Influence of the Molecular Weight of Binding Agents on the Physical Properties of Granules and Tablets

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Received March 4, 1994; accepted May 26, 1994

To improve the adhesiveness and cohesiveness of powders for granule formation, binding agents are generally used. In the wet granulation process, the binder solution plays an important role in controlling the mechanical properties of granules. In this study, the effects of the type and molecular weight of the binding agent and the effects of the concentration and viscosity of the binder solution on granule characteristics, *i.e.*, average granule size (D_{50}), granule strength (*St*) and granule compressibility, were investigated.

Polyvinylpyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC) of various molecular weights were used for the preparation of granules by the agitating-fluidized granulation method. In each polymer system, the average granule size (D_{50}) and strength (*St*) increased with increasing concentration and viscosity of the binder solution and as the molecular weight of the binding agent was increased.

The compressibility of granules was evaluated by means of the compressibility constant (*K*) of a modified version of Kawakita's equation and *K* decreased with increasing molecular weight. An approximately linear relationship was observed between the reciprocal of the compressibility constant ($1/K$) and granule strength (*St*). At the same granule strength, *K* values in the HPMC system were greater than those in the PVP system. The radial tensile strength (σ) of the tablet, obtained by the diametral compression test, increased with increasing concentrations and viscosity of binder solutions and was also affected by the molecular weight of the binding agent. These results indicate that σ is related to granule strength (*St*).

Keywords binding agent; molecular weight: granule strength; compressibility; radial tensile strength

Granule strength depends on the following factors:

1) The type and concentration of the binding agent used in the granulation process.[1]

2) The temperature and duration of the drying process (taking into account, the moisture content and flow rate of the circulating air[2]).

3) The shape and apparent density of the granule, which depend on the kind of granulating apparatus used.[3]

4) The period during which the binding solution is in contact with the granulation mass.[4]

Wells and Walker[5] have investigated the influence exerted by the properties of water/ethanol binder solutions on granule size and we have reported[6] that the physical properties were affected by adhesion in both the presence and absence of a binder. The distribution of binders within granules prepared by the agitating and fluidized bed granulation process has been investigated by Kristensen,[7] Ormos,[8] and Nouth,[9] and the effects of the concentration,[10] type and viscosity[11] of binders have been investigated by many workers. Reading and Spring[12] studied the influence of granule strength, due to the distribution of the binder within the granules, on tablet strength. However, these experiments did not address the effects exerted by the molecular weight of the binder on the physical properties of granules.

This study was carried out to investigate the effects on granule strength and compressibility of the type and molecular weight of polymers used as binding agents in the wet granulation process. Polyvinylpyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC) of varying molecular weights were selected as binders.

Materials and Methods

Materials The materials used to prepare the granules were lactose (DMV, 200 mesh), PVP (BASF, PVP, K-25, K-30, K-90), and HPMC (Shin Etsu TC-5S, TC-5RW, TC-5E).

Table I shows the physicochemical properties of the binders and the granulating fluids.

Measurement of Viscosity Binder solution viscosity was measured at 25 °C with an E type viscometer (Tokyo Keiki Co., Ltd.).

Granulation Method Granulation experiments were conducted with an agitating-fluidized bed granulator (Powrex Co., Ltd., type MP-01). Five hundred grams of lactose was pre-agitated at 350 rpm; 200 g of binder solution was then sprayed onto the lactose. The following granulating conditions were kept constant for all batches: inlet air temperature 75 °C, outlet air temperature 28—30 °C, and fluid flow-rate 14 g/min. However, after 120 g of binder solution had been sprayed, the

TABLE I. Physicochemical Properties of Binder Solutions in Relation to Granule Diameter

Binder	Mean molecular weight[a]	Concentration (w/w%)	Viscosity[b] (mPa·s)	D_{50} (μm)
PVP K-25	29000	15	9.23	229.74
		20	19.89	258.47
PVP K-30	45000	10	5.30	171.14
		15	10.12	223.15
		20	20.85	268.36
PVP K-90	1100000	5	21.00	234.24
		7	40.56	274.64
		10	95.64	375.26
HPMC TC-5E	12600	5	9.14	124.92
		7	19.44	165.15
		10	45.06	218.20
HPMC TC-5RW	29400	5	26.34	156.96
		7	76.20	256.72
		10	183.12	290.28
HPMC TC-5S	64800	3	23.61	150.21
		5	117.48	196.41
		7	379.80	312.09

a) Manufacturer's data. *b*) Measured at 25 °C.

fluid flow-rate was 12 g/min.

