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Properties of solid dispersions of piroxicam in polyvinylpyrrolidone

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Abstract

Solid dispersions of piroxicam were prepared with polyvinylpyrrolidone (PVP) K-17 PF and PVP K-90 by solvent method. The physical state and drug:PVP interaction of solid dispersions and physical mixtures were characterized by X-ray diffraction, Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). FTIR analysis demonstrated the presence of intermolecular hydrogen bonding between piroxicam and PVP in solid dispersions. These interactions reflected the changes in crystalline structures of piroxicam. The amorphousness within the PVP moeity might be predicted in piroxicam dispersions by the disappearance of N–H or O–H peak of piroxicam. Dissolution studies indicated a significant increase in dissolution of piroxicam when dispersed in PVP. The better results were obtained with the lower molecular weight PVP K-17 than with higher molecular weight PVP K-90. The non-amorphous solid dispersions in PVP K-17 showed almost equally fast dissolution rates to amorphous dispersions in PVP K-90. The mechanism of dissolution of solid dispersion in PVP K-90 is predominantly diffusion-controlled due to the very high viscosity of PVP K-90. Dissolution was maximum with the amorphous solid dispersions containing drug:PVP K-17 1:5 and 1:6 which showed a 40-fold increase in dissolution in 5 min as compared with pure drug.

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

1. Introduction

Piroxicam is one of the most potent non-steroidal anti-inflammatory drugs (NSAIDs) used in musculoskeletal and joint disorders such as

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ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis (Insel, 1991). In our previous study (Tantishaiyakul et al., 1996), solid dispersions of piroxicam prepared using PVP K-30, average molecular weight (M_w) of 45 000, were found to improve the dissolution rates of this poorly soluble drug. The drug:PVP K-30 1:4 solid dispersion, which is the X-ray amorphous, showed about a 38-fold increase in dissolution after 5 min as compared with pure drug. Since the molecular weight of the polymer might play a role in the performance of a solid dispersion, solid dispersions of piroxicam at different ratios of PVP K-17 (PVP K-17 PF, $M_w \sim 9000$) and PVP K-90 ($M_w \sim 1\,100\,000$) were then prepared and their dissolutions were investigated. The physical state and solid state interactions between piroxicam and PVP were explored using Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), and differential scanning calorimetry (DSC).

2. Materials and methods

2.1. Materials

Piroxicam was obtained from Vertex Chemicals, Hong-Kong. PVP K-17 (Kollidon 17 PF, $M_w \sim 9000$) and PVP K-90 (Kollidon 90, $M_w \sim 1\,100\,000$) were kindly supplied by BASF Thailand. All other reagents were of analytical reagent grade.

2.2. Solid dispersion preparation

Solid dispersions were prepared with drug:PVP K-17 in 1:1, 1:2, 1:3, 1:4, 1:5, 1:6 and drug:PVP K-90 in 1:1, 1:2, 1:3, 1:4 weight ratios by means of solvent method. To a solution of piroxicam (1 g) in acetone (60 ml), was added the appropriate amount of PVP K-17 or PVP K-90. The minimum amount of methanol was added to solubilize the polymer. The solvents were removed under reduced pressures at 40°C and dry 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 mixed the appropriate amount of the 0.05–0.25 mm particle size fractions of piroxicam and PVP K-17 or PVP K-90.

2.3. Fourier transform infrared spectroscopy

Fourier transform infrared spectra were obtained on a Perkin-Elmer 1620 FTIR spectrometer equipped with a deuterated triglycine sulfate (DTSG) detector. Samples were prepared in KBr discs.

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^{-1} 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^{-1} under nitrogen atmosphere (flow rate 20 ml min^{-1}).

2.6. Dissolution studies

The dissolution medium consisted of 900 ml simulated gastric fluid TS prepared without pepsin (USP 23 and NF 18, 1995), maintained at 37 ± 0.5°C. Samples were tested with the dispersed amount 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-ml aliquot was withdrawn at appropriate time intervals, and replaced with a 5 ml of fresh dissolution medium. The amount of piroxicam was determined spectrophotometrically at 334 nm without the interference from PVP. Piroxicam concentration was calculated and expressed as percentage of drug released from the mean of six determinations.

