Effect of Particle Size of Drug on Conversion of Crystals to an Amorphous State in a Solid Dispersion with Crospovidone

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The effect of particle size on amorphization of drugs in a solid dispersion (SD) was investigated for two drugs, indomethacin (IM) and nifedipine (NP). The SD of drugs were prepared in a mixture with crospovidone by a variety of mechanical methods, and their properties investigated by particle sizing, thermal analysis, and powder X-ray diffraction. IM, which had an initial particle size of 1 μm and tends to aggregate, was forced through a sieve to break up the particles. NP, which had a large initial particle size, was jet-milled. In both cases, reduction of the particle size of the drugs enabled transition to an amorphous state below the melting point of the drug. The reduction in particle size is considered to enable increased contact between the crospovidone and drug particles, increasing interactions between the two compounds.

Key words solid dispersion; crospovidone; amorphous; particle size; solid–solid interaction

Improving dissolution properties of poorly water-soluble drugs is of major interest to pharmaceutical researchers because it is a key step in enhancing the bioavailability of drugs, and many new drug candidates discovered by combinatorial chemistry and high-throughput screening have had this problem. Various methods have been reported to improve the dissolution properties, one of which is formation of a solid dispersion (SD). Conventionally, SDs have been prepared using water-soluble polymers as a carrier, and numerous methods of preparation including fusion, solvent evaporation, spray drying, and high-shear mixing[1,2] have been reported. When preparing SDs by these methods, difficulties can arise with obtaining the appropriate dosage forms and maintaining the amorphous state.[3] To solve these problems, Fujii *et al.*[4] and Shibata *et al.*[5,6] studied preparation of SDs using crospovidone as a carrier. Crospovidone is an insoluble polymer which does not melt upon heating, allowing it to remain a powder during the SD preparation process. In such SDs it is suggested that interactions occur between compounds containing proton-donor functional groups and crospovidone. Two methods for preparing SDs with crospovidone have been reported. In both methods the SD is prepared by physically mixing the drug with crospovidone (referred to hereinafter as Pmix) and heating below the melting point of the drug, but the details of each method differ. In the case of indomethacin (IM), which has a melting point of 160 °C, SD is prepared by mixing the Pmix using a high-shear mixer (theta-composer) for 30 min followed by heating for 30 min at 125 °C.[4] In the other method, the SD is obtained by mixing and heating the Pmix at 140 °C for 4 min in a one-step procedure using a twin-screw extruder or kneader.[6] It was shown that, in the former method, the high-shear mixing process allowed more drug particles to adsorb on the crospovidone, enabling the drug to become amorphous at a lower temperature. Since the IR spectra of the SD powders prepared by the different methods were similar, it is presumed that the same kind of interaction occurs irrespective of the preparation conditions.

Since crospovidone does not melt by heating, the interactions between the compound and crospovidone can be regarded as those of a solid–solid system. Sekizaki *et al.* have reported that in solid–solid systems, interaction between ibuprofen and polyvinylpyrrolidone (PVP) could be enhanced by reducing the particle size of PVP.[7] Li *et al.* studied a solid–solid phase transformation and reported that the transformation was not directly related to the crystal size but instead to the amount and activity of defects in the crystals, and that use of a milling procedure which generated defects in the crystals accelerated the transformation.[8] We hypothesize that reduction of the particle size of the drug in a Pmix system may lead to increased interaction between the drug and crospovidone. In the present study, the effect of the drug particle size on conversion to an amorphous state in a system with crospovidone was investigated. As model drugs in the study, IM and nifedipine (NP) were used.

Experimental

Materials Crospovidone (Polyplasdone® XL, USP grade) was a gift from ISP Japan (Tokyo, Japan). NP (JP grade) and IM were obtained from Nihon Bulk Yakuhin (Osaka, Japan) and Kongo Chemical (Toyama, Japan), respectively.