Measurement of Granule Diameter Distribution Granule diameter distribution was determined with JIS standard sieves vibrated on a sieve-shaking machine. The mean granule diameter (D_{50}) is equivalent to the median diameter.

Measurement of Granule Hardness Granule hardness was measured with a hardness tester, as we have described previously.[6] The measurements represent the average of 30 granules. The granule strength, St, was obtained by Hiramatsu's equation[13]:

$$St=0.7P/A \tag{1}$$

$$A=\pi d^2/4 \tag{2}$$

where P is the maximum load at the fracture of the granule, A is the sectional area, and d is the granule diameter.

Compression Test and Measurement of Radial Tensile Strength All samples were compressed on a universal tension and compression tester (Shimadzu Autograph AG 5000D) with 16 mm flat-face punches to a tablet weight of 1.0 g. Using the Autograph, we subjected the model tablets to a diametral compression test after they had been allowed to remain at room temperature for 24 h. The test consisted of applying a load diametrically, measuring the maximum load, W, at the tablet fracture, and calculating the radial tensile strength, σ, using the following equation:

$$\sigma=2W/(\pi Dt) \tag{3}$$

where D is the diameter of the tablet and t is the tablet thickness.

Measurement of Film Tensile Strength The film tensile strength was measured with the Autograph. The values represent the average of 5 measurements.

Results and Discussion

Effects of Binder Concentration and Binder Solution Viscosity on Granule Size Figure 1 shows the correlation between the concentration of binding agent and the mean granule size of lactose obtained in the liquid addition phase with binding agents of differing molecular weights. PVP K-90 gave rise to a larger mean granule size (D_{50}) than other binder solutions (Fig. 1). In addition, for HPMC, the D_{50} gradually increased as the molecular weight of the binding agents increased, as shown in Fig. 1. These findings indicate that the liquid requirement for granulation with a high molecular weight binding agent is lower than that for lower molecular weight binding agents.

Figure 2 shows the effects of binder solution viscosity on mean granule size (D_{50}). For both polymers, the mean granule size (D_{50}) increased with increasing binder solution viscosity, *i.e.*, adhesiveness between particles increased with increasing binding solution viscosity.

Schaefer *et al.*[14] reported that granule size was influenced by the diameter of the spray mist used for fluidized bed granulation and by the mechanical strength of the liquid bridge between particles. The spray mist diameter increases with binder solution viscosity and therefore the mechanical strength of the liquid bridge between particles also increases. Our results, also show that, for the same reason, binder concentration and viscosity are important factors in determining granule size.

Effects of Binder Concentration and Binder Solution Viscosity on Granule Strength We examined the effects of binder concentration, binder solution viscosity, and binder molecular weight and found that granule strength increased with increasing binder concentration (Fig. 3). For PVP K-90, granule strength increased suddently with the lowest concentration of binder and the degree of increase was considerably greater than that with other PVP binders at the same concentration. The high values for granule strength were probably due to the high viscosity of the binder solution.

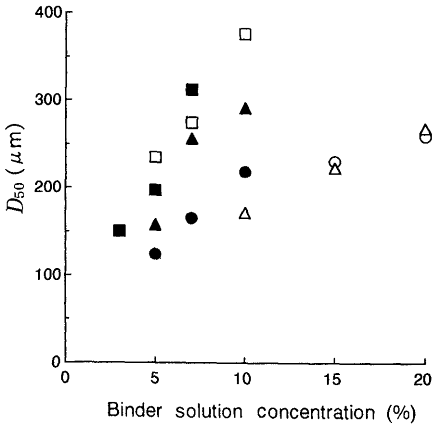

Fig. 1. Relationship between Binder Solution Concentration and Granule Size (D_{50}) as a Function of the Molecular Weight of the Binding Agents

○, K-25; △, K-30; □, K-90; ●, TC-5E; ▲, TC-5RW; ■, TC-5S.

