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The preparation of a solid dispersion powder of indomethacin with crospovidone using a twin-screw extruder or kneader

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ABSTRACT

A solid dispersion (SD) powder of indomethacin (IM) with CrosPVP was prepared continuously using a twin-screw extruder (extruder) or twin-screw kneader (kneader), which made it possible to simultaneously control kneading, mixing, and heating. For the extruder or kneader, IM existed in an amorphous state while it was treated with a screw rotation speed of 15 min^{-1} or 50 min^{-1}, respectively, while being heated to 140 °C. IM and CrosPVP interacted to maintain IM in an amorphous state. The solubility of SD powders of IM was improved about four-fold compared to crystalline IM. The retention time of the samples in the machine, screw rotation speed, and heating temperature play important roles in the preparation of SD. Although SD was prepared using a theta composer followed by heating at 125 °C for 30 min, it is more useful to be able to continuously prepare powdered SD by heating below the melting point (140 °C) in a short time (4 min) using an extruder or a kneader from the viewpoint of manufacturing.

1. Introduction

Poorly water-soluble drugs present a problem in pharmaceutical formulations. Improving dissolution properties is a major obstacle that must be overcome because many new drugs discovered by combinatorial chemistry and high-throughput screening are poorly water-soluble, making them poor candidates as new drugs. It is important to improve the solubility and/or dissolution rate for poorly water-soluble drugs because these drugs possess low absorption and bioavailability. Various methods to improve the dissolution of poorly water-soluble drugs have been reported (Simonelli et al., 1969, 1976). 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 SD including fusion, solvent evaporation, and spray drying (Chiou and Riegelman, 1971; Takeuchi et al., 2004; Asada et al., 2004). The application of these methods can be difficult because decomposition and thermal instability of the drug during melting is often a significant problem, as is selecting the appropriate solvent and residual solvent for use in the solvent method (Summers and Enever, 1976; Ford et al., 1979). There are also many difficulties associated with the preparation of SD dosage forms and maintenance of the amorphous state (Chiou and Riegelman, 1971; Serajuddin, 1999; Leuner and Dressman, 2000).

We developed SD powders of various compounds with crospovidone (CrosPVP) using a method involving mechanical mixing and heating. Interaction occurred between compounds containing proton-donor functional groups and CrosPVP, which allowed the compounds to remain in an amorphous state for at least 6 months at concentrations of ≤25–50% (w/w) (Fujii et al., 2005; Shibata et al., 2007). The SD could be manufactured by a direct compression method (Shibata et al., 2005, 2006).

An extruder is a mixer that operates continuously and involves processes such as kneading, shearing, heating, melting, and cooling. The extruder has been used for polymer processing, and in the plastics and food industries (Faubion et al., 1982; Munakata et al., 1989; Sokhey et al., 1994). This machine also is used for the preparation of SD (Nakamichi et al., 2002, 2004; Wang et al., 2005). The carrier and drug are heated and the melting mold is extruded through a die section to obtain granules of SD. A kneader, which has no extrusion function, also has been used in the preparation of SD.

This study focused on the twin-screw extruder (extruder) and twin-screw kneader (kneader), which made it possible to simultaneously control kneading, mixing, and heating and continuously

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prepare an SD powder. The effect of process parameters, such as screw rotation speed and retention time of sample in the extruder or kneader, on the preparation and characteristics of SD obtained by extruder or kneader was investigated.

2. Materials and methods

2.1. Materials

CrosPVP (Polyplasdone® XL, USP grade) was a gift from ISP Japan (Tokyo). Indomethacin (IM) was obtained from Kongo Chemical (Toyama). Other chemicals were of reagent grade.

2.2. Preparation of SD with an extruder or kneader

A 1:3 (w/w) ratio of IM:CrosPVP was used. A physical mixture (Pmix) was obtained by mixing IM and CrosPVP for 30 min using a V-type mixer (DV-1, Dalton Co., Ltd.). The extruder and kneader are illustrated in Fig. 1. The extruder (KEX-25, Kurimoto, Osaka) used in the present study consisted of a hopper, barrels, kneading screw, and heaters. The die section with extrusion function was removed for this study. The kneader (KRC-Kneader S1, Kurimoto) consisted of a hopper, kneading screw, and heaters; the die section with extrusion function was not originally attached to this machine.

A Pmix was fed into the hopper at a rate of approximately 6 g min^{-1}, carried forward by the feed screw, kneaded by the kneading screw, and discharged. In the extruder, both screws were rotated in the same direction and kept at a constant screw rotation (15–200 min^{-1}) and the 4 independent barrel heaters were set at the same constant temperature (125–150 °C). In the kneader, both screws were rotated in the same direction and kept at a constant screw rotation (50–200 min^{-1}), and the jacket heater was maintained at a constant temperature (125–150 °C). Samples processed with the extruder or kneader denoted Emix and Kmix, respectively, with the temperature and screw rotation rate in parenthesis.

