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Evaluation of the physicochemical characteristics of crospovidone that influence solid dispersion preparation

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ABSTRACT

A solid dispersion (SD) powder of indomethacin (IM) with crospovidone (CrosPVP) shows useful characteristics for manufacturing dosage forms. Four types of commercial CroPVP, Polyplasdone® XL (XL) used as the initial carrier, Polyplasdone® XL10 and INF-10® manufactured by milling XL, and Kollidon® CL (CL) marketed by another company, were compared. The limit of the IM–CrosPVP weight ratio with which an SD can be prepared (maximum IM content) was calculated on the basis of the heat of fusion of physical mixtures of IM and CrosPVP with various weight ratios. When Polyplasdone®s were used, the maximum IM content increased with the specific surface area of the CrosPVP. When CL was used, however, it was about half of that obtained with XL, even though the difference between XL and CL was not observed in the physicochemical characteristics (particle size, specific surface area, flowability, glass transition temperature, IR spectra, and solid state NMR spectra). As determined by pore size distribution measurement, the volume of pore of which size is larger than the particle size of IM was less in CL than in XL. Therefore, the effective surface area of CrosPVP that comes in contact with IM is important for the preparation of the SD.

1. Introduction

The improvement of the solubility and dissolution of poorly water-soluble drugs is a major issue for many pharmaceutical researchers because of the increase in recent years in the percentage of candidates with poor water solubility. Various methods to improve the dissolution of poorly water-soluble drugs have been reported. The formation of a solid dispersion (SD) using a carrier is one such method (Sekiguchi and Obi, 1961; Leuner and Dressman, 2000). Methods reported for the preparation of SDs include fusion, solvent evaporation, and spray drying (Chiou and Riegelman, 1971; Hirasawa et al., 2003; Wu et al., 2009). The application of these methods can be difficult because the thermal instability and decomposition of the drug during melting is often a significant problem, as is selection of the appropriate solvent and elimination of residual solvent when employing the solvent method (Summers and Enever, 1976; Serajuddin, 1999). There are also many difficulties associated with the preparation of SD dosage forms and maintenance of the amorphous state (Leuner and Dressman, 2000).

We previously developed a SD of indomethacin (IM) with crospovidone (CrosPVP) using two methods. The first involved mechanical mixing with a high-speed elliptical rotor-type blender followed by heating (Fujii et al., 2005), and the second involved heating simultaneously with mixing using a twin-screw kneader or extruder (Shibata et al., 2009a,b). In these techniques, no solvent was used and no fusion of CrosPVP occurred; the materials always remained in a powder form. The obtained powder SD could be manufactured directly into tablets using the direct compression method (Shibata et al., 2005, 2006, 2009a,b).

Because CrosPVP and the drug form a solid–solid system when using these methods, the micromeritical characteristics of the two materials are expected to influence SD preparation. Commercial grade Polyplasdone® XL (XL) was used as the SD carrier. There are seven types of commercial CrosPVP products marketed as additives by two different companies. These CorsPVP products are typically used as disintegration agents in tablets, and it is reported that the disintegrating ability of the tablet is influenced by variations in particle size and liquid uptake characteristics (Shah and Augsburger, 2001a,b).

The aim of this study was to clarify the influence of physicochemical characteristics of CrosPVP on the generation of SDs. In

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this study, we used four types of CrosPVP—XL, Polyplasdone® XL10 (XL10), and Polyplasdone® INF (INF)—to clarify the effect of milling of CrosPVP on SD generation and Kollidon® CL (CL), whose manufacturer is different, to clarify the influence of the manufacturing process of CrosPVP.

2. Materials and methods

2.1. Materials

CrosPVP: XL, XL10, and INF were a gift from ISP Japan (Tokyo). CL was a gift from BASF Japan (Tokyo). All CrosPVP products were USP grade. IM and nifedipine (NP) were obtained from Kongo Chemical (Toyama) and Nihon Bulk Yakuhin (Osaka), respectively. NP was pulverized using a jet mill.

2.2. Preparation of the SDs

SDs were prepared using a modified method of a previously reported procedure. A 1:3 (w/w) ratio of IM:CrosPVP was used. A physical mixture (Pmix) was obtained by combining the IM and CrosPVP using a spatula. The Pmix was ground with a pestle and mortar for 10 min (Gmix) followed by heating at 125, 135, or 145 °C for 30 min (hGmix) in an air incubator. The sample was described with the type of CrosPVP used (for example Pmix-XL).

