Effects of Granulation Method and Drug Dissolved in Binder Solution on Compressibility of Granules

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Acetaminophen and ascorbic acid, which are slightly and highly soluble in water, respectively, were granulated with a low viscosity grade of hydroxypropylcellulose (HPC-L) aqueous solution by high-speed mixing, fluidized bed granulation, and spray drying. The granules obtained were compacted into tablets and their strengths were evaluated.

The binding strength of acetaminophen granules increased with increase in the amount of water used, irrespective of the granulation method. On the other hand, the binding strength of ascorbic acid granules depended greatly on the granulation method and decreased when an excessive amount of water was used. The ascorbic acid granules obtained by fluidized bed and spray drying granulation with the minimum amount of water exhibited high compressibility. In these granules, the surface of crystals was found to be entirely coated with the binder. It is considered that the high solubility of the drug in the binder solution enabled such coating to occur, though excessive dissolution of the drug led to a decrease in compressibility.

Keywords acetaminophen; ascorbic acid; granulation; compressibility; binder solution

When drug powders are compressed into tablets, cracks referred to as "capping" are sometimes generated within the tablets. Therefore, powders being compacted into tablets must have adequate binding properties and uniform compressibility. In the previous papers, the authors clarified that capping was a cracking of a compact in a die by a high residual die wall pressure,[1] and that an effective means for preventing capping is to enhance the binding properties of powders and to reduce the residual die wall pressure.[2] In other papers, the authors showed that capping was prevented by mixing a polymeric powder with a low residual die wall pressure,[3] and the addition of a polymeric binder during wet granulation was more effective to prevent capping because the size of the binder particles was reduced and the binding strength was enhanced.[4]

There are several granulation methods for wet granulation of drugs to be compacted into tablets. High-speed mixing and fluidized bed granulation have often been used.[5] In the former method, powder and a binder solution are mixed with an impeller rotating at a high speed. In the latter method, the binder solution is sprayed onto the fluidized powder. In both methods, however, powders are granulated in a batch mode. Recently spray drying, in which powder dispersed in a binder solution is sprayed and dried, has been studied as a method for granulation of drugs for tablets.[6-8] This method enables continuous granulation.

In this study, the effect of the type of wet granulation method, *i.e.*, different methods of addition of a binder, on the compressibility of granules was clarified. Furthermore, the effect of the drug dissolved in the binder solution was also investigated. Water-insoluble acetaminophen and water-soluble ascorbic acid were used as drug powders for this purpose.

Experimental

Materials Acetaminophen (Yamamoto Chemical Industries, Ltd., Japan) and ascorbic acid (Takeda Chemical Industries, Ltd., Japan) were used as slightly and highly water-soluble drugs. Both powders have poor binding properties and exhibit a high capping tendency. A low viscosity grade of hydroxypropylcellulose (HPC-L, Nippon Soda Co., Ltd., Japan) was used as a binder. The density of HPC-L was 1.17 g/cm^3. The amount of HPC-L added to a drug for granulation was fixed at 3% of the total.

High-Speed Mixing A cylindrical mixer with an internal diameter of 95 mm was assembled by the authors. Drug powder weighing 24.5 g and binder solution containing 0.75 g of HPC-L were mixed and granulated for 4 min with an impeller rotating at 1300 rpm. The granules were passed through a 710 μm sieve and dried at 40 °C for 8 h.

Fluidized Bed Granulation A laboratory-scale fluidized bed granulator (Fuji Sangyo Co., Ltd., Japan) was used. Drug powder weighing 388 g was fluidized in this granulator, and the binder solution containing 12 g of HPC-L was sprayed using a two-fluid nozzle. The temperature and the volume of fluidizing air were 80 °C and 45 m^3/h, respectively. The addition rate of the binder solution and the atomizing air volume were 12 g/min and 24 l/min, respectively. After granulation, the granules were dried until the temperature of the outlet air reached 50 °C.