A Tmix was obtained by mixing Pmix with a high-speed elliptical-rotor type blender (Theta-Composer Lab® type THC, Tokujyu Kousakusyo, Kanagawa) for 30 min.

2.3. Particle size analysis

Particle size was measured by the sieve analysis method using a mechanical vibrator (Sonic sifter model L-3PS, Seishin Enterprise, Tokyo). The samples were evaluated with 83 and 200 mesh (JP14th) sieves. The particle size distribution was calculated using the ratio of residual weight on each sieve to sample weight before sieving.

2.4. Physicochemical properties of SD and related materials

Powder X-ray diffraction (XRD) patterns were obtained using a powder X-ray diffractometer (M03X-HF, Mac Science, Yokohama) with Ni-filtered CuKα radiation (40 kV and 30 mA; scanning at width of steps 0.1° per 2.0 s over the range of $2\theta = 5.0$–$30.0°$). Thermal analysis was conducted by differential scanning calorimetry (DSC, Thermoflex TAS200, Rigaku, Tokyo). Samples containing 1 mg of IM were sealed in an aluminum crimp cell and heated at 20 °C min^{-1} under a nitrogen atmosphere. A comparison of degree of crystallinity was done using the intensity of a typical IM peak of $2\theta = 21.0$–$22.0°$ and heat of fusion (ΔH) of IM, calculated from the area under the peak at approximately 160 °C. Infrared (IR) spectra were obtained using an IR spectrophotometer (IRPrestige-21, Shimadzu, Kyoto) by the diffuse reflectance method.

2.5. Dissolution studies

Dissolution of IM from various formulations containing 50 mg of IM was tested at 37 °C using a JP dissolution test apparatus with 900 ml purified water and paddle rotation set at 100 min^{-1}. IM concentration was determined by UV absorption at 320 nm.

2.6. Evaluation of kneading power

Using DSC, the samples were heated under a nitrogen atmosphere from 25 °C to 125 °C or 140 °C at a rate of 5 °C min^{-1}, held at 125 °C or 140 °C for 15–120 min, and then heated from 125 °C or 140 °C to 200 °C at a rate of 20 °C min^{-1}.

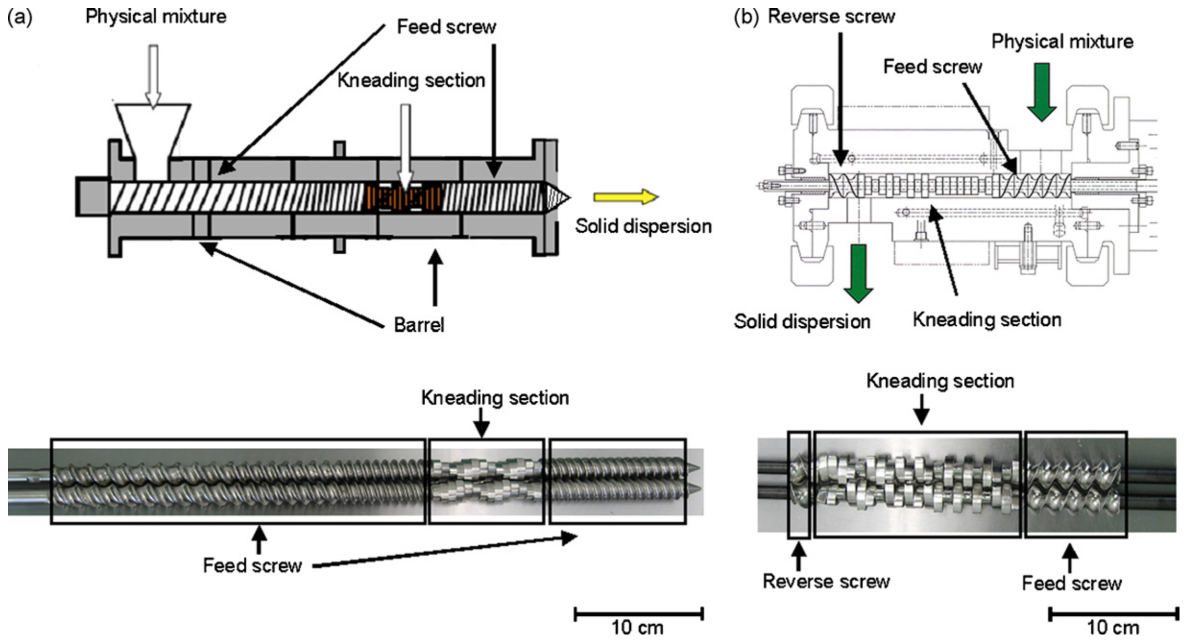

Fig. 1. Schematic view of the (a) extruder and (b) kneader.

2.7. Evaluation of retention time

Retention time was calculated as follows:

$$\text{Retention time (min)} = M\,(\text{g})/M_0\,(\text{g min}^{-1})$$

where M is retention amount in the machine and M_0 is discharge speed from the machine at a steady flow.

