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Preparation, characterization, and tableting of a solid dispersion of indomethacin with crospovidone

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Abstract

A significant problem with solid dispersion (SD) systems is the difficulty in preparing dosage forms. This difficulty can be overcome using crospovidone (CrosPVP) as a carrier. A powder SD of indomethacin (IM) with CrosPVP was prepared using mechanical mixing followed by heating to temperatures below the melting point. IM and CrosPVP interacted to produce IM in an amorphous state when its concentration was ≤40%. The solubility of IM was improved about fourfold compared to IM crystal. The SD had good fluidity, and tablets were prepared by direct compression. Tablets with small weight variation and acceptable hardness were obtained using only 1% of magnesium stearate as excipient. The dissolution of IM from tablets was similar to that of SD powder because CrosPVP, a disintegration agent, caused the tablets to break up rapidly.

Keywords: Solid dispersion; Crospovidone; Fluidity; Indomethacin; Tablet; Direct compression

1. Introduction

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, therefore efforts to increase dissolution of drugs with limited water solubility is often needed. Many methods are available to improve these characteristics, including salt formation, micronization, and addition of solvent or surface-active agent. Solid dispersion (SD) is one of these methods, and involved a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by melting, dissolution in a solvent, or melting-solvent method (Chiou and Riegelman, 1971). Since 1961 (Sekiguchi and Obi, 1961), many investigators have studied SD with various drugs and carriers; however, only a few systems are useful commercially.

There are many difficulties associated with preparing dosage forms using SD. The solvent method involves solvent residues and necessary environmental assessments because the drug and carrier are dissolved

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in an organic solvent that is subsequently removed by techniques such as vacuum evaporation and spray drying. The melting method works well for drugs that are stable at elevated temperatures. Unfortunately, the SD prepared in this way can be difficult to pulverize. Another problem involves the preparation of the dosage form because the pulverized SD is often soft and tacky and possesses poor flow characteristics. Consequently, more excipients and more complicated procedures are often required (Serajuddin, 1999; Leuner and Dressman, 2000). As a result, the amount of drug that can be incorporated into the dosage form is low and its cost is increased.

The ability to prepare a powder form SD without solvent could resolve these problems. Crospovidone (CrosPVP) has two useful characteristics in this regard. First, it is a powder with good fluidity used as a disintegration agent in tablets. Second, CrosPVP has the same chemical structure as povidone (PVP), which is commonly used as a carrier of SD (Leuner and Dressman, 2000); drugs in an SD with PVP are amorphous because of hydrogen bonding between the drug and PVP (Doherty and York, 1987a).

Reports describe the use of CrosPVP in SDs prepared with solutions of drugs in organic solvents (Takayama et al., 1982; Carli and Garbassi, 1985; Carli et al., 1986). In our study, we prepared an SD with CrosPVP and indomethacin (IM) as a model drug, using a new method that avoids solvents and their associated problems. Furthermore, tablets, a typical dosage form, can be prepared with the SD by direct compression.

2. Materials and methods

2.1. Materials

CrosPVP (Polyplasdone® XL, USP grade) was a gift from ISP Japan (Tokyo). IM (JP grade) was obtained from Nippon Bulk Yakuhin (Osaka). Magnesium stearate was obtained from Wako Pure Chemical (Osaka). Other chemicals were of reagent grade.

2.2. Preparation of SD

A physical mixture (Pmix) was obtained by combining IM and CrosPVP using a spatula. 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). 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 (Fig. 1). Tmix was heated in air in an oven for 30 min at 125 °C for 1:4 and 1:3, 130 °C for 1:2 and 145 °C for 1:1.5 to obtain the SD. The weight ratio of IM/CrosPVP ranged from 1:4 to 1:1. The IM content in SD was 20–50%; 1:3 (25%) was used unless otherwise specified.

