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Properties of solid dispersions of piroxicam in polyvinylpyrrolidone K-30

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Abstract

Solid dispersions of varying ratios of piroxicam and polyvinylpyrrolidone (PVP) K-30 were prepared by solvent method in an effort to increase the dissolution rate of the drug. The properties of solid dispersions were characterized by Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction and differential scanning calorimetry. FTIR analysis demonstrated the presence of intermolecular hydrogen bonds between piroxicam and PVP in solid dispersions. Dissolution studies indicated that the dissolution rates were markedly increased in these solid dispersion systems compared with those in physical mixtures and pure drug. The increase in dissolution rate strongly depended on the ratio of drug to PVP. The drug: PVP 1:4 solid dispersion, the only ratio that was shown to be X-ray amorphous, gave the highest dissolution rate—about a 38-fold higher than that of pure drug.

Keywords: Solid dispersion; Piroxicam; Polyvinylpyrrolidone K-30; Fourier transform infrared spectroscopy; X-ray diffraction; Dissolution rate

1. Introduction

Piroxicam is one of the most potent non-steroidal anti-inflammatory drugs (NSAIDs) used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis (Insel, 1991). Piroxicam is poorly soluble in water; its dissolution rate might be increased using solid dispersion technology. As a water-soluble polymer, polyvinylpyrrolidone has been demonstrated to retard and inhibit the crystallization of drugs, giving amorphous solid dispersions with increased drug dissolution rates and solubilities (Ford, 1986a). The solid dispersions of piroxicam at different ratios of PVP K-30 were

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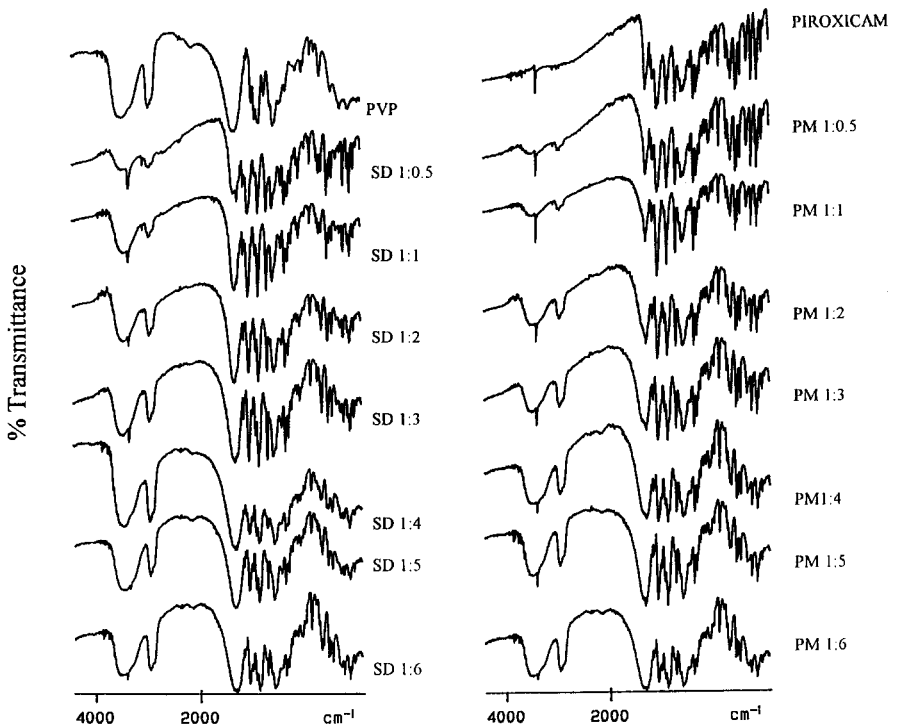

Fig. 1. FTIR spectra of piroxicam, PVP and solid dispersions (SD) and physical mixtures (PM) containing the 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 piroxicam: PVP weight ratios.

then prepared and investigated. We also explored the possible interaction between piroxicam and PVP K-30 using Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), and differential scanning calorimetry (DSC).

