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Studies on aging piroxicam-polyvinylpyrrolidone solid dispersions

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The stabilities of X-ray amorphous solid dispersions of piroxicam and polyvinylpyrrolidone (PVP) K-17 and PVP K-30 (1 : 5 and 1 : 4), respectively, were investigated after storage for 12 months. X-ray diffraction showed that in the aged solid dispersions piroxicam remained in the amorphous state. Fourier transform infrared (FTIR) spectroscopy indicated that the interactions between drug and PVP in aged solid dispersions are similar to those in freshly prepared samples. The dissolution rates of the X-ray amorphous solid dispersions during storage for 12 months at 45 °C and ambient temperature were examined. Very minor decreases in dissolution rates of aged solid dispersions were found which might be due to the coarsening of the particles. Dissolutions of these amorphous solid dispersions after aging for 12 months still showed an about 40-fold increase in dissolution in 5 min compared to pure drug.

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 [1]. Piroxicam is poorly soluble in water; its dissolution rate might be increased using solid dispersion technology. As a water-soluble polymer, polyvinylpyrrolidone (PVP) has been demonstrated to retard and inhibit the crystallization of drugs, giving amorphous solid dispersions with increased drug dissolution rates and solubilities [2]. In a previous study solid dispersions of piroxicam prepared using PVP K-17 and K-30 were found to enhance the dissolution rates of this poorly soluble drug [3, 4]. The X-ray amorphous solid dispersions of drug : PVP K-17 (1 : 5) and drug : PVP K-30 (1 : 4) showed an about 40-fold increase in dissolution after 5 min as compared with pure drug. Since the maximum *in vitro* dissolution rate for drug : PVP solid dispersion systems generally involves an amorphous drug phase and the storage time might decrease the dissolution rate [5], the dissolution properties, X-ray diffraction pattern, and FTIR analyses of solid dispersions of drug : PVP K-17 (1 : 5) and drug : PVP K-30 (1 : 4) stored for 12 months were examined.

2. Investigations, results and discussion

Solid dispersions of drug : PVP K-17 (1 : 5) and drug : PVP K-30 (1 : 4) weight ratio were prepared and stored for 12 months. All solid dispersions stored at 45 °C or at ambient temperature remained in the free-flowing states and no color changes were found.

The XRD patterns of piroxicam, PVP, freshly prepared and aged solid dispersions are shown in Fig. 1. 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 the needle form of piroxicam [6].

X-ray diffraction spectra were obtained for the freshly prepared and aged solid dispersions. No changes were observed in the aged solid dispersions spectra after storage for 12 months. The XRD of the freshly prepared and aged solid dispersions showed typical amorphous spectra, with no evidence of piroxicam diffraction peaks (Fig. 1). This is indicative of a stabilization effect of PVP.

FTIR spectroscopy was employed to study the interaction in solid dispersions between drug and PVP. As previously reported [3, 4], piroxicam which is present as enol or zwitterionic forms showed the N−H or O−H stretching vibration at 3391 cm^{-1}. This region of interest showed evidence of an 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-30 displayed broad peaks at about 3718 to 3048 cm^{-1} (Fig. 2). In spite

