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# Preparation and Characterization of Solid Dispersions of Piroxicam with Hydrophilic Carriers

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**ABSTRACT** The objective of this study was to improve the dissolution rate of a poor water soluble drug, piroxicam, by solid dispersion technique. Solid dispersions were prepared by three different methods depending on the type of carrier. The dissolution rate of piroxicam was markedly increased in solid dispersion of myrj 52, Eudragit® E100 and mannitol. Solubility studies revealed a marked increase in the solubility of piroxicam with an increase in myrj 52 and Eudragit® E100 concentrations. Data from the X-ray diffraction and FT-IR spectroscopy showed that piroxicam was amorphous in the solid dispersions prepared with dextrin and Eudragit® E100.

**KEYWORDS** Piroxicam, Solid dispersion, Coprecipitate, Coevaporate, X-ray diffraction, FT-IR spectroscopy, Dissolution

## INTRODUCTION

Incorporation of drugs into solid dispersions is one way to improve the dissolution of poorly water-soluble drugs. This approach frequently improves bioavailability that is limited or rate-controlled by dissolution (Martin, 1993). Dispersion in freely aqueous-soluble carriers has been reported to considerably increase the dissolution rate of several drugs (Chiou & Riegelman, 1971; Nagarsenker & Garad, 1998; Ntawukulilyayo et al., 1993; Okimoto et al., 1997; Shin & Chiou, 1997). If the solid dispersion is an amorphous solid solution, not only is particle size of drug decreased to the molecular level, but there could be improvement in wettability of the drug (Craig, 2002) if the carrier is readily wetted. These effects increase the surface area available for mass transfer, and can enhance dissolution rate according to the modified Noyes-Whitney equation (Proudfoot, 1988). Furthermore, there may be a decrease in the enthalpy required to separate drug molecules from each other, or from the carrier molecules, compared to the energy required to separate drug molecules within a crystalline structure. Gibbs free energy of dissolution is likely to decrease as a result, enhancing solubility (Aulton, 1994). Amorphous drugs by themselves also have this solubility advantage, but may tend to rapidly revert to the crystalline state upon exposure to small quantities of plasticizers such as

water (Hancock & Parks, 2000). The solubility advantage of amorphous drugs by themselves is thus offset by poor physical stability, because of high internal energy and corresponding thermodynamic metastability, relative to the crystalline form (Hancock & Zografi, 1997). Existence of amorphous materials is thought to rely on slow kinetics of conversion to a thermodynamically more stable crystalline form (Ediger et al., 1996). Incorporation of drugs into drug-carrier solid solutions can retard drug crystallization (Khouzagaz & Clas, 2000; Nikolakakis et al., 2000; Yoshioka et al., 1995). This is more likely when the glass transition temperature (*Tg*) of the solid solution in question is higher than that of the amorphous drug by itself (Hancock & Zografi, 1994).

Piroxicam belongs to biopharmaceutical classification system (BCS) Type II (low aqueous solubility, high permeability) (Amidon et al., 1995; Löbenberg & Amidon, 2000). The present investigation was focused on exploring mannitol, dextrin, Eudragit® E100 and myrj 52 as a carrier to increase the drug solubility and the dissolution rate of hydrophobic drugs by formation of solid dispersions. In the previous study we found that these carriers improve the dissolution rate of the indomethacin (Valizadeh et al., 2004). In this study, the dissolution enhancement of piroxicam was attempted using a solid dispersion technique with above mentioned carriers.

## MATERIALS AND METHODS

### Materials

For the preparation of solid dispersions the following materials were used: Mannitol, dextrin (Merck, Darmstadt, Germany), piroxicam (Cenateur, India), myrj 52 (Polyoxyethylene 40 Stearate, Atlas Chemical Industries, Pasadena, CA). Eudragit® E100 was a gift from Röhm Pharma (Germany). All other materials used were of analytical or HPLC grade.

### Preparation of Solid Dispersions and Physical Mixtures

Physical mixtures of piroxicam were prepared by mixing piroxicam with the hydrophillic carriers for 5 min in 100 mL bottles, until a homogenous mixture was obtained. The resulting mixtures were sieved and the 125–420 μ particle size fraction was obtained using 40 and 120 mesh screen. The powders were stored in a screw-cap vial at room temperature until use.

Solid dispersions with different concentrations of piroxicam were prepared using the following three methods:

Coevaporates of the drug with dextrin and mannitol were prepared in the following piroxicam-carrier ratios: 1:10, 1:20, 1:40. Coevaporates were prepared by dissolving the components separately in a minimum volume of acetone and distilled water respectively. The acetonic solution of piroxicam was then poured into the aqueous solution of the carrier under continuous stirring. The mixture was then heated in a water bath (70°C) under vacuum and vigorous stirring. Initially a transparent to a translucent viscous mass was observed and finally a pale yellow coevaporate was formed. The moist mass was transferred to a vacuum desicator with heating device and kept at 70°C for 120 min and finally at 40°C overnight. The solid mass was ground and the particle size fraction of 125–420 μ was obtained by sieving and kept in a screw-capped glass vial until use.

Coevaporates with Eudragit® E100: The required amounts of piroxicam and Eudragit® E100 to yield drug-carrier proportions of 1:10, 1:20, and 1:40 were dissolved in a minimum volume of acetone by heating in a water bath. Then the solution was transferred to a vacuum desicator and was handled as described in the last section.

Solid dispersions with myrj 52: Solid dispersions with different concentrations of piroxicam were prepared by adding the drug to myrj 52, which were then melted in a water bath at 70°C. The mixtures were stirred and the resulting homogeneous preparations rapidly cooled. Subsequently the dispersions were pulverized and the 125–420 μ particle size fraction was obtained by sieving and kept in a screw-capped glass vial until use.