3. Results and discussion

3.1. Preparation of solid dispersion

We developed SD powders of various compounds with CrosPVP using a mechanical mixing and heating method. The heating temperature required to obtain an amorphous state was relatively low compared to a compound's melting point (Fujii et al., 2005; Shibata et al., 2007). Experiments were conducted to determine whether SD powder could be continuously obtained with simultaneous mixing and heating using an extruder or a kneader, which allows the control of kneading, mixing, and heating. The die section with extrusion function was removed from the extruder for this study because the sample remained a powder throughout the procedure from Pmix to SD. The kneader without extrusion function also was used in the preparation of SD.

XRD patterns and DSC curves of CrosPVP, IM, Pmix, Emix (20 °C, 15 min^{-1}), Emix (125 °C, 15 min^{-1}), and Emix (140 °C, 15 min^{-1}) are shown in Fig. 2. The XRD patterns of the Pmix contained many sharp peaks attributable to the crystalline form of IM, and DSC curves showed endothermic peaks identical to those of IM. The Emix (20 °C, 15 min^{-1}) produced an XRD pattern and DSC curves similar to those of Pmix (Fig. 2). Neither the XRD patterns nor DSC curves displayed IM peaks in samples treated with a screw rotation speed of 15 min^{-1} and temperatures of 140 °C (Fig. 2). With the kneader, neither the XRD patterns nor DSC curves displayed IM peaks in samples treated at 140 °C, irrespective of screw rotation speed (data not shown). Previous studies indicated that IM exists in an amorphous state when mechanically mixed and heated to approximately 125 °C (Fujii et al., 2005); however, use of an extruder or a kneader resulted in crystalline IM in the sample at 15–200 min^{-1} and 125 °C.

The Emix (140 °C, 15 min^{-1}) and Kmix (140 °C, 50 min^{-1}), in which IM exists in an amorphous state, were defined as SD (Emix) and SD (Kmix), respectively.

As prepared, the SD is a powder that does not require crushing. The particle sizes of CrosPVP, SD (Emix), and SD (Kmix) are shown in Table 1. Particle size of the SD obtained was large because of cohered particles. Thus, the resulting SD was sieved with a 180-μm-mesh sieve, which resulted in the separation of cohered particles. The particle sizes of SD (Emix) and SD (Kmix) were larger than that of CrosPVP, probably because the surface of CrosPVP is covered with amorphous IM.

Table 1
The particle size distribution of CrosPVP and SD

	Particle size distribution (%)		
	<75 μm	75–160 μm	160 μm<
CrosPVP	52.4	41.8	5.8
SD [Emix (140 °C, 15 min^{-1})]	24.9	61.8	13.3
SD [Kmix (140 °C, 50 min^{-1})]	16.0	58.5	25.5
SD [Emix (140 °C, 15 min^{-1})][a]	33.2	65.9	0.9
SD [Kmix (140 °C, 50 min^{-1})][a]	24.5	74.2	1.3

[a] SD was sieved with a 180-μm-mesh sieve.

The SDs sieved with a 180-μm-mesh sieve was used in the following examinations.

Fig. 3 shows SEM images of the SD (Emix) and related materials. CrosPVP possessed a popcorn shape, containing many cavities. The IM existed as small particles with a diameter of 1–10 μm. For Pmix and Emix (20 °C, 15 min^{-1}), some IM crystals existed on the surface of CrosPVP, and the surface conditions of Emix (20 °C, 15 min^{-1}) were similar to those of Pmix. In contrast, IM crystals