Spray Drying A laboratory-scale spray dryer (1 m in diameter, Iwai Machinery Industries, Ltd., Japan) was used. Drug powder weighing 29.1 g was suspended in a binder solution containing 0.9 g of HPC-L, then this suspension was sprayed using a disk-type atomizer rotating at a high speed and dried instantaneously. The temperatures of inlet air, chamber, and outlet air were 200 °C, 100 °C, and 80 °C, respectively. The rate of revolution of the disk of the atomizer was 20000 rpm, and the addition rate of the suspension was about 50 g/min.

Measurement of Characteristics of Granules Particle size of granules was measured by sieving them, and 50%-mean particle size was determined. The surface of granules was observed using a scanning electron microscope (JSM-T330A, Nihon Denshi, Ltd., Japan). The X-ray diffraction of powder was measured with an X-ray diffraction apparatus (RAD-IC, Rigaku Denki, Ltd., Japan); LiF in powder form of the same mass as the granules was added to the sample powder as an internal standard by mixing lightly in a mortar.

Tablet Preparation The water content of granules was controlled by keeping the granules in a desiccator, where the relative humidity was maintained at 15% with a saturated LiCl aqueous solution, for a period longer than 12 h before compaction. The granules were compacted into tablets using a hand-operated oil press (Riken-Seiki, Ltd., Japan). A die with an internal diameter of 8 mm and flat-faced punches were used. Granules weighing 200 mg were compacted into tablets. Before each compaction, the die and punches were lubricated with a very small amount of magnesium stearate. The tablets obtained were kept in the desiccator at 15% relative humidity for more than 12 h, and thus the moisture content of tablets was controlled at the same level.

Measurement of Characteristics of Tablets The diameter and the thickness of tablets were measured with a dial-gauge. The apparent density and porosity of a tablet were calculated using these values. The strength of tablets was measured using a compression test apparatus (Rheo-Robot, Kyowa Seiko Co., Ltd., Japan). The tablets were compressed in a diametrical direction at a speed of about 1 mm/min, and fracturing forces (F, kg) were determined. The tensile strength (S, kg/cm^2) of the tablet was calculated through Eq. 1.[9]

$$S=2F/(\pi DT) \quad (1)$$

where D and T are the diameter and the thickness of the tablet, respectively. The values for 3—5 tablets were averaged.

Results and Discussion

Characteristics of Original Powders The mean particle size, the density of particles, and the solubility in water at 20 °C of the original powders are shown in Table I. These values were determined using a microscope and an air compaction pycnometer, and by measurement of the absorbance to determine concentration, respectively. Ascorbic acid is highly soluble in water, and its solubility is 25 times that of acetaminophen.

The original powders were compressed into tablets under pressures of 1000 and 2000 kg/cm^2. As shown in Table II, neither of the powders could be compacted to form tablets because of their strong capping tendency. However, when these powders were subjected to compaction using a loaded-ejection type compactor in which a tablet is ejected from the die under a mild compressive pressure,[2,10,11] they could be compacted to form uniform tablets with no capping. In Table II, the tensile strengths of these uniformly compacted tablets are listed. Both powders exhibited an extremely low tensile strength. From these results, it was assumed that the high capping tendency of these powders was due to the low binding strength relative to the residual die wall pressure.[2]

Granulation of Acetaminophen Acetaminophen was granulated with HPC-L aqueous solution containing various amounts of water by high-speed mixing, fluidized bed granulation, and spray drying.

Figure 1 indicates the relationship between granule size and the amount of water used. The amount of water needed for granulation depended on the granulation method. In the high-speed mixing, 0.16 ml/g of water gave the optimum result. Departure from this value led to more or less unsuccessful granulation. The amount of water for the fluidized bed granulation was restricted by the viscosity of the binder solution to be sprayed. Minimal water for spraying was about 0.5 ml/g. In the case of the spray drying, the fluidity of the suspension was a determinant of the minimum amount of water required. More than 2 ml/g of water was needed for spraying acetaminophen suspension in HPC-L aqueous solution. As shown in Fig. 1, the particle size of granules depended on the granulation method, and was little influenced by the amount of water used. The high-speed mixing gave larger granules while the spray drying gave smaller granules.