Powder X-ray diffraction patterns (PXRD) and thermal analysis data were obtained to examine the drug crystallinity in the hGmix. PXRD data were obtained using a PXRD diffractometer (Ultima 4, Rigaku, Tokyo), with Ni-filtered CuKα radiation (40 kV and 40 mA; scanning speed at 4.0°/min over the range of 2θ = 5–40°). Thermal analysis was conducted using differential scanning calorimetry (DSC, Thermoflex TAS200, Rigaku, Tokyo). Samples containing 1 mg of IM were sealed in an aluminum crimp cell and heated at a rate of 20 °C/min under a nitrogen atmosphere. The SD was considered formed when no peaks related to the drug were observed by either method.

2.3. Determination of the heat of fusion of the drug crystal residue

Gmixes containing 25–90% (w/w) of IM were prepared. The sample that contained 1 mg of IM was heated using DSC at a rate of 5 °C/min to 140 °C, held isothermally for 60 min, and then heated at a rate of 20 °C/min to 200 °C. The heat of fusion (J/g) was calculated from the peak area for the IM crystal at 160 °C. In the case of NP, a similar procedure was used with holding at 165 °C for 90 min and determination of the heat of fusion of the NP crystal at 173 °C.

2.4. Micromeritical characterization of CrosPVP

Particle size was determined by microscopic analysis. The photos of CrosPVP samples were taken with a digital microscope (VC3000, Omron, Kyoto), and the particle sizes (Feret diameter) of about 1000 particles were measured using image processing software (Image J).

Specific surface area was determined using a micromeritics automatic surface area and porosimetry analyzer (TriStar 3000, Shimadzu, Kyoto). Nitrogen gas was used as the adsorption gas. Prior to the experiment, preadsorbed gases and vapors were removed from the surface of CrosPVP for 6 h or more at 130 °C in vacuo.

Particle density was determined using a gas pycnometer (Accupyc 1330, Shimadzu, Kyoto) with nitrogen gas.

Bulk density, tapped density, and the compressibility index (CI) were calculated using the data obtained with a tapping density analyzer (Tapdenser KYT-3000, Seishin Enterprise, Tokyo) with a 20 mL cylinder. The weight of powder in the cylinder (W) was measured. Bulk density was calculated by dividing W by V_0, the powder volume before tapping (20 mL). V_f, the powder volume after tapping infinitely, was calculated using Kawakita's equation and the data collected after tapping 200 times. The tapped density was calculated by dividing W by V_f. CI was calculated using the following Eq. (1):

$$\mathrm{CI} = \frac{V_0 - V_f}{V_0} \times 100 \quad (1)$$

2.5. Characterization of the SDs

Dissolution of IM from various formulations containing 5 or 50 mg of IM was tested at 37 °C using a JP dissolution test apparatus with 900 mL purified water and a paddle rotation of 100 min^{-1}. IM concentration was determined by UV absorption at 318 nm.

FT-IR spectra were obtained by the diffuse reflectance method using an IR spectrophotometer (IRPrestige-21, Shimadzu, Kyoto) over a scanning range of 4000–400 cm^{-1}. The samples were diluted with KBr.

Carbon-13 solid-state NMR spectra were recorded with cross polarization, magic-angle spinning FT-NMR (DRX-500, Bruker) operating at 125 MHz. Typical operating conditions utilized a spinning rate of 8.5 kHz, a 90° H^+ pulse of 4.9 μs, a contact time of 1.75 ms, a recycle delay of 5 s, an acquisition time of 34 ms, and a spectral width of 4.5 kHz.

2.6. Comparison of XL and CL

Glass transition temperatures (Tg) were measured using DSC (DSC-60, Shimadzu, Kyoto). The CrosPVP (3 mg) was sealed in an aluminum pan. The samples were heated at 5 °C/min to 240 °C, held isothermally for 10 min, cooled to 25 °C, and then reheated at 10 °C/min to 240 °C. The Tg was determined from the DSC thermograms using software (TA-60WS, Shimadzu, Kyoto).

Photographs were obtained with a scanning electron microscope (SEM) JSM-5200 (JEOL, Tokyo). The Au–Pd spattered samples were observed at magnifications of 350 and 3500.