### Solubility Measurement of Piroxicam

Solubility measurements were performed according to Higuchi and Connors method (Higuchi & Connors, 1965): In brief an excess amount of piroxicam was weighed into test bottles to which 10 mL of dissolution medium (simulated gastric fluid without pepsin or simulated intestinal fluid without pancreatin) containing various concentrations of carriers was

added. The samples were sonicated (Metler Electronics, model ME5.5, USA) for 2 hr at room temperature, thereafter, the capped test tubes were shaken at 37±0.1°C for 48 hr in a water bath (This duration was previously tested to be sufficient to reach equilibrium). Subsequently, the suspensions were filtered through a 0.22 μm membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at the wavelength of 334 nm using a spectrophotometer (Shimadzu–120, Japan). All solubility experiments were done in duplicate. The solubility of piroxicam in these mediums was determined following the same procedure as above.

The Gibbs free energy of transfer $(\Delta G^0_{tr})$ of piroxicam from pure water to the aqueous solution of carrier was calculated as follows:

$$\Delta G^0_{tr} = -2.303\text{RT} \log S_0 / S_S$$

where $S_0/S_s$ is the ratio of the molar solubility of piroxicam in aqueous solutions of carrier to that of the same medium without carrier.

## Dissolution Studies

Hand-filled, hard gelatin capsules of the formulations, containing 20 mg of the drug, were used for the dissolution studies. The test was conducted with USP 27 Apparatus I at 50 rpm. The dissolution medium consisted of 900 mL simulated gastric fluid without pepsin (pH = 1.2) or simulated intestinal fluid without pancreatin (pH = 7.2) which was maintained at 37(±0.5)°C. The duration of the test was 30 min. A 5-mL aliquot was withdrawn at appropriate time intervals, and replaced with a 5 mL of fresh dissolution medium. The samples were filtered through a filter paper and assayed by UV spectrophotometry at 334 nm without the interference from carriers. Cumulative percentages of the drug dissolved from the preparations were calculated. Three replicates of each dissolution test were performed.

## Powder X-Ray Diffraction

The powder X-ray diffraction (PXRD) pattern of all ingredients and all binary systems were recorded using an automated siemens X-ray diffractometer (Siemens D5000, Munich, Germany). Cross-sections of the ingredients and all binary systems were taken and held in place on a quartz plate to Cu Kα radiation of wave length 1.5406 Å. The samples were analyzed at room temperature ovesr a range of 5–70° 2θ with sampling intervals of 0.02° 2θ and scanning rate of 6°/min.

## Fourier-Transform Infrared Spectroscopy

Fourier-transform infrared Spectroscopy (FT-IR) were obtained on a Bomem 2000 FT-IR system (Bomem Quebec, Canada) using the KBr disk method. Samples were mixed with KBr powder and compressed to 10-mm discs by hydraulic press at pressure of 10 tons for 30 s. The scanning range was 450–4000 $cm^{-1}$ and resolution was 2 $cm^{-1}$.

# RESULTS AND DISCUSSION

## Solubility Studies

The solubility of piroxicam in simulated gastric fluid and simulated intestinal fluid at 37°C was found to be 0.23 mmol/L (74.72 μg/mL) and 0.845 mmol/L (280 μg/mL), respectively. Therefore, according to the USP solubility definition, piroxicam can be considered as a practically insoluble drug at pH 1.2 and very slightly soluble at pH 7.2. Aqueous solutions of mannitol did not seem to increase the solubility of piroxicam (Table 1, Fig. 1). The solubility data and phase solubility diagram of piroxicam in solutions containing myrj 52 at 37°C in simulated gastric fluid and simulated intestinal fluid are shown in Table 1 and Fig. 1. At 4% of myrj 52 the increase in solubility at 37°C in simulated gastric fluid and simulated intestinal fluid was about 2.3-fold and 3.2-fold, respectively, compared to pure piroxicam. The increase in solubility in the presence of myrj 52 can probably be explained by micellar solubilization. Table 2 presents the thermodynamic parameters associated with the aqueous solubility of piroxicam in the presence of different carriers. An indication of the process of piroxicam transfer from pure water to the aqueous solutions of myrj 52 may be obtained from the values of Gibbs free energy change. $\Delta G^0_{tr}$ values were negative indicating the spontaneous nature of the drug solubilization. The values decreased by increasing myrj 52 concentration, demonstrating that the reaction became more favorable as the concentration of myrj 52 increased.

**TABLE 1** **Solubility Data (Mmol/L) for Piroxicam at pH 1.2 and 7.2 Water-carrier Systems in 37°C**

| Carrier concentration(%w/w) | | 0.25 | 1 | 4 | 8 | 16 |
|---|---|---|---|---|---|---|
| pH 1.2 | Mannitol | 0.218 ± 0.014 | 0.266 ± 0.026 | 0.266 ± 0.046 | 0.266 ± 0.045 | 0.245 ± 0.050 |
| | Dextrin | 0.166 ± 0.015 | 0.168 ± 0.013 | – | – | – |
| | Myrj 52 | 0.200 ± 0.017 | 0.222 ± 0.021 | 0.519 ± 0.053 | 0.647 ± 0.085 | 1.185 ± 0.144 |
| | Eudragit® E100 | 1.483 ± 0.097 | 1.383 ± 0.082 | 1.816 ± 0.132 | 2.299 ± 0.157 | 3.465 ± 0.264 |
| pH 7.2 | Mannitol | 0.849 ± 0.082 | 0.873 ± 0.105 | 0.817 ± 0.118 | 0.821 ± 0.157 | 0.809 ± 0.124 |
| | Dextrin | 0.843 ± 0.164 | 0.825 ± 0.206 | – | – | – |
| | Myrj 52 | 1.460 ± 0.213 | 1.75 ± 0.224 | 2.661 ± 0.364 | 3.324 ± 0.326 | 3.49 ± 0.433 |
| | Eudragit® E100 | – | – | – | – | – |