These granules were compacted into tablets and their tensile strengths were estimated. The results are shown in Fig. 2, where the strengths are plotted against the amount of water used to dissolve the binder. The strength of tablets was slightly increased in the following order; high-speed mixing < fluidized bed < spray drying. Considering the relation with the amount of water used, however, the tensile strength of tablets did not depend on the granulation method, but depended only on the amount of water used, and slightly increased with an increase in amount of water. The moisture contents of tablets are considered to be the

TABLE I. Characteristics of Original Powders

	Particle size (μm)	Particle density (g/cm^3)	Solubility in water (g/100 ml)
Acetaminophen	40	1.29	1.3
Ascorbic acid	15	1.65	32.6

TABLE II. Tensile Strength of Tablets of Original Powders (kg/cm^2)

	Ordinary method		Loaded ejection method	
	1000 kg/cm^2	2000 kg/cm^2	1000 kg/cm^2	2000 kg/cm^2
Acetaminophen	Capped	Capped	3.6	6.1
Ascorbic acid	Capped	Capped	6.2	13.5

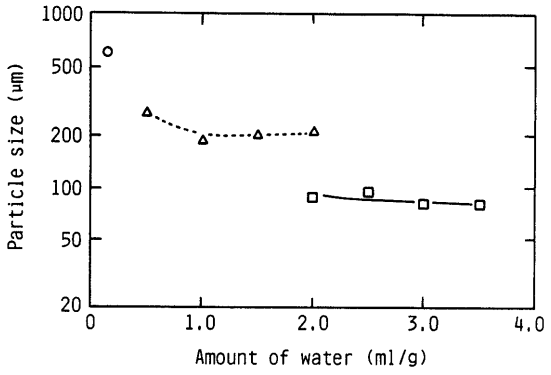

Fig. 1. Mean Particle Size of Acetaminophen Granules

○, high-speed mixing; △, fluidized bed; □, spray drying.

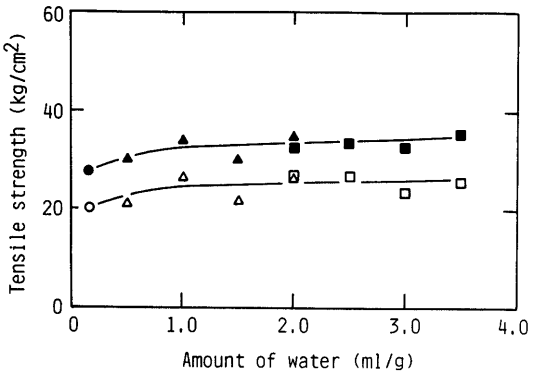

Fig. 2. Tensile Strength of Acetaminophen Tablets

Compaction pressure: open symbols, 1000 kg/cm^2; solid symbols, 2000 kg/cm^2. ○●, high-speed mixing; △▲, fluidized bed; □■, spray drying.

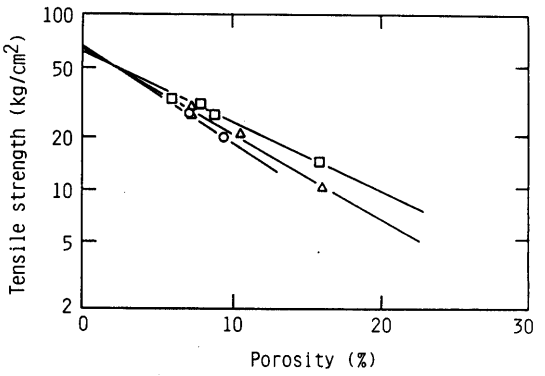

Fig. 3. Relationship between Tensile Strength and Porosity of Acetaminophen Tablets

○, high-speed mixing (0.16 ml/g); △, fluidized bed (0.5 ml/g); □, spray drying (2.0 ml/g).

same because the tablets were kept in a desiccator. These results indicate that the HPC-L was scattered more finely on the acetaminophen crystals when the binder was dissolved in a large amount of water. However, an especially effective granulation method to improve the compressibility was not found for acetaminophen.