The pore size distribution and total intrusion volume of CrosPVP were determined using a mercury intrusion porosimeter (TraisterII 3200, Shimadzu, Kyoto) at a pressure range of 0.7–7.0 kPa.

3. Results and discussion

3.1. Effect of CrosPVP particle size on solid dispersion preparation

The micromeritical characteristics of CrosPVP are shown in Table 1. The median diameter of XL is 39 μm, while XL10 and INF, which were milled from XL, have a median diameter of 17 μm. The median particle size of INF was equal to that of XL10, however the percentage of particles smaller than 10 μm was greater in the case of INF (Fig. 1). The specific surface area increased in the order XL < XL10 < INF, a trend that is reasonable because smaller particles are expected to have a larger specific surface area. There was little difference in particle density and bulk density, however the tapped density and CI showed a wide range of values in the order XL < XL10 < INF. XL had a good flowability, with that of XL10 and INF inferior to XL because of the decrease in particle size. The bulk density of XL was rather low considering its good flowability, indicating that XL was highly porous.

We developed SD powders of various types of CrosPVP using two methods. When the SD with XL was prepared via mechanical mixing with a high-speed elliptical rotor-type mixer (Theta-Composer Lab® type THC, Tokuju Kousakusyo, Kanagawa) followed by heating, the IM existed in an amorphous state when heated at 125 °C (Fujii et al., 2005). In this study, a mortar and pestle were used

Table 1
Micromeritical characteristics of CrosPVP.

	Particle size (μm)	Specific surface area (m^2/g)	Particle density (g/cm^3)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	CI (%)
XL	39	0.69	1.23	0.29	0.35	19
XL10	17	0.94	1.24	0.29	0.47	41
INF	17	1.13	1.27	0.27	0.49	55
CL	31	0.79	1.25	0.33	0.41	22

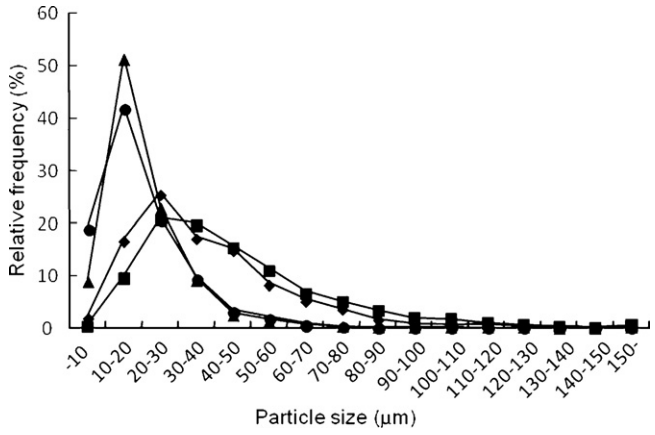

Fig. 1. Particle size distribution of CrosPVP powders measured using the microscope method (Feret diameter). (■) XL; (▲) XL10; (●) INF; and (♦) CL.

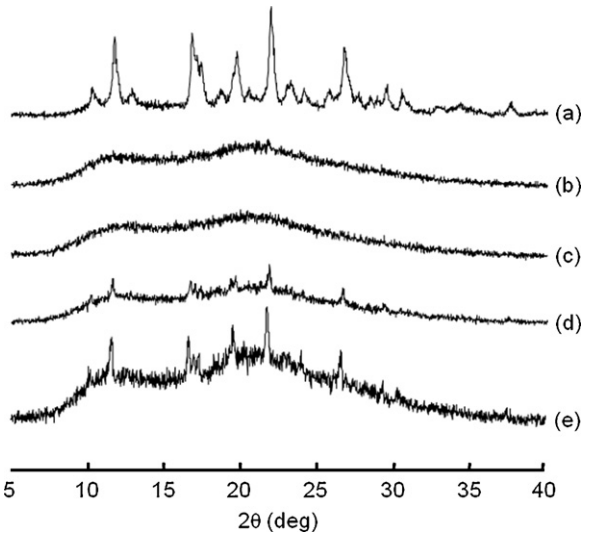

Fig. 2. X-ray diffraction patterns of Pmix and hGmix after heating the Gmix at 125 °C. (a) Pmix-XL; (b) hGmix-XL; (c) hGmix-XL10; (d) hGmix-INF; and (e) hGmix-CL.

