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Characterization of solid dispersions of piroxicam/polyethylene glycol 4000

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Summary

Piroxicam is a nonsteroid anti-inflammatory that is poorly soluble in water. The present study describes the formulation of solid dispersions of the drug designed to increase solubility. X-ray diffraction, infrared spectroscopy and DSC were used to examine the physico-chemical characteristics of solid dispersions of piroxicam and polyethylene glycol 4000 (PEG 4000) prepared by the melting-solvent method, using percentage proportional compositions ranging from 10:90 to 80:20. The results showed that there was no chemical interaction between the drug and the polymer, and that a solid solution of piroxicam:PEG 4000 formed at concentrations of the drug below 30%. In addition, dispersions of small crystals of piroxicam were noted in the soluble carrier, however, a eutectic mixture of the drug:polymer binary system tested was not obtained.

Introduction

Since Sekiguchi and Obi (1961) first proposed solid dispersions as a way to improve the solubility and bioavailability of drugs poorly soluble in water, this approach has been widely applied. The utility of solid dispersions has been documented in a number of studies (Hajratwal, 1974; Puisieux and Henry, 1981; Lefebvre et al., 1985; Ford, 1986).

We designed the present study to examine solid dispersions of piroxicam (oxicam type NSAI), a nonsteroid anti-inflammatory characterized by its poor solubility in water, in the soluble carrier polyethylene glycol 4000 (PEG 4000). We investigated the possible interaction between solid-state formulations of piroxicam and PEG 4000 using infrared (IR) spectroscopy, X-ray diffraction, and differential scanning calorimetry (DSC). As described by Ford and Francomb (1985) and Yang and Swarbrick (1986), we used the peak melting point and heat of fusion to construct the phase diagram and determine the possible solubility in the solid state.

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Materials and Methods

Materials

Piroxicam (Medichem SA), polyethylene glycol (PEG 4000) (Glyco Ibérica) and analytical grade chloroform (Panreac) were used.

Sample preparation

Solid dispersions (SD) were prepared according to the melting-solvent method (Chiou and Riegelman, 1971). The carrier was melted in a water bath (approx. 70°C), and piroxicam was dissolved in a minimal amount of chloroform. The two components were mixed with constant shaking until most of the solvent had evaporated. The remainder of the solvent was removed (constant weight) in a vacuum oven at room temperature. The resulting solid was pulverized and sieved to separate the desired granulometric fraction (0.175 mm). For purposes of comparison, physical mixtures (PM) were prepared by simple mixture and homogenization of the two pulverized components, and 0.175 mm particles were obtained by sieving.

Combinations of piroxicam : PEG 4000 of the following percentage proportions were prepared: 10 : 90, 20 : 80, 30 : 70, 40 : 60, 50 : 50 and 80 : 20. These mixtures were placed in sealed, opaque recipients and stored away from light and humidity.

Infrared spectroscopy

IR spectra were taken on a Perkin Elmer 782 infrared spectroscope connected to a Perkin Elmer 3700 data station. The samples were prepared in KBr discs.

X-ray diffraction patterns

X-ray diffraction studies were performed using an automatic powder diffractometer equipped with a curved graphite monochromator and an automatic slit width adjuster (Philips Pw 1710/100), using CuKα radiation (CuKα = 1.5418 Å). Diffractograms were obtained from powdered samples.

Thermal analyses

DSC (Mettler 3000 calorimeter) was used to obtain thermograms at a heating rate of 10°C/min, over the temperature range from 20–250°C, and in samples ranging in weight from 3.24 to 7.25 mg. Peak transition temperature and heat of fusion were determined for all samples.

Results and Discussion

Kozjeck et al. (1985) characterized two distinct and interconvertible crystalline polymers of piroxicam. One crystal took the form of white needles (monoclinic system), with a melting point of 198°C, the other appeared as yellow cubes (triclinic system), with a melting point at 202°C. Both forms were distinguishable by their IR absorption spectrum (Azcona et al., 1987), X-ray diffraction capacity, and solubility in 0.1 N HCl. However, these physico-chemical differences did not affect their activity, and according to Kosjeck et al. (1985), both produced similar plasma concentration curves in dogs.