A linear relationship has been reported between porosity and the logarithm of tensile strength of tablets.[12] The relationship between these two values for acetaminophen tablets is shown in Fig. 3. Figure 3 indicates that the tensile strength of the tablet at the same porosity was increased in the same order as that in Fig. 2, *i.e.*, high-speed mixing < fluidized bed < spray drying. This fact implies that an increase in the tablet strength can be attributed to an increase in the binding strength at the points of contact between particles, because the number of total contact points between particles within a tablet is assumed to be the same at the same value of porosity. An increase in the strength at contact points will be caused by an increase in the probability of existence of the binder at a contact point. Figure 3 also shows that the difference in strength between granulation methods is reduced with a decrease in porosity, *i.e.*, an increase in compaction pressure. This implies that the binder was slightly spread during compaction.

Granulation of Ascorbic Acid The particle size of ascorbic acid granules is shown in Fig. 4. In the high-speed mixing, 0.1 ml/g of water was optimal. In the spray drying, ascorbic acid suspension containing more than 0.4—0.5 ml/g of water could be sprayed. These values were much less than those for acetaminophen. This is due to the high solubility of ascorbic acid in water. When dichloromethane, in which ascorbic acid did not dissolve, was used as a solvent in the spray drying, more than 1.5 ml/g was needed to fluidize the suspension. The granules obtained by the high-speed mixing and by the fluidized bed method showed larger particle sizes while those formed by spray drying resulted in smaller sizes. A marked effect of the amount of water on granule size was not observed.

These granules were compacted into tablets, and their tensile strengths were determined. The results are shown in Fig. 5. The strength greatly depended on the granulation method. It was found that granules with high binding strength were obtained by fluidized bed granulation and by spray drying with 0.4—0.5 ml/g of water. The granules formed by the high-speed mixing and the fluidized bed methods with 0.3 ml/g of water showed lower strengths. This is due to the uneven distribution of the binder. The binding strength of granules formed by spray drying was remarkably reduced with an increase in the amount of water used, and that in the case of the fluidized bed method was slightly reduced with an increase of water above 0.5 ml/g. This phenomenon was quite different from the case of acetaminophen. The decrease in strength with an increased

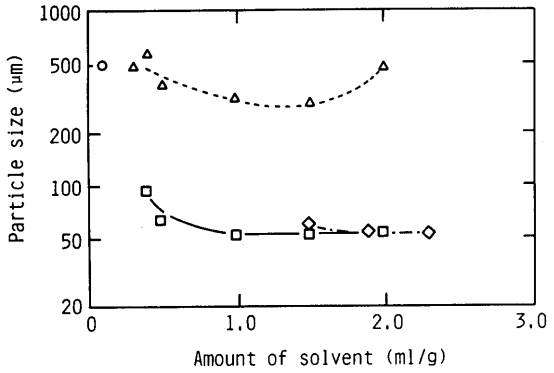

Fig. 4. Mean Particle Size of Ascorbic Acid Granules

○, high-speed mixing; △, fluidized bed; □, spray drying; ◇, spray drying with dichloromethane.

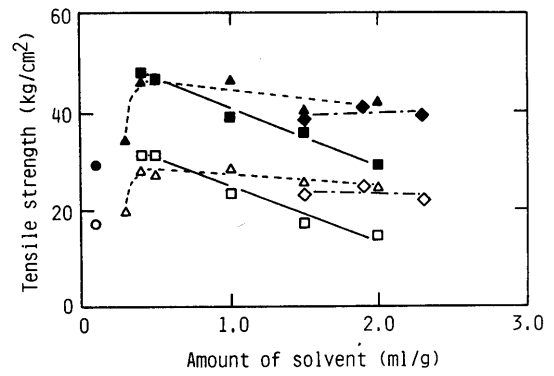

Fig. 5. Tensile Strength of Ascorbic Acid Tablets

Compaction pressure: open symbols, 1000 kg/cm²; solid symbols, 2000 kg/cm². ○●, high-speed mixing; △▲, fluidized bed; □■, spray drying; ◇◆, spray drying with dichloromethane.