instead of the Theta-Composer for grinding the Pmix. The IM existed in an amorphous state when heating the Gmix at 125 °C (Fig. 2b). Thus it was confirmed that the SD could be made with the same properties as the previous method. Therefore, the method of heating the Gmix was used in this study. PXRD patterns of IM, the Pmix using XL, and the hGmixes are shown in Fig. 2. When XL10 was used as the carrier, the IM existed in an amorphous state when heated at 125 °C, whereas the IM remained slightly crystalline when INF was used, and it was necessary to heat the SD at 145 °C to observe the IM in an amorphous state. The flowability of INF was inferior compared with XL and XL10. IM readily forms aggregates, and the miscibility of the INF and IM powders might be inferior because of such behavior. IM must come in contact with the CrosPVP to interact in the SD, and we propose that heating at high temperature was necessary to prepare the SD with INF because of the poor miscibility of the system.

In a previous study, we reported that IM maintained an amorphous state in the SD when the Pmix-XL containing 40% (w/w) IM was heated at 140 °C (Fujii et al., 2005). It was thought that IM content could also be increased when XL10 or INF was used. It was suggested that agglomerates of IM sometimes prevent preparation of amorphous SDs (Sugamura et al., 2011). These results indicated that the immiscibility of the drug and CrosPVP interferes with the determination of the maximum ratio of IM in the SD. Thus the relationship between the limits of the IM–CrosPVP weight ratio as a function of the carrier was evaluated with the assumption that the heat of fusion of the IM crystal increases along with the amount of IM crystal exceeding the limit of the IM–CrosPVP weight ratio. Gmixes, which contained 25–90% (w/w) IM were heated at 140 °C for 60 min using DSC, and then each heat of fusion of the IM crystal at 160 °C was plotted against IM content (Fig. 3a). Gmix-INF containing 25% (w/w) IM showed a small endothermic peak (1.7 J/g) at 160 °C, however the peak area was nearly the same in the case of the 50% (w/w) IM. It is considered that the immiscibility of the two materials influenced SD formation in the case of INF. Gmix-XL, XL10, and INF containing 60% (w/w) or more IM showed the linear relationship between IM content in the Gmix and the heat of fusion (R^2 = 0.9954, 0.9873, and 0.9980, respectively). It is thought that the

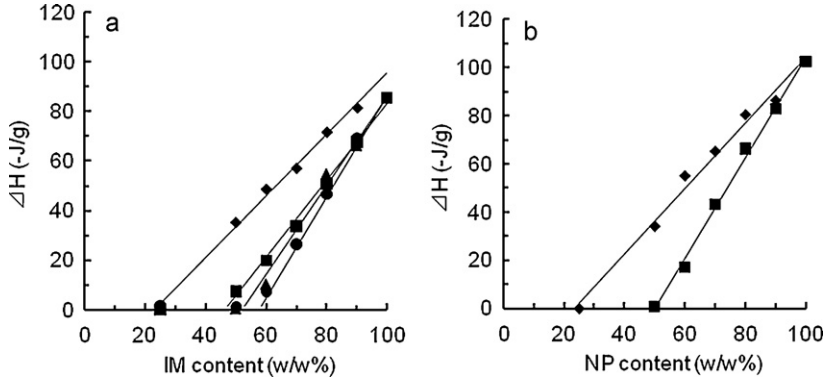

Fig. 3. Relationship between the IM (a) or NP (b) content in the Gmix and the heat of fusion after heating the Gmix. (■) XL; (▲) XL10; (●) INF; and (♦) CL. IM-Gmixes and NP-Gmixes were heated at 140 °C for 60 min and 165 °C for 90 min, respectively.

heat of fusion of the IM crystal increased along with the amount of remaining IM crystal exceeding the limit of the IM–CrosPVP weight ratio. Therefore, the *x*-intercept of the obtained regression line is assumed to be the maximum IM content for the amorphous state.