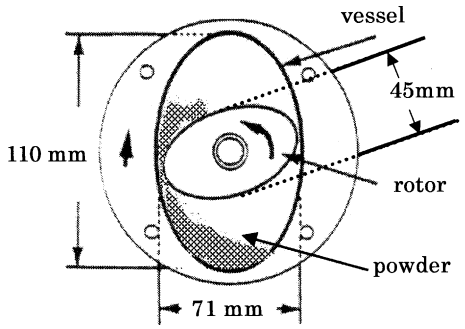

Fig. 1. Structure of the mixing portion of the Theta-Composer®.

2.3. Physicochemical properties of SD and related materials

Powder X-ray diffraction (XRD) patterns were examined in a diffractometer (M03X-HF, Mac Science, Yokohama). The X-rays were Ni-filtered Cu Kα radiation (40 kV and 30 mA; scanning at width of steps 0.1° per 2.0 s over the range of $2\theta = 5$–$30°$). Thermal analysis was conducted using differential scanning calorimetry (DSC, Thermoflex TAS200, Rigaku, Tokyo). The samples containing 1 mg IM were sealed in an aluminum crimp cell and heated at 20 °C/min under a nitrogen atmosphere. Infrared (IR) spectra were obtained on an IR spectrophotometer (FT/IR-8000, JASCO, Tokyo) by the diffuse reflectance method.

2.4. Dissolution studies

Dissolution of IM from various forms containing 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 rpm. IM concentration was determined by UV absorption at 320 nm.

2.5. Powder fluidity of SD and related materials

Angle of repose of the SD and related materials was measured with a turn-table type apparatus (Tsutsui Rikagaku Kikai, Tokyo).

Compressibility index (CI) was calculated as follows:

$$\mathrm{CI} = \frac{V_0 - V_f}{V_0} \times 100$$

where V_0 is powder volume before tapping and V_f is powder volume after tapping infinitely. CI was calculated using Kawakita's equation (Kawakita, 1956):

$$\frac{V_0 - V}{V_0} = \frac{abn}{1 + bn} \quad (1)$$

where n is the tapping number, V is the volume of powder after n times tapping and a and b are constants. Eq. (1) was transformed as Eq. (2):

$$\frac{V_0}{V_0 - V} = \left(\frac{1}{ab}\right)\frac{1}{n} + \frac{1}{a} \quad (2)$$

The data obtained by 200 times tapping using a tapping density analyzer (Tapdenser KYT-1000, Seisin Enterprise, Tokyo) with a 20-mL cylinder was plotted along with Eq. (2). V_f is the volume of powder after tapping infinitely, namely $n = \infty$ and $1/n = 0$. Thus, the y-intercept of Eq. (2) indicates $V_0/(V_0 - V_f)$, and was calculated by the least squares method.

2.6. Tableting condition

The SD with 1% magnesium stearate as lubricant was directly compressed to tablets (200 mg) by a tablet-hitting pressure displacement system (Sratt Press, model N-20E, Okada Seiko, Tokyo) equipped with a flat-faced punch (8 mm diameter), using a compression force of 500 kgf. For comparison, Pmix and Tmix were also directly compressed to tablets.

2.7. Characterization of tablets

The weight variation among tablets was based on a sample of 20 tablets. The crushing strength of the tablets (hardness) was measured with a digital crushing tolerance-measuring instrument (TS-50N, Okada Seiko, Tokyo).

3. Results and discussion

3.1. Preparation of solid dispersion

Preparing an SD without solvent by dissolving the drug in a molten carrier followed by cooling is a common method. However, CrosPVP does not melt. CrosPVP is a powder with good fluidity and is difficult to crush using a mortar and pestle. Therefore, Pmix was mechanically blended using a Theta-Composer, and the characteristics of the Tmix examined. XRD patterns of Tmix and related materials show that while the intensities of the peaks related to IM crystal were lower in Tmix than in Pmix, the differences were not significant (Fig. 2a). Intensity of a typical IM peak ($2\theta = 21.8°$) in the XRD pattern decreased with duration of mixing to about half of the Pmix with 30 min mixing; no additional change occurred with additional mixing up to 120 min (Fig. 3a). Fig. 2b, which shows DSC curves of Tmix and related materials, reveals that IM has an endothermic peak of melting at 162 °C. Pmix also had an endothermic peak near 160 °C, but it was not as sharp as that of IM. For Tmix, a small endothermic peak occurred near 160 °C, and a new peak appeared around 140 °C. Heat of fusion (ΔH) of IM, calculated by the area of peak near 160 °C, decreased to 1/3 of Pmix with 15 min mixing and became negligible after 120 min mixing (Fig. 3b).