Particle Size Analysis Particle size was measured by laser diffraction using a particle size distribution analyzer (Seishin LMS-24, Seishin Enterprise, Tokyo, Japan) by dry measurement at an air pressure of 1.0 kgf/cm^2. Particle size distribution was shown as particle size of 10% (D10), 50% (D50) and 90% (D90) of cumulative percent distribution curve.

Preparation of Pmix and Tmix Pmix was obtained by mixing the drug and crospovidone in the weight ratio of 1 : 3 using a spatula. Pmix samples of NP and crospovidone are hereinafter referred to as NP-Pmix, with the method of preparation of NP (*i.e.*, non-mill, jet-milled) given in parenthesis. IM-Pmix-sieved was prepared by sieving the IM-Pmix using a mesh sieve (mesh size 180 μm) and a spatula. A theta-composed mixture (Tmix) was obtained by mixing 15 g of Pmix with a high-speed elliptical rotor type blender (Theta-Composer Lab type THC, Tokujyu Kousakusyo, Kanagawa, Japan). In this method, the rotor and vessel were rotated counterclockwise at 3000 rpm and clockwise at 100 rpm, respectively, with a clearance of 0.5 mm between the rotor and vessel.

Evaluation of NP-Pmix Powder. Thermal Analysis Using a differential scanning calorimeter (DSC, Thermoflex TAS200, Rigaku, Tokyo, Japan), a sample containing 1 mg of NP was sealed in an aluminum crimp cell and

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heated under nitrogen from 25 to 200 °C at a rate of 2 °C/min. The heat of fusion at 173 °C was calculated from the DSC thermogram.

Powder X-Ray Diffraction (PXRD) Analysis Equipped with DSC Apparatus PXRD analysis was conducted using a powder X-ray diffractometer (Ultima4, Rigaku, Tokyo) equipped with a DSC apparatus. Samples were heated from 25 to 150 °C at a rate of 5 °C/min, and held at 150 °C for 120 min, and PXRD analysis was conducted simultaneously with Ni-filtered Cu$K\alpha$ radiation (40 kV and 40 mA; scanning over the range of 2θ=10.0—20.0°).

Evaluation of IM-Pmix Powder. Thermal Analysis Thermal analysis was conducted using DSC. Samples containing 1 mg of IM were sealed in an aluminum crimp cell and heated under nitrogen using the following heating program: from 25 to 125 °C or 140 °C at a rate of 5 °C/min, held at 125 °C or 140 °C for 15—120 min, and then heated to 200 °C at a rate of 20 °C/min. The heat of fusion at 160 °C was calculated from the DSC thermogram.

PXRD Analysis Equipped with DSC Apparatus PXRD analysis was conducted similar procedure with NP-Pmix. Samples were heated from 25 to 125 °C at a rate of 5 °C/min, and held at 125 °C for 120 min. PXRD scanned over the range of 2θ=15.0—25.0°.

Evaluation of Samples Heated Using a Dry Block Bath The sample (0.65 g) was placed in a test tube (diameter: 1.3 cm) and was heated at 125 °C or 140 °C for 2—20 min, using a dry block bath without mixing. The heated samples were cooled to room temperature, and analyzed by PXRD. PXRD analysis was conducted using a powder X-ray diffractometer (M03X-HF, Mac Science, Yokohama, Japan) with Ni-filtered Cu$K\alpha$ radiation (40 kV and 30 mA; scanning at intervals of 0.1° per 2.0 s over the range of 2θ=5.0—30.0°). The intensity ratio of peak at 2θ=21° was calculated using the following equation.

$$\text{intensity ratio (\%)} = \frac{\text{peak intensity of sample (counts)}}{\text{peak intensity of Pmix before heating (counts)}} \times 100 \quad (1)$$

The data was expressed the mean and standard deviation of 3 or 4 experiments.

