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Preparation and Characterization of Solid Dispersions of Dipyridamole with a Carrier "Copolyvidonum Plasdone®S-630"

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Solid dispersions (SDs) of dipyridamole (DIP) with a novel carrier copolyvidonum Plasdone®S-630 (CoPVP) were developed by solvent evaporation method. The solid state of SDs of DIP with CoPVP (SDs CoPVP) was characterized by fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), X-ray diffraction (XRD) and polarizing microscopy, compared with that of SDs of DIP with polyvinylpyrrolidone Plasdone®K-29/32 (SDs PVP). FT-IR analysis demonstrated the presence of intermolecular hydrogen bonding between DIP and CoPVP or PVP in SDs. DSC and XRD studies indicated that DIP presented in amorphous state in both SDs CoPVP and SDs PVP at higher weight ratios. The dissolution property of SDs CoPVP was significantly improved in comparison of pure DIP and physical mixtures with CoPVP (PM CoPVP). Both SDs CoPVP and SDs PVP powder showed the favorable flowability. However, SDs CoPVP showed better compressibility than SDs PVP. The lower hydroscopicity of SDs CoPVP could be advantageous to the stability to SDs. This study proves the potential of CoPVP as a carrier in the formulations of SDs for poorly soluble drugs.

Keywords solid dispersion; dipyridamole; copolyvidonum; PVP; hydroscopicity; compressibility

INTRODUCTION

The solubility and/or dissolution rate of a drug is an important factor for its oral bioavailability. Therefore it is often needed to increase dissolution of drugs with limited water solubility. The use of solid dispersions (SDs) has been recognized as an attractive strategy to improve the dissolution behavior of poorly soluble drugs for many years. However, the number of different polymeric carriers that have been used during the past 40 years is still rather limited. Indeed, polyethylene glycol or PVP are used in the majority of studies that have been published so far (Leuner & Dressman, 2000). Although several new carriers such as crosprovidone (Fujii et al., 2005) and Inutec SP1 (Van den Mooter et al., 2006) have been proposed in an attempt to tailor the physicochemical properties of the polymeric carriers to those of the dispersed drugs, there is definitely a need to explore new carrier materials.

One such potential carrier is copolyvidonum Plasdone® S-630 (CoPVP). CoPVP is a derivative of PVP by the addition of the vinyl acetate groups to the vinylpyrrolidone polymer chain. The structures of CoPVP and PVP are depicted in Figure 1. CoPVP has good compressibility and consequently it is often used with poorly compressible actives to improve tablet hardness or to lower compression force and reduce punch wear (Moroni, 2001). Due to its relatively lower glass transition temperature (T_g), CoPVP is also a better film former than vinylpyrrolidone homopolymers. Therefore, CoPVP can be used with other coating materials as film coating to modify drug release behavior (Chan et al., 2005). Here, CoPVP is used as a carrier of SDs. Some researches on the use of CoPVP in the preparation of SDs have been carried out (Chokshi et al., 2005; Ghebremeskel et al., 2006; Kondo et al., 1994; Moneghini et al., 1998; Zingone & Rubessa, 1994). In this study, CoPVP is used to improve solubility of a poorly soluble drug—dipyridamole by manufacturing solid dispersions.

In comparison of PVP, CoPVP has several useful characteristics in the preparation of SDs. First, addition of vinyl acetate groups to the vinylpyrrolidone polymer chain decreases hydrophilicity relative to PVP homopolymer. This has two effects: (1) it makes CoPVP copolymer perform as a polymeric surfactant and consequently it is of much greater wetting characteristics than PVP and (2) it reduces the hydroscopic property of the vinylpyrrolidone, therefore it is highly desirable when formulating with moisture sensitive actives or under humid conditions since it reduces the uptake of moisture. These two effects are advantageous to improving the dissolution behavior of drugs and reducing the hydroscopic property of SDs. The

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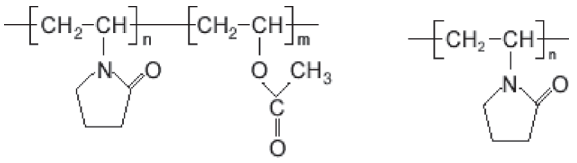

[1] [2]

FIGURE 1. Structures of: [1] CoPVP; [2] PVP.

physicochemical stability of SDs might be improved by decreasing the water absorption of SDs powder (Ahlneck & Zografi, 1990; Carstensen, 1974; Ford & Rubenstein, 1979; Kontny et al., 1987). Meanwhile, incorporating vinyl acetate into PVP polymers decreases its T_g. The T_g of CoPVP copolymer is 106°C while it is 164°C for PVP homopolymer of similar K-value. The lower T_g of CoPVP copolymer allows it to undergo plastic deformation on compression and makes it an excellent direct compression binder aid. This property is beneficial to improving the compressibility of SDs powder during the manufacturing process of dosage forms.

Just like PVP homopolymer, CoPVP is also soluble in water and a wide variety of pharmaceutically acceptable organic solvents, including alcohols, esters and ketones. Due to its good solubility in a wide variety of solvents, it is also particularly suitable for the preparation of SDs by the solvent evaporation method.

Therefore, the aim of this study was to evaluate the potential of this polymer as a novel carrier in the formulation of SDs. On the other hand, a new application of CoPVP to the preparation of SDs was investigated besides direct compression and film coating.

In the present work, a poorly soluble drug DIP, acting as an antiplatelet agent, was selected as a model drug. The SDs of DIP was prepared with CoPVP by solvent evaporation method. The solid state properties of SDs CoPVP were investigated to contribute to our understanding how materials behave in the SDs system. Furthermore, the flowability, compressibility and hydroscopic property of SDs CoPVP powder were investigated in this study. To elucidate the difference between the novel carrier CoPVP copolymer and conventional carrier PVP homopolymer, the comparison has been done between the physicochemical characteristics of SDs CoPVP and those of SDs PVP. In order to eliminate the difference of the products from different pharmaceutical excipient companies, CoPVP and PVP from the same company were applied in this study.

MATERIALS AND METHODS

Materials

Plasdone®K-29/32 and Plasdone®S-630 were donated from International Specialty Products Incorporate (ISP Inc.). Dipyridamole was purchased from Shanxi Yabao Pharmaceutical Group Corporation, China. The ethanol used in the study was 99.5% (Nanjing Chemical Reagent Corporation, China). Magnesium stearate was purchased from Wenzhou Chemical Materials Factory, China.

Preparation of Solid Dispersions

SDs CoPVP at four weight ratios (1:1, 1:2, 1:3, 1:5), denoted as SDs CoPVP 1/1, 1/2, 1/3, 1/5, respectively, were prepared by solvent-evaporation method as described below. DIP was dissolved in appropriate volumes of ethanol and then the required amount of CoPVP was added. Next, the solvent was removed under reduced pressure at about 50°C in a rotary evaporator (ZFQ 85A, the eleventh radio tube factory, Shanghai, China) and dried under vacuum at room temperature for 24 hr. The dried powder was pulverized using a mortar and sieved through a 100-mesh screen (about 154 μm).

SDs PVP at four weight ratios (1:1, 1:2, 1:3, 1:5) were prepared by the same method as above described, and denoted as SDs PVP 1/1, 1/2, 1/3, 1/5, respectively. These powders were stored in a brown desiccator prior to be evaluated.