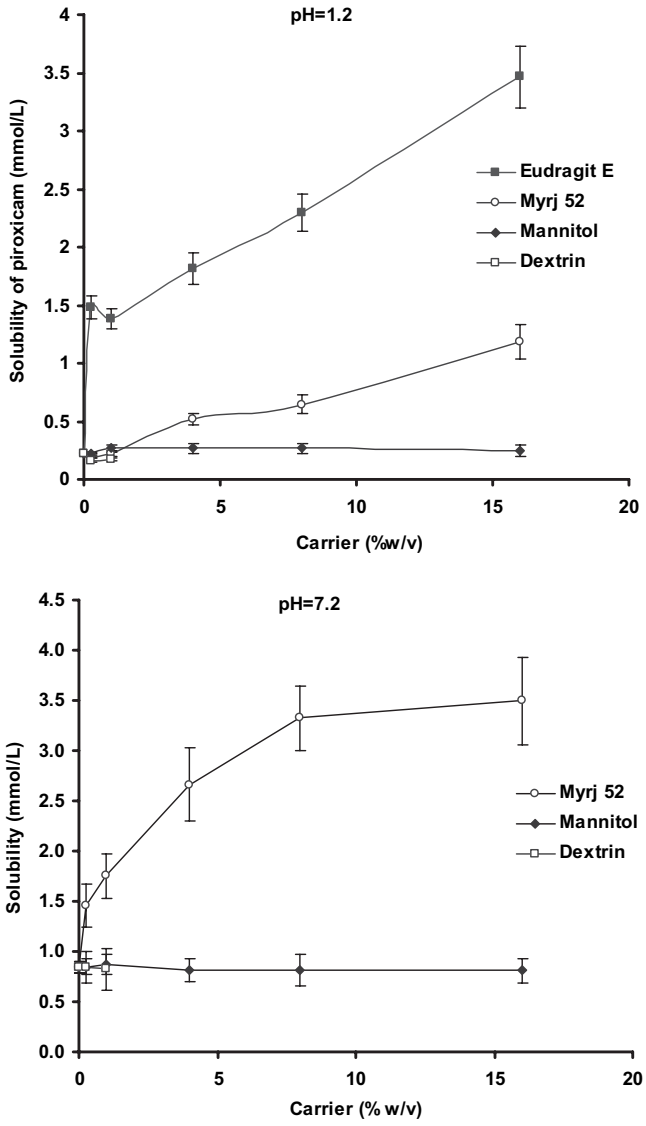


**FIGURE 1** **Phase Solubility Diagram of Piroxicam in Aqueous Solutions of Different Carriers at 37°C, in Two Medium.**

**TABLE 2** **The Value of Gibbs Free Energy of Transfer for the Solubility Process of Piroxicam at pH 1.2 and 7.2 Water-carrier Systems in 37°C**

| | | $\Delta G^{\circ}_{tr}$ | |
|---|---|---|---|
| Carrier | % w/w | pH 1.2 | pH 7.2 |
| Mannitol | 0.25 | 33 | –804.59 |
| | 1 | –89.52 | –826.76 |
| | 4 | –89.52 | –780.92 |
| | 8 | –89.52 | –783.92 |
| | 16 | –38.92 | –774.86 |
| Dextrin[a] | 0.25 | 219.74 | –800.22 |
| | 1 | 193.52 | –786.92 |
| | 4 | – | – |
| | 8 | – | – |
| | 16 | – | – |
| Myrj 52 | 0.25 | 86.1 | –1138.59 |
| | 1 | 21.81 | –1250.21 |
| | 4 | –501.38 | –1508.17 |
| | 8 | –637.16 | –1664.71 |
| | 16 | –1010.01 | –1675.48 |
| Eudragit® E100[a] | 0.25 | –1148.22 | – |
| | 1 | –1105.22 | – |
| | 4 | –1273.01 | – |
| | 8 | –1418.01 | – |
| | 16 | –1671.05 | – |

[a]Measurement of the drug solubility in the presence of Edragit E100 at pH 7.2 and high amounts of dextrin at both pHs was not possible because of carrier solubility problems.

The results for Eudragit® E100 were interesting. The solubility of piroxicam in an 8% aqueous solution of Eudragit® E100 at pH 1.2 was 2.299 mmol/L (761.52 μg/mL). But when piroxicam was first mixed with this carrier and then put into pH 1.2 medium, there was a considerable increase in solubility as compared to the aqueous solution of Eudragit® E100 [3.85 mmol/L (1275.9 μg/mL)]. In addition to the solubilizing effect, the increase in solubility in the presence of this carrier can be explained by an increase in medium pH. Addition of Eudragit® E100 raises the pH of the medium, which results in a considerable increase in the solubility of piroxicam. In

fact when 0.8 g Eudragit® E100 was added to 10 mL pH 1.2 medium, the pH was determined to be 6.5. Phase solubility diagram obtained for piroxicam in the presence of Eudragit® E100 at 37°C in simulated gastric fluid is shown in Fig. 1. A content of 8% w/w Eudragit® E100 at pH 1.2 and 37°C increased the solubility about 10-fold compared to piroxicam by itself. From our data it is clear that aqueous solutions of Dextrin did not seem to increase the solubility of piroxicam. Measurement of the piroxicam solubility in the presence of Eudragit® E100 at pH 7.2 and high amounts of dextrin at both pHs was not possible because of carrier solubility problems.

## Dissolution Studies

The release of piroxicam from solid dispersions and physical mixtures was analyzed in simulated gastric fluid without pepsin and simulated intestinal fluid without pancreatin. $Q_{5min}$ and $Q_{15min}$ values (percent drug dissolved within 5 and 15 min) are reported in Table 3. From Table 3 it is evident that the dissolution rate of pure piroxicam is low (less than 22% of the drug being dissolved within 15 min). Solid dispersions of piroxicam with hydrophilic carriers, except Eudragit® E100 at pH 7.2 and dextrin, considerably enhanced dissolution rate compared to the physical mixtures of ingredients. The dissolution rate of all physical mixtures was higher compared to pure piroxicam. Possible explanations of the increased dissolution rate of solid dispersions have been proposed by Ford and Craig (Craig, 2002; Ford, 1986), and include: reduction of drug crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug, dissolution of the drug in the hydrophilic carrier, conversion of the drug to the amorphous state and finally the combination of the above mentioned mechanisms.