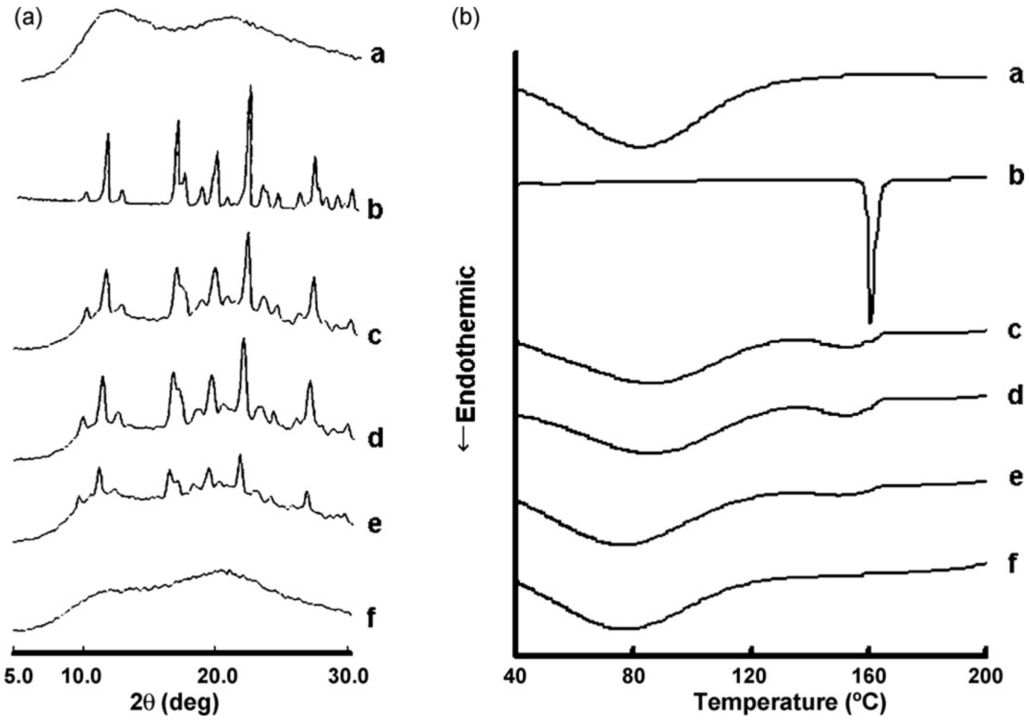

Fig. 2. XRD patterns (a) and DSC curves (b) of solid dispersions and related materials: (a) CrosPVP; (b) IM; (c) Pmix; (d) Emix (20 °C, 15 min^{-1}); (e): Emix (125 °C, 15 min^{-1}); (f) Emix (140 °C, 15 min^{-1}).

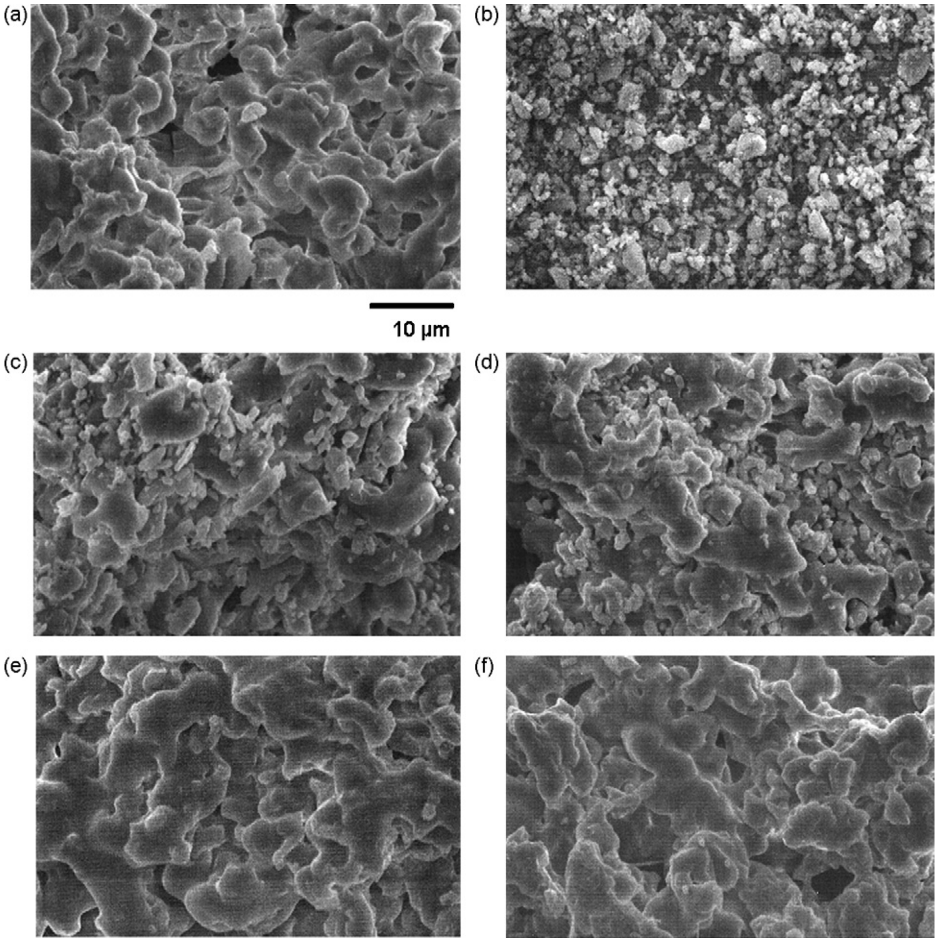

Fig. 3. Scanning electron micrographs of solid dispersions prepared with an extruder or a kneader and related materials: (a) CrosPVP; (b) IM; (c) Pmix; (d) Emix (20 °C, 15 min^{-1}); (e) SD (Emix); (f) SD (Kmix).

were not found in the SD (Emix). Similar results were obtained for SD (Kmix).