IR spectroscopy

The IR spectra of piroxicam and PEG 4000 alone, and of the SDs and PMs, are shown in Fig. 1. The two piroxicam polymorphs showed slightly different fingerprint regions in the IR spectrum. Mihalic (1986) found variations in the band of -NH and -OH stretching, which gave values of 3385 cm^{-1} for needle-shaped crystals, and 3330 cm^{-1} for the cube-shaped form. Another characteristic band was detected for amide carbonyl stretching at 1635 cm^{-1}.

The 3336 cm^{-1} band was clearly visible in the spectrum of piroxicam, and is also discernible in the spectra for SDs and PMs, becoming more intense as the percentage of drug in the mixture increased. The signal was generally stronger in PMs than in SDs.

A new band at 3399 cm^{-1} was barely visible in the spectrum for the 20 : 80 SD, but became more evident with that of 30 : 70 SD. This band appears to represent the monoclinal form of piroxicam.

A series of poorly resolved peaks was also seen between 3000 and 3100 cm^{-1}; these signals were partly masked by the band of -OCH_3 stretching produced by PEG 4000 in the first three SDs (10 : 90, 20 : 80 and 30 : 70). The signals were first detectable in the 40 : 60 dispersion, owing to the lower content of carrier.

The 1724 cm^{-1} band was not observed in this spectrum, suggesting that piroxicam was present as an enol.

The above-mentioned results suggest that there

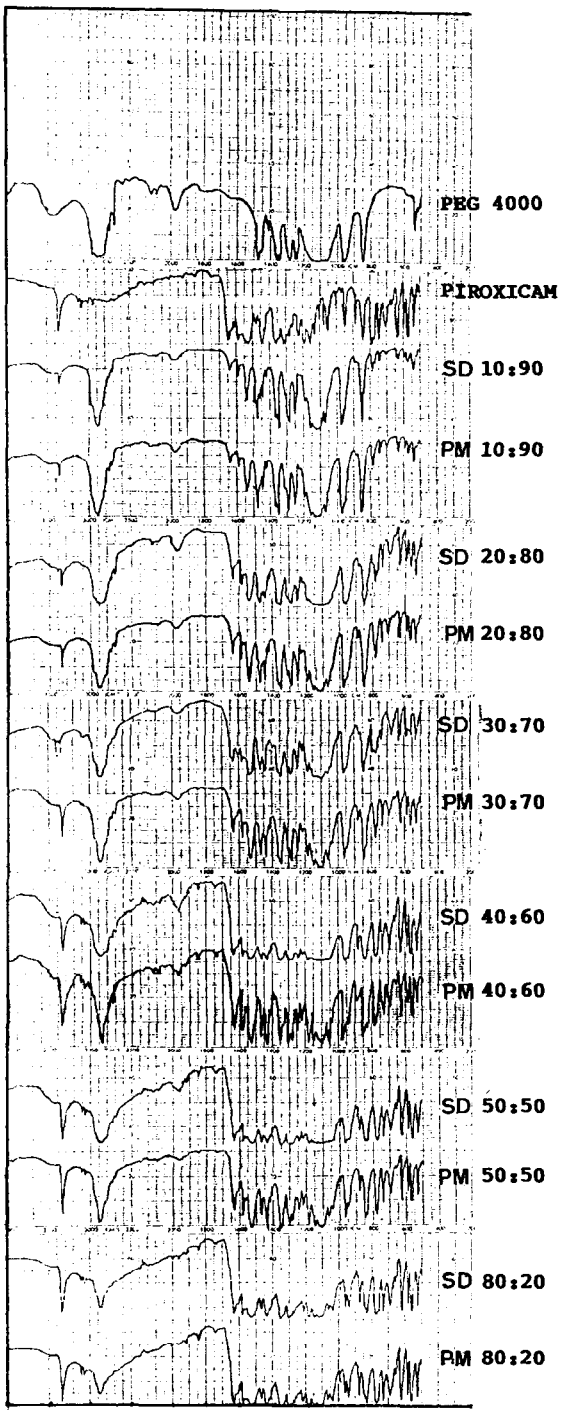

Fig. 1. Infrared spectrograms of piroxicam and PEG 4000 alone and in solid dispersions and physical mixtures.

was no chemical interaction between piroxicam and PEG 4000.