3. Results and discussion

The solid dispersions of drug:PVP K-17 1:1, 1:2, 1:3, 1:4, 1:5, 1:6 and drug:PVP K-90 1:1, 1:2, 1:3, 1:4 weight ratios were prepared and their dissolutions and physical state properties were characterized. The properties of solid dispersions of drug:PVP K-90 lower than 1:4 were not investigated due to the stickiness of the preparations with the increasing amount of this polymer.

3.1. X-ray diffraction analysis

The XRD patterns of piroxicam, PVP K-17, PVP K-90, solid dispersions and physical mixtures were shown in Figs. 1 and 2. PVPs are 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).

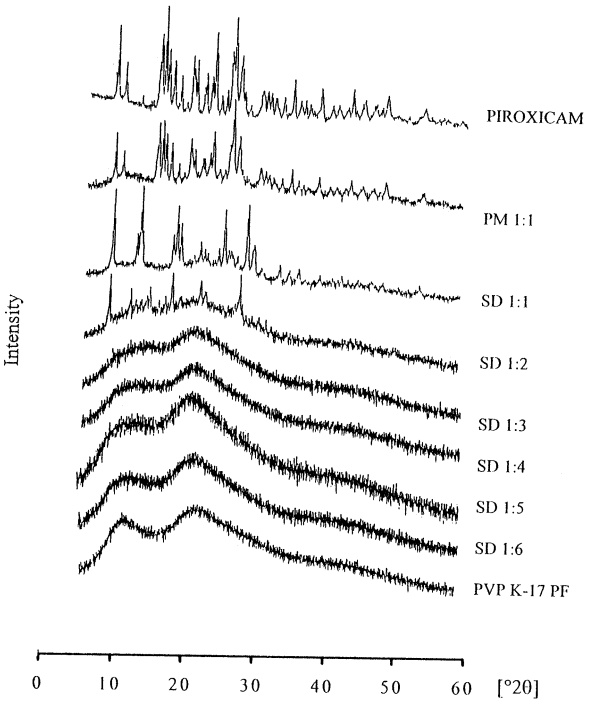

Fig. 1. X-ray diffraction patterns of piroxicam, PVP K-17, and solid dispersions (SD) and physical mixtures (PM) of drug:PVP K-17.

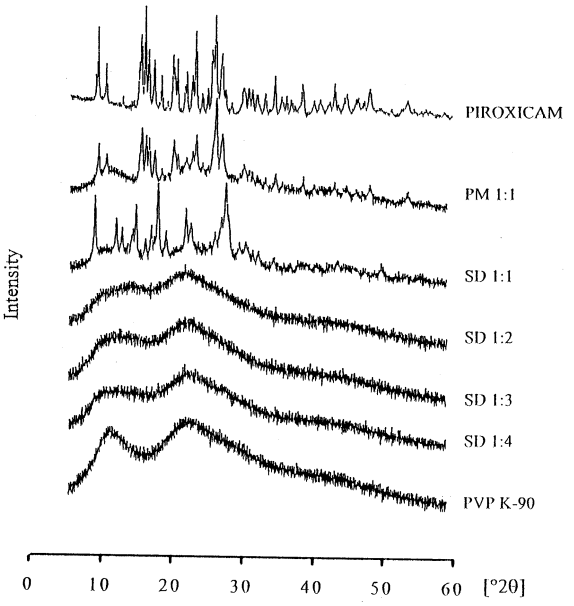

Fig. 2. X-ray diffraction patterns of piroxicam, PVP K-90, and solid dispersions (SD) and physical mixtures (PM) of drug:PVP K-90.1

The XRD peaks of crystalline piroxicam in all physical mixtures of both drug:PVP K-17 and drug:PVP K-90 were similar to those in pure drug, indicating that the crystallinity of piroxicam did not change in the physical mixtures.