Results and Discussion

Influence of Primary Particle Size We evaluated the effect of the primary particle size using NP as a model system. NP was pulverized using a jet mill (NP-jet-milled) and compared with the NP as received (NP-non-mill). The particle size distributions of the NP samples are shown in Table 1. NP-non-mill shows a broad distribution (D90=51.9 μm), whereas after pulverization, crushing of the large particles results in a sharper distribution (D90=18.8 μm). NP-Pmix samples were then prepared using the two types of NP to make NP-Pmix (non-mill) and NP-Pmix (jet-milled).

Figure 1 shows the DSC thermograms of NP and NP-Pmix samples for heating at a rate of 2 °C/min. NP-jet-milled shows little difference from NP-non-mill indicating that while pulverizing affected the particle size it had little effect on the crystal structure with both samples exhibiting a sharp endothermic peak at 173 °C. NP-Pmix (non-mill) shows a significantly larger endothermic peak (11.9 J/g at 173 °C) than NP-Pmix (jet-milled) (1.0 J/g at 173 °C), which in one case did not show any peak (c-2, Fig. 1). These results suggest that almost all of the NP in NP-Pmix (jet-milled) became amorphous below its melting point during heating, while some of the NP in NP-Pmix (non-mill) remained in crystal form. For comparison a Tmix sample prepared using NP-non-mill was also evaluated. The DSC thermogram showed a slight endothermic reaction from 140 °C and a peak at 173 °C, which was smaller (6.6 J/g) than the case of NP-Pmix (non-mill), indicating that after high-shear mixing, more NP was able to become amorphous at below 173 °C than the non-milled sample.

Figure 2 shows the PXRD pattern of the NP samples collected upon heating at 150 °C. At 25 °C (initial), the two patterns are similar. At 150 °C, however, a decrease in peak intensity was observed in NP-Pmix (jet-milled) while no changes were observed in NP-Pmix (non-mill). The peaks of NP-Pmix (jet-milled) had largely disappeared after 60 min heating. NP-Pmix (non-mill) showed peaks of the remaining NP crystals after 120 min heating. These results show that by reducing the primary particle size of the drug, it is possible for the Pmix sample to turn amorphous below the melting point of the drug.

These results indicate that reducing the primary particle size of a drug through physical mixing allows the drug to turn amorphous below its melting point. One possible mech-

Table 1. Particle Size Distribution of Drug and Crospovidone

	Size distribution (μm)		
	D10	D50	D90
NP-non-mill	5.6	19.7	51.9
NP-jet-milled	3.0	7.8	18.8
IM	3.0	6.4	13.2
Crospovidone	25.7	77.5	186.2

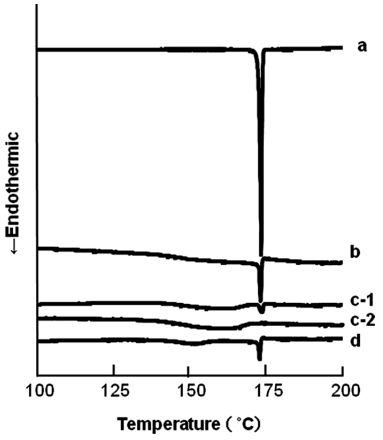

Fig. 1. DSC Thermograms of NP and Related Samples

(a) NP crystals (b) NP-Pmix (non-mill), (c-1, c-2) NP-Pmix (jet-mill), (d) NP-Tmix (non-mill). In the experiments, samples containing 1 mg of NP were heated at 2 °C/min.