The change in crystallinity of IM during mixing based on XRD pattern and DSC was different. This indicated that the heating process associated with DSC affected crystallinity of IM; the new peak observed near 140 °C suggested a new interaction between IM and CrosPVP. Thus, Tmix was heated for 30 min at temperatures ranging from 115 to 140 °C (Fig. 4). No IM peak was observed in either the XRD pattern or DSC curve after heating Tmix above 125 °C. In the case of Pmix, peaks of IM crystals were observed until it was heated above 160 °C. This indicated that IM in Tmix interacted with CrosPVP at temperatures lower than its melting point, but melting temperatures were required to permit IM and CrosPVP interactions in Pmix.

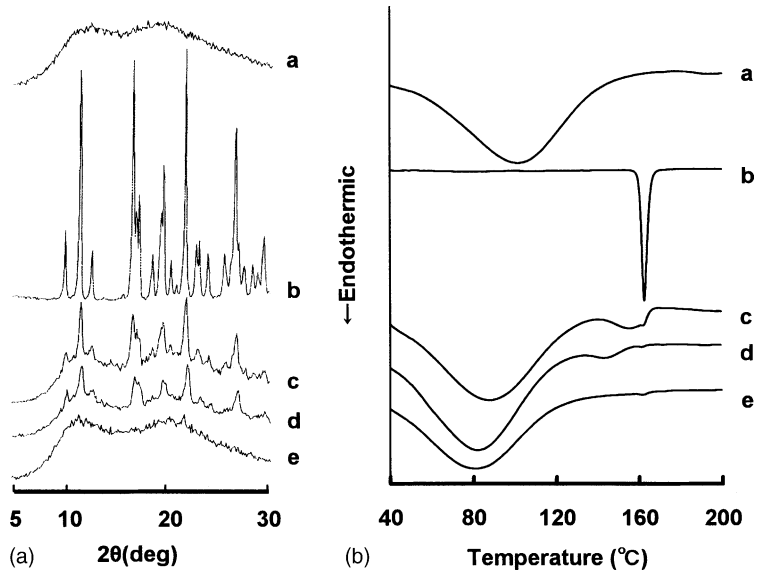

Fig. 2. XRD patterns (a) and DSC curves (b) of solid dispersion and related materials: a, CrosPVP; b, IM; c, Pmix; d, Tmix (30 min); e, SD (Tmix heated 30 min at 125 °C), weight ratio of IM: CrosPVP = 1:3.

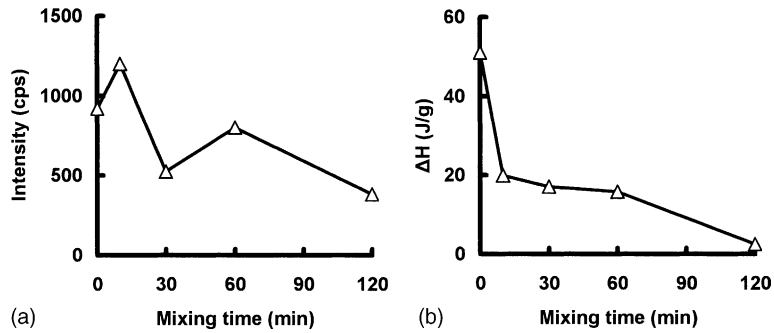

Fig. 3. Influence of mixing time on crystallinity of IM in Tmix with Theta-Composer® (a) intensity of the peak at $2\theta = 21^\circ$ observed in XRD pattern, (b) heat of fusion of the peak at 160 °C calculated from DSC curve, weight ratio of IM: CrosPVP = 1:3.