The IR spectra of SD (Emix) and related materials are shown in Fig. 4. CrosPVP absorption was found at 1676 cm^{-1}, which indicates C═O stretching. The IM produced absorptions at 1716 and 1691 cm^{-1}, which indicate C═O stretching. In amorphous forms of IM, C═O stretching occurs at lower wavenumbers, suggesting that conformational restrictions may be reduced, and non-hydrogen-bonded acid was observed at 1718 cm^{-1}. Pmix and Emix (20 °C, 15 min^{-1}) possessed the combined spectra of IM and CrosPVP. In contrast, SD (Emix) showed new absorptions at 1718 cm^{-1} and 1683 cm^{-1}. Similar results were obtained for SD (Kmix) (data not shown). These changes correspond to results reported by Taylor and Zografi (1997) and Fujii et al. (2005). Watanabe et al. (2003) also reported interaction between IM and PVP as shown by a C-CP/Mass-NMR study. Since CrosPVP has the same chemical structure as PVP, these observations suggest an interaction between IM and CrosPVP, as in the case of IM and PVP.

Fig. 5 shows dissolution patterns of IM from SD and related materials. The solubility of IM in purified water is 8.5 μg/ml (Fujii et al., 2005), but this level was not achieved within 90 min for IM powder. The dissolution rate increased when Pmix, Emix (20 °C, 15 min^{-1}), and Kmix (20 °C, 50 min^{-1}) were used, and IM dissolved to its solubility limit within 30 min; however, there was no increase in solubility. Emix (20 °C, 15 min^{-1}) and Kmix (20 °C, 50 min^{-1}) showed the same IM dissolution pattern as Pmix. These results suggest that mixing IM with CrosPVP, which has good wettability, might improve wettability along with dissolution in Pmix, Emix (20 °C, 15 min^{-1}), and Kmix (20 °C, 50 min^{-1}). However, IM existed in a crystalline form and solubility was not improved for Pmix, Emix (20 °C, 15 min^{-1}), or Kmix (20 °C, 50 min^{-1}).

When SD (Emix) or SD (Kmix) was used, IM dissolved to its solubility limit within 5 min, and achieved a concentration greater than 30 μg/ml. The solubility of IM increased about four-fold using SD. These improvements in solubility and dissolution rate were the same as those for SD prepared using a method previously reported (Fujii et al., 2005). CrosPVP does not dissolve in water, but increases the solubility of amorphous drugs. In this study, SD improved both the dissolution rate and solubility of IM because IM existed in an amorphous state in SD.

The physicochemical characteristics of SD prepared using an extruder or a kneader were the same as those of SD reported previously (Fujii et al., 2005).

3.2. The relation between degree of amorphous state and preparation conditions of solid dispersions

We investigated the degree of amorphous state and the preparation conditions of SD. Use of an extruder decreased the intensity of a typical IM peak in the XRD pattern as screw rotation speed decreased and heating temperature increased, and the Δ*H* of IM was similar (Fig. 6).

Neither the XRD patterns nor DSC curves displayed IM peaks for samples treated with a screw rotation speed of 15–50 min^{-1} and

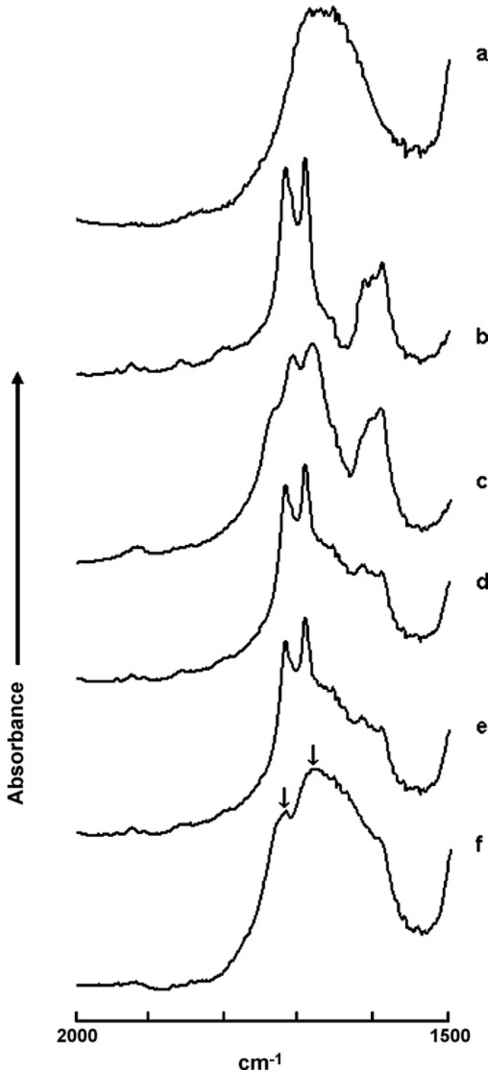

Fig. 4. IR spectra of solid dispersions prepared with an extruder and related materials: (a) CrosPVP; (b) IM; (c) amorphous IM; (d) Pmix; (e) Emix (20 °C, 15 min^{-1}); (f) SD (Emix).