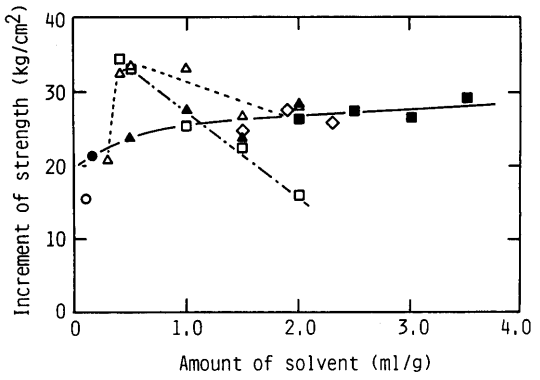

Fig. 6. Increment of Tensile Strength of Tablets Caused by Added HPC-L under 2000 kg/cm² Compaction Pressure

●, acetaminophen by high-speed mixing; ▲, acetaminophen by fluidized bed; ■ acetaminophen by spray drying; ○, ascorbic acid by high-speed mixing; △, ascorbic acid by fluidized bed; □, ascorbic acid by spray drying; ◇, ascorbic acid by spray drying with dichloromethane.

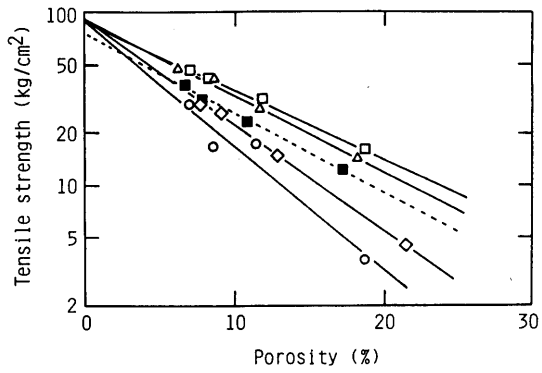

Fig. 7. Relationship between Tensile Strength and Porosity of Ascorbic Acid Tablets

○, high-speed mixing (0.1 ml/g); △, fluidized bed (0.5 ml/g); □, spray drying (0.5 ml/g); ◇, spray drying (2.0 ml/g); ■, spray drying with dichloromethane (1.5 ml/g).

amount of water is considered to be attributed to the reduction in the binding strength of HPC-L caused by ascorbic acid dissolved in the binder solution. In the case of the fluidized bed, the binder solution sprayed on the particles will dry immediately and only a limited amount of ascorbic acid will dissolve in the binder solution. Thus the lowering in binding strength should be slight.

In order to clarify the effect of dissolution of the drug in the binder solution on the strength of tablets, ascorbic acid was spray dried using dichloromethane, in which ascorbic acid did not dissolve. The results are illustrated in Fig. 5. The tensile strengths were not influenced by the amount of dichloromethane, but were lower than those in the case of the fluidized bed or spray drying method with a minimum amount of water. This fact means that the dissolution of the drug in the binder solution does not act merely to reduce the compressibility of the granules.

The increment of tensile strength caused by added HPC-L was determined by subtracting the strength of the tablet formed from the original powder in Table II from the strength of the tablet made of granules (Fig. 2 or 5). The results are shown in Fig. 6. The ascorbic acid granules obtained by spray drying with dichloromethane showed a similar strength to acetaminophen granules, but the granules formed by the fluidized bed method or by spray drying with 0.4—0.5 ml/g of water showed considerably higher values than the others. This result implies that high solubility of the drug in the binder solution serves to enhance the compressibility when the amount of the solvent is limited.