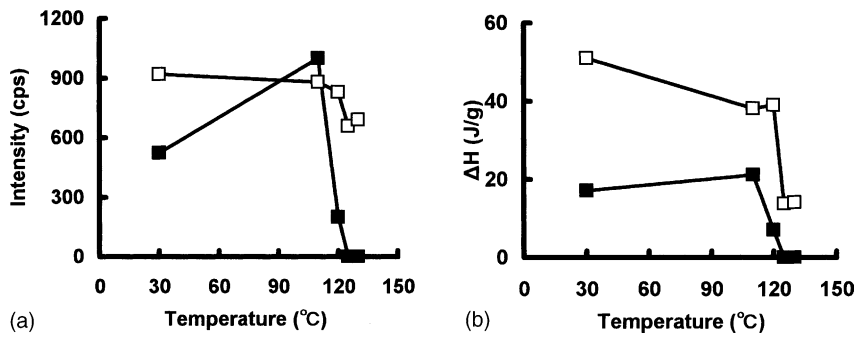

Fig. 4. Influence of heating temperature on crystallinity of IM when Tmix (30 min) (■) or Pmix (□) was heated in an oven in air, (a) intensity of the peak at $2\theta = 21^\circ$ observed in XRD pattern, (b) heat of fusion of the peak at 160 °C calculated from DSC curve, weight ratio of IM: CrosPVP = 1:3.