Dry mixing of piroxicam with dextrin, mannitol, myrj 52 or Eudragit® E100 brings the drug in close contact with the hydrophilic carrier. The increased dissolution rate observed in these cases can be contributed to several factors such as a solubilization effect of the carrier, improved wettability of the drug and inhibition of particle aggregation. Piroxicam alone exhibited the slowest dissolution rate with only about 21.7% of drug release in 15 min. As shown in Table 3, the dissolution rate of piroxicam from all physical mixtures of the drug-mannitol were almost the same, but considerably is higher than that of piroxicam alone. This might be caused by the reduction in surface tension of the medium caused by the presence of mannitol, resulting in a better wetting of piroxicam (Sekikawa et al., 1979; Valizadeh et al., 2004). The dissolution rates for solid dispersions prepared with mannitol were greater than those for physical mixtures or

**TABLE 3** **Percent Drug Dissolved Within 5 and 15 Min ($Q_{5min}$ and $Q_{15min}$) of Piroxicam-carrier Binary Systems at pH 1.2 and 7.2 (Standard Deviations Were All Less Than 10%)**

| | | pH=1.2 | | | | pH=7.2 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Physical mixture | | Solid dispersion | | Physical mixture | | Solid dispersion | |
| Sample | | $Q_{5min}$ | $Q_{15min}$ | $Q_{5min}$ | $Q_{15min}$ | $Q_{5min}$ | $Q_{15min}$ | $Q_{5min}$ | $Q_{15min}$ |
| Pure piroxicam | | 10.97 | 21.68 | – | – | 4.01 | 22.59 | – | – |
| Mannitol | 1:10 | 28.51 | 57.37 | 63.52 | 93.57 | 54.23 | 81.59 | 87.65 | 98.56 |
| | 1:20 | 32.54 | 54.84 | 70.14 | 95.29 | 55.57 | 69.34 | 94.58 | 98.26 |
| | 1:40 | 33.45 | 58.43 | 76.34 | 99.31 | 61.28 | 78.51 | 97.65 | 100 |
| Dextrin | 1:10 | 27.12 | 42.71 | 26.14 | 39.18 | 51.65 | 79.65 | 38.56 | 60.19 |
| | 1:20 | 37.18 | 65.92 | 22.93 | 39.24 | 53.84 | 80.16 | 25.26 | 56.34 |
| | 1:40 | 45.32 | 67.33 | 17.64 | 34.56 | 54.23 | 79.84 | 22.55 | 50.3 |
| Myrj 52 | 1:10 | 50.16 | 72.64 | 90.26 | 100 | 68.33 | 85.24 | 96.33 | 100 |
| | 1:20 | 53.46 | 79.94 | 100 | 100 | 69.84 | 88.74 | 100 | 100 |
| | 1:40 | 56.24 | 83.55 | 100 | 100 | 74.29 | 93.58 | 100 | 100 |
| Eudragit® E100 | 1:10 | 25.31 | 39.54 | 66.6 | 91.65 | 18.54 | 40.21 | 4.08 | 9.26 |
| | 1:20 | 19.48 | 43.72 | 74.62 | 98.42 | 15.45 | 33.06 | 3.38 | 7.23 |
| | 1:40 | 20.34 | 43.22 | 93.39 | 100.34 | 11.88 | 28.64 | 2.6 | 5.84 |

piroxicam alone (Fig. 2). The enhanced dissolution rates of solid dispersions in this case may be attributed to many factors such as decreased particle size of the drug (Ford, 1986), and the specific form of the drug (Simonelli et al., 1976) in the solid dispersions. However, the earlier mentioned mechanisms like increase in drug wettability and prevention of drug aggregation by carrier may also apply (Leuner & Dressman, 2000). With respect to the drug alone, an improvement in the dissolution rate was achieved for the formulations containing dextrin (Fig. 2). However, the release of piroxicam from physical mixtures was slightly faster than the release from coevaporates. This could be attributed to the fact that, dissolution mechanism of solid dispersion with dextrin might be predominantly diffusion-controlled, and presumably the high viscosity of this carrier in stagnate layer is the main factor to control the dissolution rate. Similar observation has been reported for indomethacin (Valizadeh et al., 2004).

An improved dissolution rate of piroxicam from formulations prepared with myrj 52 was obtained. From Fig. 3 it is evident that the dispersion of drug in this carrier considerably enhances the dissolution rate of piroxicam compared to physical mixtures. The $Q_{5min}$ for all systems prepared with myrj 52 was more

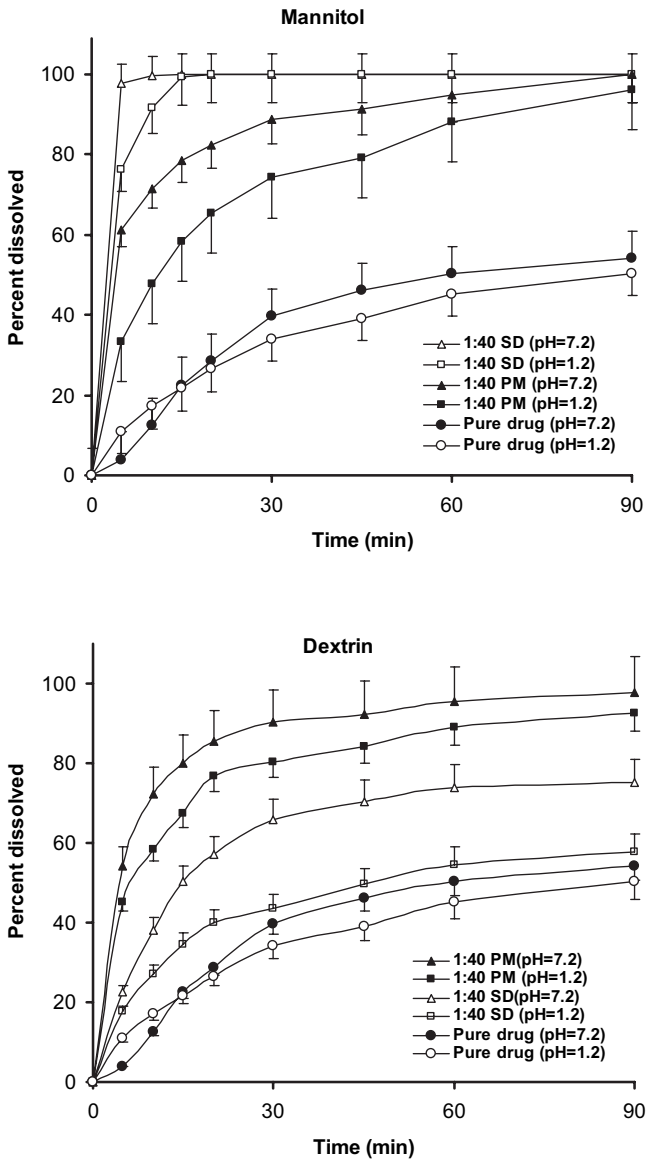


**FIGURE 2** **Dissolution Profiles of Physical Mixtures (PM) and Solid Dispersions (SD) of Piroxicam With Mannitol and Dextrin in pH 1.2 and 7.2.**