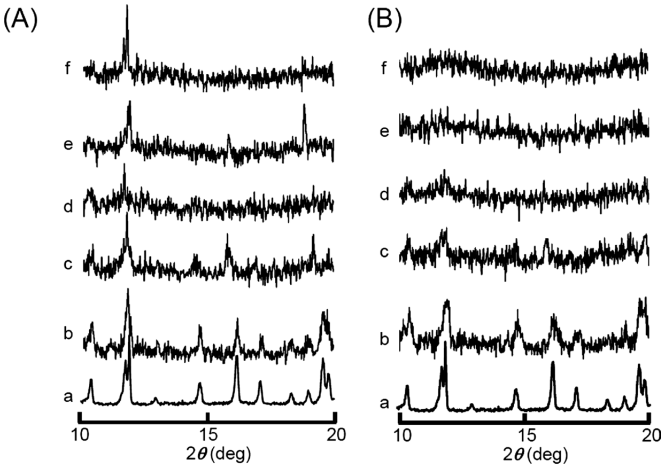

Fig. 2. Changes in PXRD Profiles of NP-Pmix During Heating at 150 °C

(A) NP-Pmix (non-mill), (B) NP-Pmix (jet-mill). NP crystals (a) is described in different intensity scale. Profiles of NP-Pmix were taken at 25 °C (b), 150 °C (c), and after holding at 150 °C for 30 min (d), 60 min (e), and 120 min (f).

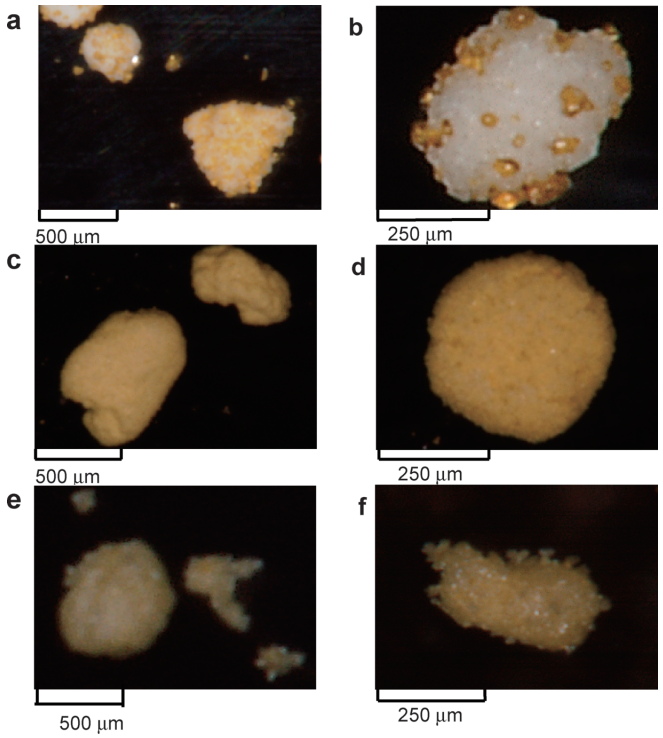

Fig. 3. Microscope Photographs of NP and Crospovidone Mixtures
(a, b) NP-Pmix (non-mill), (c, d) NP-Pmix (jet-milled), (e, f) NP-Tmix (non-mill).

anism for this change is the increase in surface area of the drug particles as a result of reduced particle size, which provides increased contact area between the drug particles and crospovidone particles. In a solid–solid system, this increase in contact area would lead increased interaction.

To determine the microstructure of the samples of NP and crospovidone we examined them using a digital microscope. Since NP is a yellow substance and crospovidone is white, we can easily observe the mixing of drug particles and the crospovidone particles in the NP-Pmix. Figure 3 shows photographs of the NP-Pmix (non-mill) (a, b), NP-Pmix (jet-milled) (c, d), and NP-Tmix (non-mill) (e, f) powders. As can be seen, the NP particles are more finely mixed with the crospovidone particles in the case of NP-Pmix (jet-milled) compared to NP-Pmix (non-mill). For NP-Tmix (non-mill), the large NP particles seem to be effectively crushed with small particles adsorbed on the crospovidone particles. It has been reported that the mechanical force provided by mixing using a theta-composer leads to smaller drug particles adsorbing on the crospovidone particles.[4] The results shown here indicate that the smaller particles are able to provide increased contact with the crospovidone particles. Thus by reducing the particle size of the drug prior to mixing with crospovidone, more drug particles can come into contact with crospovidone, enabling the drug to turn amorphous below its melting point, without the need for any high shear forces during mixing. In other words, some of the effect of high-shear mixing in enabling the drug to become amorphous at a lower temperature may be simply a result of a reduction in particle size of the drug. Because the Pmix and Tmix samples are not homogeneous mixtures at the micro level it was not possible to reliably characterize changes in the adsorption of drug particles onto the crospovidone particles. However, based on the examples shown in Fig. 3, the changes in adsorption are considered to be a major factor in lowering the temperature at which the drug crystals turn amorphous.