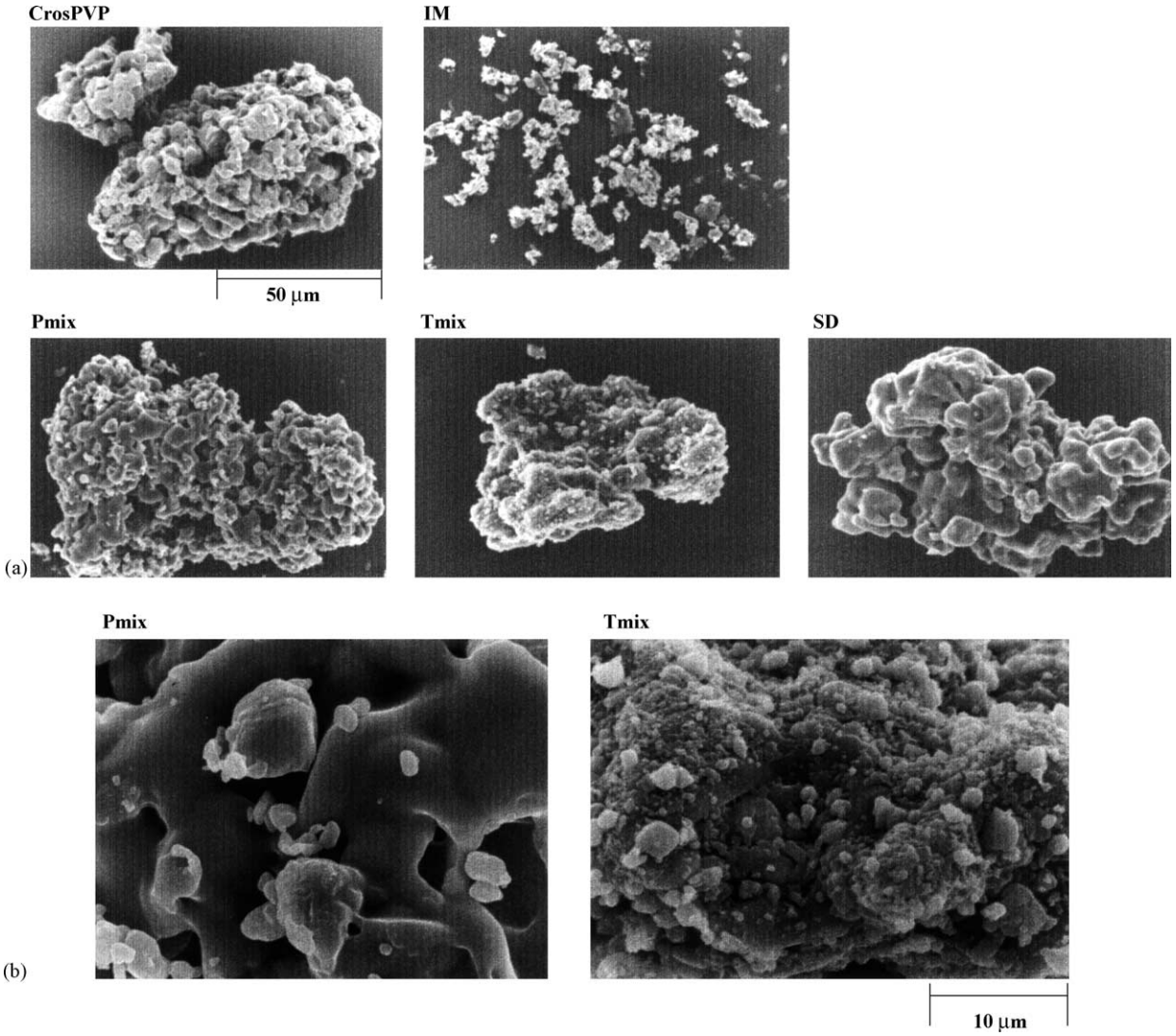

Fig. 5. Scanning electron microscopy of solid dispersion and related materials. Weight ratio of IM: CrosPVP = 1:3. Mixing time of Tmix was 30 min. SD was obtained by heating Tmix (30 min) at 125 °C.

Shin et al. (1998) reported that co-grinding of furosemide and CrosPVP for 24 h in a ball mill produced amorphous furosemide. The mixing mechanism of the Theta-Composer, which differs from that of a ball mill, produces good surface modifications (Kawashima et al., 1998) and small particle adsorption on large particles. Tmix was slightly yellow, which indicated that a portion of IM was amorphous state but most of it remained crystalline after mechanical mixing. IR spectra and dissolution studies supported this conclusion. Characteristics similar to those of Tmix were obtained when CrosPVP and IM were mixed with a mortar and pestle for 10 min; however, when these components were mixed in a V-shape mixer, the character of the powder obtained was similar to Pmix. Thus, mechanical force was necessary to change Pmix to Tmix.

Fig. 5a shows the SEM of the SD and related materials. CrosPVP possessed a “popcorn” shape, containing many cavities. The IM existed as small particles with

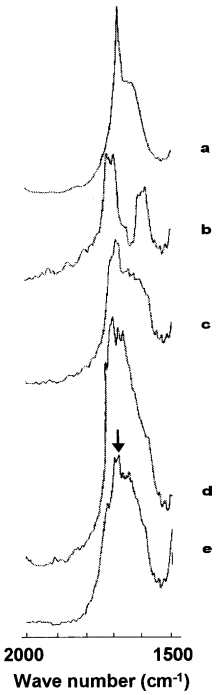

Fig. 6. IR spectra of solid dispersion and related materials: a, CrosPVP; b, IM; c, Pmix; d, Tmix (30 min); e, SD (Tmix heated 30 min at 125 °C), weight ratio of IM: CrosPVP = 1:3.

a diameter of 1–2 μm. For Pmix, some IM crystals existed on the surface of CrosPVP, although most of the IM crystals existed apart from CrosPVP. The difference in the IM crystals on the surface can be seen in Fig. 5b. The surface of CrosPVP was covered with IM crystals, and some of the crystals were found in the cavities of CrosPVP in Tmix. The decrease in the XRD intensity for IM may be due to IM positioned in the CrosPVP cavities.

The IR spectra of SD and related materials are shown in Fig. 6. CrosPVP absorption was found at 1700 cm^{-1}, which indicates C=O stretching. IM had C=O stretching absorptions at 1710 and 1591 cm^{-1}. Pmix gave a spectrum that combined those of IM and CrosPVP. In contrast, SD showed a new absorption at 1684 cm^{-1}. Tmix produced a spectrum that combined those of Pmix and SD. These changes in the SD correspond to the results reported by Taylor and Zografi (1997). Watanabe et al. (2003) also reported interaction between IM and PVP through a C-CP/Mass-NMR study. Since CrosPVP has the same chemical structure as PVP, these observations suggest an interaction between the carboxyl group of IM and the amide carbonyl group of CrosPVP, as in the case of IM and PVP.