X-ray diffraction

Fig. 2 shows the X-ray diffractograms for piroxicam, PEG 4000 and the SDs and PMs tested. The diffraction spectrum for piroxicam confirmed the triclinal nature of the sample (Mihalic, 1986). Characteristic peaks appeared at a diffraction angle of 2θ, at 8.80, 17.90, 22.65 and 27.60°. These values were similar to those recorded by Mihalic (1986) (8.7, 17.7, 22.5 and 27.4°). PEG 4000 produced peaks at 19.35 and at 35.55°.

In the 10:90, 20:80 and 30:80 samples, the piroxicam spectrum was almost completely masked by the signals from PEG 4000, suggesting that an interstitial solid may have formed. Such an occurrence is not infrequent in this type of carrier when mixed with small amounts of a low molecular weight drug. As the proportion of piroxicam increased, the peaks for the drug became more intense, while those for the carrier became weaker. Since the peaks produced by SDs and PMs of the same composition were comparable, we conclude that the drug was insoluble in the solid carrier, i.e., in formulations containing more than 40% piroxicam, no solid solution formed between the drug and polymer.

Thermal analysis

The thermograms for piroxicam, PEG 4000, and the SDs and PMs are shown in Figure 3. The DSC curves of the pure products show a single fusion endotherm, with a melting point of 201.5°C for the drug (triclinal form) and 59.9°C for the polymer. All thermograms for the SDs showed the fusion endotherm of the carrier, with no change in the melting point. As the proportion of piroxicam decreased, the endotherm for the drug shifted toward melting points lower than that for the pure product. The fusion endotherm for PEG 4000 increased with the proportion of polymer, while that of the drug decreased, and was not detected at proportions of piroxicam below 30%.

In the DSC curves for the PMs (Fig. 3) the fusion endotherm of PEG 4000 showed no shift, while that of the drug was barely visible in sam-

ples containing less than 30% piroxicam. As in previous assays (see above) no chemical interaction between the drug and the polymer was evident.

The peak melting points were used to construct a phase diagram for SDs (Fig. 4). As the resulting diagram did not permit us to determine the degree of solid solubility, we used the heats