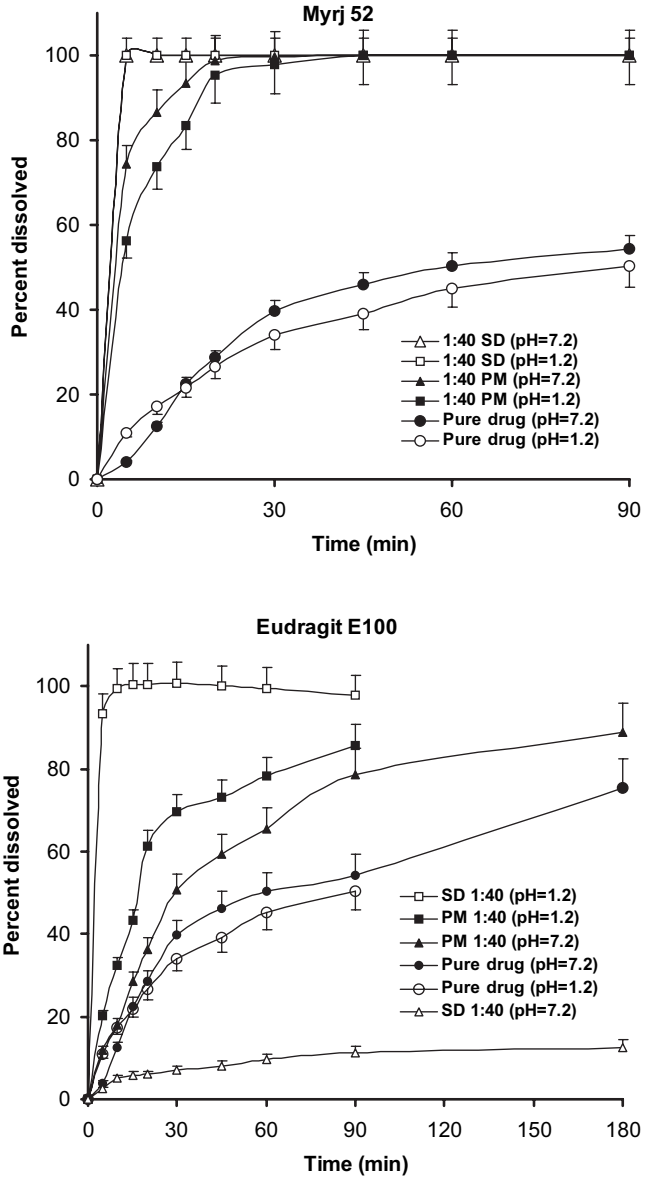


**FIGURE 3** **Dissolution Profiles of Physical Mixtures (PM) and Solid Dispersions (SD) of Piroxicam With myrj 52 and Eudragit® E100 in pH 1.2 and 7.2.**

than 90% (Table 3). This phenomenon can be attributed to the solubilization effect of these carrier, improved wettability and dispersibility of the drug from the dispersion.

Fig. 3 shows the amount of piroxicam dissolved from physical mixtures and coevaporates of piroxicam with Eudragit® E100 at pH 1.2 and 7.2. The $Q_{5min}$ values of 66.6 and 93.39 were observed for 1:10 and 1:40 coevaporates respectively at pH 1.2 (Table 3). The rapid drug release can be attributed to the high solubility of the polymer at this pH, solubilizing effect of Eudragit® E100 as well as a microenvironmental pH increase around particles, which is favorable to the piroxicam dissolution (Fig. 3).

Coevaporates with Eudragit® E100 delayed and decreased the dissolution of the piroxicam in a simulated intestinal fluid (pH 7.2) (Table 3, Fig. 3). After 3 hr, only 23.45% of the drug was released from 1:10 coevaporate and 12.57 from 1:40 coevaporate. However, the dissolution rates of physical mixtures were higher compared to pure piroxicam that may be caused by the absence of aggregation of drug crystallites. Compared to the piroxicam alone and physical mixtures, the lower dissolution rate of the drug in coevaporates can be associated to the insolubility of the Eudragit® E100 at this pH. The mechanism of drug release in this case depends on the penetration of the dissolution medium into coevaporate, the dissolution and subsequent diffusion of the drug through the polymeric matrix, and hence the diffusional process within the drug-polymer system as shown by Abd El-Fattah et al. (Abd El Fattah et al., 1984), and Valizadeh et al. (Valizadeh et al., 2004).

## Powder X-Ray Diffraction (PXRD)

The extent of crystallinity influences dissolution of drugs. An amorphous or metastable form will dissolve at the fastest rate because of its higher internal energy and greater molecular motion, which enhance thermodynamic properties compared to crystalline materials (Hancock & Zografi, 1997; Matsumoto & Zografi, 1999).

Kuhnert et al. reported that piroxicam has three crystalline forms. Only β (I) polymorph with the highest melting point was found to be stable under mechanical and thermal stress. Form α (II) is metastable and Form III is very unstable which rapidly is changed to the other polymorphs (Kuhnert-Brandstätter & Völlenklee, 1985; Vrecer et al., 2003). Dominant peaks at 2θ of 8.99°, 15.76°, 23.02° and 25.85° has been reported for α (II) crystalline form; 2θ of 8.99°, 14.46°, 17.67°, 21.83° and 27.36° for β (I) crystalline form and 2θ of 8.99°, 12.86°, 18.22°, 24.88°, 28.52° and 29.22° for III crystalline form (Vrecer et al., 2003).