Figure 7 shows the relationship between porosity and tensile strength. The same tendency as that seen in the case of acetaminophen was observed. Thus, the results in Fig. 5 may be attributed to the binding strength at contact points between particles. Figure 7 also indicates that the difference in the tensile strength is diminished as the porosity approaches zero. This means that HPC-L on ascorbic acid also spread during compaction. However, the value of tensile strength of the granules formed by spray drying with dichloromethane at zero porosity was the lowest. This

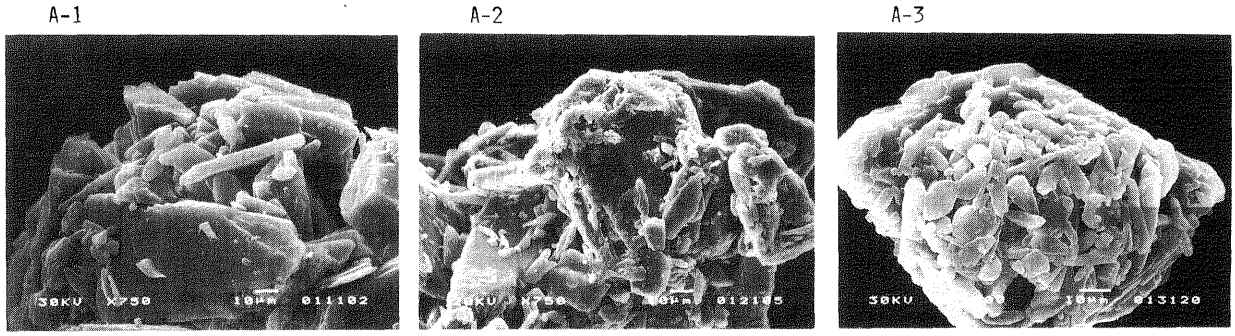

Fig. 8. Scanning Electron Micrographs of Acetaminophen Granules
A-1, high-speed mixing (0.16 ml/g); A-2, fluidized bed (0.5 ml/g); A-3, spray drying (2.0 ml/g).