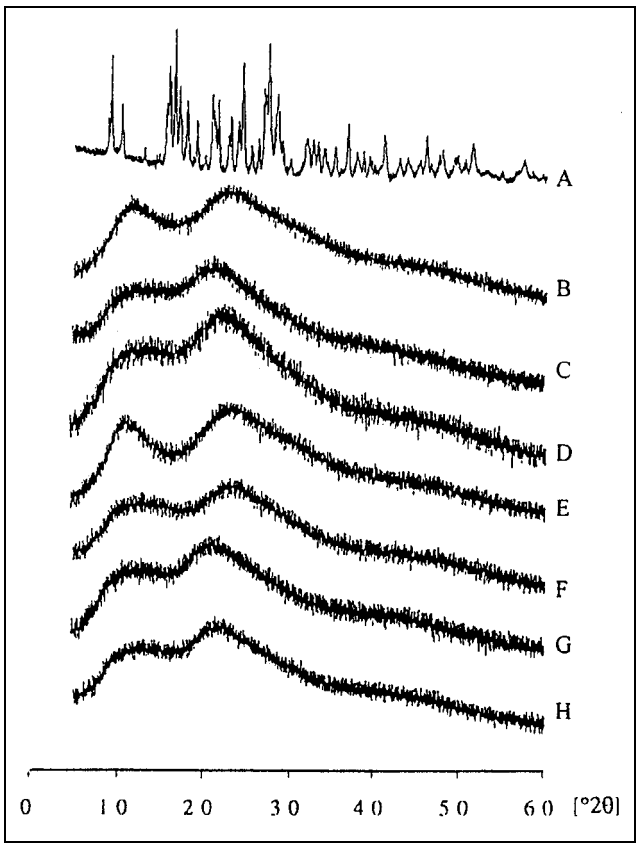

Fig. 1: X-ray diffraction patterns of A) piroxicam, B) PVP K-17, C) solid dispersion (SD) of drug : PVP K-17 (1 : 5) freshly prepared, D) aged SD drug : PVP K-17 (1 : 5) stored at ambient temperature, E) PVP K-30, F) SD drug : PVP K-30 (1 : 4) freshly prepared, G) aged SD drug : PVP K-30 (1 : 4) stored at ambient temperature, H) aged SD drug : PVP K-30 (1 : 4) stored at 45 °C.