2. Materials and methods

2.1. Materials

Piroxicam (Vertex Chemicals, Hong-Kong) and polyvinylpyrrolidone (PVP) K-30 (Kollidon 30, BASF) were employed in this study. All other reagents were of analytical grade.

2.2. Solid dispersion preparation

Solid dispersions were prepared with drug:PVP in the 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 weight ratios by means of the solvent method. To a solution of piroxicam (1 g) in acetone (60 ml), was added the appropriate amount of PVP K-30. The minimum amount of methanol was added to solubilize the polymer. The solvents were removed under reduced pressures at 40°C and dried under vacuum at room temperature for 5 h. The samples were pulverized using a mortar and pestle, and the 0.05–0.25 mm particle size fractions were obtained by sieving.

Physical mixtures were prepared by manually mixing the appropriate amount of the 0.05–0.25 mm particle size fractions of piroxicam and PVP K-30.

2.3. Fourier transform infrared spectroscopy

Fourier transform IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer equipped with a DTSG detector. Samples were prepared in KBr discs. A polystyrene filter was used to check the spectrophotometer calibration.

2.4. X-ray diffraction

X-ray diffraction (XRD) patterns were obtained using a PW 3710 diffractometer (Philips) with CuK_{α} radiation, collimated by a 0.08° divergence slit and a 0.2° receiving slit and scanned at a rate of 2.4°/min over the 2θ range of 5–60°.

2.5. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was performed on a Perkin-Elmer DSC7. Samples (5–10 mg) were heated in hermetically sealed aluminium pans with a heating rate of 10°C/min under a nitrogen atmosphere (flow rate 20 ml/min).

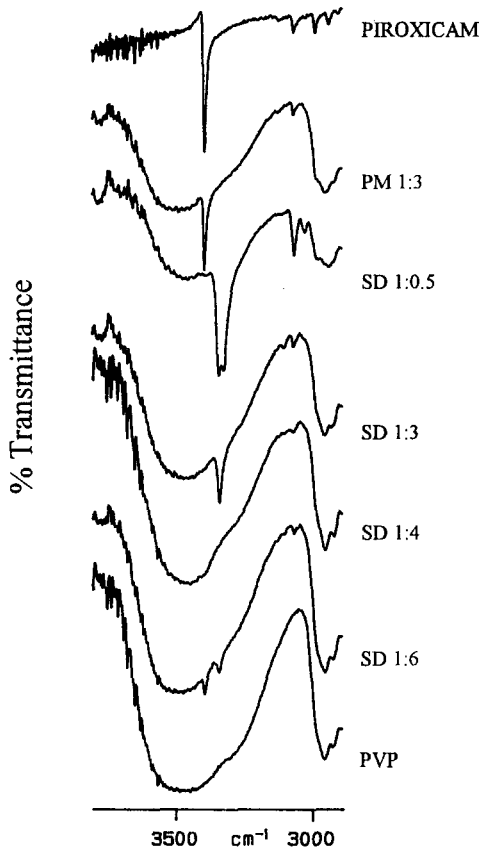

Fig. 2. FTIR spectra of piroxicam, PVP, physical mixture of drug: PVP 1:3 (PM1:3) and solid dispersions (SD) containing the 1:0.5, 1:3, 1:4 and 1:6 piroxicam: PVP weight ratios.

2.6. Dissolution studies

The dissolution medium consisted of 900 ml simulated gastric fluid TS prepared without pepsin (USP23 and NF18, 1994), maintained at 37 ± 0.5°C. Samples were tested with the dispersed amounts method (Kim et al., 1985) by placing 10 mg of piroxicam or its equivalent in solid dispersions or physical mixtures on the surface of the dissolution medium. A 5.0 ml aliquot was withdrawn at appropriate time intervals, filtered and replaced with 5 ml of fresh dissolution medium. The amount of piroxicam was determined spectrophotometrically at 334 nm without the interference from PVP. The piroxicam concentration was calculated and expressed as percent drug released from the mean of six determinations.