The maximum IM content using XL, XL10, and INF was calculated as 47, 52, and 57% (w/w), respectively. As the specific surface area of CrosPVP increased, the maximum IM content in the SD also increased. From the maximum IM content and specific surface area of CrosPVP, the IM weight per unit surface area of CrosPVP was calculated using Eq. (2).

$$\text{Drug weight per unit surface area of CrosPVP } (\text{g/m}^2) = \frac{\text{Maximum IM content } (\text{w/w, \%})}{\text{Specific surface area of CrosPVP } (\text{m}^2/\text{g}) \times (100 - \text{Maximum IM content } (\text{w/w, \%}))} \quad (2)$$

The maximum amount of amorphous IM per unit surface area of XL, XL10, and INF was 1.29, 1.15, and 1.13 g/m^2, respectively. These results indicate that the maximum IM content for preparing an SD is affected by the specific surface area of the CrosPVP.

CrosPVPs with a small particle size showed a high limit for the IM content in the SDs, however preparation of the SDs was also influenced by the flowability of the CrosPVP and was thus easier with XL because of its good flowability.

3.2. Effect of CrosPVP source on solid dispersion preparation

There are two main sources of CrosPVP: the Polyplasdone series from ISP and the Kollidon series from BASF. All of the products are USP grade; however, it is well known that the characteristics of a polymer differ among commercial sources (Tallon et al., 2008). Thus, the behavior of XL and CL with regard to SD preparation was compared.

As shown in Table 1 and Fig. 1, no obvious differences were observed in the particle size, specific surface area, or particle density of XL and CL. However, the bulk density and tapped density of CL were larger than those of XL. This result suggested that the porosity was different between XL and CL. On the other hand, IM crystals remained when Gmix-CL containing 25% (w/w) IM was heated at 125 °C (Fig. 2e). In addition, the maximum IM content using CL (22%, w/w) was half that obtained when using XL (Fig. 3a), and the maximum amount of amorphous IM per unit surface area of CL was 0.36 g/m^2. Clearly, XL and CL differ from each other from the point of view of SD formation.

The reaction processes for manufacturing XL and CL are different (Tallon et al., 2008). XL is made using alkali metal hydroxide and a small amount of added water, whereas CL is produced using *N*,*N*′-divinylimidazolidone as a crosslinker. If the alkali metal hydroxide remains in the XL product, the acidic drug IM may show a higher solubility in the polymer. Thus, a similar experiment was carried out using NP as a model basic drug (Fig. 3b). XL and CL as carriers exhibited similar maximum drug content values as obtained with IM, 50% (w/w) for XL and 24% (w/w) for CL, and the maximum amount of amorphous NP per unit surface area with XL and CL was 1.45 and 0.40 g/m^2, respectively, which were similar to the results obtained with IM. It was confirmed from these experiments that it was not the characteristics of the drug but the characteristics of the CrosPVP that influenced the maximum drug content and the maximum amount of amorphous drug per unit surface area of CrosPVP. Furthermore, these results suggested that XL is superior to CL for SD formation.

3.3. Characteristics of the SDs

Because there were differences between XL and CL in the preparation temperature and maximum IM content in the SDs, it was possible that the characteristics of the SDs obtained were also different. Thus, SDs using XL and CL were prepared by heating each Gmix at 145 °C for 30 min and their characteristics were compared.

The dissolution patterns of IM from the SDs and related materials are shown in Fig. 4. The IM dissolution profiles from SDs using XL and CL were similar. When an excess amount (50 mg) of IM was used, the concentration of IM after 90 min was compared. Even if the kinds of CrosPVP were different, the IM achieved a concentration of 40 μg/mL, which was 4 times the solubility of IM. It was shown that the dissolution and solubility of IM from the SDs was equal, even if the kind of CrosPVP was different.

The IR spectra of XL, CL, and each SD are shown in Fig. 5. A C=O stretching absorption was found at 1647 cm^{-1} for the SD prepared with XL, which has been reported to be related to the interaction of XL with the drug (Fujii et al., 2005). A C=O stretching absorption was also found at 1649 cm^{-1} for the SD prepared with CL, indicating a similar interaction between this CrosPVP and the drug. When the IR spectra in the region 2000–1500 cm^{-1} were compared for the two SDs, no difference was observed, indicating that the IM–CrosPVP interaction was the same, even though the types of CrosPVP were different.

To evaluate the molecular states of the two kinds of CrosPVP further, samples of IM, the CrosPVPs and the two Pmixes and SDs were analyzed by ^{13}C solid state NMR. Fig. 6 shows ^{13}C CP/MAS-NMR spectra of XL and CL and the related materials. In the spectra for both XL and CL, a peak is seen at 177 ppm that is indicative of an amide carbonyl group. In addition, no differences were observed in the spectra of the two kinds of CrosPVP. Furthermore, the spectra for both SDs using either CrosPVP showed a peak at 175 ppm, which is indicative of the interaction between IM and the CrosPVP, and again there were no differences.