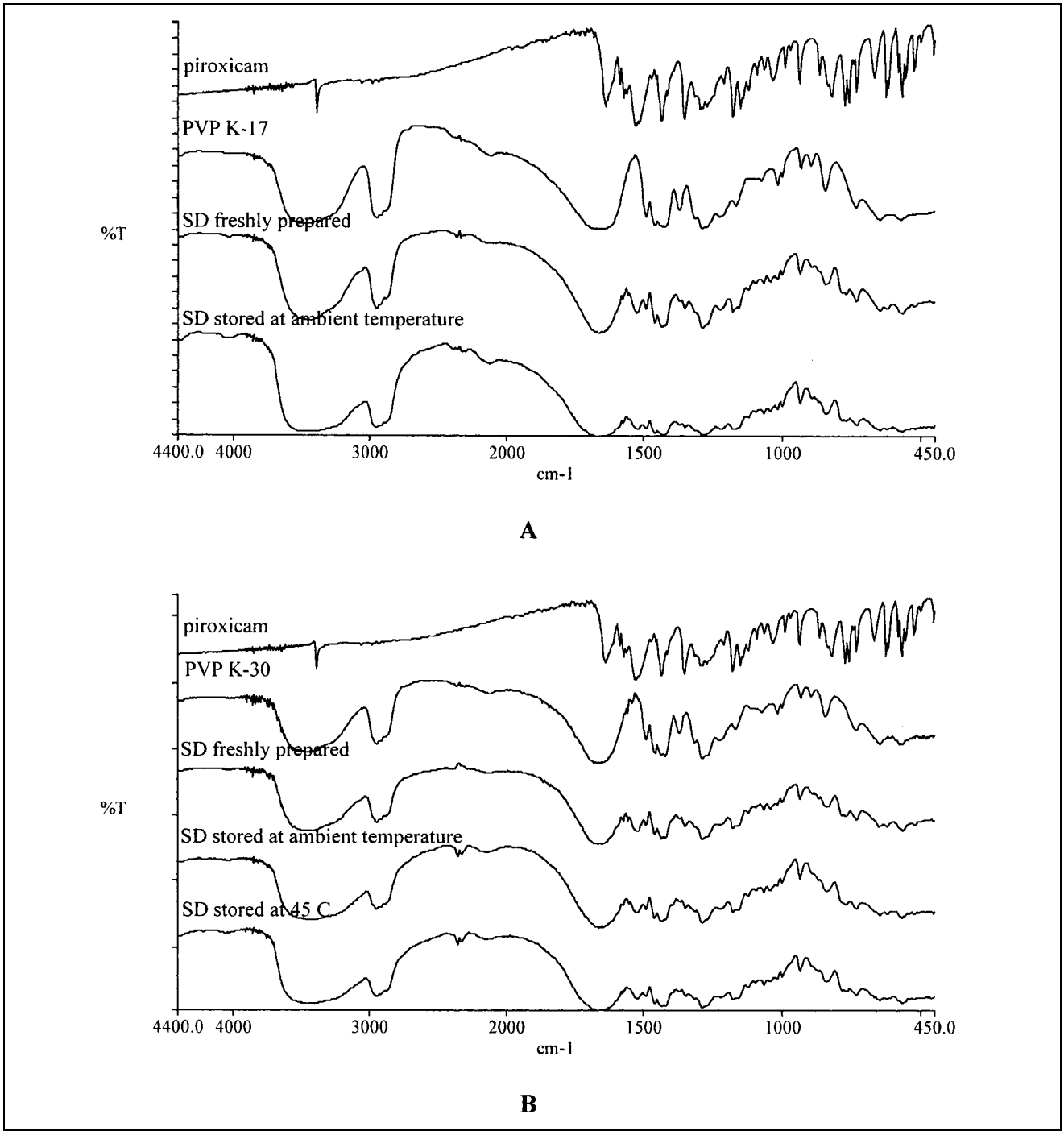

Fig. 2: FTIR spectra for A) drug : PVP K-17 (1 : 5); B) drug : PVP K-30 (1 : 4) freshly prepared and after storage for 12 months.

of this broad peak, the FTIR spectra of all physical mixtures of drug : PVP and some ratios of drug : PVP solid dispersions showed peaks of N−H or O−H stretching vibration of piroxicam. Due to the different solid-state hydrogen bond systems between drug and PVP [3, 4], the solid dispersion of drug : PVP which are in crystalline states showed peaks in different shape and position at the range of 3341–3337 cm^{-1}. However, the N−H or O−H stretching vibration was not detected in solid dispersions of drug : PVP K-17 (1 : 5) and drug : PVP K-30 (1 : 4) which are X-ray amorphous. 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. Accordingly, the amorphousness within the PVP moiety might be predicted in piroxicam solid dispersions by the disappearance of this N−H or O−H peak.

The aged solid dispersions of PVP K-17 (1 : 5) and PVP K-30 (1 : 4) were analyzed using FTIR. There was no peak of N−H or O−H obtained for the aged solid dispersions, indicating the amorphous form of these solid dispersions. This was consistent with the results obtained by X-ray diffraction studies.

The dissolution profiles of piroxicam, freshly prepared and aged solid dispersions stored at 45 °C and ambient temperature, are shown in Figs. 3 and 4. The freshly prepared dissolution rate in the first 15 min was analysed by plotting the log of the percentage undissolved piroxicam

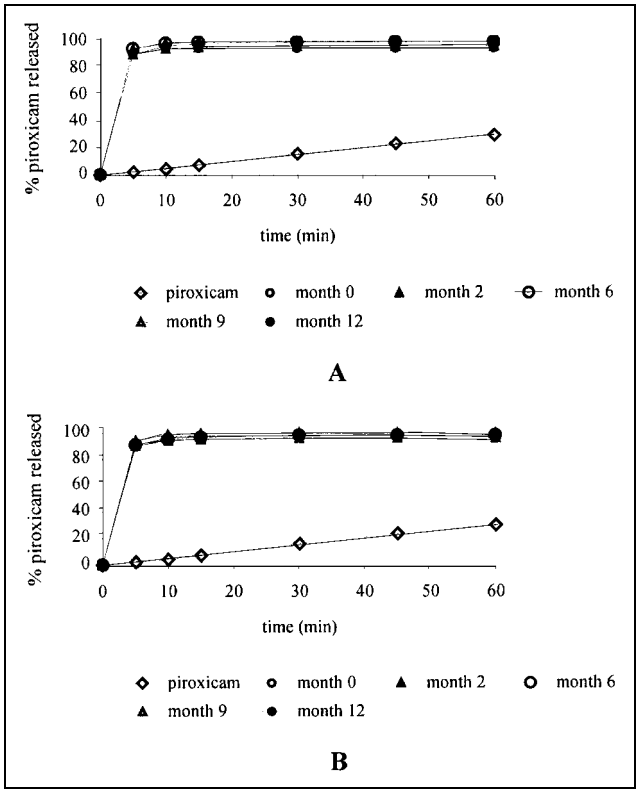

Fig. 3: Dissolution profiles of piroxicam alone and piroxicam in solid dispersions of drug : PVP K-30 (1 : 4) freshly prepared and after storage for 12 months A) at 45 °C and B) at ambient temperature.

over the function of time. A linear relationship was obtained, indicating first order dissolution process. The dissolution rate constant was calculated from the slope of the regression line and is listed in the Table.

As shown in the Table, piroxicam alone yielded the slowest dissolution rate (0.0025 min^{-1}) with only 10% of drug released in 15 min. The dissolution rates of freshly prepared solid dispersions of drug : PVP K-17 (1 : 5) and drug : PVP K-30 (1 : 4), 0.1187 and 0.1130 min^{-1} respectively, are faster than that of drug alone. These freshly prepared amorphous solid dispersions showed an about 40-fold increase in dissolution in 5 min as compared with pure drug.