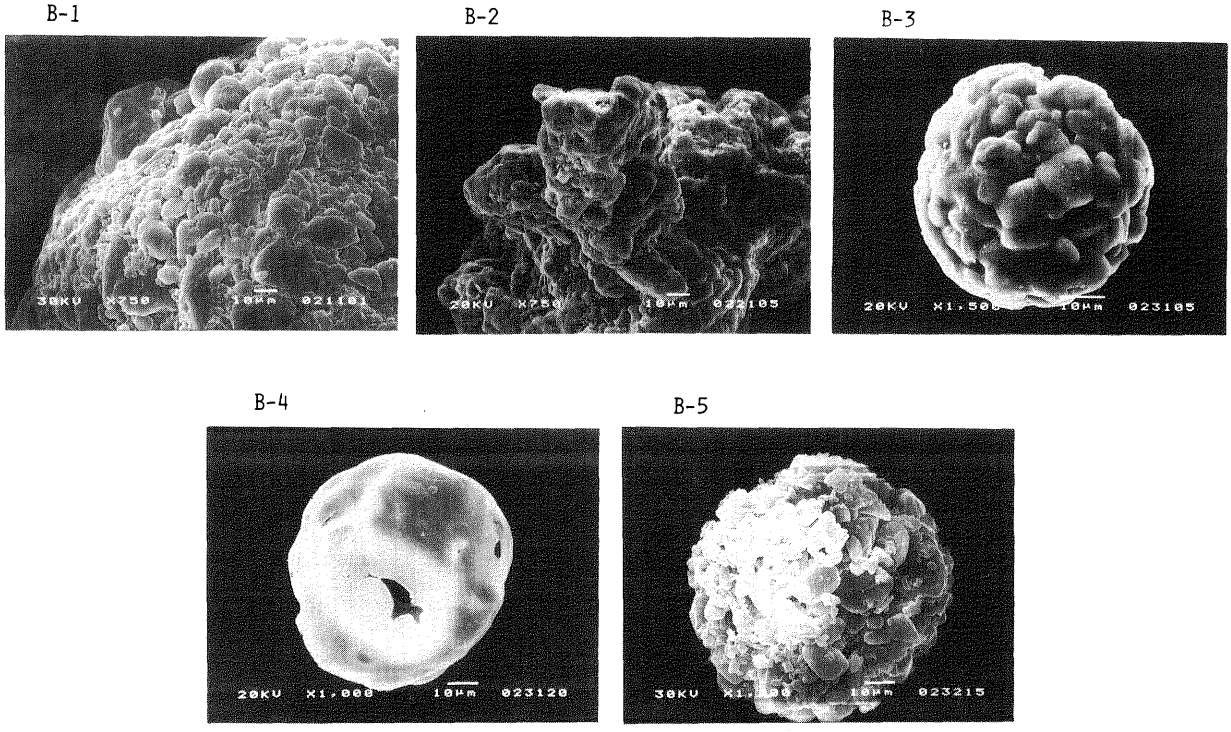

Fig. 9. Scanning Electron Micrographs of Ascorbic Acid Granules
B-1, high-speed mixing (0.1 ml/g); B-2, fluidized bed (0.5 ml/g); B-3, spray drying (0.5 ml/g); B-4, spray drying (2.0 ml/g); B-5, spray drying with dichloromethane (1.5 ml/g).

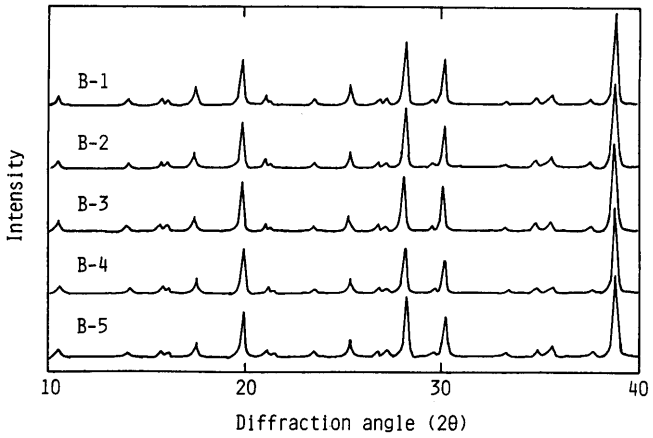

Fig. 10. X-Ray Diffraction of Ascorbic Acid Granules

B-1, high-speed mixing (0.1 ml/g); B-2, fluidized bed (0.5 ml/g); B-3, spray drying (0.5 ml/g); B-4, spray drying (2.0 ml/g); B-5, spray drying with dichloromethane (1.5 ml/g).

TABLE III. X-Ray Diffraction of Ascorbic Acid Granules

Granulation	Solvent (ml/g)	Peak height (ratio to LiF)		
		$2\theta=28.09°$	$2\theta=19.85°$	$2\theta=30.07°$
High-speed mix	Water (0.1)	0.69	0.54	0.48
Fluidized bed	Water (0.5)	0.68	0.54	0.47
Spray dry	Water (0.5)	0.60	0.55	0.45
Spray dry	Water (2.0)	0.55	0.53	0.38
Spray dry	CH_2Cl_2 (1.5)	0.73	0.55	0.46

suggests that the adhesion state of HPC-L differed depending on the kind of solvent.

Electron Micrography and X-Ray Diffraction In order to confirm the adhesion state of the binder, the surface of granules was observed using a scanning electron microscope. Micrographs of acetaminophen granules are shown in Fig. 8. The surface of the granules obtained by high-speed mixing was covered with many raw acetaminophen crystals and the binder was unevenly dispersed (A-1). In the case of the fluidized bed granulation, the binder partially coated the surface of the crystals (A-2). For the granules formed by spray drying, the binder was scattered on the surface of crystals, but did not entirely coat the surface (A-3). This suggests that HPC-L solution around the crystals in the suspension was localized during the spray drying process and resulted in an insufficient increase in the binding strength of the granules.