3. Results and discussion

3.1. Fourier transform infrared spectroscopy

Fourier transform IR spectra for piroxicam, PVP, solid dispersions and physical mixtures were shown in Fig. 1. Different polymorphic forms of piroxicam have been reported to exhibit different FTIR spectra. According to Mihalic (1986), the band of N–H and enolic O–H stretching of piroxicam lay at 3385 cm^{-1} for the needle forms and 3330 cm^{-1} for the cubic forms. These absorption bands were detected by Vrecer et al. (1991) to shift by 30 cm^{-1} to higher wavenumbers.

In the present study, the N–H or O–H stretching vibration of piroxicam occurred at 3391 cm^{-1}. The position and shape of this peak was not changed after treating piroxicam with acetone and methanol in the same procedure used for preparing solid dispersions. This result suggested that in the absence of PVP piroxicam remained in the same crystal structures.

Piroxicam structure might exist as mixtures of tautomeric keto, enol or zwitterionic forms (Kojic-Prodic and Ruzic-Toros, 1982). Due to the lack of a normal absorption of conjugated ketone in the FTIR spectrum recorded, piroxicam would be present as enol or zwitterionic forms.

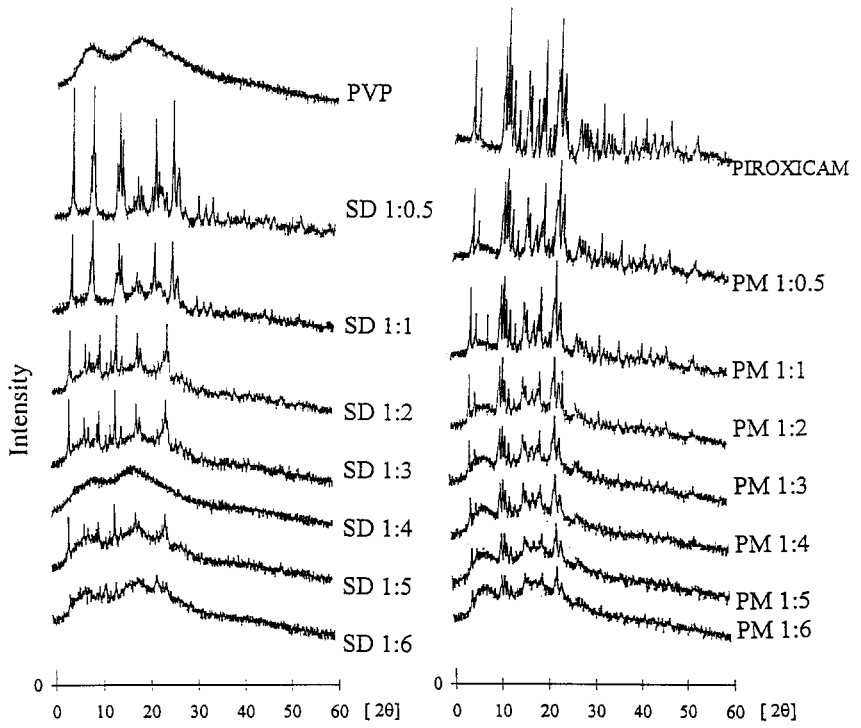

Fig. 3. X-ray diffraction patterns of piroxicam, PVP and solid dispersions (SD) and physical mixtures (PM) containing the 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 piroxicam: PVP weight ratios.