Both IM and CrosPVP existed in powder form and no media existed between them without solvent. IM, which did not contact CrosPVP in Pmix, required heating near the melting point for an interaction to occur. In contrast, IM in Tmix was adsorbed on the surface of CrosPVP, and appeared to stick to CrosPVP during mixing in the Theta-Composer. The DSC curve of Pmix with IM and PVP was similar to that of Tmix with IM and CrosPVP—an endothermic peak near 140 °C. IM and CrosPVP did not melt; however, they interacted with each other upon heating, which resulted in physical adsorption and depressed the melting point of IM.

CrosPVP interacted with IM, and IM was in an amorphous state in SD, which was prepared by mixing with the Theta-Composer and heating. Based on XRD and DSC data, IM maintained an amorphous state for at least 1 year (data not shown).

When the ratio of IM and CrosPVP was changed to 1:4, the SD could be prepared using the same procedure. When ratios were 1:2 and 1:1.5, heating to 130 and 145 °C, respectively, was required. If the ratio of IM in Tmix was above 50% (1:1), then heating above 160 °C was necessary to obtain an amorphous state of IM. Recrystallization of IM occurred relatively quickly when the ratio was 1:1.

The SD could be prepared when the ratio of IM/CrosPVP was 1:1.5, or the IM content in SD was 40%. A major problem with an SD is the low concentration of a drug it can contain. An SD prepared with CrosPVP as a carrier solves this problem. Furthermore, this SD exists as a powder that does not require crushing.

3.2. *Dissolution of IM*

Fig. 7 shows dissolution patterns of IM from the SD and related materials. The solubility of IM in purified water is 8.5 μg/ml, and this level was not achieved within 90 min. Dissolution rate increased when using Pmix, and IM dissolved to its solubility limit within 30 min; however, there was no increase in solubility. Tmix showed the same IM dissolution pattern as Pmix. These results suggest that mixing IM with CrosPVP, which has good wettability, might improve wettability

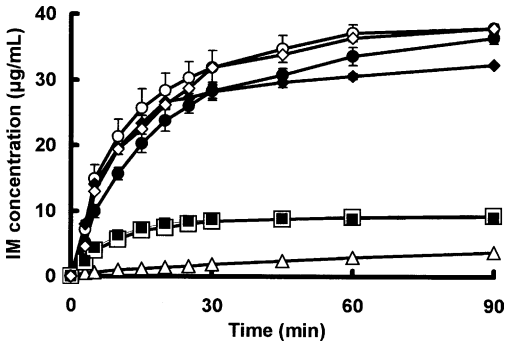

Fig. 7. Dissolution of IM from SD and related materials: △, IM powder; □, Pmix; ■, Tmix; ◊, SD (1:4); ◯, SD (1:3); ●, SD (1:2); ♦, SD (1:1.5). Each data point represents the mean ± S.D. of three experiments.

and dissolution in Pmix or Tmix. Unfortunately, IM existed in a crystalline form and solubility was not improved in the cases of Pmix and Tmix.

When an SD 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 approximately fourfold using the SD. The improved solubility of drugs from SDs can be explained by the microenvironment of the drugs, which promotes dissolution from the carrier polymers (Doherty and York, 1987b). CrosPVP does not dissolve in water, but increases the solubility of amorphous state drugs, such as fulfenamic acid (Takayama et al., 1982), griseofulvin (Carli et al., 1986) and furosemid (Shin et al., 1998). In this study, SD improved both the dissolution rate and solubility of IM because the IM existed in an amorphous state in the SD. Changing the ratios of IM in SD produced similar dissolution patterns.

3.3. Fluidity of SD

The flow properties of powders are important for preparing dosage forms (Wadke et al., 1990). When fluidity is poor, it must be improved by granulation or addition of excipients.