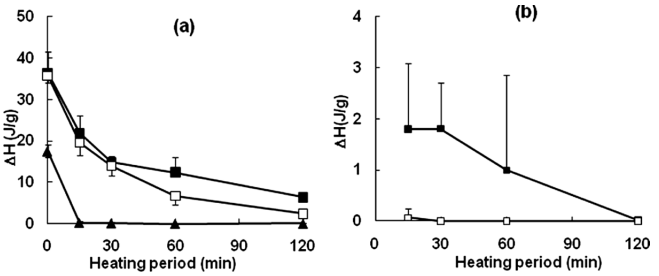

Fig. 4. Comparison of Heat of Fusion Calculated from Thermogram of Samples after Heating at 125 °C (a) or 140 °C (b) Using a DSC Apparatus
(■) IM-Pmix, (□) IM-Pmix-sieved, (▲) IM-Tmix. Each data represents the mean±S.D. of 3 or 4 experriments.

Influence of Secondary Particle Size The particle size distribution of IM is shown in Table 1. The median diameter of the particles was 6.4 μm and most particles were in the range of 1—10 μm. The particle size of IM was similar or smaller than that of NP-jet-milled, however, some crystals remained after heating of Pmix.[4] Because IM has a tendency to agglomerate, some large (over 1 mm) secondary particles were observed in IM-Pmix. To break up the large agglomerates of IM in IM-Pmix, the sample was sieved through a 180 μm mesh using a spatula (IM-Pmix-sieved). For comparison, we also prepared IM-Tmix, which was obtained by mixing the IM-Pmix mechanically using a theta-composer for 30 min.

The IM-Pmix, IM-Pmix-sieved, and IM-Tmix samples were heated at 125 °C using DSC and the heat of fusion was calculated by the DSC thermogram. Figure 4a shows the relationship between the heating period at 125 °C and the heat of fusion. For IM-Tmix, the heat of fusion before heating was about half of that of IM-Pmix. A decrease in drug crystallinity by cogrinding with a polymer has been reported by Crowley and Zografi,[9] Jayasankar *et al.*[10] and Bahl and Bogner,[11] and is thought to be caused by the high-shear mixing. In our case, for IM-Tmix heated at 125 °C for 30 min, there was no melting peak. On the other hand, the heat of fusion of IM-Pmix decreased with prolonged heating; however, IM crystals still existed after 120 min heating at 125 °C. These results are in agreement with previous reports.[4—6] In the case of IM-Pmix-sieved, the heat of fusion was almost the same as for IM-Pmix. After 120 min, however, the heat of fusion was slightly smaller than that of IM-Pmix, indicating that more IM crystals had become amorphous. In the X-ray patterns of IM-Pmix and IM-Pmix-sieved collected upon heating at 125 °C also showed the difference between them. The peaks of IM-Pmix-sieved showed smaller peaks than IM-Pmix when they were heated 125 °C for the same period (Fig. 5). Since IM-Pmix and IM-Pmix-sieved were found to have IM crystals remaining after heating at 125 °C, the same experiment was performed at 140 °C for these two samples (Fig. 4b). For heating at 140 °C, IM-Pmix-sieved showed no melting peak within 30 min while IM-Pmix still had IM crystals remaining even after 120 min heating.