Electron micrographs of ascorbic acid granules are shown in Fig. 9. The surface of the granules obtained by high-speed mixing was covered with many raw ascorbic acid crystals, similarly to the case of acetaminophen (B-1). For the granules formed by the fluidized bed method, the crystals partially dissolved and the binder seemed to entirely coat the crystals (B-2). A similar surface was observed for the granules formed by spray drying with a minimum amount of water (B-3). These results mean that the high compressibility of granules was achieved by complete coating of the binder on the crystals. The crystals of the granules formed by spray drying with 2.0 ml/g of water were considerably dissolved (B-4). For the granules formed by spray drying with dichloromethane, though the crystals were not dissolved, the binder did not entirely coat the surface, but was merely scattered on the surface of crystals (B-5).

Figure 10 indicates the X-ray diffraction of ascorbic acid granules. The peak at $2\theta=38.7°$ is owing to LiF, the internal standard. Slight differences in peak height were observed though the peak positions were the same. The heights of three main peaks (expressed as ratios to the peak height of LiF) are listed in Table III. The granules from the spray drying with 2.0 ml/g of water showed lower values. This suggests that a part of the ascorbic acid crystals which dissolved in the binder solution had changed to an amorphous state together with HPC-L and the binding strength of HPC-L was reduced.

Granulation to Improve Compressibility The results obtained suggest that the entire coating of particles with a binder is effective to improve the compressibility. However, such coating is not always achieved by spray drying. A strong affinity of the binder solution to the drug particles, as represented by a high solubility of the drug in the solution, is a prerequisite. On the other hand, the dissolution of the drug in a binder solution leads to the reduction of binding strength of the binder. Therefore, the use of a solvent with a high solubility for the drug should be limited to the minimum amount that allows a uniform distribution over the particle surface.

In the case of ascorbic acid, fluidized bed granulation and spray drying with a minimum amount of water were found to be effective approaches to granulation for increasing the binding strength. Spray drying with a minimum amount of water is an especially useful method for the mass production of granules because it enables continuous granulation.

References

1) K. Sugimori, S. Mori, and Y. Kawashima, *Powder Technol.*, **58**, 259 (1989).
2) K. Sugimori, S. Mori, and Y. Kawashima, *Chem. Pharm. Bull.*, **37**, 458 (1989).
3) K. Sugimori, S. Mori, and Y. Kawashima, *Advanced Powder Technology*, accepted.
4) K. Sugimori, S. Mori, and Y. Kawashima, *Chem. Pharm. Bull.*, **37**, 1064 (1989).
5) H. G. Kristensen and T. Schaefer, *Drug Dev. Ind. Pharm.*, **13**, 803 (1987).
6) P. J. Rue, H. Seager, J. Ryder, and I. Burt, *Int. J. Pharm. Tech. & Prod. Mfr.*, **1**, 2 (1980).
7) M. J. Gamlen, H. Seager, and J. K. Warrack, *Int. J. Pharm. Tech. & Prod. Mfr.*, **3**, 108 (1982).
8) H. Seager, P. J. Rue, I. Burt, J. Ryder, J. K. Warrack, and M. J. Gamlen, *Int. J. Pharm. Tech. & Prod. Mfr.*, **6**, 1 (1985).
9) J. T. Fell and J. M. Newton, *J. Pharm. Sci.*, **59**, 688 (1970).
10) Y. Funakoshi, T. Kajiura, and T. Asogawa, *Zairyo*, **18**, 547 (1969).
11) Y. Funakoshi, *Zairyo*, **24**, 673 (1975).
12) M. Hasegawa, A. Otsuka, and F. Higashide, *Yakuzaigaku*, **46**, 50 (1986).