Effect of Several Cellulosic Binders on Particle Size Distribution of Granules Prepared by a High-Speed Mixer

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A model system consisting of lactose-cornstarch-microcrystalline cellulose was used to study the effect of five cellulosic binders [hydroxypropylcellulose (HPC) (6 cP), hydroxypropylmethylcellulose 2910 (HPMC) (3, 6, 15 cP), and methylcellulose (MC) (15 cP)] on particle size distribution of granules prepared by a high-speed mixer under fixed operating conditions. The distribution of binder in different size fractions of granules was 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 percentage of coarse particles generated in the granules being increased without an increase in the median particle size. The granules prepared by the dry mixing method with HPC (6 cP) or HPMC (3 cP) showed a good correlation between their median particle size and binder level. Other binders did not show such a correlation, as higher concentrations of the binders were present in smaller particle fractions of the granules with an increase in binder level. When binders were dissolved completely in the dry mixing method, a good correlation between median particle size and binder level was observed. The analysis of granule size dependency of binder content appeared to be useful for evaluating the effectiveness of binders in the dry mixing method.

Keywords cellulose ether; wet granulation; binder distribution; granule size distribution; high-speed mixer; dry mixing

Water-soluble cellulose ethers are defined in official publications, such as the Japanese Pharmacopoeia, and are commonly applied as binders in various granulation methods for pharmaceutical preparations. In particular, wet granulation allows both mixing and granulation to be performed in the same granulating vessel in a short time, and is thus widely employed for the production of granules for tablets and fine granule preparations. Granule size distribution is a critical factor directly affecting the flowability in tablet production, and consequently, the compressibility and tablet hardness. Thus, analysis of the effects of the characters of various water-soluble cellulose ethers on granulation should provide important information for formulating solid dosage forms.

Granulation has been extensively studied in the drug industry. Methods have been developed to determine the end point of granulation from the power consumption during wet granulation, and the effects of amounts of binder solution and operating conditions on the yield of granules processed have been examined.[1–5] The uniformity of drug content in granules has also been the subject of many studies,[6–8] and it has been suggested that the distribution of a drug in granules is influenced by the adhesion of drug particles on the surface of carrier powders and in inter-particulate spaces.[7–9] In wet granulation processes, 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, no clear information is yet available regarding differences among various water-soluble cellulosic binders, though various species of binders have been compared and differences among methods of binder addition have been reported.[10–12]

The objective of this study was to examine the effects of changes in the binder grade, the amount of binder applied and the method of binder addition on the relationship between the distribution of the binders in different size fractions and the physical properties of granulated products. A model system of lactose–cornstarch–microcrystalline cellulose was used as the excipient in both the solution method and the dry mixing method under fixed granulating conditions in a highspeed mixer, and the distribution of binder was determined by measuring the content of methoxyl and hydroxypropoxyl groups. Based on the powder properties of the granules and the binder content in different size fractions of granules, we discuss the role of the binder in wet granulation processes, especially the dry mixing method.

Experimental

Materials Powder materials used were lactose (Pharmatose 200M, DMV Co.), cornstarch (Cornstarch W, Nihon Shokuhin Kako Co.) and microcrystalline cellulose (Avicel PH-101, Asahi Chemical Industry Co.).

TABLE I. 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
Methylcellulose (MC)	15.8	55

TABLE II. Formulation of Powder Mixture

Component	Solution	Dry mixing
Lactose	3360 g	3360 g
Cornstarch	1440 g	1440 g
Microcrystalline cellulose	200 g	200 g
Total	5000 g	5000 g
Binder	25, 50, 100 g	50, 150, 250 g
Water	1000 g	1000 g

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 I 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 II, the basal material was prepared by mixing lactose and cornstarch at a ratio of 7:3 (3360 g and 1440 g) and by adding microcrystalline cellulose to make 4% (200 g) of the total (5000 g) for both the solution and dry mixing methods. The amounts of each binder tested were 25 g, 50 g and 100 g for the solution method, and 50 g, 150 g and 250 g for the dry mixing method (Table II).