Preparation of Physical Mixtures

PM CoPVP was prepared by mixing the required amount of DIP and CoPVP in a mortar. The resulting mixtures were sieved through a 100-mesh screen and denoted as PM CoPVP 1/1, 1/2, 1/3, 1/5, respectively.

The physical mixtures of DIP with PVP (PM PVP) were also prepared as above and denoted as PM PVP 1/1, 1/2, 1/3, 1/5, respectively. The powder was stored in a brown desiccator at room temperature until use.

X-Ray Diffraction

The X-ray diffraction (XRD) patterns were obtained at room temperature using a diffractometer (D8, Bruker, Germany), with Cu Kα radiation. The scanning angle ranged from 5º to 60º of 2θ, steps were 0.3º of 2θ per 1.0 sec. The current used was 30 mA and the voltage 40 kV.

Differential Scanning Calorimetry

Thermal analyses of various samples were performed on a DSC-204 (NETSCH, Germany) differential scanning calorimeter. Samples were accurately weighed (about 10 mg) and heated in hermetically sealed aluminum pans with a heating rate of 10°C min^{-1} from 50 to 200°C under nitrogen flow (20 mL/min). An empty aluminum pan was used as reference.

Microscopy Study

The surface morphology of DIP and related materials were examined by means of a polarizing microscopy (Leica DM LP, Leica Microsystem, Germany). The samples were placed on the glass slides and then observed under the microscopy. The micrographs were taken with a microcamera (PL-A662, Pixelink, Canada).

Fourier Transform Infrared Spectroscopy

FT-IR spectra of SDs and related materials were obtained in a FT-IR-8400S spectrophotometer (Shimadzu, Japan) by the diffuse reflectance method. Samples were previously ground and mixed thoroughly with potassium bromide (KBr), an infrared transparent matrix (2 mg sample in 200 mg KBr). The KBr discs were prepared by compressing the powders at a pressure of 5 tons. The scanning range was from 4000 to 400 cm^{-1}.

Determination of Solubility

Solubility studies were carried out by adding SDs or physical mixtures (PMs) powders equivalent to 10 mg of DIP to 15 mL of pH 6.8 phosphate buffer solution in screw-capped test tubes, respectively. The tube was vortexed for 30 min and kept in water bath (25ºC) under magnetic stirring for 36 hr. Then, suspensions were filtered through a 0.45 μm membrane filter and the supernatant was analyzed on an Ultraviolet-visible spectrophotometer (Model 752C, Shanghai Analytical Instrument Factory, China) at a wavelength of 283 nm after appropriate dilution. The average of triplicate determinations was reported.

Dissolution Study

Dissolution studies of 10 mg of DIP and its equivalent in SDs and PMs were performed by using a dissolution test apparatus (ZRS-4 Dissolution Tester; Tianjin University Radio Factory, China) at the paddle rotation speed of 50 rpm in 900 mL simulated intestinal juice without enzyme as a dissolution media at 37 ± 0.5°C. The SDs or PMs powder equivalent to 10 mg of DIP were weighed using an electronic balance (AE240, METTLER, Switzerland) and added into the dissolution medium. At predetermined time intervals, 5 mL of samples were withdrawn, filtered through a 0.45 μm membrane filter and then assayed for DIP content by measuring the absorbance at 283 nm using an Ultraviolet-visible spectrophotometer (Model 752C, Shanghai Analytical Instrument Factory, China). Fresh medium (5 mL) prewarmed at 37°C was added into the dissolution medium after each sampling to maintain its constant volume throughout the test. Dissolution studies were performed in triplicate, and calculated mean values of cumulative drug release were used while plotting the release curves.

The similarity factor (f_2) was evaluated to compare DIP release profiles.

$$f_2 = 50 \log\{[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\}$$

where R_t and T_t were the cumulative percentage of drug released for reference and test assay at time t respectively, n was the number of time points. The FDA suggests that two dissolution profiles are declared to be similar if the value of f_2 is between 50 and 100 (Moore & Flanner, 1996; Peh & Wong, 2000).

Flowability of Solid Dispersion Powder

About 100 g of each kind of SDs samples were placed in SOTAX FT300 powder flowability tester (SOTAX, Switzerland) to determine the angle of repose of powder to evaluate their flowability. To evaluate the flow property of powder, the bulk and tapped density were also measured, and Carr's Flowability Index (Carr's Index) (Carr, 1965) was calculated according to the following relationship to:

$$\text{Carr's Index} = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

where ρ_b was the bulk density, ρ_t was the tapped density. 100 mL of each powder was placed in a 250 mL measuring cylinder. Then the weight of 100 mL of solid dispersion powder was determined and the bulk density (ρ_b) was calculated thereafter. The measuring cylinder was tapped manually by falling freely from 1-cm height until the volume of powder could not decrease any more, and the final volume was recorded to calculate the tapped density (ρ_t). The average of triplicate determinations was reported.

Hygroscopic Property of Solid Dispersion Powder

Approximately 0.4 g of powder particles were put into small dishes and dried. Then each dishes was placed in a desiccator containing a saturated solution of NaCl (75% relative humidity, 25°C). The total weight of every sample and corresponding dish were accurately weighed using an electronic balance (AE240, METTLER, Switzerland) at 0, 1, 2, 3, 4, 5, 6 days, and the moisture absorption percentages at each sampling time were calculated to plot the hygroscopic curves of SDs powders. Results were the mean values of three determinations.

Tabletting and Determination of Tensile Strength of Tablets

The SDs CoPVP 1/1, 1/2, 1/3, 1/5 mixed with 0.5% w/w magnesium stearate as lubricant, respectively, was directly compressed to tablets (200 mg) by a tablet machine (MiNi PRESS-IISF, Karnavati Engineering Ltd., India) equipped with a circular, 9 mm diameter flat-faced punch and die set. The compression force of every tablet was recorded. Ten of tablets were prepared at each pressure setting to obtain the average of tablet strength.

The tablets of SDs PVP 1/1, 1/2, 1/3, 1/5 were prepared by the same method described above.

The crushing strength was determined by measuring the load force to fracture the compacts across the diameter using a universal materials testing machine (Model 5569, Instron) at a compression rate of 10 mm/min. The tablet dimensions were

determined by a vernier caliper (Shanghai measurement tools factory, Shanghai, China). Tensile strength of tablets was calculated from the formula:

$$\text{Tensile strength} = \frac{2P}{\pi DL}$$

where P is the crushing load, D is the tablet diameter, and L is its thickness.