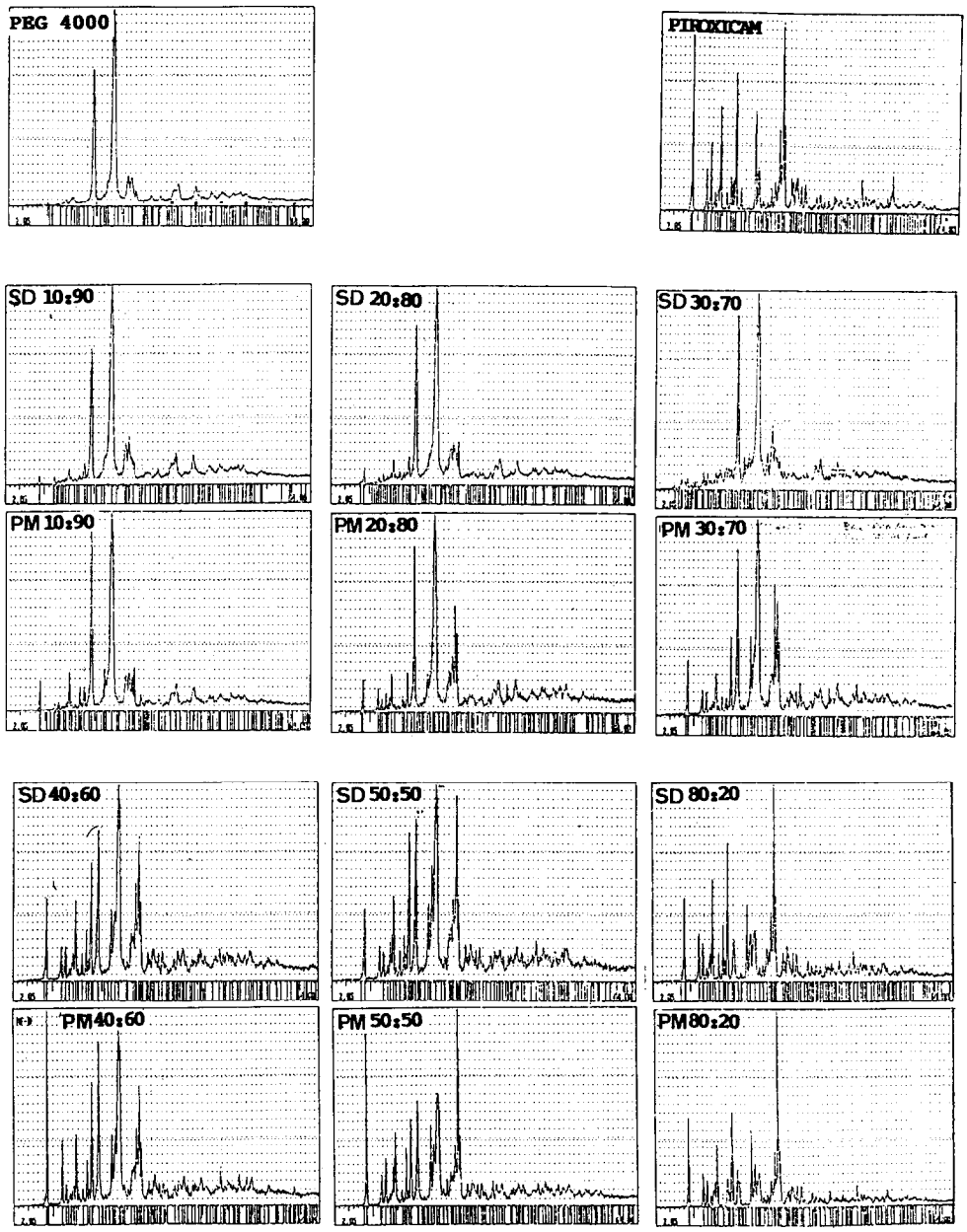

Fig. 2. X-ray diffraction data for piroxicam and PEG 4000 alone and in solid dispersions and physical mixtures.

of fusion (Fig. 5), as described by Yang and Swarbrick (1986), to analyze the phase diagram. There was a linear relation between composition and the heats of fusion, with a correlation coefficient close to unity ($r = 0.99$). The intercept on the abscissa did not cross the origin, however, when the heat of fusion was zero, the resulting values of solubility for piroxicam and PEG 4000 were compatible with those obtained with X-ray diffraction.