These results therefore suggest that the characteristics of the SD are independent of the method for manufacturing the CrosPVP, and the CrosPVPs prepared by the two different companies are essentially equivalent.

3.4. Difference between XL and CL

There were, however, differences between XL and CL in the preparation temperature and maximum IM content in the SD, even though the characteristics of the SD were independent of the type of CrosPVP used.

It is known that the glass transition temperature of the carrier influences the preparation of SDs by the solvent method or melting method. The Tgs of XL and CL were thus compared. Fig. 7 shows

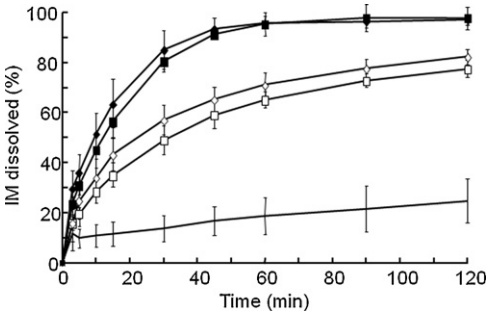

Fig. 4. Dissolution profiles of IM from various samples. (·) IM crystals; (□) Pmix-XL; (◊) Pmix-CL; (■) SD-XL; and (♦) SD-CL. Each data point represents the mean ± SD of three experiments.

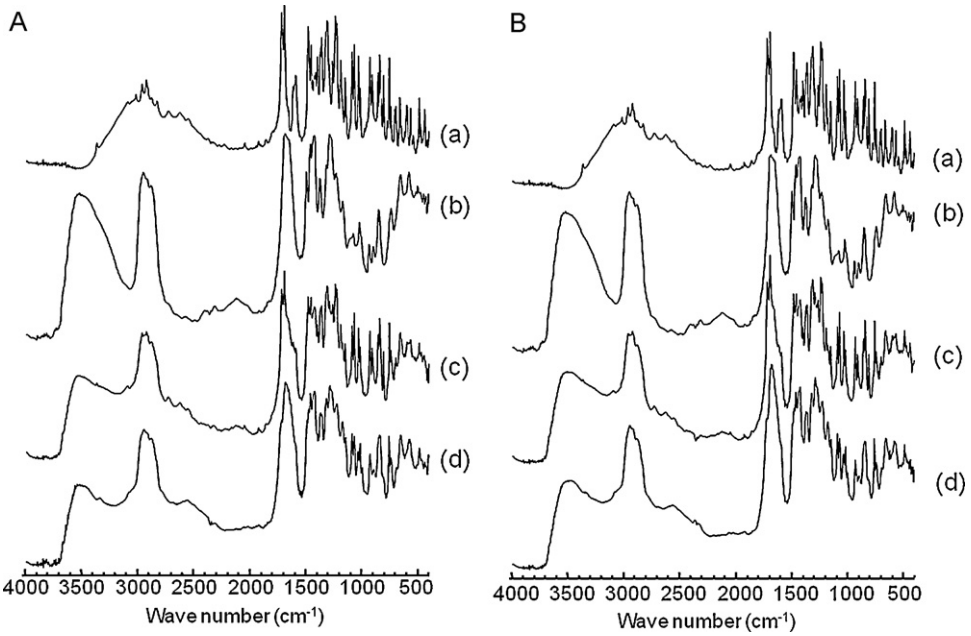

Fig. 5. FT-IR spectra of SDs and related materials. (A) XL, (B) CL; (a) IM; (b) CrosPVP; (c) Pmix; and (d) SD.