RESULTS AND DISCUSSION

X-Ray Diffraction

The XRD patterns of pure DIP, CoPVP, SDs CoPVP and PM CoPVP were shown in Figure 2, compared with those of PVP and corresponding SDs PVP or PM PVP. The powder X-ray diffractogram of pure DIP from 5 to 60° 2θ (Figure 2a) showed numerous distinctive peaks indicating a high crystallinity. There was no diffraction peaks in the XRD diagrams of either CoPVP or PVP as shown in Figure 2g and f, demonstrating that both these two polymers were amorphous powder. The

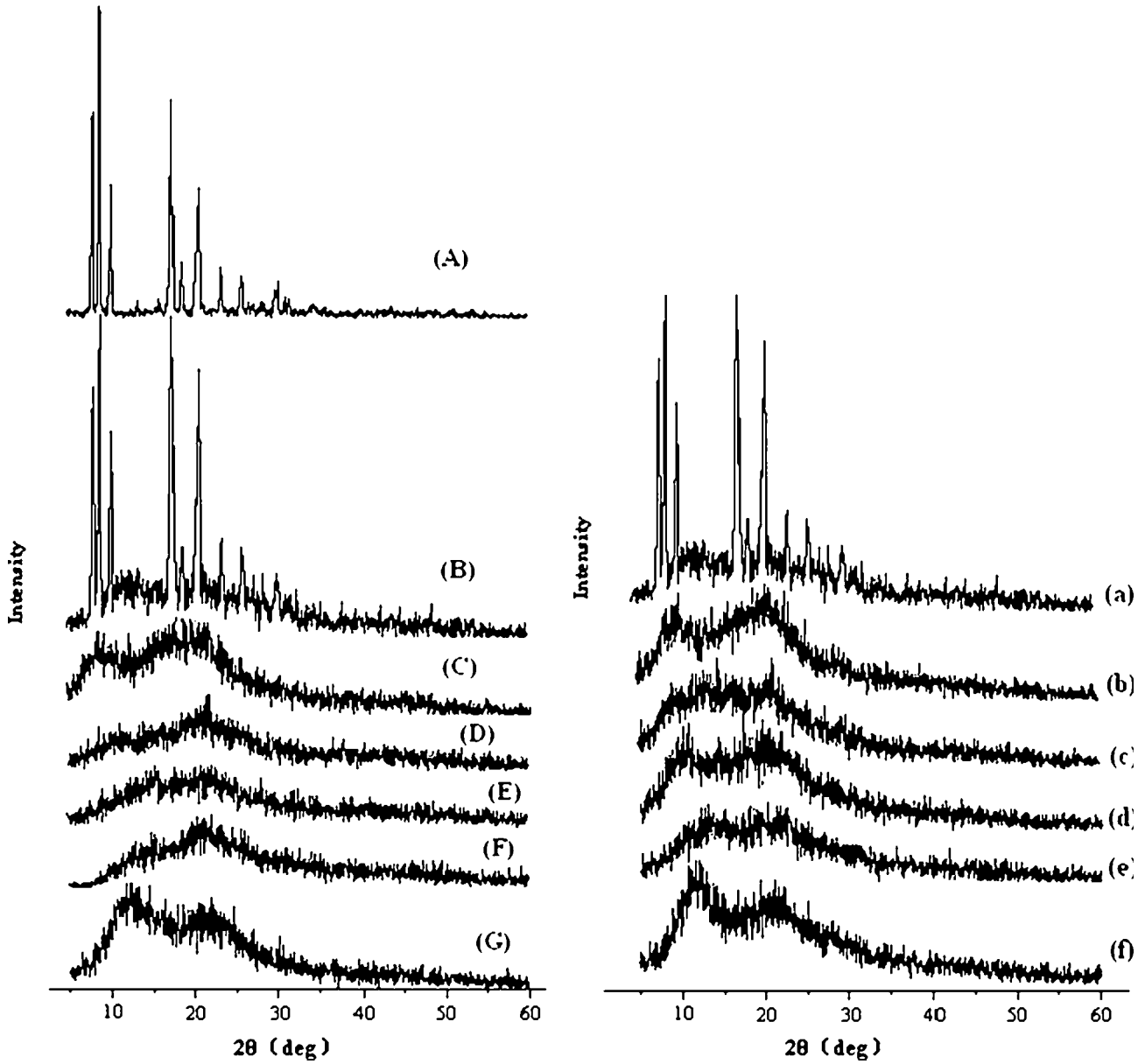

FIGURE 2. X-ray diffraction patterns of: (A) Pure DIP; (B) PM CoPVP 1/1; (C) SDs CoPVP 1/1; (D) SDs CoPVP 1/2; (E) SDs CoPVP 1/3; (F) SDs CoPVP 1/5; (G) CoPVP; (a) PM PVP 1/1; (b) SDs PVP 1/1; (c) SDs PVP 1/2; (d) SDs PVP 1/3; (e) SDs PVP 1/5; (f) PVP.

characteristic peaks of crystalline DIP were detectable in the XRD diagram of PM CoPVP 1/1, indicating that the crystallinity of DIP had not change (Figure 2b). On the other hand, SDs CoPVP showed the absence of diffraction peaks pointing to the loss of crystallinity as a consequence of the preparation procedure (Figure 2c–F). However, if the content of crystalline was under 5–10%, it can not be generally detected with XRD (Leuner & Dressman, 2000).

The characteristic peaks of crystalline DIP were also observed in the XRD pattern of PM PVP 1/1 as shown in Figure 2a, while they were not found in the XRD diagram of SDs PVP at various ratios (Figure 2b–e). These results indicated that DIP existed in crystalline form in PM PVP and in amorphous state in SDs PVP at various ratios. These results of XRD patterns were similar to those of SDs CoPVP due to possible similar intermolecular-interaction mechanism which was stated by FT-IR spectra in the Section 3.3.

Some reports proposed that PVP might inhibit the association of the drug molecule to form the crystal nucleus and inhibit the crystal growth; and the interaction of drug and PVP should be the inhibitory or retardatory factor in the crystallization (Sekikawa et al., 1978; Tantishaiyakul et al., 1996). In this study, CoPVP might have the same effects as PVP in the SDs. The interaction between DIP and CoPVP present in the SDs CoPVP at various ratios inhibited the formation of crystal nucleus and the crystal growth. As a result, the crystalline structure of DIP in the SDs CoPVP was transformed to the form of amorphism.

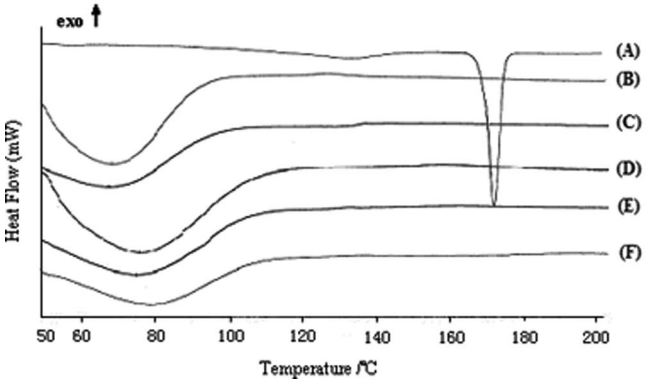

FIGURE 3. Thermograms of DSC of: (A) Pure DIP; (B) SDs CoPVP 1/1; (C) SDs CoPVP 1/2; (D) SDs CoPVP 1/3; (E) SDs CoPVP 1/5; (F) CoPVP.