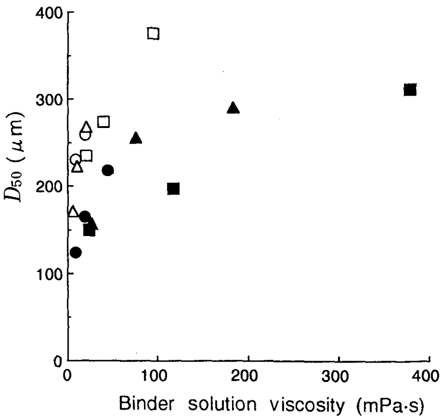

Fig. 2. Relationship between Binder Solution Viscosity and Granule Size (D_{50}) as a Function of the Molecular Weight of the Binding Agents

○, K-25; △, K-30; □, K-90; ●, TC5E; ▲, TC-5RW; ■, TC-5S.

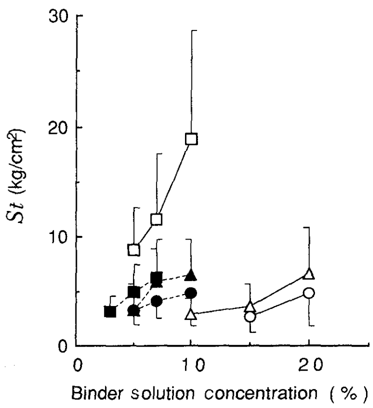

Fig. 3. Effects of Binder Solution Concentration (%) on Granule Strength (St)

○, K-25; △, K-30; □, K-90; ●, TC-5E; ▲, TC-5RW; ■, TC-5S.

Indeed, we found that granule strength increased with increasing binder solution viscosity (Fig. 4).

The tensile strength of films made with 5% HPMC solution increased with the increasing molecular weight of

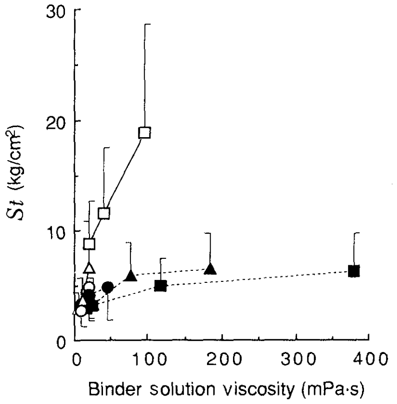

Fig. 4. Effects of Binder Solution Viscosity (η) on Granule Strength (St)

○, K-25; △, K-30; □, K-90; ●, TC-5E; ▲, TC-5RW; ■, TC-5S.

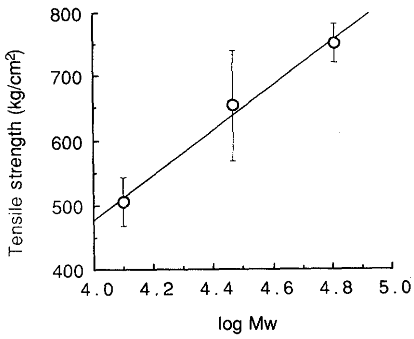

Fig. 5. Relationship between the Logarithm of the Molecular Weight (Mw) and the Tensile Strength of Polymer HPMC Films

HPMC, as shown in Fig. 5. These findings suggest that granule strength is affected by the molecular weight of the binding agent. However, since the tensile strength of PVP films of very weak, we did not measure the tensile strength of these films. However, Healey *et al.*[15] have measured the tensile strength of PVP, gelatin, and methylhydroxyethylcellulose films and found that the tensile strength of PVP film was the weakest. Our present results for the tensile strength of films agree with those of Healey *et al.* Krycer *et al.*[16] have reported that, for the granulation of acetoaminophen, the granule strength in an HPMC system is greater than that in a PVP system at the same binder solution viscosity. On the other hand, Cutt *et al.*[17] and Horisawa *et al.*[18] found that, for the granulation of hydrohobic materials, the granule strength in a PVP system was greater than that in an HPMC system. It is considered that granule fracture occurs at the center of the neck of the binder between particles when the affinity of the particle and binder agent is strong, and at the joining of the binder and particles, when the affinity is weak. The present results for granule strength support the findings of Cutt *et al.*[17] and Horisawa *et al.*[18] This greater granule strength may be related to the work of immersion of PVP being greater than that of HPMC, as reported by Horisawa *et al.*[18]