The crystalline structures of piroxicam in all solid dispersions were different from that of pure drug as indicated from the differences in their XRD patterns. Three different XRD patterns were found for these solid dispersions. The first diffraction pattern was observed in solid dispersions prepared with low molecular weights and lower proportions of PVPs that included drug:PVP K-17 1:1 and drug:PVP K-30 1:0.5, 1:1 (Tantishaiyakul et al., 1996). The second XRD pattern was detected for solid dispersions of drug:PVP K-17 1:2, drug:PVP K-30 1:2, 1:3, 1:5 and drug:PVP K-90 1:1. The third one was observed in solid dispersions of drug:PVP K-17 1:3, 1:4, 1:5, 1:6 and drug:PVP K-90 1:2, 1:3, 1:4. In contrast to the former two XRD patterns which contained diffraction peaks, no peak was displayed from the third XRD pattern. The absence of diffraction peaks indicated the presence of

piroxicam in amorphous form. In general, the process of the crystallization of drug from supersaturated solution consisted of two processes; creation of the crystal nucleus and growth of the crystal. Sekikawa et al. (1978) pointed out that PVP might inhibit the association of the drug molecule to form the crystal nucleus and inhibit the crystal growth; and the interaction between drug and PVP should be the inhibitory and/or retardatory factor in the crystallization. In this study, the certain type of hydrogen bonding interaction between piroxicam and PVP, verified by FTIR analysis, would inhibited drug recrystallization and causing piroxicam precipitated out in an amorphous form. This inhibitory effect was associated with molecular weight and proportion of PVP. Hence, a suitable molecular length and proper amounts of PVP may be required to form the polymer net upon the crystal surface or among the drug molecule, resulting in the optimum orientation of the proton-donating and receiving groups and strong interaction between drug and polymer.

3.2. Fourier transform infrared spectroscopy

FTIR spectroscopy was employed to study the interaction in solid dispersions between drug and PVP. As our previous report (Tantishaiyakul et al., 1996), piroxicam which is present as enol or zwitterionic forms showed the N–H or O–H stretching vibration at 3391 cm^{-1}. And this region of interest showed the evidence of the interaction between piroxicam and PVP via intermolecular hydrogen bonding between the > N– or C=O functions on pyrrolidone moiety with the amide (N–H) group or protonated pyridine N atom of piroxicam.

FTIR spectra of PVP K-17 and PVP K-90 displayed broad peaks at about 3048–3718 cm^{-1} (Fig. 3). In spite of this broad peak, the FTIR spectra of all physical mixtures of drug:PVP K-17 and drug:PVP K-90 still showed peaks of N–H or O–H stretching vibration of piroxicam at 3391 cm^{-1}. The FTIR spectra of all physical mixtures were similar to the synthetic spectra producing by the addition of piroxicam and PVP, the selected spectra were shown in Fig. 3. This indicated that physical mixture spectra were only the summation of piroxicam and PVP spectra and reflected that there was no interaction between piroxicam and PVP in physical mixtures. This was consistent with the results obtained by X-ray diffraction studies.

As shown in Fig. 3, the N–H or O–H stretching vibration of solid dispersions was different from those of physical mixtures and piroxicam. The solid dispersion of drug:PVP K–17 1:1 displayed a peak at 3341 cm^{-1} and a shoulder at about 3322 cm^{-1} (Fig. 3 B). The doublets at this position were shown in the spectra of drug:PVP K-30 1:0.5 and 1:1 solid dispersions (Tantishaiyakul et al., 1996). The absorption band at wavenumber of 3337 cm^{-1} was observed from the FTIR spectra of drug:PVP K-17 1:2, drug:PVP K-90 1:1 and drug:PVP K-30 1:2, 1:3, 1:5 solid dispersions. The N–H or O–H stretching vibration was not detected in solid dispersions of drug:PVP K-17 1:3, 1:4, 1:5, 1:6 and drug:PVP K-90 1:2, 1:3, 1:4 which are X-ray amorphous.