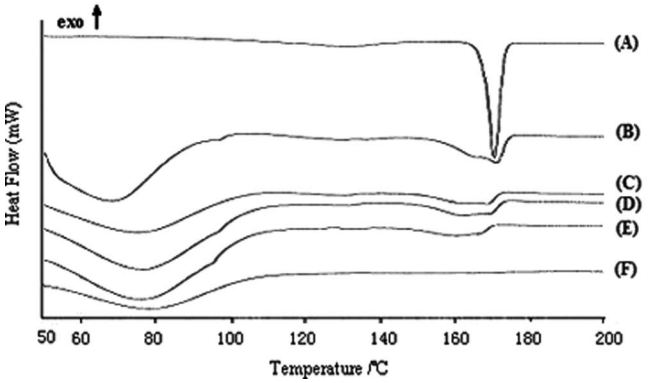

FIGURE 4. Thermograms of DSC of: (A) Pure DIP; (B) PM CoPVP 1/1; (C) PM CoPVP 1/2; (D) PM CoPVP 1/3; (E) PM CoPVP 1/5; (F) CoPVP.

Differential Scanning Calorimetry

DSC enabled the quantitative detection of all processes in which energy was required or produced (i.e., endothermic and exothermic phase transformations). Lack of a melting peak in the DSC of a solid dispersion indicated that the drug presented in an amorphous rather than a crystalline form.

The DSC thermograms of DIP, CoPVP, SDs CoPVP and PM CoPVP at various ratios were shown in Figures 3 and 4. The DSC curve of pure DIP showed an endothermic peak at about 166.8°C corresponding to the melting point of the drug (Figures 3a or 4a). The melting endothermic peak of DIP disappeared in SDs CoPVP at various ratios (Figure 3b–e). This result indicated that DIP in SDs presented in the amorphous state and explained why no diffraction peaks were observed during X-ray diffraction. Whereas in the DSC thermograms of PM CoPVP, the endothermic peaks corresponding to the melting point of DIP could be observed and the intensity of melting peaks decreased with lowering amount of the drug in the binary mixtures (Figure 4'b–e), demonstrating that the crystalline form DIP did not change in PM CoPVP at various ratios. Based on the DSC thermograms of both SDs CoPVP and PM CoPVP, broad endothermic peaks between about 60 and 120°C could be observed. This phenomenon may be explained that the residual solvent and absorbed water in the samples evaporated when heated and as a consequence of the production of broad endothermic peaks during the evaporation process (Marín et al., 2002; Van den Mooter et al., 2006).

The similar results of the DSC thermograms of SDs PVP and PM PVP as shown in Figures 5 and 6 indicated that DIP present in form of crystalline structure in PM PVP while in the amorphous form in SDs PVP.

Fourier Transform Infrared Spectroscopy

FT-IR studies were performed to detect the possible interactions between DIP and polymeric carrier in the SDs leading to amorphous state of DIP. Figure 7 showed the FT-IR spectra of DIP, CoPVP, SDs CoPVP, and PM CoPVP, compared with those of SDs PVP and PM PVP. FTIR spectra of DIP showed the O–H stretching vibration at 3377 and 3303 cm^{-1} (Figure 7a). And this region of interest could produce the interaction between DIP and polymeric carrier via intermolecular hydrogen bonding between the > N– or C=O functions on pyrrolidone moiety with the hydroxyl (O–H) group of DIP. However, steric hindrance precluded the involvement of nitrogen atom in

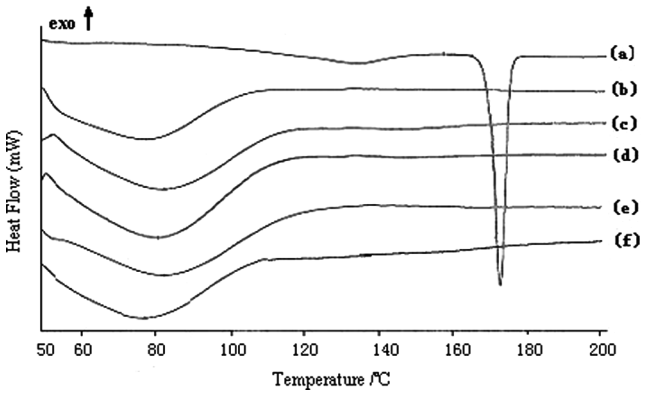

FIGURE 5. Thermograms of DSC of: (a) Pure DIP; (b) PVP; (c) SDs PVP 1/1; (d) SDs PVP 1/2; (e) SDs PVP 1/3; (f) SDs PVP 1/5.

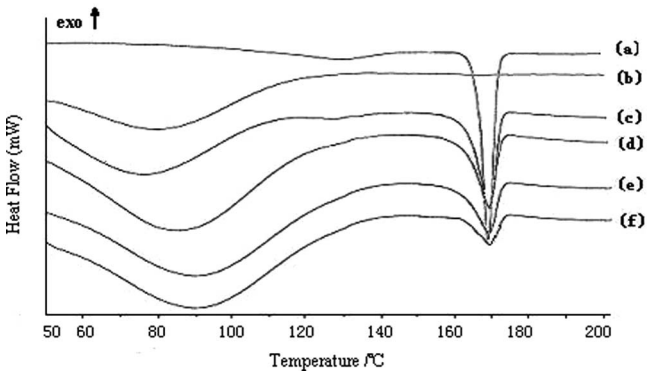

FIGURE 6. Thermograms of DSC of: (a) Pure DIP; (b) PVP; (c) PM PVP 1/1; (d) PM PVP 1/2; (e) PM PVP 1/3; (f) PM PVP 1/5.

intermolecular interactions, thus making the carbonyl group more favorable for hydrogen bonding (Taylor & Zografi, 1997).

The FT-IR spectra of CoPVP displayed important peaks at 2960 cm^{-1} (C–H stretch), 1738 cm^{-1} carbonyl (–N–CO–R vibration) group, 1658 cm^{-1} carbonyl (–O–CO–R vibration) group (Figure 7g). A very broad band was also visible at 3400–3600 cm^{-1} and it was probably due to the presence of water (Sethia & Squillante, 2004; Van den Mooter et al., 1998) confirming the broad endothermic peak detected in the DSC experiments. In spite of this broad peak, the FTIR spectra of PM CoPVP 1/1 still showed peaks of O–H stretching vibration of DIP at about 3377 and 3303 cm^{-1} (Figure 7b). The FT-IR spectra of PM CoPVP 1/1 seemed to be only a summation of DIP and CoPVP spectra. It reflected that there was no interaction between DIP and CoPVP in PM CoPVP 1/1. And DIP still maintained its crystallinity as observed in the DSC thermograms. These were also consistent with the results obtained by XRD studies.

However, the O–H stretching vibration of DIP at about 3377 and 3303 cm^{-1} was not detected in SDs CoPVP 1/1, 1/2, 1/3 (Figure 7c–e) and almost disappeared in SDs CoPVP 1/5 (Figure 7f). It was attributed to the presence of the intermolecular hydrogen bonds which caused the O–H stretching vibration to weaken. This led to the production of a weak and broad peak that was completely covered by broad bond stretches of CoPVP (Porubcan, 1978). The new chemical bonds and strong complexation (hydrogen bonding) could alter the crystalline structure of drug, resulting in a changed XRD pattern. The hydrogen bonding interaction between DIP and CoPVP in SDs might cause changes in DIP crystalline structure which could be reflected in different XRD patterns of SDs from that of DIP alone. Therefore, the amorphousness of DIP within carriers might be predicted in DIP dispersions by the disappearance of the O–H peaks in the FT-IR spectra of DIP.