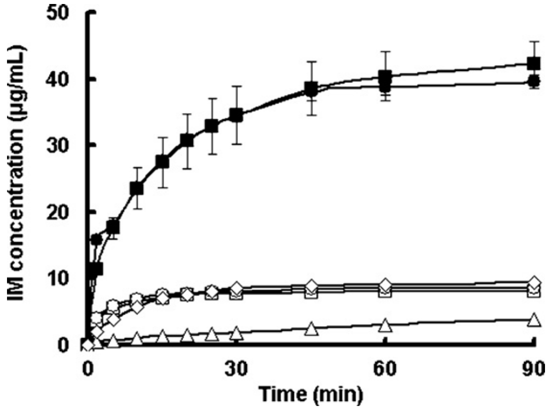

Fig. 5. Dissolution profiles of IM from a solid dispersion and related materials. (△) IM; (◇) Pmix; (○) Emix (20 °C, 15 min^{-1}); (□) Kmix (20 °C, 50 min^{-1}); (●) SD (Emix); (■) SD (Kmix). Each data point represents the mean ± S.D. of three experiments.

temperature of 140 °C. When screw rotation speed was fast, e.g., 200 min^{-1}, an IM peak was observed in for the sample treated at 200 min^{-1} and 140 °C, but no IM peak in the XRD and Δ*H* of IM were observed at temperatures greater than 145 °C, irrespective of the screw rotation speed. These results suggest that screw rotation speed influences the preparation of SD. The mechanical shear usually becomes greater as screw rotation speed increases. However, in this study, as screw rotation speed slowed, IM peak in the XRD and Δ*H* of IM decreased at a constant heating temperature.

Use of a kneader decreased the intensity of a typical IM peak in the XRD pattern as screw rotation speed decreased and heating temperature increased, and the Δ*H* of IM was similar (Fig. 7). Irrespective of screw rotation speed, neither the XRD patterns nor DSC curves displayed IM peaks in samples heated at 140 °C. Similar to results for the extruder, as screw rotation speed slowed, IM peak in the XRD and Δ*H* of IM decreased at a constant heating temperature.

The results suggest that IM in Emix and Kmix interacted with CrosPVP at temperatures lower than its melting point through simultaneous kneading and heating. When results for Emix and Kmix are compared at the same screw rotation speed and heating temperature, the intensity of a typical IM peak in the XRD pattern and Δ*H* of IM were relatively small for Kmix (Figs. 6 and 7). These results indicate that kneading power, retention time, or packing power can influence the crystallinity of IM.

3.3. *Factors influencing the preparation of solid dispersions in an extruder or kneader*

Important factors associated with the use of the extruder or the kneader includes kneading power and screw rotation speed. Thus, an evaluation of Emix and Kmix at different screw speed rotation speeds was conducted using DSC to examine the difference of kneading power. For DSC, temperature was maintained at 125 °C (Fig. 8a) or 140 °C (Fig. 8b). In the case of Pmix, Δ*H* of IM decreased with time at 125 °C; however, IM crystals were observed with additional time up to 120 min. Previous reports indicated that IM exists in an amorphous state when Tmix is heated at 125 °C, although IM crystals remained in Pmix (Fujii et al., 2005). Thus, we used Tmix to compare kneading power with Emix and Kmix in this study. For Tmix, Δ*H* of IM became negligible by heating for 30 min (Fig. 8a). Emix and Kmix treated without heating showed the same Δ*H* as Pmix, and no obvious differences were seen by changing rotation speed and between the extruder and kneader. Namely, no difference existed in kneading power by rotation speed or between the extruder and kneader. Also, kneading itself had no effect on preparation of SD, probably because the periods of kneading by the extruder and kneader were shorter than that of the theta composer.

IM mixed by screw rotation with heating interacted with CrosPVP at temperatures lower than its meting point as shown in Figs. 6 and 7. For Emix (20 °C, 15 or 50 min^{-1}) and Kmix (20 °C, 50 min^{-1}), Δ*H* of IM heated for 30 min became negligible (Fig. 8b). For Pmix heated at 140 °C for 15–120 min using DSC, Δ*H* of IM decreased with longer heating times, however, it did not become negligible and produced small values throughout the heating period (Fig. 8b). Thus, simultaneously mixing and heating appears important. In preliminary experiments, IM existed in an amorphous state while Pmix was heated for about 16 min at 130–140 °C in a test tube with mixing by a spatula (data not shown).

In the case of Pmix, SD could not be prepared at temperatures below the melting point without mixing because IM crystals remained in the mass, some of them existing apart from CrosPVP. In contrast, SD could be prepared at 140 °C, below its melting point, because any IM crystals remaining were mixed in by the extruder or kneader. In addition, SD could be prepared with heating at low temperatures (125 °C) because the Δ*H* of IM decreased with prolonged