Wet Granulation In the dry mixing method, lactose (3360 g), cornstarch (1440 g), microcrystalline cellulose (200 g) and a test binder (50, 100 or 250 g) were mixed for 1 min in a high-speed mixer (Vertical granulator, Model FM-VG-25, Powrex Co.) at a blade speed of 300 rpm and a chopper speed of 3000 rpm. Water (1 l) was then added and granulation was conducted for 10 min. In the solution method, lactose (3360 g), cornstarch (1440 g) and microcrystalline celloluse (200 g) were similarly mixed for 1 min, then binder solution, which contained 1 l of water, was added and granulation was conducted for 10 min. 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 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.

To determine the binder content in granules, a portion of each granule fraction, (1 g accurately weighed) was decomposed in a flask according to the substituent analysis method for hydroxypropyl methylcellulose described in the JP XII, then the content of hydroxypropoxyl or methoxyl groups was measured by gas chromatography.

Results and Discussion

The Solution Method The results obtained by granulation using an aqueous solution of various binders (water-soluble cellulose ethers) are shown in Table III. The relationship between binder content and mean 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.

As shown in Table III, the median particle size of product granules was not greatly affected by differences in the species and content of binders used. In general, the median particle size is strongly affected by the amount of water added.[12] Thus, when the amount of water was kept constant, as in the present experiment, and when the amount of a binder

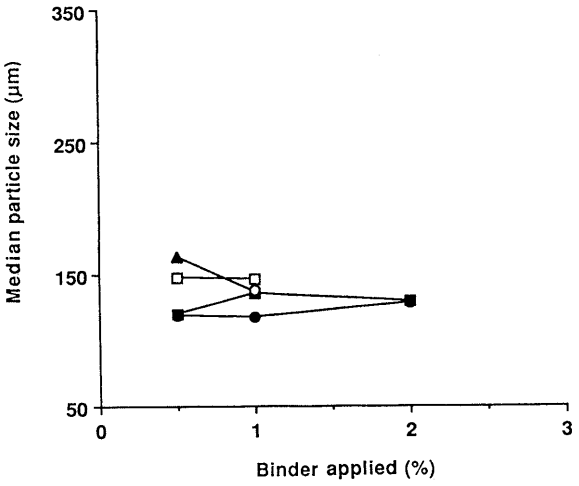

Fig. 1. Effect of Binder Applied on Median Particle Size of Granules Prepared by the Solution Method in a High-Speed Mixer
●, HPC; ○, HPMC (3 cP); ■, HPMC (6 cP); □, HPMC (15 cP); ▲, MC.

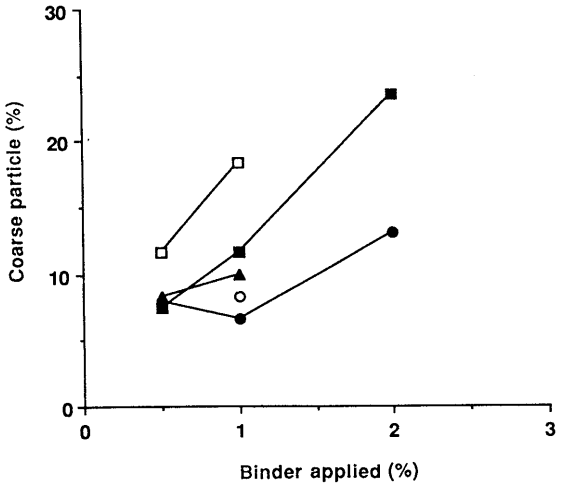

Fig. 2. Effect of Binder Applied on Coarse Particle Generation of Granules Prepared by the Solution Method in a High-Speed Mixer
●, HPC; ○, HPMC (3 cP); ■, HPMC (6 cP); □, HPMC (15 cP); ▲, MC.

TABLE III. Particle Size Distribution and Granule Strength for Some Batches Prepared by the Solution Method in a High-Speed Mixer