The important peaks of PVP in FT-IR spectra were 2955 cm^{-1} (C–H stretch) and 1657 cm^{-1} (C=O) as shown in Figure 7g. From the FTIR spectra of PM PVP 1/1 (Figure 7b) and SDs PVP at various ratios (Figure 7c–f), the same conclusion could be drew that there was no interaction between DIP and PVP in PM PVP 1/1. The presence of the intermolecular hydrogen bonds in the SDs PVP caused the O–H stretching vibration of DIP to be weakened. This resulted in a weak and broad peak that was completely covered by broad bond stretches from PVP.

Though there were some differences between the chemical structures of these two kinds of polymer carriers (Figure 1 [1] and [2]), the chemical bonds generated between DIP and CoPVP were similar to those between DIP and PVP. This phenomenon could be explained that both the carbonyl groups (–N–CO–R and –O–CO–R) of CoPVP (Figure 1 [1]) and the carbonyl groups (–N–CO–R) of PVP (Figure 1 [2]) were hydrogen-bond receptors and the hydroxyl groups of DIP acted as the hydrogen-bond donors when the intermolecular interactions generated between DIP and each kind of polymer carriers, i.e., the formation of hydrogen bonds due to the interactions between the similar chemical groups. Therefore, the groups participated in the intermolecular interactions were similar and resulted in the similar chemical bonds formed between DIP and each kind of carriers. Furthermore, the chemical bonds between DIP and polymer carriers could change the crystalline structures of DIP in SDs and this was also confirmed by the similar XRD patterns and DSC diagrams of SDs.

Microscopy Study

Polarizing microscopic photographs of DIP, CoPVP, SDs CoPVP 1/2 and PM CoPVP 1/2 were shown in Figure 8, compared with those of PVP, SDs PVP 1/2 and PM PVP 1/2. The DIP rodlike crystal structure was observed from the micrograph magnified 50 times, while the microstructure photograph of CoPVP was shown as loosened spherical particles aggregates. The photograph of PM CoPVP 1/2 showed only the summation of DIP crystals and CoPVP particles, whereas the micrograph of SDs CoPVP 1/2 showed the platy and transparent solid structure which was completely different from PM

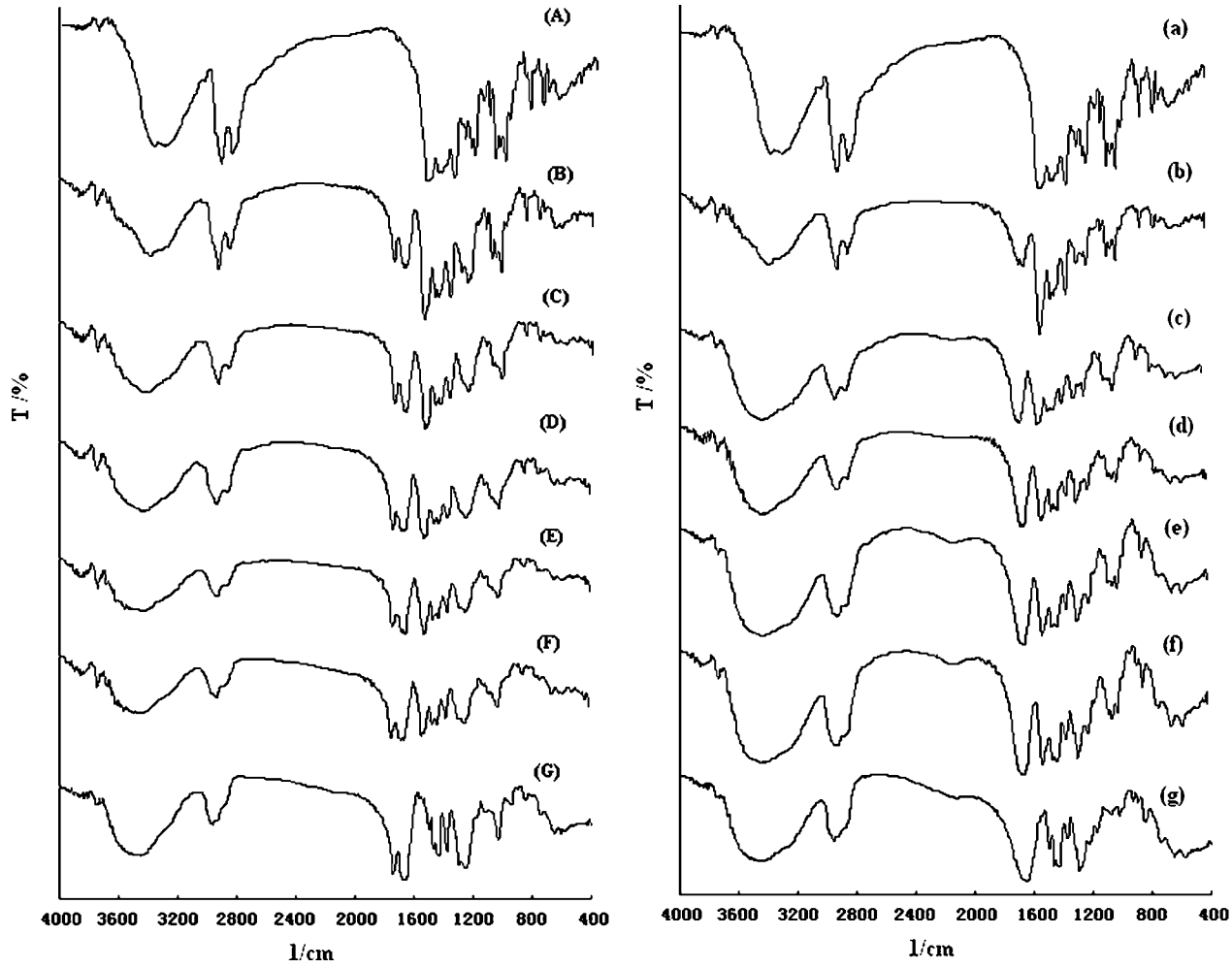

FIGURE 7. FTIR Spectra of : (A) Pure DIP; (B) PM CoPVP 1/1; (C) SDs CoPVP 1/1; (D) SDs CoPVP 1/2; (E) SDs CoPVP 1/3; (F) SDs CoPVP 1/5; (G) CoPVP; (a) Pure DIP; (b) PM PVP 1/1; (c) SDs PVP 1/1; (d) SDs PVP 1/2; (e) SDs PVP 1/3; (f) SDs PVP 1/5; (g) PVP.

CoPVP 1/2 or DIP alone. This indicated that a kind of new structure formed in SDs CoPVP.

The micrograph of PVP was shown as spherical particles like CoPVP. The photographs of PM PVP 1/2 showed only the summation of DIP crystals and PVP particles, whereas the micrographs of SDs PVP 1/2 also showed the platy and transparent solid structure like the microstructure of SDs CoPVP 1/2.

The similar microscopic photographs of SDs might be attributed to the similar intermolecular interaction between DIP and each kind of carrier which was confirmed in the XRD, DSC and FTIR studies.