The shifted towards lower wavenumber of N–H or O–H stretching vibration were attributed to a solid-state hydrogen bonding interaction between piroxicam and PVP in the solid dispersions. The differences in shape and position of this peak reflecting the substantially different hydrogen bonding networks among these solid dispersions. The intermolecular hydrogen bonding occurred in amorphous solid dispersions might be stronger than those containing crystalline drug, 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 phenomenon was previously observed for amorphous solid dispersion of drug:PVP K-30 1:4 (Tantishaiyakul et al., 1996). Therefore, the amorphousness within the PVP moiety might be predicted in piroxicam dispersions by the disappearance of this N–H or O–H peak.

Porubcan et al. (1978) demonstrated that new chemical bonds and strong complexations (hydrogen bonding) could alter the crystalline structure of drug, resulting in a changed XRD pattern. In present study, the hydrogen bonding interaction between piroxicam and PVP in solid dispersions may cause changed in piroxicam crystalline struc-

ture reflecting in different XRD patterns of solid dispersions from that of piroxicam alone. Solid dispersions showing difference in hydrogen bonding interaction between drug and PVP, i.e. the shifted towards different wavenumber, exhibited different XRD pattern. Interestingly, and also support the role of hydrogen bonding interaction on crystal structure, solid dispersions prepared with different proportion or molecular weight of PVP, such as those of drug:PVP K-17 1:2,

