	1.52	2.35	3.26	1.50	2.38	3.26	0.84	2.25
Theoretical value (%)	1.96	4.76	7.41	1.96	4.76	7.41	1.96	4.76	7.41	1.96	4.76	7.41	1.96	4.76

liquid bridging occurs initially, then further growth results from cutting, compaction and adhesion of the agglomerates with the formation of solid bridges resulting from hardening of the binders or crystallization of the dissolved substances.[7] The dry mixing method thus requires a higher moisture content than the solution method, as shown in Table 3. In addition, in the solution method, the continuous supply of binder solution results in a more uniform distribution of the binder than in the case of wet granulation with a high-speed mixer. Accordingly, for fluidized bed granulation, the solution method is more favorable for achieving uniform distribution of the binder, and for suppressing aggregation of the binder and the generation of coarse particles.

Conclusion

We have examined the effects of changes in the binder grade of various water-soluble cellulose ethers, in the amount of binder applied and in the method of binder addition on the distribution of the binders in different size fractions and the relationship of these changes to the physical properties of the granulated products obtained by fluidized bed granulation. The results were as follows: 1) In the solution method, the difference among the cellulosic binders tested was small, at least when lactose–cornstarch was used as a starting material. Higher viscosity of the binder solution resulted in a larger granule size. 2) In the dry mixing method, the amount of water required for the dissolution of binder particles affected the granulation. HPC and HPMC (3 cP) were good as binders because they were soluble and adhesive at a low water content per binder. 3) In both the solution and dry mixing methods, the binder content was higher in larger granule fractions when the binder was sprayed as a solution or when it was completely dissolved. When the binder dissolution was incomplete, the medium-sized granule fraction showed a higher content of the binder due to aggregation of the binder itself. In contrast with high-speed mixer granulation,[15] aggregation of some binders was observed in the medium-sized fraction in fluidized bed granulation with the dry mixing method of binder addition. This may be explained by insufficient mechanical agitation in the fluidized bed at a high binder level or poor solubility of the binder used (MC).

The amount of a binder for the dry mixing method that will be effective for granulation can be estimated by measuring the binder distribution in the product granules, and this will be useful in the design of solid dosage forms.

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