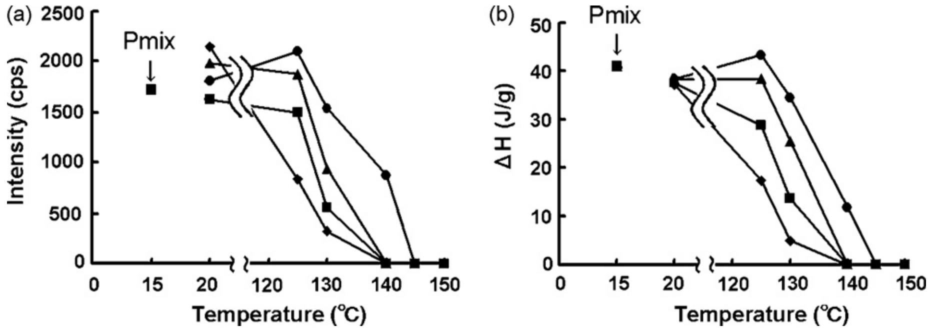

Fig. 6. Influence of heating temperature and rotation speed of an extruder on intensity of the peak at $2\theta = 21.0–22.0^\circ$ observed by (a) XRD and (b) heat of fusion of the peak near 160 °C from the DSC curve. (●) 200 min^{-1}; (▲) 50 min^{-1}; (■) 30 min^{-1}; (◆) 15 min^{-1}.

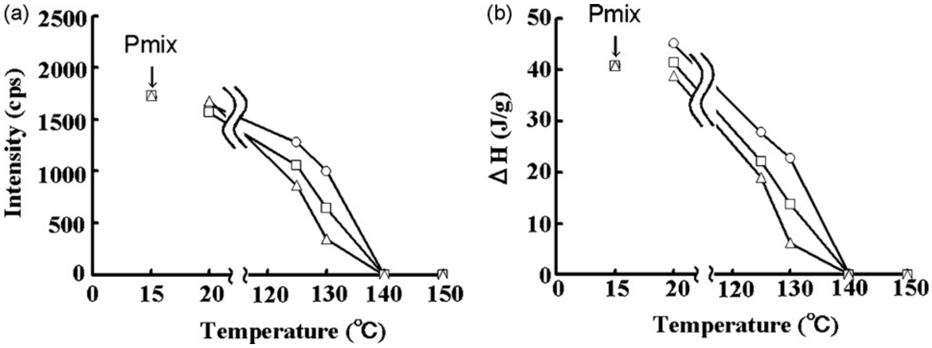

Fig. 7. Influence of heating temperature and rotation speed of a kneader on (a) intensity of the peak at $2\theta = 21.0–22.0^\circ$ observed by XRD and (b) heat of fusion of the peak at 160 °C calculated from the DSC curve. (○) 200 min^{-1}; (□) 100 min^{-1}; (△) 50 min^{-1}.

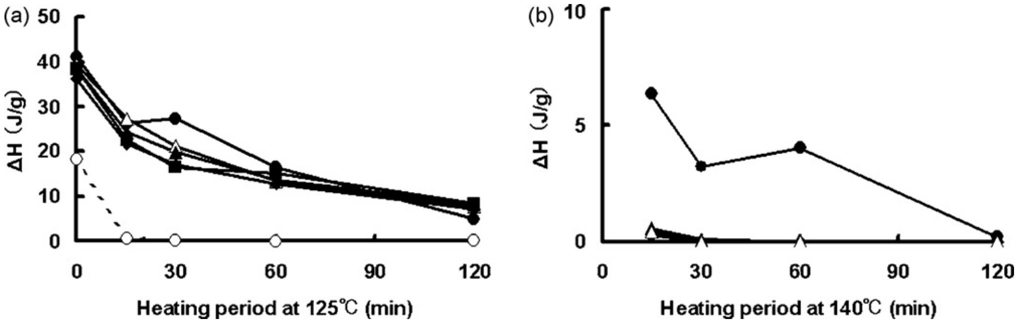

Fig. 8. Relation between heating duration at (a) 125 °C or (b) 140 °C and heat of fusion of the peak near 160 °C calculated from the DSC curve after heating. (●) Pmix; (◆) Emix (20 °C, 15 min^{-1}); (▲) Emix (20 °C, 50 min^{-1}); (■) Emix (20 °C, 200 min^{-1}); (△) Kmix; (20 °C, 50 min^{-1}); (○) Tmix.

heating period in Pmix, Emix, and Kmix. These results suggest that the decrease in IM mass and the adsorption of IM to the surface of CrosPVP are important for the preparation of SD when heating at temperatures below its melting point.