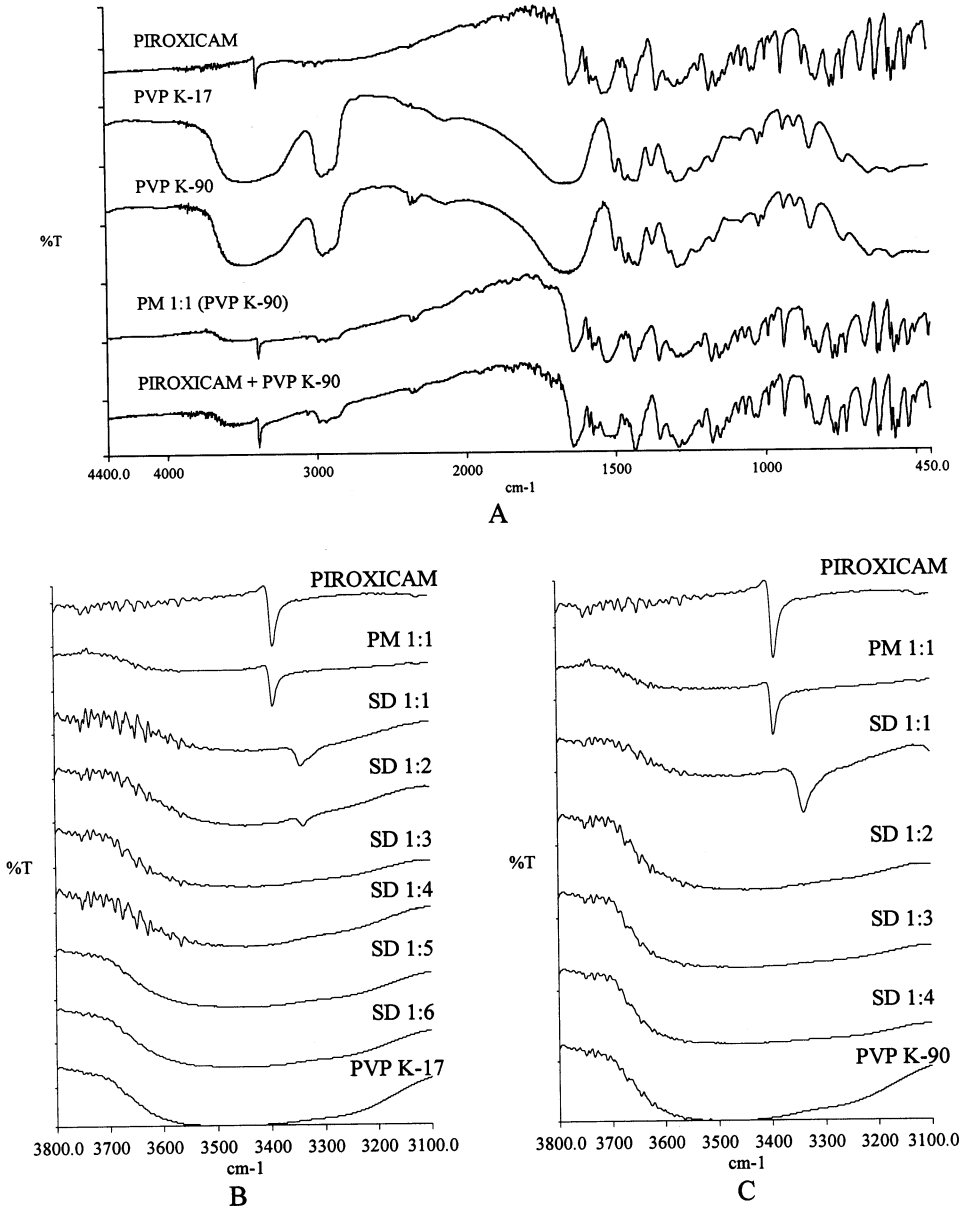

Fig. 3. FTIR spectra of (A) piroxicam, PVP K-17, PVP K-90, physical mixture and additive of piroxicam and PVP K-90 spectra; (B) solid dispersions (SD) and physical mixtures (PM) of drug:PVP K-17; (C) solid dispersions and physical mixtures of drug:PVP K-90.

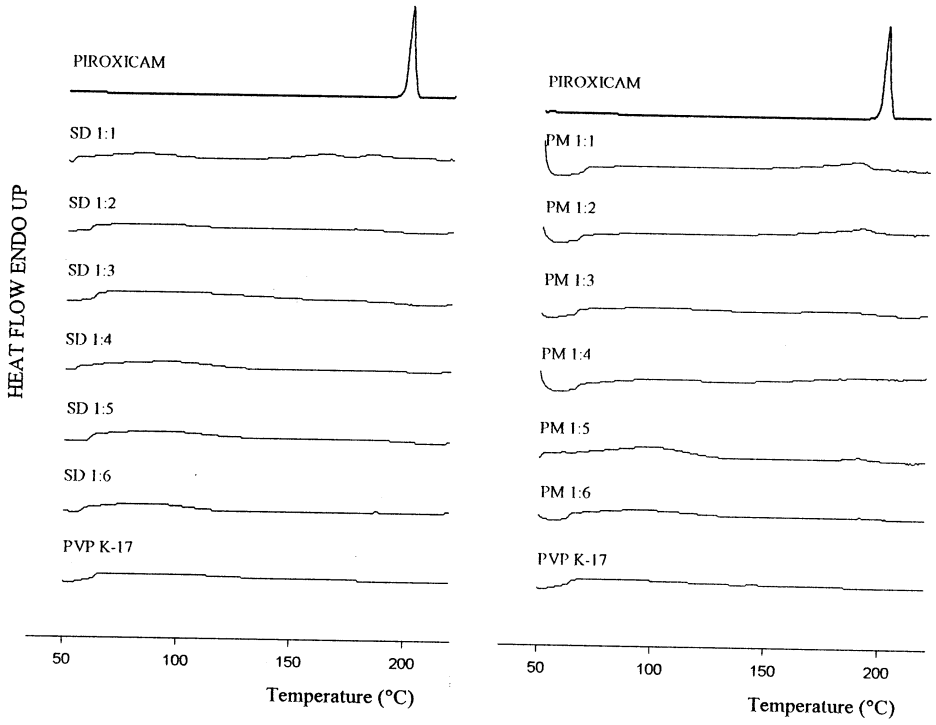

Fig. 4. DSC thermograms of piroxicam, PVP K-17, solid dispersions (SD) and physical mixtures (PM) of drug:PVP K-17.

drug:PVP K-30 1:3 and drug:PVP K-90 1:1, which displayed the same shifted of N–H or O–H stretching exhibited the identical of XRD pattern. Hence, these solid dispersions contained the same crystal structure of piroxicam as a result of the same interaction between drug and PVP.