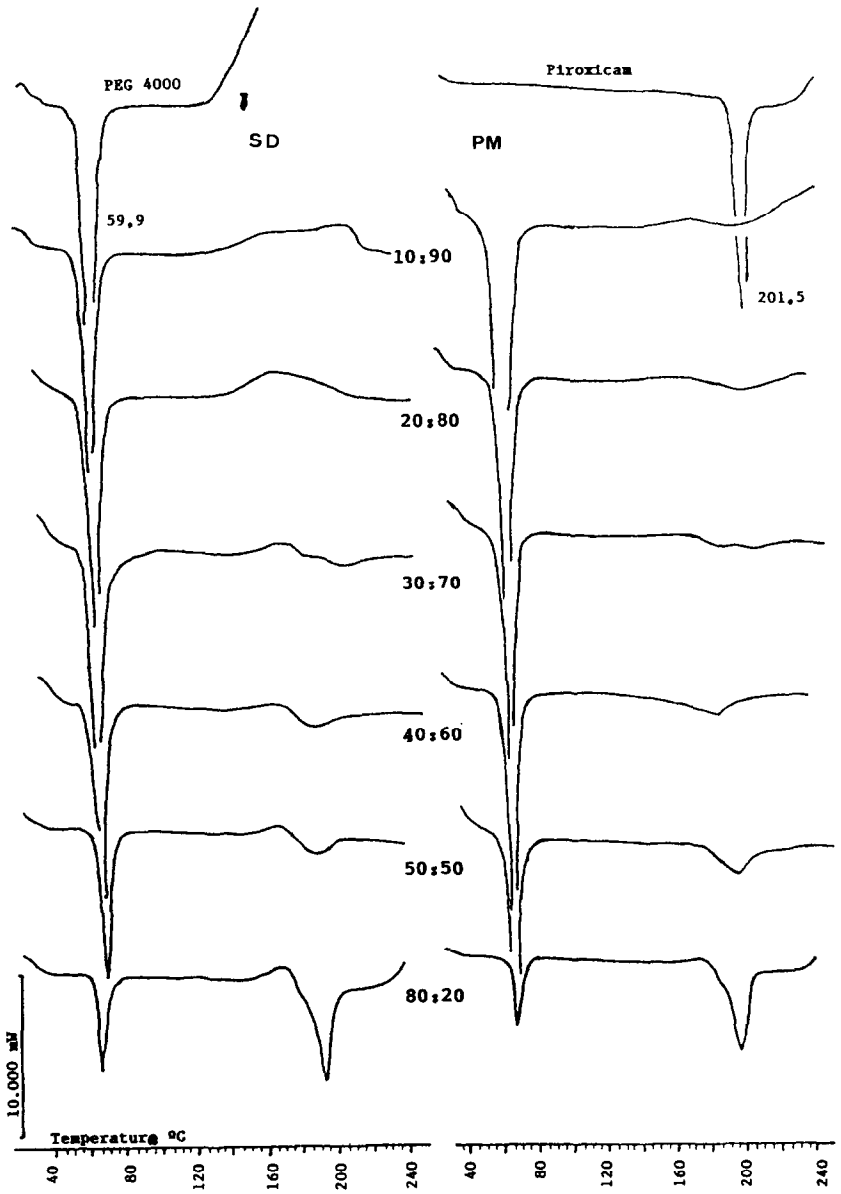

Fig. 3. Differential scanning calorimetric data for piroxicam and PEG 4000 alone and in solid dispersions and physical mixtures.

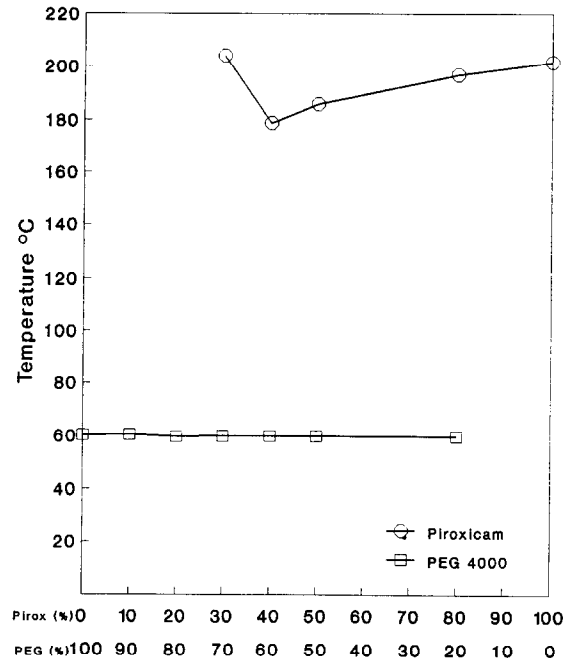

Fig. 4. Phase diagram for solid dispersions of piroxicam in polyethylene glycol 4000.

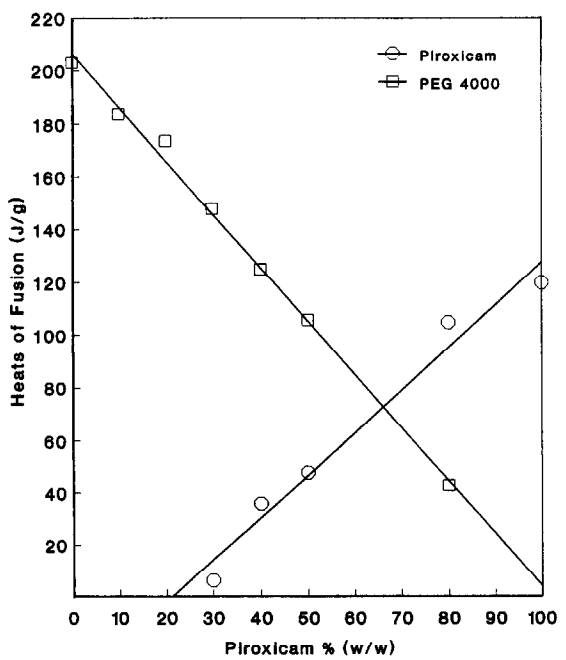

Fig. 5. Relation between piroxicam concentration in solid dispersions and heat of fusion.

In conclusion, solid-state solutions were obtained for combinations containing less than 30% piroxicam. The findings obtained with IR spectroscopy, X-ray diffraction and DSC detected no chemical interaction between the drug piroxicam and the inert carrier PEG 4000. The melting-solvent method was used to prepare solid dispersions of piroxicam in PEG 4000. Solid-state solutions of the binary system were obtained with samples containing less than 30% piroxicam.

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