Drug Solubility

The solubility of DIP in phosphate buffer solution (pH 6.8) from pure drug, SDs and PMs at different weight ratios was shown in Table 1. It could be noted from this table that the drug solubility was enhanced as the polymer content in the samples increased. This phenomenon could be ascribed in the PMs to a higher wettability of drug in presence of CoPVP. In the SDs, it was due to a highly dispersed state of the drug. The solubility of DIP in SDs CoPVP at various ratios was much greater than those of DIP alone and in PM CoPVP. These results could be explained that the reduction in crystallinity of DIP led to a decrease of the energy required in the dissolving process and also to a highly dispersed state of the drug in SDs. The latter resulted in the local increase in the solubility and maximizing the surface area of the drug that came in contact with the dissolution medium as the carrier dissolved. From the solubility data as shown in Table 1, it could be also found that the solubility of DIP in PM CoPVP at various ratios was higher than drug alone. The solubility of DIP in PM CoPVP 1/1, 1/2, 1/3, 1/5 was about 8.5-, 22.4-, 36.9- and 41.9-fold of pure DIP, respectively. This might due to the surface tension lowering effect of polymer to the medium, resulting in wetting of hydrophobic DIP crystalline surface.

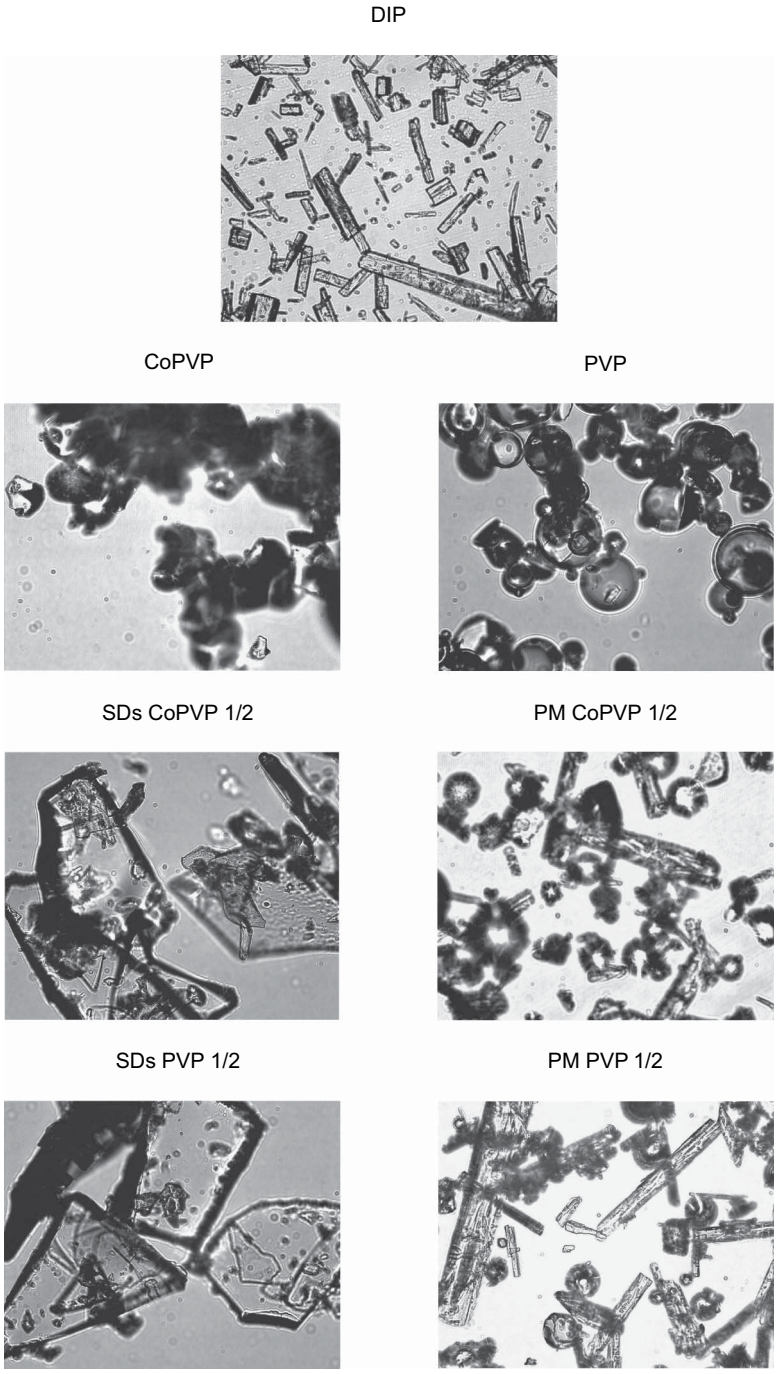

FIGURE 8. Photographs of DIP, CoPVP, PVP and Relate materials (weight ratio of DIP: polymer = 1:2). (Polarizing microscope, 50 ×).

As shown in Table 1, the solubilitiy of DIP in SDs PVP 1/1, 1/2, 1/3, 1/5 had about 10.2-, 17.0-, 20.7-, and 33.7-fold of pure DIP, respectively. The solubility of DIP in PM PVP 1/1, 1/2, 1/3, 1/5 was about 7.9-, 14.0-, 17.6-, and 27.5-fold of pure DIP, respectively. And the solubility of DIP in various SDs was greater than those of DIP alone and in PMs for each kind of polymer in the samples, while the solubility of DIP in PM PVP at various ratios was higher than drug alone. Similarly, these results could be explained that the highly dispersed state of DIP in the SDs and the wettability of polymer in presence of PVP in PMs.

Furthermore, it was found that there were statistically significant differences ($P < 0.05$) between the solubility of DIP in SDs CoPVP and that of DIP in SDs PVP by the comparison of

TABLE 1
Solubilities of Pure DIP and in SDs or PMs in Phosphate Buffer Solution (pH 6.8). (mean ± *SD*, *n* = 6)

	Solubility (μg/ml) DIP to Carriers Weight Ratio				
	–	1:1	1:2	1:3	1:5
DIP	2.01 ± 0.18	–	–	–	–
SDs CoPVP	–	30.22 ± 0.21*	55.13 ± 0.70*	80.79 ± 1.62*	128.91 ± 0.79*
SDs PVP	–	20.49 ± 0.42	34.16 ± 0.73	41.46 ± 1.02	67.49 ± 1.52
PM CoPVP	–	16.93 ± 0.27	44.83 ± 0.13	53.67 ± 1.52	83.72 ± 1.69
PM PVP	–	15.67 ± 0.53	28.16 ± 0.47	35.28 ± 0.92	54.94 ± 0.88

*indicated that there was statistically significant difference ($P < 0.05$) in comparison of the solubility of DIP in SDs CoPVP and that in PM CoPVP at the same weight ratio.

the average values obtained (Table 1). This phenomenon was probably attributed to a higher wettability of CoPVP than that of PVP. In the structure of CoPVP, the addition of vinyl acetate groups to the vinylpyrrolidone polymer chain lowered hydrophilicity relative to PVP homopolymer, but it made CoPVP copolymer perform as a polymeric surfactant which allowed it much greater wetting characteristics than PVP. The difference of molecular structures between CoPVP copolymer and PVP homopolymer resulted in the difference of surface activity of the polymers and ultimately caused the difference of wettability of polymers. The wettability of polymers was of great benefit to the solution of drug from SDs in the media. The solubility of DIP in PM CoPVP was also significantly higher than that of DIP in PM PVP. It could also be explained that CoPVP was of higher wettability than PVP due to the molecular structure difference of these two kinds of polymers as described above.