3.3. Differential scanning calorimetry

DSC thermograms of piroxicam, PVP K-17, PVP K-90, physical mixtures and solid dispersions were shown in Figs. 4 and 5. Piroxicam gave a melting endotherm at 199.6°C. Piroxicam melting was absent in all the X-ray amorphous solid dispersions, as expected. The melting peak of piroxicam in solid dispersions containing crystalline piroxicam was also absent. This may be due to the interaction between piroxicam and PVP in these solid dispersions.

Melting of piroxicam could be observed in physical mixtures of drug:PVP K-90 and more prominent in those with lower proportions of PVP (Fig. 5). In contrast to physical mixtures of drug:PVP K-90, fusion of piroxicam for physical mixtures of drug:PVP K-17 occurred in the broad range of 170–195°C (Fig. 4), the final temperature was lower than piroxicam melting point. This indicated a piroxicam:PVP K-17 solid state interaction induced by heating. This type of interaction was previously observed in the physical mixture of naproxen:PVP K-15 (Bettinetti and Mura, 1994).

3.4. Dissolution rate studies

In dissolution study, 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.

Piroxicam alone yielded the slowest initial dissolution rate with only about 10% of drug was released in 15 min. As shown in Table 1, the dissolution rate constants of piroxicam from all physical mixtures of drug:PVP K-17 and drug:PVP K-90 were almost the same but significantly higher than piroxicam alone. This might due to the surface tension lowering effect of PVP to the medium, resulting in wetting of hydrophobic piroxicam crystalline surface (Sekikawa et al., 1979).

Dissolution rates for solid dispersions were greater than those for physical mixtures and piroxicam alone (Table 1; Figs. 6 and 7). The enhanced dissolution rates of solid dispersions may be due to many factors such as decreased particle size of drug (Ford, 1986), specific form of drug (Simonelli, et al., 1976) in these solid dispersions in addition to the increase in drug wettability and preventing the aggregation of drug by PVP.

The dissolution rate constants for solid dispersions prepared with different molecular weight of PVP were shown in Fig. 8 and Table 1. Interestingly, amorphous dispersions prepared with drug:PVP K-90 1:2, 1:3 and 1:4 ratio have almost equally fast dissolution rates to non-amorphous dispersions of drug: PVP K-17 1:1 and 1:2. To explain this result, the dissolution processes and factors involving dissolution rate would be considered. In general, dissolution may be described by two rate processes: the rate of the interfacial or solid-solvent reaction leading to solubilization of the molecule, and the rate associated with the diffusional or transport process of the solvated molecule to bulk of the dissolution medium. Solid dissolving can occur if there are bonds between the solvent and the dissolved molecules with a strength at least comparable with that between the molecules of the solid. The transfer of a molecule from the solid to the liquid is then not opposed and dissolving can take place. Since water is strongly polar because of its O–H groups, it readily forms hydrogen bonds with polar groups such as >N– and C=O group on pyrrolidine moiety of PVP and electronegative atoms or amide group on piroxicam molecule. The strength of bonds between water–PVP and water–drug molecules may be stronger than or comparable with that between the molecules of the solid dis-