Solid dispersions and physical mixtures showed slightly different FTIR spectra in the fingerprint regions, the substantial differences were shown in the N–H or O–H stretching regions. This region was expanded to show differences between the spectra in Fig. 2. The largest spectral differences in this region were also reported for polymorphs of some compounds which reflected the different hydrogen bonding networks (Threlfall, 1995). Each pyrrolidone moiety of PVP has two groups (>N- and C=O) that can potentially hydrogen bond with the amide (N–H) group or protonated pyridine N atom of piroxicam. In spite of the broad peak at about 3048–3718 cm^{-1} from PVP, the FTIR spectra of all physical mixtures still showed small peaks of N–H or O–H stretching vibrations at the same position as that of piroxicam (Figs. 1 and 2). The FTIR spectra of physical mixtures seemed to be only the summation of piroxicam and PVP spectra. This result suggested that there was no interaction between piroxicam and PVP in physical mixtures.

The N–H or O–H stretching vibrations were also observed in the FTIR spectra of solid dispersions as shown in Figs. 1 and 2. However, the FTIR spectra in this region were different from those of physical mixtures and piroxicam. The drug: PVP 1:0.5 and 1:1 showed doublets at 3341 and 3322 cm^{-1}. The single absorption bands at 3337 cm^{-1} were observed in the FTIR spectra of the drug: PVP 1:2, 1:3 and 1:5. The drug:PVP 1:6 gave two absorption bands at 3391 and 3337 cm^{-1}. Interestingly, the drug:PVP 1:4 solid dispersion which showed to be X-ray amorphous (Fig. 3), gave no peak of this N–H or O–H stretching vibration. Comparing with piroxicam and physical mixtures, these peaks for solid dispersions were shifted toward lower wavenumbers, indicating the presence of intermolecular hydrogen bonds between piroxicam and PVP. Different ratios of drug to PVP showed different FTIR

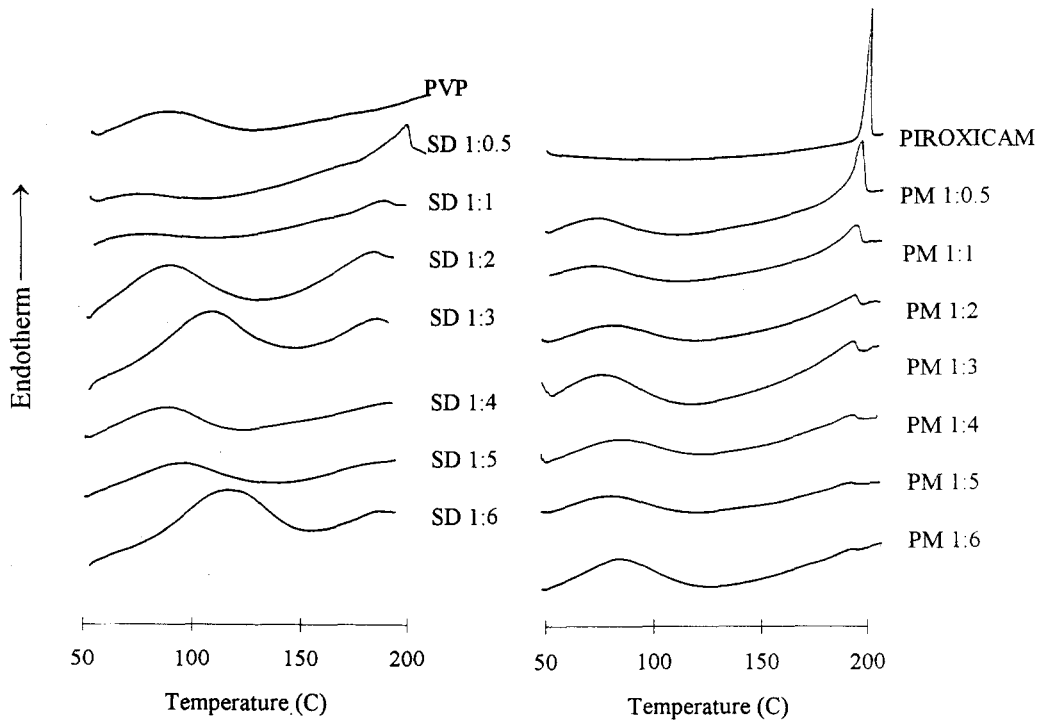

Fig. 4. DSC curves of piroxicam, PVP, and solid dispersions (SD) and physical mixtures (PM) containing the 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 piroxicam: PVP weight ratios.