Characteristic peaks of pure intact piroxicam appeared at diffraction angles (2θ) of 8.99°, 14.46°, 17.67°, 21.83°, and 27.36°. These values are comparable to those reported for modification I (β, cubic form) (Fig. 4). Our finding revealed that piroxicam was in its crystalline forms in the physical mixtures prepared with mannitol, dextrin and Eudragit® E100. However solid dispersions prepared with mannitol did not show any peak at 2θ of 14.46°, 17.67° and 27.36° instead small peaks appeared at 2θ of 15.76° and 23.02°, that are related to modification II (α, needle form) of piroxicam (Fig. 4). Solid dispersions prepared with dextrin and Eudragit® E100 were characterized by the complete absence of any diffraction peaks, suggesting a complete amorphization or drug salvation in these amorphous carriers (Figs. 5 and 6).

## Fourier-Transform Infrared Spectroscopy

Fourier-transform infrared (FT-IR) spectroscopy was used to further characterize possible interactions between the drug and carrier in the solid state.

As is well known (Mihalic et al., 1982; Mihalic et al., 1986; Vrecer et al., 2003), the most significant differences in the IR spectra of different polymorphic piroxicam modifications concern the positions of the amide N–H or enol O–H stretching absorption bands at 3393 $cm^{-1}$ for modification II (needle form) and 3334 $cm^{-1}$ for modification I (cubic form). In this study pure intact piroxicam showed the N–H or O–H stretching vibration at 3335 $cm^{-1}$ (attributed to modification I) and this region of interest showed the evidence of interaction between piroxicam and carriers via intermolecular hydrogen bonding.

From the structures of the piroxicam and carriers it can be assumed that possible interactions could occur between the hydroxyl group and amide group of piroxicam with hydroxyl groups of mannitol, myrj 52, dextrin and the basic amine group of the Eudragit® E100. Any sign of interaction would be reflected by a

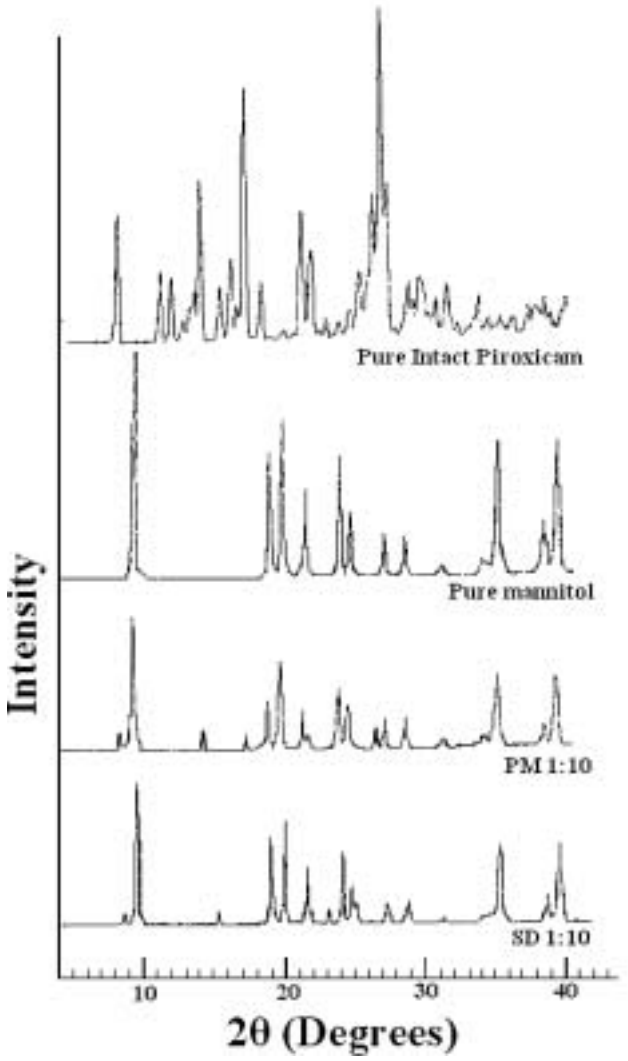


**FIGURE 4** X-ray Diffraction Patterns of Solid Dispersions (SD) and Physical Mixtures (PM) of Piroxicam With Mannitol.

change in O–H and N–H vibration, depending on the extent of interaction.

Fig. 7 shows the FT-IR spectra for pure piroxicam, pure mannitol, physical mixture and solid dispersion system prepared using mannitol. Physical mixture exhibits a characteristic band at 3335 $cm^{-1}$ (OH stretching), that is attributed to β (I) crystalline form of piroxicam, whereas related solid dispersion system exhibits a characteristic band at 3399 $cm^{-1}$, that is attributed to α (II) crystalline form of piroxicam.

This observation indicates that dispersion of piroxicam in mannitol gives crystals of modification II, which has higher solubility than modification I (Vrecer et al., 2003). This confirms the results obtained from PXRD and dissolution studies.

The spectrum of dextrin showed, amongst others, important bands at 2953 $cm^{-1}$ (C–H stretching) and 1109 $cm^{-1}$ (C–O stretching). A very broad band was also visible at 3446 $cm^{-1}$, which attributed to the presence of water (Fig. 7). An expected interaction between piroxicam and dextrin in the solid state, involve the OH or NH function of piroxicam and OH groups of the dextrin in hydrogen bonding. Indeed, the absorption bands, which can be assigned to the free OH and NH, disappeared, and the OH band because of intermolecular association increased in intensity. The reason for this observation can be interpreted as a consequence of hydrogen bonding between OH or NH groups of piroxicam and the OH of dextrin; this will result in a decreased stretching frequency. Our findings are in accordance with previous reports (Sekikawa et al., 1979; Tantishaiyakul et al., 1999; Valizadeh et al., 2004).