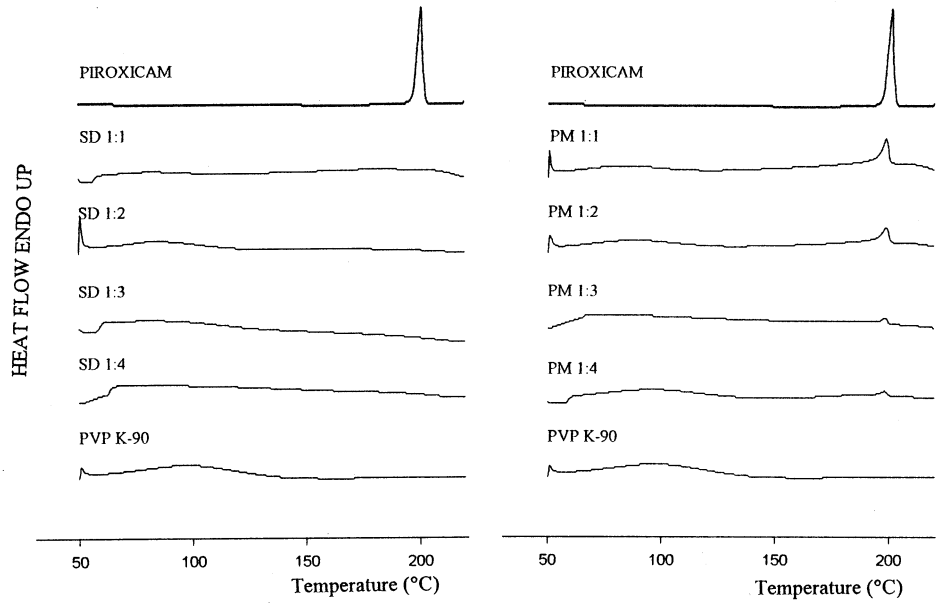

Fig. 5. DSC thermograms of piroxicam, PVP K-90, solid dispersions (SD) and physical mixtures (PM) of drug:PVP K-90.

Table 1
Dissolution rate constants of piroxicam alone and piroxicam in solid dispersions and physical mixtures

	Dissolution rate constant (min^{-1}) piroxicam to PVP weight ratio						
	–	1:1	1:2	1:3	1:4	1:5	1:6
Piroxicam	0.0025	–	–	–	–	–	-
Drug:PVP K-17 solid dispersion	–	0.0305	0.0365	0.0545	0.1051	0.1187	0.1184
Drug:PVP K-90 Solid dispersion	–	0.0287	0.0343	0.0427	0.0399	–	–
Drug:PVP K-17 physical mixture	–	0.0146	0.0153	0.0129	0.0162	0.0140	0.0152
Drug:PVP K-90 physical mixture	–	0.0131	0.0127	0.0130	0.0137	–	–

persions. Upon contact, water molecules can then solvate polymer and drug molecules, either in the crystalline or in amorphous form, and break the hydrogen bonds between drug:PVP complex. During the process of solubilization, a stagnant layer which surrounds the particle is saturated with dissolved PVP and drug molecules. The dissolution rate of drug is related to many factors. According to Noyes and Whitney equation:

$$\frac{dm}{dt} = \frac{DA(C_x - C)}{h},$$

the rate of change of mass dissolved (m) with time (t) is governed by diffusion coefficient (D), surface area (A) of the solid, thickness of the diffusion layer (h), solubility of the solid (C_s), and concentration of solute in the bulk solution and at time t (C). From the Stokes–Einstein equation, the diffusion coefficient is inversely proportional to viscosity. The viscosity of 10% w/v solution of PVP K-90 at 20°C is 500 mPa s which is about 200 times higher than that of PVP K-17 (Kollidon grades, 1990). With the high viscosity of PVP K-90, the diffusion coefficient is largely decreased resulting in the low dissolution rate of drug even though the solubilization process can occur fast for the high energy amorphous form of drug. The mechanism of dissolution of solid dispersion in PVP K-90 might be predominantly diffusion-controlled, and the high viscosity of this polymer is the main factor to control the dissolution rate.