patterns, suggesting that hydrogen bond systems might be different in these solid dispersions. In the case of the drug: PVP 1:4 solid dispersion, intermolecular hydrogen bond might be stronger than the others, therefore the N–H or O–H stretching might be weakened, resulting in a weak and broad peak that was completely covered by bond stretches from PVP. This FTIR pattern was previously observed for the N–H stretching of the amorphous furosemide-PVP solid dispersion (Doherty and York, 1987). The drug: PVP 1:6 solid dispersion yielded another peak at 3391 cm^{-1}, the same wavenumber for N–H or O–H stretching of pure piroxicam, suggesting that there might be some portion of piroxicam that did not interact with PVP.

3.2. X-ray diffraction

XRD patterns for piroxicam, physical mixtures, solid dispersions and PVP were shown in Fig. 3. PVP is an amorphous powder having no-crystalline structure. Characteristic peaks of piroxicam appeared at a diffraction angle of 2θ, at 8.99, 15.76, 23.02 and 25.85°. These values were comparable to those reported for needle form of piroxicam (Mihalic, 1986) (9.18, 15.78, 22.85, and 25.22°). The XRD pattern of piroxicam was similar to those of physical mixtures indicating that the crystallinity of piroxicam did not change in the physical mixtures. This was consistent with the results obtained by FTIR studies.

The XRD patterns of solid dispersions were different from those of piroxicam and physical mixtures (Fig. 3). The XRD patterns for the drug: PVP 1:0.5 and 1:1 solid dispersions were similar but different from those for the other solid dispersions. The drug: PVP 1:2, 1:3 and 1:5 yielded the same XRD patterns, indicating the same crystal structures of piroxicam in these solid dispersions.

No detectable diffraction peak was observed for the drug: PVP 1:4 solid dispersion, indicating the presence of the drug in an amorphous form. The