The site of interaction between piroxicam and myrj 52 is expected to be at the oxygen atoms of myrj 52 with OH and NH groups of piroxicam, but the results showed that there were no significant differences between FT-IR spectrum of solid dispersions and FT-IR spectrum of physical mixtures prepared with myrj 52 (Fig. 8). The absence of any other new peaks in the solid dispersion systems indicates that piroxicam is not undergoing any polymorphic change during their preparation, confirming the PXRD results. Furthermore the absence of shift in the wave numbers of the FT-IR peaks of the solid dispersion compared to the physical mixture indicate lack of significant interaction between the drug and the components in the solid dispersion systems (Fig. 8).

In the case of Eudragit® E100, the peak, which was assigned to the hydroxyl at 3335 $cm^{-1}$, disappeared in the solid dispersion systems (Fig. 8). The reason for this observation can be interpreted as a consequence of hydrogen bonding between amide group of piroxicam and oxygen atoms of Eudragit® E100, and as a result there will be a decrease in stretching frequencies of OH and NH groups.

## CONCLUSION

Solubility studies showed a solubilizing effect of myrj 52 on piroxicam at pH 1.2 and pH 7.2. The negative values of the Gibbs free energy and enthalpy of transfer from water to an aqueous solution of myrj 52 indicated the spontaneity of the transfer. Increased

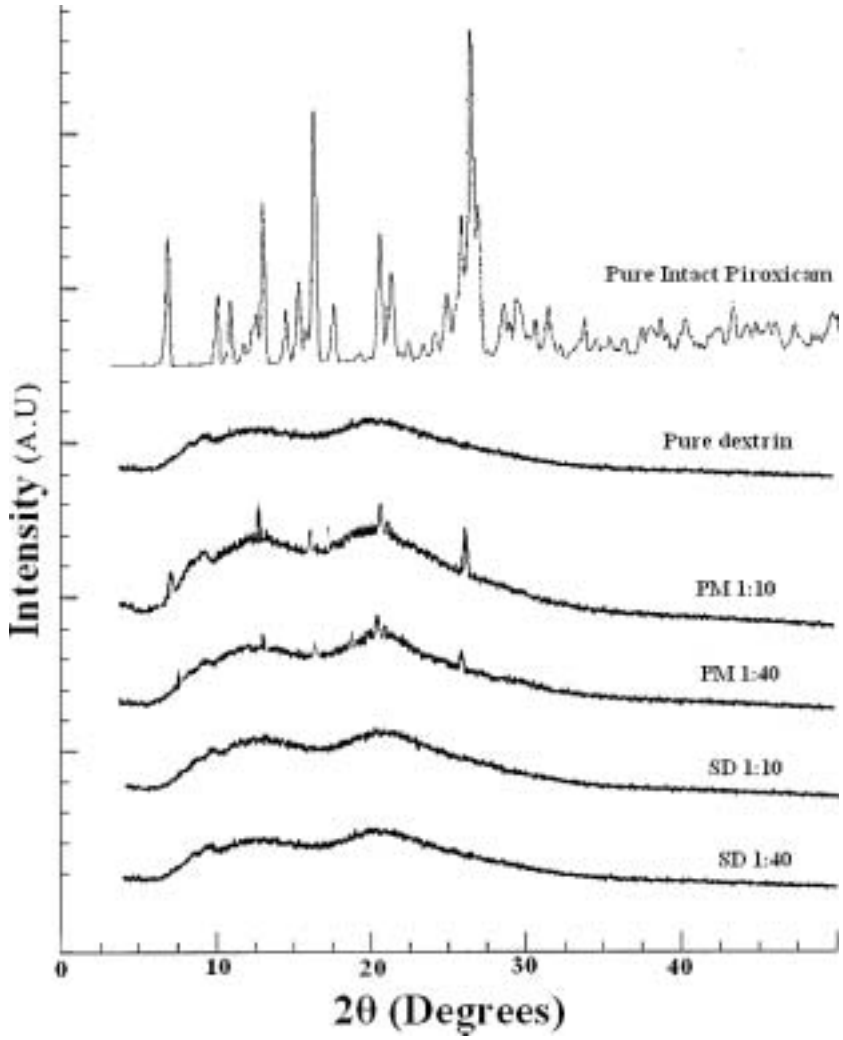


**FIGURE 5** X-ray Diffraction Patterns of Solid Dispersions (SD) and Physical Mixtures (PM) of Piroxicam With Dextrin.

solubility was also observed in aqueous solutions of Eudragit® E100 at pH 1.2. An increased dissolution rate of piroxicam at pH 1.2 and pH 7.2 was observed when the drug was dispersed in myrj 52 and mannitol. The solubilization effect of myrj 52 as well as the reduction of particle aggregation and an alteration of the surface properties of the drug particles might be responsible for the enhanced dissolution rate. In the case of mannitol, an alteration of surface properties as well as a reduction of the particle size might be responsible for the enhanced dissolution rate. Solid dispersions of piroxicam with Eudragit® E100 markedly improved the dissolution rate and extent at pH 1.2 because of a microenvironmental pH change induced by this polymer.

Results from IR spectroscopy concluded that there was no well-defined interaction between piroxicam and Mannitol or myrj 52. But in the cases of Dextrin and Eudragit® E100 a drug-carrier interaction through intermolecular hydrogen bonding was demonstrated using FT-IR. Powder X-ray diffraction indicated that piroxicam was in the amorphous state when dispersed in Dextrin or Eudragit® E100, and crystallinity reduced in solid dispersion systems prepared with mannitol but in the case of myrj 52 there was not difference between the crystallinity of piroxicam in physical mixtures and solid dispersions.

Since the coevaporates with dextrin and mannitol could be prepared by using two different but mutually soluble solvents, the need of a common solvent for the drug and the carrier should not be considered an absolute requirement for preparation of co-evaporates. Use of two mutually soluble solvents will broaden the application of the co-evaporation technique for a wider range of drugs and carriers.