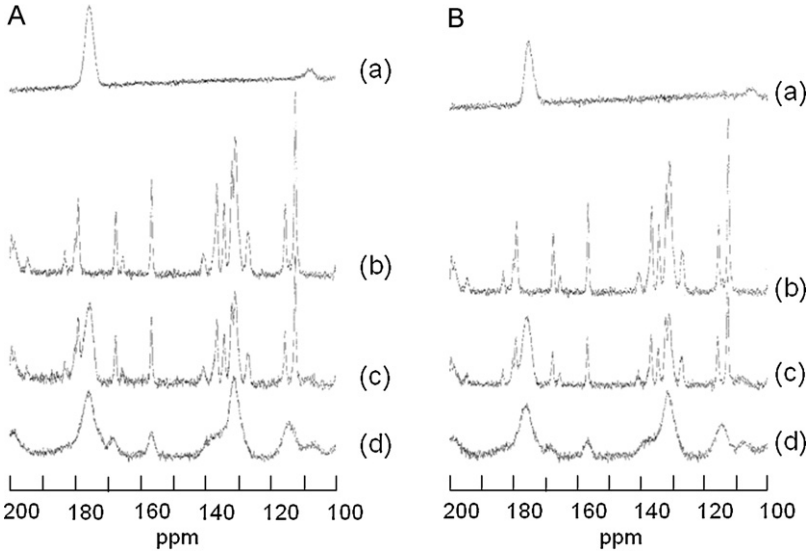

Fig. 6. Solid state ^{13}C NMR of SDs and related materials. (A) XL, (B) CL; (a) IM; (b) CrosPVP; (c) Pmix; and (d) SD.

DSC thermograms of XL and CL. For both kinds of CrosPVP, the baseline shifts of the DSC thermograms were similar and the Tgs were observed at about 185 °C.

Because the particle size, specific surface areas, Tgs, IR spectra, and NMR spectra of XL and CL were equal, we turned our attention to the shape of the XL and CL particles. SEM images of XL and CL are shown in Fig. 8. The particle surface of CrosPVP is not smooth, but has pore openings (open pores). XL appeared highly porous with a popcorn-like shape, whereas CL was observed to possess a rod-like shape, with the surface morphology of CL clearly quite different from that of XL. The specific surface area of the CrosPVPs was determined from their nitrogen adsorption isotherms. Because nitrogen invaded the pores of the CrosPVPs whose size diameters are 2 nm or less, the specific surface area of XL was found to be equal to that of CL. However, as the particle sizes of IM and NP were 3–20 μm, there was the possibility that the pore sizes on the XL and CL particle surfaces might vary. If that were the case, the ability of the drug

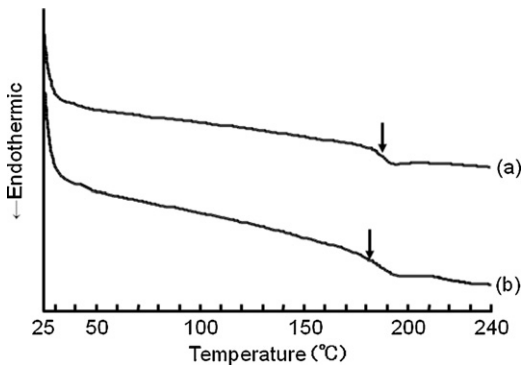

Fig. 7. DSC thermograms of CrosPVPs: (a) XL and (b) CL. Arrows represent the glass transition temperatures (Tg).

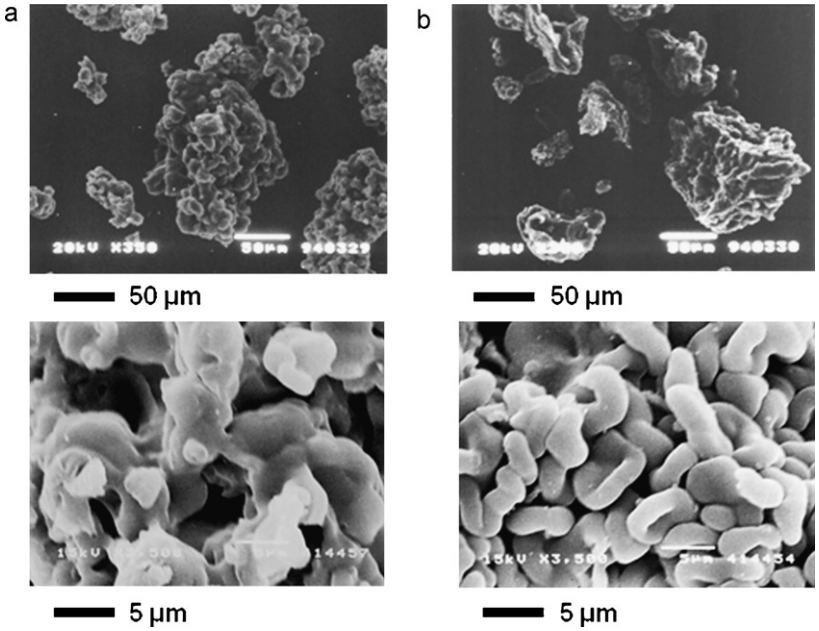

Fig. 8. SEM images of XL (a) and CL (b).