Batch	A	B	C	D	E	F	G	H	I	J	K
Binder	HPC			HPMC (3 cP)[c]	HPMC (6 cP)[c]			HPMC (15 cP)[c]		MC	
Content (%)	0.5	1.0	2.0	1.0	0.5	1.0	2.0	0.5	1.0	0.5	1.0
Particle size distribution (%)											
500 μm on	7.9	6.6	13.1	8.3	7.5	11.6	23.5	11.6	18.4	8.3	10.0
355 μm on	5.9	5.0	4.0	6.1	5.5	6.0	4.2	6.4	4.5	6.4	4.4
250 μm on	5.5	4.4	3.6	6.5	5.1	4.6	3.0	7.0	4.3	6.6	3.6
180 μm on	9.9	8.2	6.7	13.5	10.5	7.4	4.0	14.0	9.1	17.9	9.2
150 μm on	7.9	7.8	7.5	9.7	8.1	8.4	4.3	10.4	11.3	19.3	11.6
106 μm on	19.6	25.6	32.6	24.4	20.8	38.2	24.3	18.5	30.0	29.4	42.4
75 μm on	32.8	22.5	21.0	17.0	19.0	17.8	21.9	14.0	11.9	10.7	12.0
75 μm pass	10.5	19.9	11.5	14.5	23.5	6.0	14.4	18.1	10.5	1.4	6.8
Median particle size (μm)[a]	119	118	128	138	120	135	129	148	146	163	137
Granule strength (%)[b]	12.3	2.6	3.1	5.5	4.9	4.9	5.4	1.5	5.3	4.4	9.5

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

TABLE IV. Binder Content Distribution According to Particle Size for Batches Prepared by the Solution Method in a High-Speed Mixer

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 (%)	0.5	1.0	2.0	1.0	0.5	1.0	2.0	0.5	1.0	0.5	1.0
Binder content (%)											
250—355 μm	0.65	1.38	2.75	1.30	0.70	1.40	2.73	0.77	1.51	0.81	1.56
106—150 μm	0.47	0.80	1.77	0.88	0.46	0.81	1.70	0.48	0.95	0.45	0.94
75 μm pass	0.42	0.75	1.13	0.80	0.41	0.73	1.23	0.36	0.76	0.44	0.74
Theoretical value (%)	0.50	0.99	1.96	0.99	0.50	0.99	1.96	0.50	0.99	0.50	0.99

TABLE V. Particle Size Distribution and Granule Strength for Some Batches Prepared by the Dry Mixing Method in a High-Speed Mixer

Batch	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
Binder	HPC			HPMC (3 cP)			HPMC (6 cP)			HPMC (15 cP)			MC		
Content (%)	1.0	3.0	5.0	1.0	3.0	5.0	1.0	3.0	5.0	1.0	3.0	5.0	1.0	3.0	5.0
Particle size distribution (%)															
500 μm on	7.1	8.8	18.2	8.1	11.9	22.8	7.1	12.5	21.7	10.5	20.3	27.6	6.5	8.7	11.4
355 μm on	11.3	10.2	27.4	8.7	10.9	19.7	11.2	6.0	3.7	10.5	7.8	4.3	5.9	4.2	3.5
250 μm on	13.0	16.1	26.0	13.6	18.1	21.9	12.8	6.7	4.1	17.3	11.6	4.7	7.4	3.6	3.0
180 μm on	11.9	15.9	6.8	17.6	22.9	9.7	12.0	10.9	8.5	20.1	20.4	8.5	17.2	9.7	5.3
150 μm on	5.9	8.0	3.0	8.3	7.5	3.6	6.5	10.9	9.9	7.5	10.2	8.9	19.2	13.1	13.0
106 μm on	14.2	21.8	7.6	16.1	13.1	9.1	18.0	31.3	30.7	11.5	13.5	22.9	27.6	45.2	49.4
75 μm on	17.4	12.6	14.0	15.4	12.2	4.0	14.4	8.9	7.1	10.7	8.6	12.8	11.7	12.3	7.7
75 μm pass	21.2	7.0	7.0	13.2	6.7	6.1	15.0	9.1	7.4	11.9	7.6	10.3	4.7	3.2	6.9
Median particle size (μm)	147	184	335	172	219	315	149	145	146	206	212	163	159	138	136
Granule strength (%)	4.8	2.1	0.2	6.9	2.0	0.1	5.6	1.8	2.6	0.0	0.2	0.0	10.5	10.6	16.1