Effects of Binder Properties on Compressibility The effect of the granulating fluid as a binder solution governing the compressibility of the granules was examined. We assumed that the relationship between porosity and compression force conformed to the following modified version of Kawakita's equations for the com-

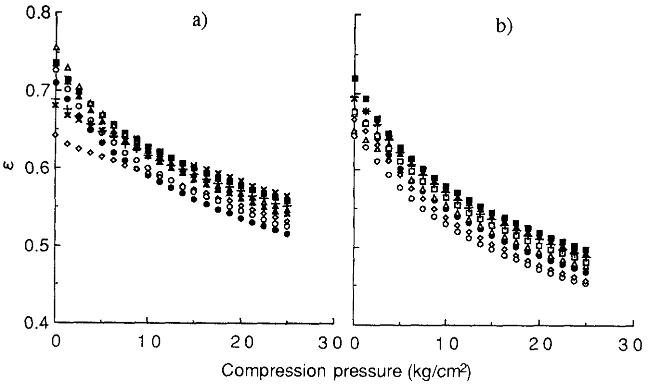

Fig. 6. Relationship between Compression Pressure (P) and Porosity (ε)

a) ○, 15% K-25; △, 20% K-25; ●, 10% K-30; ▲, 15% K-30; ■, 20% K-30; ◇, 5% K-90; +, 7% K-90; ×, 10% K-90. b) ○, 5% TC-5E; △, 7% TC-5E; □, 10% TC-5E; ●, 5% TC-5RW; ▲, 7% TC-5RW; ■, 10% TC-5RW; ◇, 3% TC-5S; +, 5% TC-5S; ×, 7% TC-5S.

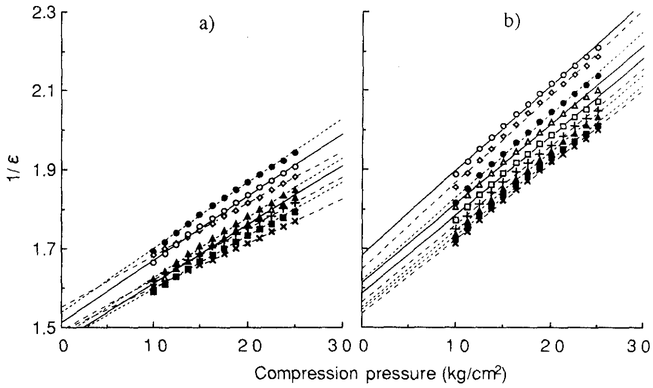

Fig. 7. Plots of the Modified Kawakita's Equation as a Function of Binder Solution Concentration

a) ○, 15% K-25; △, 20% K-25; ●, 10% K-30; ▲, 15% K-30; ■, 20% K-30; ◇, 5% K-90; +, 7% K-90; ×, 10% K-90. b) ○, 5% TC-5E; △, 7% TC-5E; □, 10% TC-5E; ●, 5% TC-5RW; ▲, 7% TC-5RW; ■, 10% TC-5RW; ◇, 3% TC-5S; +, 5% TC-5S; ×, 7% TC-5S.

paction process[19]:

$$-(d\varepsilon/dP)=K\varepsilon^2 \tag{4}$$

where ε is the porosity of the compaction layer, P is the compression force, and K is a constant. Equation 4 represents the following linear relationship:

$$1/\varepsilon=1/\varepsilon_0+KP \tag{5}$$

where ε_0 is the initial porosity at $P=0$.

Porosity (ε) decreased with increasing compression force (P) for each sample, as shown in Fig. 6.

Figure 7 shows the relationship between compression force (P) and inverse porosity ($1/\varepsilon$). Each specimen showed a good linearity ($r^2=0.997-0.999$). Here, we will consider the constant, K, which is related to the compressibility of granules. At a high K value, granules were easily compacted.

Figure 8 shows the effects of binder solution viscosity on the constant K and can be seen that K decreased with increasing binder solution viscosity.