Table 2
Pore size distribution of SD containing 25% IM and related materials.

	XL			CL		
	Pore volume (mL/g)	Pore size (μm)		Pore volume (mL/g)	Pore size (μm)	
		Mode	Median		Mode	Median
CrosPVP	2.31	32.0	26.6	1.80	26.8	18.0
Gmix	1.40	9.00	7.88	1.29	6.96	6.44
SD	2.00	33.7	29.1	1.94	17.1	16.6

particle to invade the pores would also vary, and thus the adhesion of the drug to the XL and CL particle surfaces would also be different. The pore size distributions for XL and CL were therefore measured using mercury porosimetry. This method is more useful for measurement of pores with sizes of 2 nm or greater compared with the nitrogen adsorption isotherm method. The total intrusion volume for XL particles in the pore size range from 0.1 to 180 μm was 2.31 mL/g, whereas that of the CL particles was 1.80 mL/g. CL therefore has a smaller pore volume than XL. The pore size distribution curves for XL and CL can be seen in Fig. 9. The pore volume of pores 1 μm or more in size was larger for XL than for CL. These results indicate that the pore volume that the drug particles could invade was less in CL than that in XL. Table 2 shows the change of pore volume and size in the process of preparation of SD containing 25% (w/w) of IM. Both pore volume and size decreased by grinding CrosPVP and IM (Gmix). It suggests that IM particles filled in pore of CrosPVP. After heating, the shape of SD was similar to original CrosPVP (Fujii et al., 2005), and pore volume and size were also similar to original CrosPVP. Even though the specific surface areas of XL and CL were equal, the effective surface area of the CrosPVP that was able to come in contact with the drug particle influenced the preparation of the SD.

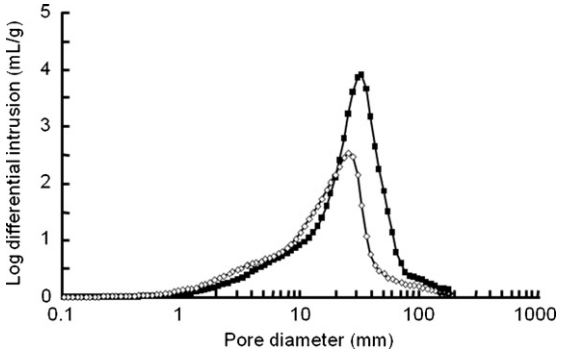

Fig. 9. Pore size distribution curves of XL (■) and CL (◊) measured using a mercury porosimeter.

4. Conclusion

Characteristics of the CrosPVP had a direct impact on the preparion of the solid dispersions. The difference in flowability of XL, XL10, and INF due to the decrease in particle size resulting from milling affected the formation of the amorphous state. As a result, IM existed in an amorphous state when heated at 125 °C if XL or XL10 was used as a carrier, whereas heating to 145 °C was necessary for preparation of the SD when INF was used. It was confirmed that the specific surface areas of XL10 and INF were increased by milling XL. Maximum IM content for the amorphous state increased as the specific surface area of the CrosPVP increased, and thus it was clear that specific surface area of the CrosPVP influences SD preparation.

On the other hand, the physicochemical characteristics of XL and CL, which are manufactured by different companies, were equal but the shapes of these particles were different. When SDs were prepared using the two kinds of CrosPVPs, it was necessary to heat the CL SD 10 °C higher than the XL SD in order to get the IM into the amorphous state. Because the pore volume of the CrosPVPs was different because of the presence of more pore diameters larger than the drug particle size in XL, it was thought that

even though the specific surface areas of XL and CL were equal, a larger effective specific surface area of the XL CrosPVP allowed greater contact with the drug particle and thus influenced SD preparation.

It is possible that maximum drug content increases for the amorphous state because of an increase in the amount of adhesion of the drug particle. Therefore, it is useful in preparing SDs to select a CrosPVP that possesses a larger effective specific surface area.

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