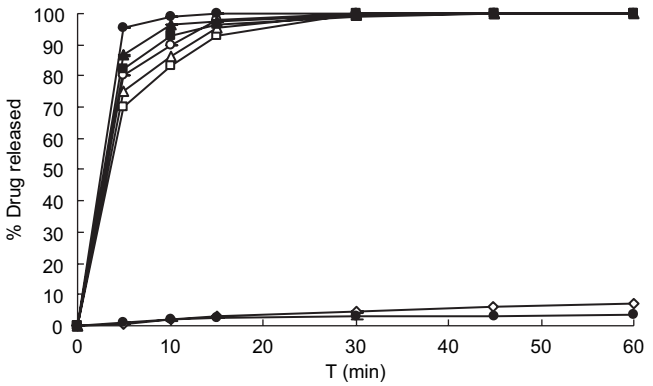

FIGURE 9. Dissolution Profiles of SDs CoPVP and SDs PVP at Various Ratios. Key: (□) SDs CoPVP 1/1; (■) SDs CoPVP 1/2; (▲) SDs CoPVP 1/3; (●) SDs CoPVP 1/5; (◇) SDs PVP 1/1; (▫) SDs PVP 1/2; (▯) SDs PVP 1/3; (○) SDs PVP 1/5.

Dissolution Study

Dissolution profiles of DIP from SDs CoPVP at various ratios were shown in Figure 9. The cumulative release percentages of DIP from SDs CoPVP 1/2, 1/3, 1/5 were close to 100% within 30 min. Possible mechanisms of increased dissolution rates of SDs had been proposed by Ford (Ford, 1986) and include: reduction of crystal size, a solubilization effect of the carrier, absence of aggregation of drug crystals, improved wettability, dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, conversion of drug to amorphous state, and finally, the combination of the abovementioned methods.

However, the drug release percentage of SDs CoPVP 1/1 was not over 10% within 60 min. This phenomenon was probably due to the part presence of the crystal form of DIP in the SDs CoPVP 1/1, which could not be detected by XRD. If the content of crystal was under 5–10%, it can not generally be detected with XRD (Leuner & Dressman, 2000) and DSC thermograms. Therefore, this result could be explained that a lot of energy was required to break up the structure of crystal during the dissolution process of DIP present completely or partly in the form of crystal. According to the results above, in order to obtain the correct information of SDs, when the solid state of SDs was discussed, all of the XRD patterns, DSC thermograms, FT-IR spectra and dissolution behaviors should be systematically analyzed.

The drug cumulative release percentages from PM CoPVP at various ratios and pure drug powder were not over 10% within 60 min, as Figure 10 shown. This could be explained that DIP in the PM CoPVP was not a molecularly dispersed system and the drug presented in a crystal form. When DIP in the form of crystal dissolved, much energy was required to break up the crystal structure of DIP. Therefore, the cumulative release percentages of pure DIP and PM CoPVP were significantly lower than those of DIP in SDs CoPVP.

The drug release behaviors of SDs PVP and PM PVP were observed from Figure 9 and Figure 10, respectively. The cumulative release percentages of DIP from SDs PVP 1/2, 1/3, 1/5 were near to 100% within 30 min, while the release percentages of SDs PVP 1/1 were not yet over 10% within 60 min probably due to be partly present in the crystal form of DIP in

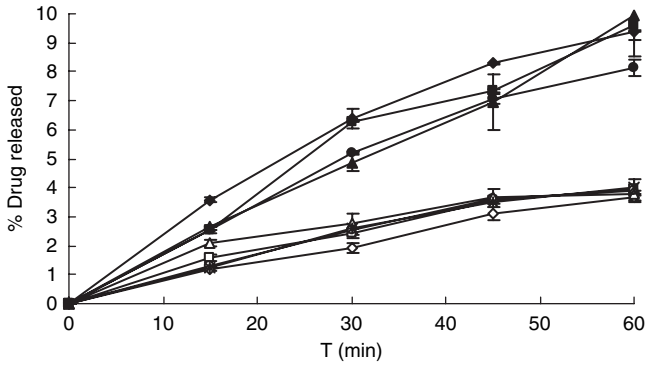

FIGURE 10. Dissolution Profiles of Pure DIP, PMs of DIP and CoPVP or PVP. Key: (□) PM CoPVP 1/1; (■) PM CoPVP 1/2; (▲) PM CoPVP 1/3; (●) PM CoPVP 1/5; (◇) PM PVP 1/1; (▫) PM PVP 1/2; (▯) PM PVP 1/3; (○) PM PVP 1/5.

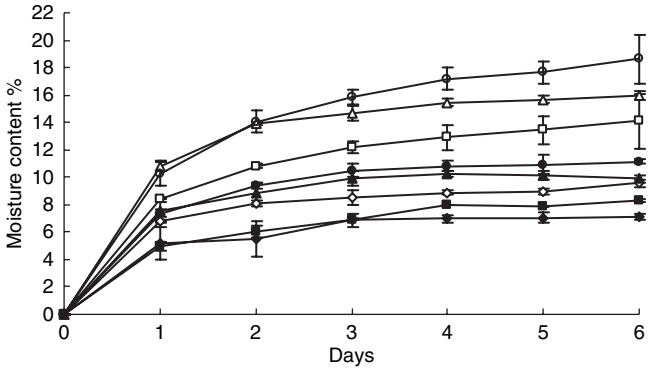

FIGURE 11. Hygroscopicity Profiles of SDs CoPVP and SDs PVP Powders. Key: (□) SDs CoPVP 1/1; (■) SDs CoPVP 1/2; (▲) SDs CoPVP 1/3; (●) SDs CoPVP 1/5; (◇) SDs PVP 1/1; (▫) SDs PVP 1/2; (▯) SDs PVP 1/3; (○) SDs PVP 1/5.

the SDs PVP 1/1. The drug cumulative release percentages from PM PVP were not over 10% within 60 min, as Figure 10 showed.

The dissolution of SDs CoPVP was similar to those of SDs PVP at the same weight ratio ($f_2 > 50$). And the DIP dissolution rates of PM PVP 1/1, 1/2, 1/3, 1/5 were similar to those of pure DIP and PM CoPVP 1/1, 1/2, 1/3, 1/5 ($f_2 > 50$).

Hygroscopic Property of Solid Dispersions Powder

Hygroscopic property was the intrinsic tendency of a material to absorb moisture from its surroundings. The stability of drug in SDs could probably be affected by the hygroscopicity of SDs powder during the process of storage. Therefore, it was necessary to decrease the hygroscopicity of SDs powder as far as possible in order to maintain the stability of drug in SDs. To reduce the moisture absorption of SDs powder, it was very important to choose the polymer carrier with lower hygroscopic property in the preparation of SDs.

The hygroscopic property of SDs CoPVP powder was investigated in RH 75%, 25°C surrounding, compared with that of SDs PVP at various ratios (Figure 11). It was found that the final uptake of moisture was increased with the increase of the proportion of carriers containing in the SDs. This result suggested that the hygroscopic property of carriers added in SDs was a critical factor during the process of the moisture uptake of SDs powder.