Figure 9 shows the relationship between granule strength (St, abscissa) and the inverse constant K

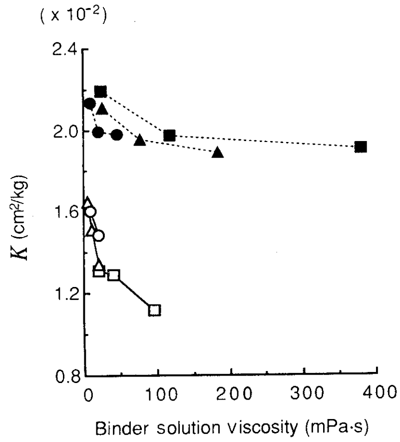

Fig. 8. Effects of Binder Solution Viscosity (η) on the Compressibility Constant (K)

○, K-25; △, K-30; □, K-90; ●, TC-5E; ▲, TC-5RW; ■, TC-5S.

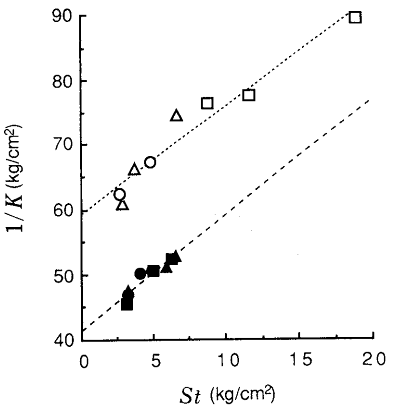

Fig. 9. Relationship between Granule Strength (St) and Inverse Compressibility Constant ($1/K$)

○, K-25; △, K-30; □, K-90; ●, TC-5E; ▲, TC-5RW; ■, TC-5S.

(ordinate) at a compression force of 25 kg/cm^2. All experimental data points in Fig. 9 lie approximately on a straight line for both binding agents. The inverse constant K increased with increasing granule strength and this implies that the compression force requirements for compression with a high molecular weight binding agent are higher than those required for low molecular weight binding agents. These results suggest that HPMC is more easily compressed than PVP when granules of the same strength are used.

Effects of Binder Agent Properties on Tablet Strength As stated above, tablet strength is known to be affected by many factors, such as compression force and speed, granule size and hardness, and type of binder; however, to our knowledge, the effects of granule strength on tablet strength have never been reported. We therefore examined these effects. Figure 10 shows the relationship between radial tensile strength, σ, and the concentration of binder solution.

Figure 11 shows the effects of binder solution viscosity (abscissa) on radial tensile strength, σ. These findings show that the radial tensile strength, σ, increased with increasing binder concentration and binder solution viscosity. Again, radial tensile strength depended markedly on the molecular

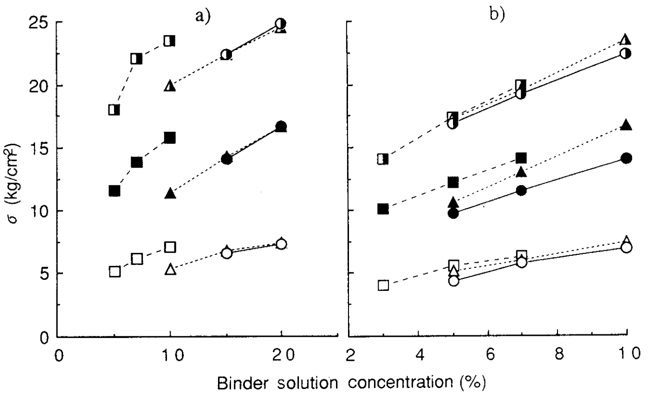

Fig. 10. Relationship between Binder Solution Concentration (%) and Radial Tensile Strength (σ) as a Function of Compression Force

a) ○, K-25 500 kg/cm^2; ●, K-25 1000 kg/cm^2; ○, K-25 1500 kg/cm^2; △, K-30 500 kg/cm^2; ▲, K-30 1000 kg/cm^2; △, K-30 1500 kg/cm^2; □, K-90 500 kg/cm^2; ■, K-90 1000 kg/cm^2; ◨, K-90 1500 kg/cm^2. b) ○, TC-5E 500 kg/cm^2; ●, TC-5E 1000 kg/cm^2; ◑, TC-5E 1500 kg/cm^2; △, TC-5RW 500 kg/cm^2; ▲, TC-5RW 1000 kg/cm^2; ◭, TC-5RW 1500 kg/cm^2; □, TC-5S 500 kg/cm^2; ■, TC-5S 1000 kg/cm^2; ◨, TC-5S 1500 kg/cm^2.