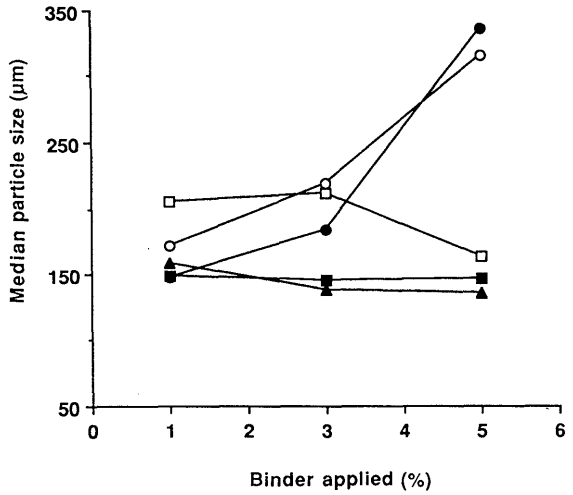

Fig. 3. Effect of Binder Applied on Median Particle Size of Granules Prepared by the Dry Mixing Method in a High-Speed Mixer

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

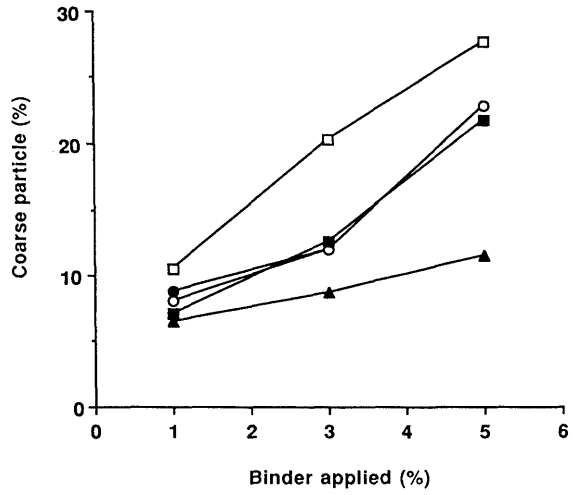

Fig. 4. Effect of Binder Applied on Coarse Particle Generation of Granules Prepared by the Dry Mixing Method in a High-Speed Mixer

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

was increased or a binder with a greater degree of polymerization was used, the percentage of coarse particles generated was increased. This finding might be attributed to an increase in the viscosity of the binder solution and the consequent heterogeneous distribution of the solution throughout the whole granulating mixture.

The relationship between the granule strength and binder level was not clear in this study. However, at 1% binder applied, the use of HPC gave stronger granules than when other binders were used; *i.e.*, the difference of the percentages passing through a 75 μm sieve was great. These effects are considered to be due to differences in adhesiveness among the binders.

The binder content in each granule fraction is shown in Table IV. For all binders tested, the greater the particle size, the higher was 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 V. The relationship between binder content and median particle size is illustrated in Fig. 3, and that between binder content and the percentage generation of coarse granules greater than 500 μm is shown in Fig. 4.

As shown in Fig. 3, when HPC or HPMC (3 cP) was

TABLE VI. Binder Content Distribution According to Particle Size for Batches Prepared by the Dry Mixing Method in a High-Speed Mixer

Batch	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
Binder	HPC			HPMC (3 cP)			HPMC (6 cP)			HPMC (15 cP)			MC		
Content (%)	1.0	3.0	5.0	1.0	3.0	5.0	1.0	3.0	5.0	1.0	3.0	5.0	1.0	3.0	5.0
Binder content (%)															
250—355 μm	1.86	3.84	4.78	1.69	3.90	4.80	1.75	3.97	5.82	1.43	4.06	5.71	1.90	4.02	5.31
106—150 μm	0.94	2.79	2.25	0.77	2.65	2.77	0.80	2.99	5.15	0.67	2.81	4.90	0.91	3.55	4.82
75 μm pass	0.30	0.62	0.49	0.40	0.53	0.63	0.49	0.89	2.29	0.29	0.87	2.84	0.40	2.91	3.50
Theoretical value (%)	0.99	2.91	4.76	0.99	2.91	4.76	0.99	2.91	4.76	0.99	2.91	4.76	0.99	2.91	4.76

used, the median particle size increased as the binder content was raised, while use of other binders, HPMC (6 cP), HPMC (15 cP) and MC, led to slight decreases in the median particle size at 5% binder applied. This reduction of the median particle size may be due to insufficient dissolution of these binders in the dry mixing method, *i.e.*, the amount of dissolved binder particles was not sufficient for granulation. At 5% binder applied, water per binder applied was decreased. HPC did not lose its adhesive power even at a low water content, while HPMC having a low degree of polymerization, such as HPMC (3 cP), was as soluble and as adhesive as HPC at a low water content. MC undergoes gel-formation at about 35 °C,[13] and since the final temperature during granulation was 50—55 °C in the present experiments, the solubility of MC was inferred to be reduced by this high temperature to a greater extent than that of other binders.