The dissolution rate data for the aged solid dispersions are shown in the Table. Very slight decreases in piroxicam

Table: Dissolution rate constant of piroxicam alone and piroxicam in solid dispersions freshly prepared and after aging.

	Dissolution rate constant (min^{-1})				
	Storage time (months)				
	0	2	6	9	12
Piroxicam	0.0025	–	–	–	–
Piroxicam : PVP K-30 (1 : 4) solid dispersion (ambient)	0.1130	0.1143	0.1006	0.0933	0.0971
Piroxicam : PVP K-30 (1 : 4) solid dispersion (45 °C)	0.1130	0.1151	0.1142	0.0964	0.0988
Piroxicam : PVP K-17 (1 : 5) solid dispersion (ambient)	0.1187	–	–	–	0.1081

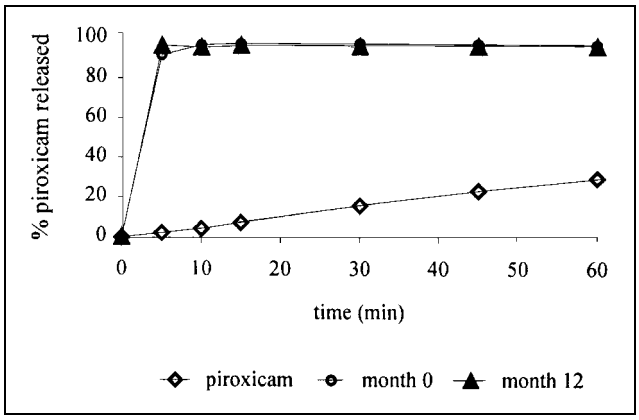

Fig. 4: Dissolution profiles of piroxicam alone and piroxicam in solid dispersions of drug : PVP K-17 (1 : 5) freshly prepared and after storage for 12 months at ambient temperature.

dissolution rates were observed for drug-PVP solid dispersion after storage for 12 months. The results might be due to the coarsening of the solid dispersion particles. However the storage for 12 months did not appear to have any marked effect on the dissolution profiles (Figs. 3 and 4). The dissolution of aged solid dispersions still showed a drug release as high as 90% of the freshly prepared solid dispersions.

3. Experimental

3.1. Materials

Piroxicam was obtained from Vertex Chemicals, Hong-Kong. PVP K-30 (Kollidon 30) and PVP K-17 (Kollidon 17 PF) were kindly supplied by BASF Thailand. All other reagents were of analytical grade.

3.2. Solid dispersion preparation

Solid dispersions were prepared by the solvent method. An appropriate amount of PVP was added to a solution of piroxicam (1 g) in acetone (60 ml). An minimum amount of methanol was added to solubilize the polymer. The solvents were removed under reduced pressure at 40 °C and dried under vacuum at room temperature for 5 h. The sample was pulverized using a mortar and pestle, and the 0.05–0.25 mm particle size fractions were obtained by sieving.

Solid dispersions of drug : PVP K-17 (1 : 5) and drug : PVP K-30 (1 : 4) which showed the best dissolution rates, 0.1187 and 0.1130 min^{-1} respectively, from each group [3, 4] were used for aging studies. All solid dispersions were stored in screw-capped bottles for 12 months. Drug:PVP K-17 solid dispersion was stored at ambient temperature. Drug:PVP K-30 samples were kept separately at 45 °C and ambient temperature.

3.3. X-ray diffraction

X-ray diffraction (XRD) patterns were obtained using a PW 3710 diffractometer (Philips, Almelo, Netherlands) 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°.

3.4. Fourier transform infrared spectroscopy

Fourier transform infrared spectra were obtained on a Perkin-Elmer 1620 FTIR spectrometer (Norwalk, CT, USA) equipped with a deuterated triglycine sulfate (DTSG) detector. Samples were prepared in KBr discs. The spectra were analyzed and compared using Spectrum lite software package (Perkin-Elmer, Norwalk, CT, USA).

3.5. Dissolution studies

The dissolution medium consisted of 900 ml simulated gastric fluid TS prepared without pepsin [7], maintained at 37 ± 0.5 °C as previously reported. Shortly, sample was tested with the dispersed amounts method [8] by placing 10 mg of piroxicam or its equivalent in solid dispersions 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.

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