Figure 6 shows the comparison of IM-Pmix and IM-Pmix-sieved in a test tube heated at 125 °C or 140 °C using a dry

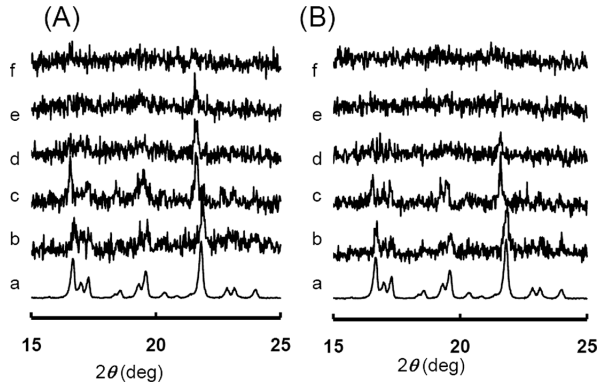

Fig. 5. Changes in PXRD Profiles of IM-Pmix (A) and IM-Pmix Sieved (B) During Heating at 125 °C

IM crystals (a) is described in different intensity scale. Profiles were taken at 25 °C (b), 125 °C (c), and after holding at 125 °C for 30 min (d), 60 min (e), and 120 min (f).

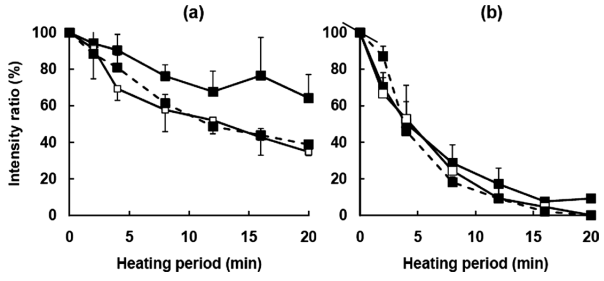

Fig. 6. Comparison of Intensity Ratio of Peak at $2\theta=21°$ in PXRD for Samples after Heating at 125 °C (a) or 140 °C (b) Using a Dry Block Bath to Pmix before Heating

(■) IM-Pmix, (□) IM-Pmix-sieved; without mixing while heating (line), with mixing while heating (dashed line). Each data represents the mean±S.D. of 3 or 4 experriments.

block bath. The extent of drug crystals remaining in the heated sample was expressed by the intensity ratio of the PXRD peaks as given in Eq. 1. At 125 °C, the intensity ratio decreased with heating, falling to about 70% after 12 min for IM-Pmix, however, the ratio did not appear to change with longer heating. In contrast, the ratio for IM-Pmix-sieved decreased with prolonged heating, reaching a value of about 40% after 20 min. When IM-Pmix was heated mixing with a spatula, the change of intensity ratio was similar to that of IM-Pmix-sieved (Fig. 6a). At 140 °C, IM-Pmix-sieved had converted to an amorphous state after heating for 20 min, while IM-Pmix still had crystals remaining (Fig. 6b).

As shown in Figs. 4 and 6, IM-Pmix-sieved, the sample prepared by forcing the IM-Pmix through a sieve using a spatula, became amorphous at 140 °C, while IM-Pmix was not. At 140 °C, a sample in which Pmix was heated while mixing with a spatula showed no IM peak after heating for 20 min. By sieving the Pmix or mixing Pmix during heating, the large secondary particles of IM in IM-Pmix were broken up, allowing a greater number of IM particles to come into contact with the crospovidone particles. In other words, the sieving procedure improved the homogeneity of Pmix at the micro level improving the contact area. In a solid–solid system, this change enabled a greater amount of IM to become amorphous below its melting point without the need for any intensive mechanical force during the mixing procedure.

Conclusion

By reducing the particle size of the drug in Pmix, it was possible to lower the temperature at which the drug became amorphous. This may be caused by a change in the degree of contact between the drug particles and crospovidone particles. Smaller drug particles seem to be able to adsorb more readily on the crospovidone as compared to larger particles. As more drug particles come into contact with the crospovidone, greater interaction with crospovidone is possible, allowing the drug to turn amorphous below its melting point. It indicates that the reaction similar to fusion method, the typical preparation method of SD, occurred at the interface between drug and crospovidone.

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