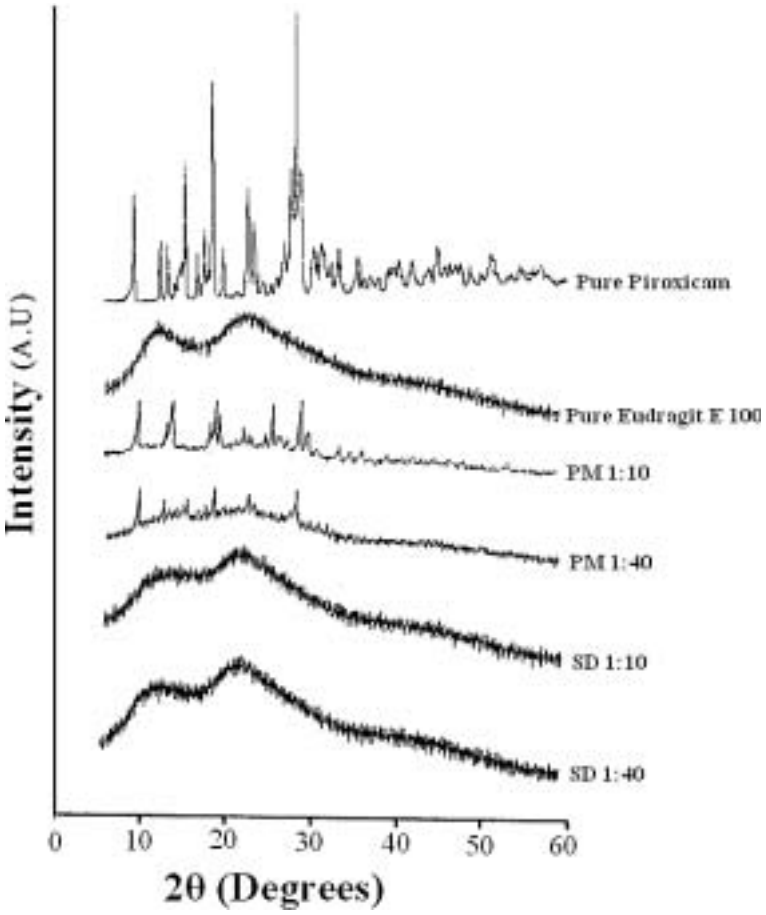


**FIGURE 6** X-Ray Diffraction Patterns of Solid Dispersions (SD) and Physical Mixtures (PM) of Piroxicam With Eudragit® E100.

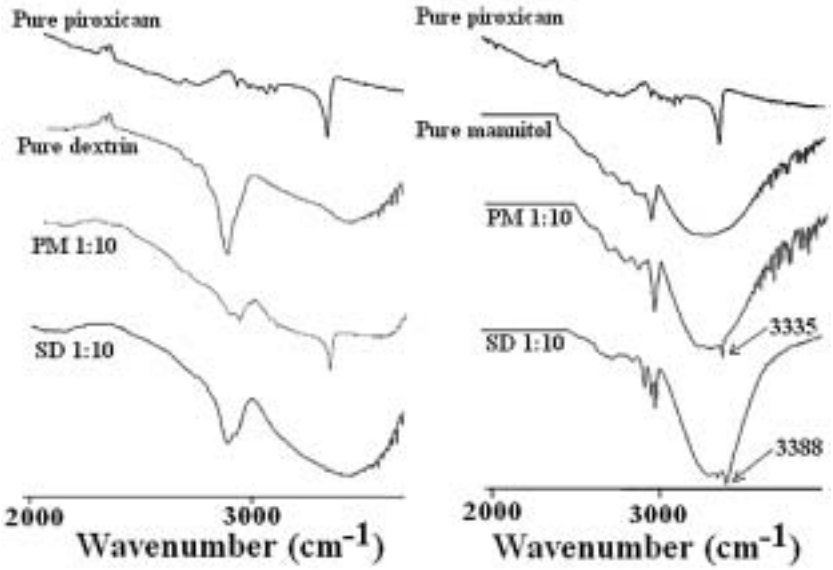


**FIGURE 7** FT-IR Spectra of Pure Piroxicam, Mannitol, Dextrin, 1:10 Physical Mixture (PM) of Piroxicam With Mannitol or Dextrin, and 1:10 Solid Dispersion (SD) of Piroxicam With These Carriers.

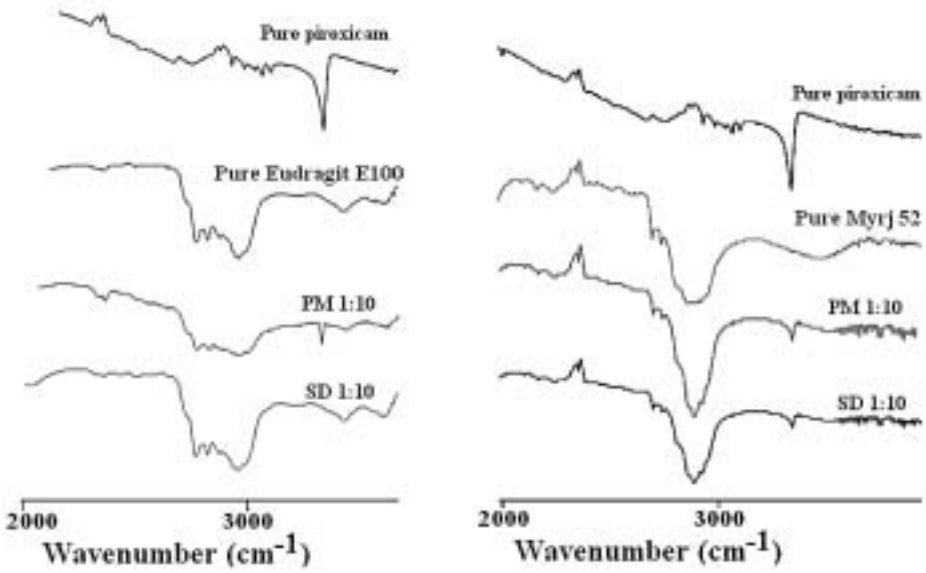


**FIGURE 8** **FT-IR Spectra of Pure Piroxicam, myrj 52, Eudragit® E100, 1:10 Physical Mixture (PM) of Piroxicam With myrj 52 or Eudragit® E100, and 1:10 Solid Dispersion (SD) of Piroxicam With These Carriers.**

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