Figure 11 showed that the water uptake percentages of SDs CoPVP were always lower than those of SDs PVP at the same weight ratio of DIP and carriers. This result was possibly attributed to the difference between the chemical structures of two kinds of carriers. For the structure of CoPVP, the addition of vinyl acetate groups to the vinylpyrrolidone polymer chain lowered hydrophilicity relative to PVP homopolymer and therefore, the hygroscopic of CoPVP were lower than that of PVP. As a result, the hygroscopic of SDs CoPVP was less than that of SDs PVP. And the decrease of hygroscopic of SDs powder would be of more advantage to the stability of drug in the SDs or the final pharmaceuticals.

Flow Properties of Solid Dispersions Powder

The flow properties of powders were very important for direct compression. The flowability of solid dispersion powder was evaluated by angle of repose and the Carr's Index value. The flowability of SDs CoPVP powder was similar to that of SDs PVP (Table 2). Since powder with an angle of repose less than 45° was suitable for direct compression (Wadke et al., 1989), both SDs CoPVP and SDs PVP powder were suitable for direct compression.

The Carr's Index value was an important parameter to evaluate the flowability of powder. The results indicated that these SDs powders showed the favorable flow properties and they were easy manufactured by direct compression. This was consistent with the measurement result of angle of repose of powders.

Compressibility of Solid Dispersions Powder

The tensile strengths of tablets of SDs CoPVP 1/1, 1/2, 1/3, 1/5 were determined at various pressure settings, compared with those of tablets of SDs PVP 1/1, 1/2, 1/3, 1/5 (Figure 12). The tensile strengths of tablets were slightly increased with the higher polymer content in SDs. This was probably explained that the compressibility of drug was of less effect on the tensile strengths of tablets. It was also found that the tensile strengths of tablets made up of SDs CoPVP at various ratios were always higher than those of tablets of SDs PVP at the same compression pressure. This indicated that the SDs CoPVP powder had relatively better compressibility than the SDs PVP powder. This result could be explained that the chemical structure difference between CoPVP and PVP caused the difference of

TABLE 2
Parameters Described the Flowability of Solid Dispersion Powder. (mean ± *SD*, *n* = 6)

	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index %	Angle Repose
SDs PVP 1/1	0.2798 ± 0.0036	0.4258 ± 0.0091	34.2857 ± 0.0115	36.3819 ± 4.1035
SDs PVP 1/2	0.3145 ± 0.0074	0.4477 ± 0.0005	29.7503 ± 0.0122	40.1813 ± 0.3626
SDs PVP 1/3	0.3728 ± 0.0129	0.5761 ± 0.0253	35.2941 ± 0.1012	38.2450 ± 1.1998
SDs PVP 1/5	0.3712 ± 0.0329	0.5556 ± 0.0801	33.1818 ± 0.1325	32.4556 ± 0.3538
SDs CoPVP 1/1	0.3733 ± 0.0124	0.5194 ± 0.0034	28.1250 ± 0.1088	31.8056 ± 0.0005
SDs CoPVP 1/2	0.2864 ± 0.0042	0.4296 ± 0.0097	29.4118 ± 0.0901	35.8365 ± 0.4426
SDs CoPVP 1/3	0.4027 ± 0.0620	0.5448 ± 0.0454	26.0870 ± 0.1287	38.4190 ± 0.3348
SDs CoPVP 1/5	0.2857 ± 0.0201	0.3999 ± 0.0341	28.5714 ± 0.1212	35.0091 ± 0.0012

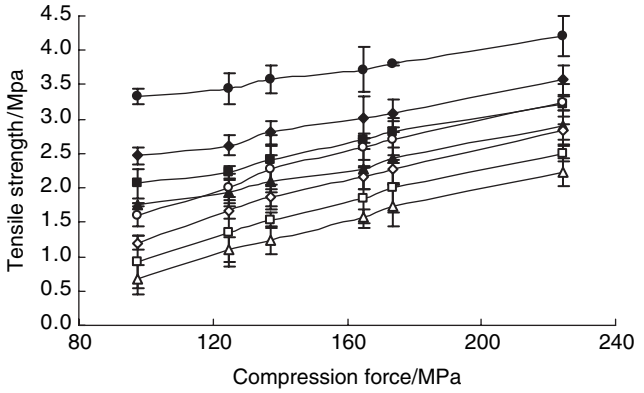

FIGURE 12. Relationship Between Compaction Pressure and Tensile Strength of Tablets Made up of Two Kinds of Solid Dispersion Powder. Key: (▲) SDs CoPVP 1/1; (■) SDs CoPVP 1/2; (□) SDs CoPVP 1/3; (•) SDs CoPVP 1/5; (◇) SDs PVP 1/1; (▫) SDs PVP 1/2; (▯) SDs PVP 1/3; (○) SDs PVP 1/5.

the compressibility of corresponding SDs. Because of the incorporating vinyl acetate into PVP polymers, the T_g of CoPVP copolymer was lower than that of PVP homopolymer. The lower T_g of CoPVP made it an excellent direct compression binder aid and allowed it to undergo plastic deformation during compression.

CONCLUSION

In this study, CoPVP copolymer was employed to prepare the SDs of DIP. The XRD, DSC, FT-IR spectroscopy and polarizing microscopy were performed to investigate the physicochemical characteristics of these samples. FT-IR analysis demonstrated the presence of the hydrogen bonding between DIP and CoPVP in the SDs CoPVP. DSC and XRD studies indicated that DIP in the SDs CoPVP presented in an amorphous state or very small amount of crystal which could not be detected by XRD. To elucidate the difference between the novel carrier CoPVP copolymer and conventional carrier PVP homopolymer, the physicochemical characteristics of SDs CoPVP were in comparison with those of SDs PVP. And the similar results for SDs PVP were given by FT-IR, DSC and XRD studies. The solubility of DIP of SDs CoPVP was higher than that of SDs PVP at the same weight ratio because the wettability of CoPVP copolymer was higher than that of PVP. The dissolution properties of SDs CoPVP of high drug-carrier ratios were faster than those of pure drug and PM CoPVP. The dissolution behavior of SDs CoPVP was similar to that of SDs PVP. Both SDs CoPVP and SDs PVP powder showed the favorable flowability and they were easily manufactured by direct compression. Meanwhile, the compressibility of SDs CoPVP was better than that of SDs PVP due to the lower T_g of CoPVP. And the hydroscopic property studies indicated that the hydroscopicity of SDs CoPVP was lower than that of SDs PVP because in the chemical structure of CoPVP, the addition of vinyl acetate groups to the vinylpyrrolidone polymer chain lowered hydrophilicity relative to PVP homopolymer and reduced the hydroscopic property of the vinylpyrrolidone. Therefore, copolyvidonum CoPVP is a good candidate for a carrier of solid dispersions. In particular, when the drug is sensitive to moisture, or when the compressibility of drug powder is not good, CoPVP may be a better material than PVP. On the other hand, the results in this study also demonstrated the importance of combining the information from the XRD patterns, DSC thermograms, FT-IR spectra and dissolution behaviors when the solid state of SDs was discussed.

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