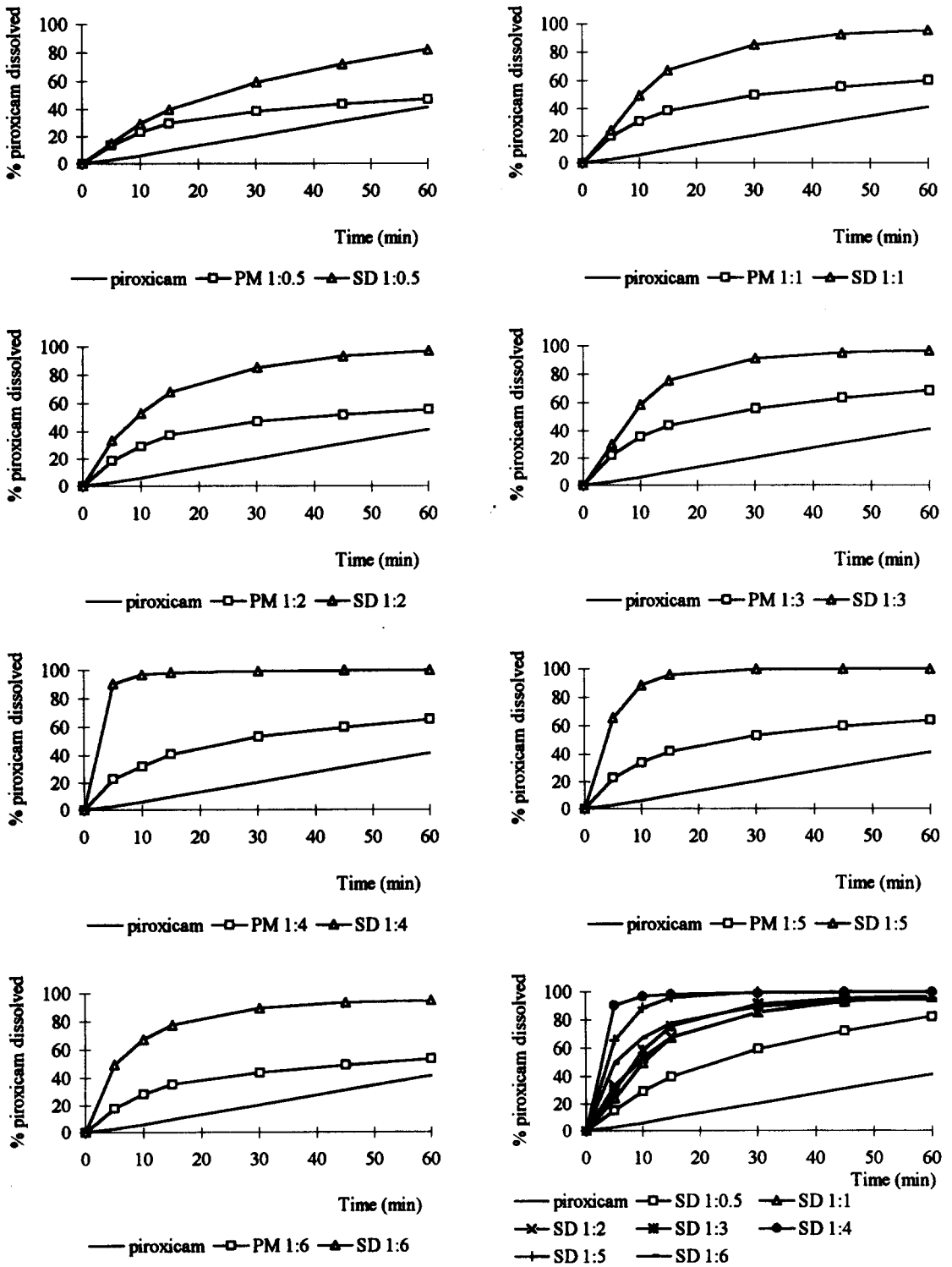

Fig. 5. Dissolution profiles of piroxicam alone and piroxicam in solid dispersions (SD) and physical mixtures (PM) containing the 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 piroxicam: PVP weight ratios.

Table 1
Dissolution rate constants (k) of piroxicam alone and piroxicam in solid dispersions and physical mixtures containing the 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 piroxicam: PVP weight ratios

	Piroxicam to PVP ratio							
	—	1:0.5	1:1	1:2	1:3	1:4	1:5	1:6
k (min^{-1}) of piroxicam	0.003	—	—	—	—	—	—	—
k (min^{-1}) of solid dispersion	—	0.015	0.033	0.033	0.041	0.113	0.093	0.043
k (min^{-1}) of physical mixture	—	0.010	0.014	0.014	0.017	0.015	0.016	0.013

certain type of intermolecular hydrogen bonding interaction between piroxicam and PVP (FTIR analysis) possibly retarded or inhibited drug recrystallization and causing piroxicam to be precipitated out in an amorphous form.

The relatively intense peaks of the drug: PVP 1:5 were also present in the drug: PVP 1:6. The intense diffraction peaks of piroxicam (e.g. 15.76, 23.02°) were also present in the drug: PVP 1:6 solid dispersion. These peaks were less prominent or absent in other solid dispersions. These results suggested that some portion of piroxicam still existed in the same crystal structures of pure drug.