The fluidity of SD was determined by angle of repose and compressibility. CrosPVP, which was used as a disintegrating agent, is a free-flowing material, and its angle of repose and CI were 28° and 29%, respectively (Table 1). IM is a fine powder (Fig. 5), and has poor fluidity; its CI could not determined because of static electricity. The fluidity of CrosPVP decreased with IM (Pmix). The fluidity of Tmix was better than that of Pmix because the IM powder in Pmix adsorbed onto the surface of CrosPVP, which improves its fluidity. The fluidity of SD was similar to that of Tmix. Since powder with an angle of repose less than 45° is suitable for direct tableting (Wadke et al., 1990), Pmix, Tmix, and SD should be suitable for direct tableting.

Table 1
Characteristic of SD and related materials from the point of powder fluidity

	Angle of repose (°)	Compressibility index (%)
CrosPVP	28	28
IM	58	ND
Pmix	44	40
Tmix	36	37
SD	37	30

ND: not determined. The weight ratio of IM: CrosPVP = 1:3.

3.4. Tableting of SD by direct compression

While SD and related materials possessed good fluidity, other factors are required for preparing tablets (Parrott, 1990). Tablets were prepared using the direct compression method because it is a simple procedure that depends on the characteristics of the powder. Magnesium stearate was used as a lubricant at a level of 1%.

More than 100 consecutive tablets could be made by direct compression when Tmix or SD was used. Difficulties were encountered when compressing tablets using Pmix. The weight variation, which depends on the weight of powder filling the die, decreased in the order Pmix > Tmix > SD (Table 2). The good fluidity of SD probably contributed to more uniform filling of the die. Hardness increased in the order Pmix < Tmix < SD. Hardness of the tablets containing CrosPVP was 13.9 kg; IM reduced tablet hardness, and

Table 2
Characteristics of tablets prepared with SD and related materials

	Weight variation (%)	Hardness (kg)
Pmix	3.9	5.9 ± 0.9
Tmix	2.5	8.6 ± 1.3
SD	1.2	11.3 ± 0.5

The weight ratio of IM: CrosPVP = 1:3. Magnesium stearate was added 1% as lubricant.

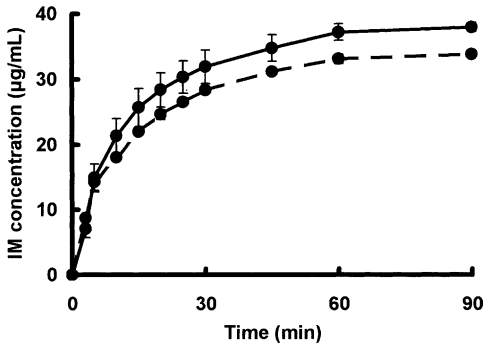

Fig. 8. Dissolution of IM from tablets prepared by SD. Broken lines and lines represent dissolution from tablets and powder form, respectively. Weight ratio of IM: CrosPVP = 1:3. Magnesium stearate at 1% was added as lubricant.

its degree seemed different with IM condition. Since many factors affect hardness, this change associated with IM may be caused by some other phenomenon.

The dissolution of drugs from SD can be reduced by the choice of dosage form because addition of excipients changes the characteristics of the SD (Serajuddin, 1999). Thus, we compared the dissolution of IM from SD tablets made with SD powder (Fig. 8). The improved solubility of IM was maintained with these tablets. Since CrosPVP was the original disintegrating agent, the tablet broke up very quickly. The simple procedure and few excipients prevented changes in the SD characteristics.

Therefore, SD could be compressed directly and continuously, and the resulting tablets possessed good characteristics including low weight variation, appropriate hardness, rapid disintegration, and rapid dissolution of IM.

4. Conclusion

IM existed in an amorphous state when it was mechanically mixed with CrosPVP and heated to approximately 125 °C. IM and CrosPVP interacted in a manner similar to IM and PVP. The good powder fluidity of CrosPVP was maintained in the SD, and tablets of SD could be prepared by direct compression using only 1% magnesium stearate as a lubricant. These tablets contained high concentrations of IM, and had low weight variation and convenient hardness. IM solubility and dissolution rate were improved in both SD powders and tablets. Therefore, CrosPVP is a good candidate as a carrier of SD for easy preparation of dosage forms.

Acknowledgement

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