Even though rotation speed had no obvious effect on kneading power, a low rotation speed was beneficial for the preparation of SD. Therefore, the influence of screw rotation speed on retention time of samples was evaluated. Because Emix or Kmix heated at 140 °C is in an amorphous state, neither can be used to examine the influence of retention time on the crystallinity of IM. Therefore, heating temperature was set at 130 °C. Irrespective of the machine, retention time was prolonged when screw rotation speed was slow. The intensity of a typical IM peak in the XRD pattern decreased as retention time was prolonged (Fig. 9), and the ΔH of IM was similar (data not shown). The body compartment for the kneader was shorter than that for the extruder. But when results from an extruder and kneader are compared at the same screw rotation speed, the kneader produced longer retention

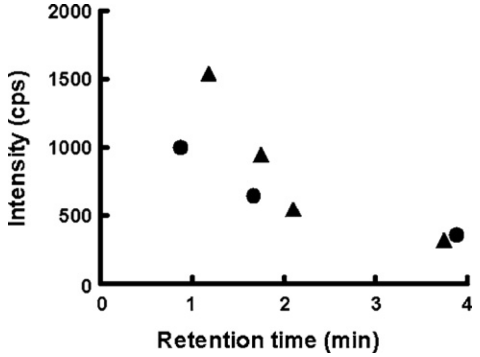

Fig. 9. The relation between screw rotation speed, retention time, and intensity of the peak at $2\theta = 21.0–22.0^\circ$ observed in the XRD pattern. (▲) Extruder; (●) kneader.

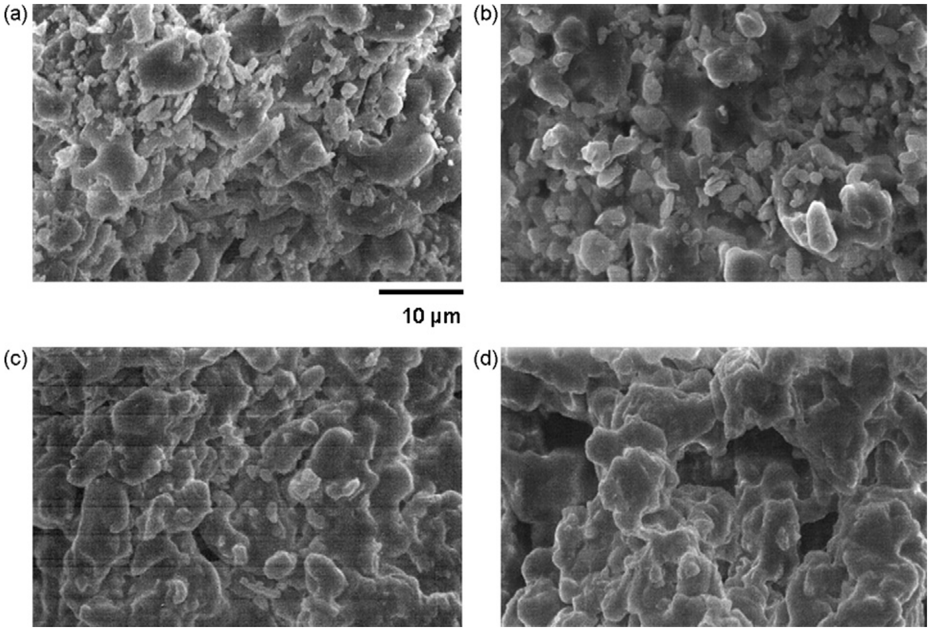

Fig. 10. Scanning electron micrographs of samples after passing through the extruder and related materials: (a) Pmix; (b) Pmix heated at 130 °C for 30 min; (c) Emix (130 °C, 15 min^{-1}); (d) Emix (130 °C, 15 min^{-1}) after passing through the extruder twice.

times than the extruder, possibly because of a weaker feeding mechanism.

The influence of retention time was evaluated using an extruder or kneader. Retention time was about 4 min in the case of Emix (130 °C, 15 min^{-1}) or Kmix (130 °C, 50 min^{-1}) and the intensity of a typical IM peak in the XRD pattern and the ΔH of IM were small. To examine the effect of retention time at 130 °C, retention time was prolonged by passing through the extruder or kneader twice. A typical IM peak was not observed after two passes through the extruder or kneader, and no ΔH for IM was observed. Fig. 10 shows SEM pictures of samples after passing through the extruder. For samples that passed through the extruder once and for Pmix heated at 130 °C for 30 min, some IM crystals were present on the surface of CrosPVP. In contrast, IM crystals could not be detected in samples that passed through the extruder twice. Similar results were obtained for the kneader. Retention time in the machine is thought to play a role in SD preparation.

Any IM crystals remaining in the mass are assumed to decrease by mixing and heating simultaneously, allowing preparation of SD below the melting point.

Although SD was prepared by the theta composer followed by heating at 125 °C for 30 min, for manufacturing it is more useful to continuously prepare powdered SD by heating below the melting point (140 °C) in a short time (4 min) using an extruder or a kneader.

4. Conclusions

A powder of SD with IM and CrosPVP was prepared continuously by heating at a temperature below the melting point, kneading and mixing with an extruder or a kneader without the extrusion die section. The IM and CrosPVP interacted to maintain IM in an amorphous state. The IM solubility and dissolution rate were improved in SD powders. Consequently, no differences in the characteristics of SD obtained in an extruder and SD obtained in a kneader could be detected in this study. Operating conditions, such as screw rotation speed, heating temperature, and the retention time of the samples in the machine were important parameters for the preparation of SD. For manufacturing purposes, an extruder or a kneader is more useful than a theta composer for the preparation of powdered SD.

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