3.3. Differential scanning calorimetry

DSC thermograms for piroxicam, PVP, solid dispersions and physical mixtures were shown in Fig. 4. Pure piroxicam gave a melting endotherm at 199.6°C. DSC thermograms of PVP, physical mixtures and solid dispersions showed the broad endotherms due to water removal at about 110–140°C. Physical mixtures gave a broad range of endotherms at about 186–193°C. Melting of piroxicam could be observed in all physical mixtures and was more prominent in those with lower ratios of PVP. As the proportion of piroxicam decreased, the endotherm for the drug shifted toward melting points lower than that for pure piroxicam. Melting with decomposition occurred both in solid dispersions and physical mixtures. Piroxicam melting endotherms of solid dispersions were lower than those of physical mixtures. Melting of piroxicam solid dispersions could not be observed when the ratio of drug to PVP lower than 1:3. As expected, the drug: PVP 1:4 solid dispersion which was X-ray amorphous did not show a melting endotherm.

3.4. Dissolution rate studies

The dissolution profiles of piroxicam, solid dispersions and physical mixtures were shown in Fig. 5. The initial dissolution rate in the first 15 min was examined by plotting the log of the percentage undissolved of piroxicam to a function of time. A linear relationship was obtained, indicating an apparent first order of dissolution process. The dissolution rate constant was calculated from the slope of the regression line and listed in Table 1.

In all cases, solid dispersions exhibited faster dissolution rates than pure drug and their corresponding physical mixtures. Piroxicam yielded the slowest initial dissolution rate with only about 10% of the drug dissolved in 15 min. Its hydrophobic property caused the powder to float on the surface of the dissolution medium and prevented its surface contacting the medium. As shown in Table 1, piroxicam in all physical mixtures released almost at the same rate, but faster than piroxicam alone. The faster dissolution rate of a physical mixture compared to pure drug was also observed in the physical mixture of phenytoin and PVP (Sekikawa et al., 1978). This might be caused by the surface tension lowering effect of PVP to the medium, resulting in wetting of hydrophobic piroxicam crystalline surface. The enhanced dissolution rate of piroxicam from the solid dispersions might be due to the increase in drug wettability and also the interactions of drug to PVP indicated in FTIR analysis.

As indicated in Table 1, the dissolution rate of piroxicam in solid dispersion was strongly dependent on the relative concentration of the drug to PVP ratio. The dissolution rates increased with

the increment in PVP proportions up to the drug to PVP ratio of 1:4, then decreased with further increase in amount of PVP. This result was similar to that found by Akbuga et al. (1988) and Ford (1986b). Pandit and Khakurel (1984) suggested that the decrease in dissolution rate of the solid dispersion containing higher proportions of the polymer might be caused by the leaching out of the carrier during dissolution which could form a concentrated layer of solution around the drug particles, therefore, the migration of the released drug particles to the bulk of the dissolution medium was slowed down. The drug: PVP 1:4 solid dispersion provided almost a 38-fold increase in the dissolution rate with the initial dissolution rate constants for the drug: PVP 1:4 solid dispersion and pure drug of 0.113 min^{-1} and 0.003 min^{-1}, respectively. This was due to the formation of high energy amorphous form.

4. Conclusions

The amorphous piroxicam-PVP solid dispersion was formed only at the 1:4 drug to PVP weight ratio. FTIR analysis indicated different intermolecular hydrogen bonding interactions between piroxicam and PVP in the solid dispersions. The dissolution rates of physical mixtures were higher than that of pure drug, this was possibly caused by the increase in drug wettability. Solid dispersions exhibited better dissolution rates than those of physical mixtures, resulting from the increase in drug wettability and the drug-PVP interactions. The increase in dissolution rates of solid dispersions reached up to a certain amount of PVP, and decreased with further increase of PVP. This maximum dissolution rate, which was about 38-fold higher than drug alone, was obtained with the solid dispersion containing the amorphous form of the 1:4 drug to PVP ratio. This amorphous solid dispersion should be useful for further formulation of dosage forms.

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