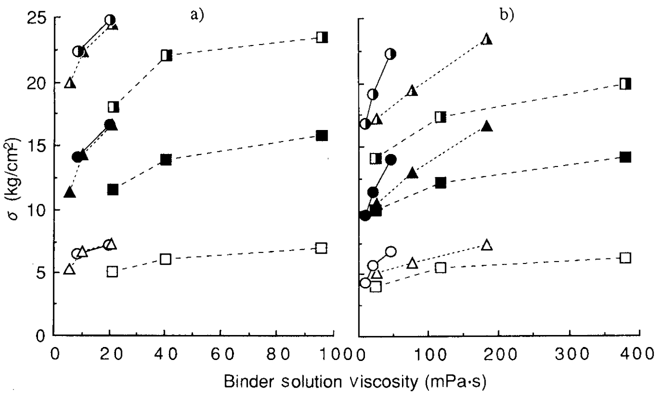

Fig. 11. Effects of Binder Solution Viscosity (η) on Radial Tensile Strength (σ)

a) ○, K-25 500 kg/cm^2; ●, K-25 1000 kg/cm^2; ◑, K-25 1500 kg/cm^2; △, K-30 500 kg/cm^2; ▲, K-30 1000 kg/cm^2; ◭, K-30 1500 kg/cm^2; □, K-90 500 kg/cm^2; ■, K-90 1000 kg/cm^2; ◨, K-90 1500 kg/cm^2. b) ○, TC-5E 500 kg/cm^2; ●, TC-5E 1000 kg/cm^2; ◑, TC-5E 1500 kg/cm^2; △, TC-5RW 500 kg/cm^2; ▲, TC-5RW 1000 kg/cm^2; ◭, TC-5RW 1500 kg/cm^2; □, TC-5S 500 kg/cm^2; ■, TC-5S 1000 kg/cm^2; ◨, TC-5S 1500 kg/cm^2.

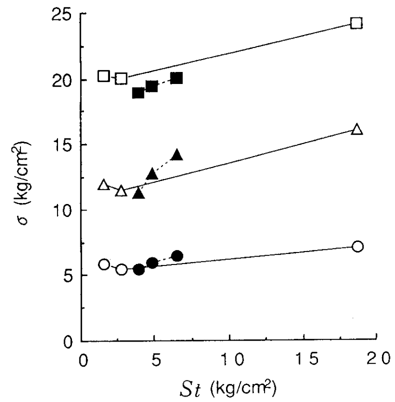

Fig. 12. Relationship between St and σ

○, PVP 500 kg/cm^2; △, PVP 1000 kg/cm^2; □, PVP 1500 kg/cm^2; ●, HPMC 500 kg/cm^2; ▲, HPMC 1000 kg/cm^2; ■, HPMC 1500 kg/cm^2.

weight of the binder. It would seem that the radial tensile strength is affected by the physical properties of the granule, *i.e.*, its size and strength. We therefore examined the effects of granule strength on the radial tensile strength.

We investigated the relationship between granule strength and radial tensile strength at the same binder concentration, 10% for PVP and 7% for HPMC.

Figure 12 shows the effects of granule strength, *St*, on the radial tensile strength, σ. The radial tensile strength, σ, gradually increased with increasing *St*, however, there was no significant difference between the results for the different types of binder.

Conclusion

Granule strength was influenced by the concentration, viscosity, and molecular weight of the binding agent. The granule size and strength increased as the viscosity and molecular weight of the binding agent increased due to the mechanical strength of the bridge between particles increasing as these factors increased. The effects of these factors on the physical properties of granules depended on the type of binding agent used. Again, using the modified version of Kawakita's equation, we showed in this study that granule compressibility decreased with increasing granule strength, while the radial tensile strength increased, because granules were fractured by compression stress.

Acknowledgment The authors gratefully acknowledge the support for this research by a grant from the Hosokawa Advancement of Powder Technology Foundation.

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