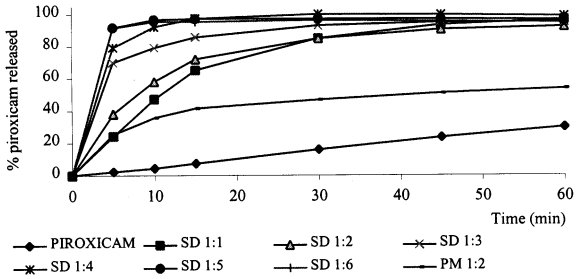

Fig. 6. Dissolution profiles of piroxicam alone and piroxicam in solid dispersions (SD) and physical mixtures (PM) of drug:PVP K-17.

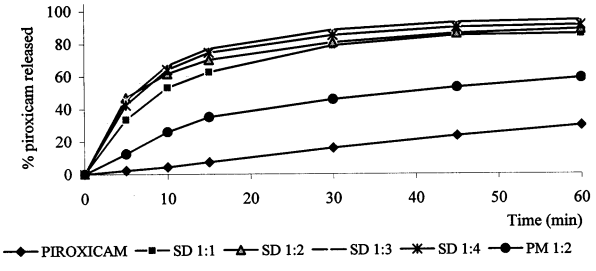

Fig. 7. Dissolution profiles of piroxicam alone and piroxicam in solid dispersions (SD) and physical mixtures (PM) of drug:PVP K-90.

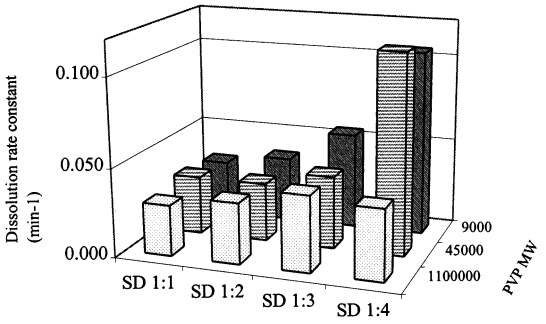

Fig. 8. Dissolution rate constants of solid dispersions (SD) prepared using different molecular weight of PVPs.

For solid dispersions prepared with PVP K-17, diffusional process might not be the major factor to govern the dissolution process. In the solubilization process, the formation of a high energy amorphous phase of drug attributed to rapid dissolution rates which were faster than the solid dispersions containing crystalline drug. The dissolution rate of solid dispersion was increased until the ratio 1:5 and then increase in the proportion of PVP did not affect drug release. The increase amount of PVP may prevent drug aggregation, decrease drug particle size or increase drug wettability resulting in higher solubility. However, at the higher ratio of PVP, the solubilization process might be neutralized by the diffusion process by increasing the viscosity of the solution around the solid particle. The maximum release was obtained with 1:5 and 1:6 ratios; which showed about a 40-fold increase in dissolution in 5 min as compared with pure drug.

4. Conclusions

Amorphous piroxicam:PVP solid dispersion was formed either at or the lower ratios of 1:3 and 1:2 for drug:PVP K-17 and drug:PVP K-90, respectively. FTIR analysis indicated the differences in intermolecular hydrogen bonding interactions between piroxicam and PVP among solid dispersions that reflected the differences in XRD patterns. The absence of piroxicam melting was observed for the amorphous solid dispersion, as expected. DSC thermograms exhibited broad endotherms for physical mixtures of drug:PVP K-17, as a consequence of solid state interaction induced by heating. This phenomenon was not observed for drug:PVP K-90 physical mixtures. According to dissolution study, drug releases from physical mixtures were higher than that of pure drug, possibly caused by the increase in drug wettability. Solid dispersions exhibited better dissolution rates than physical mixtures, resulted from the increase in drug wettability, reduce drug particle size, or prevent drug aggregation. The maximum result was obtained from amorphous solid dispersion of drug:PVP K-17 1:5 and 1:6 which showed about a 40-fold increase in dissolution as compared with drug alone.

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