As shown in Fig. 4, the percentage generation of coarse granules increased as the binder content was raised due to the small amount of water per binder applied. This result might be attributed to an increase in non-uniformity in the distribution of water associated with the rise in binder content.

Except for MC, the granule strength was increased as the binder content was raised (Table V) in a manner similar to that in the case of the solution method, indicating that the binder content contributes to the granule strength in the dry mixing method as well. The granules produced with MC were extremely weak compared with those produced with the other binders. As mentioned above, the low gelling temperature of MC causes reduced dissolution of MC particles, and thus is thought to be responsible for this low granule strength.

The binder content in granules at each particle size is shown in Table VI. In the cases of HPC and HPMC (3 cP), the granule size increased with increasing amount of binder applied, and the binder content interpolated at median particle size came close to the theoretical value. On the other hand, in the cases of HPMC (6, 15 cP) and MC, where the granule size did not increase with increasing amount of binder applied, a higher amount of binder was found in the small size fractions in comparison with the former cases. This latter result is thought to be due to failure of the binder to dissolve completely, and indeed, undissolved binder particles were recovered in these small particle size fractions. The granules which were prepared with 5% MC and passed through a 75 μm sieve showed the largest binder content (Table VI), suggesting an interrelationship between the amount of water required for the dissolution of binder particles and the distribution of binder in the granulation product.

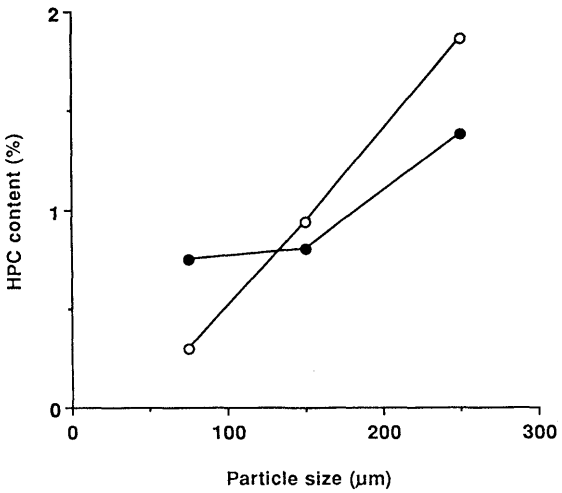

Fig. 5. Effect of the Method of Binder Addition on the Distribution of Binder in Different Size Fractions of Granules

●, HPC 1% solution method; ○, HPC 1% dry mixing method.

Differences between the Solution Method and the Dry Mixing Method Granules were prepared using 1% 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. 5 (plotted data from Tables IV and VI), at a fixed amount 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 IV and VI). In the solution method, the binder is already dissolved, whereas in the dry mixing method, a binder has to be dissolved first and then distributed, and this may result in high local water content in a manner similar to that occurring in the distribution of a high concentration solution. Thus, the use of an aqueous solution of a binder in the wet granulation method results in easy spreading over the excipient particles to give a uniform distribution of the binder. It is also evident that granules with the same strength can be prepared with a smaller amount of a binder in a solution method than in a dry mixing method.

Conclusion

The effects of changes in the binder grade of water-soluble cellulose ethers, the amount of binder applied and the method of binder addition on the relationship between the distribution of the binders in different size fractions and the physical properties of granulated products were investi-

gated.

1) In the solution method, the difference among the cellulosic binders tested was small, at least when lactose/cornstarch was used as a carrier in the presence of a fixed amount of water, and the percentage generation of coarse granules increased as the viscosity rose.

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 method and the dry mixing method, the binder content was higher in larger granule fractions when the binder was added as a solution or had dissolved. However, in the dry mixing method, the binder content was higher in smaller granule fractions when the binder had not completely dissolved. In addition, the granule strength was lower when a binder had not completely dissolved than when it had completely dissolved.

A granulation method using a powder binder does not require the preparation of a binder solution, and is thus labor-saving. The amount of a binder that will be effective for granulation can be estimated by measuring the binder distribution in the product granules, and this information will be useful in the design of solid dosage forms.

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