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RESEARCH PAPER

Solubility of Solid Dispersions of Pizotifen Malate and Povidone

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ABSTRACT

We analyzed the physicochemical characteristics of solid dispersions of pizotifen malate and povidone (Kollidon 12) at different proportions; we used X-ray diffraction, infrared spectrometry, and differential scanning calorimetry (DSC) and tested the solubility of the solid dispersions in equilibrium. The results were compared with findings for physical mixtures with the same proportions. A solid dispersion with a drug proportion of 16%–17% formed a eutectic mixture. Solubility of pizotifen malate increased with the proportion of drug in the solid dispersion up to a drug : polymer ratio of 40 : 60. The hydrotropic effect of the polymer also favored solubility: In physical mixtures, this effect was greatest at a drug : polymer ratio of 10 : 90; solubility at this proportion was equal to that of the solid dispersion at the same proportion.

Key Words: *Differential scanning calorimetry; Infrared spectroscopy; Physical mixture; Pizotifen malate; Povidone; Solid dispersion; Solubility in equilibrium; X-ray diffraction.*

INTRODUCTION

Pizotifen malate (piz-M), a potent antagonist of 5-HT_2 and histamine H_1 receptors, is widely used for prophylaxis for migraine headaches (1); it is poorly soluble in water (2). Solid dispersions (3,4), polymorphic transformations (5), and surfactants and cosolvents (6,7) have been tested to search for ways to increase the solubility of such drugs.

We prepared solid dispersions (SDs) of piz-M with povidone as the carrier. This polymer was chosen because it is well tolerated physiologically and is readily soluble in water and because it has been used as a carrier by several others; it results in an increase of dissolution

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and oral absorption (8–10). Furthermore, it was demonstrated to have a hydrotropic effect in other substances (11). The solubility of piz-M in the SDs prepared could be increased by this hydrotropic effect.

The physicochemical properties of the SDs were investigated with X-ray diffraction, infrared spectroscopy, and differential scanning calorimetry (DSC). In addition, we determined the solubility in equilibrium. The results were compared with the findings for physical mixtures (PMs) prepared at the same proportions of drug : polymer as the SDs.

For evaluating piz-M solubility in equilibrium assays, we used a spectrophotometric method (12).

EXPERIMENTAL

Materials

Pizotifen malate, $C_{19}H_{21}NS,C_4H_6O_5$ (Sandoz Pharma SAE, Barcelona, Spain); povidone (polyvinylpyrrolidone [PVP] Kollidon 12 PF, BASF, Seville, Spain); chloroform and methanol (analytical grade, Panreac, Granada, Spain); monobasic potassium phosphate and sodium hydroxide (analytical grade, Merck, Granada, Spain) were used.

Methods

The SDs containing different percentage proportions of piz-M/PVP (Table 1) were prepared according to the dissolution method described by Puisieux and Henry (13). Chloroform : methanol (1 : 1) was used as the solvent, and the mixture was evaporated in an oven at 40°C. Desiccation was completed in a vacuum oven until a constant weight was achieved, and the resulting solid was pulverized. PMs were prepared by homogenizing the two components at the proportions shown in Table 1.

Table 1

Composition of Samples and Thermal Parameters of Pizotifen Malate (piz-M) and Solid Dispersions of Pizotifen Malate/ Povidone (piz-M/PVP)

Samples Composition (% w/w)		Melting Point	Heat of Fusion
Piz-M	PVP	(°C)	(J/g)
10	100	—	—
20	90	—	—
30	80	—	—
40	70	—	—
50	60	—	—
70	50	188.1	81.1
90	30	189.1	125.0
100	10	191.8	173.0
—	—	197.8	200.0

Both SDs and PMs were placed in sealed, opaque recipients and stored away from light and humidity until assay.

Infrared spectra were recorded on a Perkin Elmer 298 infrared spectroscope from pure piz-M and PVP and from SD and PM samples prepared in KBr discs. The scanning range was 4000 to 600 cm^{-1} at a scan period of 14 min.

X-ray diffraction patterns of powdered samples were obtained with a Rigaku-Miniflex Ca 2005 apparatus equipped with a nickel filter using CuK_α radiation. For qualitative studies, the samples were scanned from 5° to 40° 2θ. The scan rate selected was 2°/min.

Differential scanning calorimetry (Mettler FP 80 calorimeter) was used to obtain thermograms of 7 mg samples using a heating rate of 5°C/min over the range 100°C to 250°C.

Peak transition temperature was determined for all samples, and heat of fusion H_f was estimated by the integration of the heat flow-versus-temperature peak data with Mettler System Software FP89.

For equilibrium solubility studies, weighed amounts of pure piz-M alone, in SD, and in PM (corresponding to 0.05 g of drug) were placed in 10-ml glass tubes containing 3 ml distilled water. The tubes were sealed and agitated at 120 rpm in a thermostated shaking water bath (Julabo SW21) set at 37°C ± 0.1°C. After 5 days, the samples were filtered through a 0.45-μm Millipore filter (Ireland), and 1 ml of each solution was diluted to 100 ml with phosphate buffer (pH 7.0). Diluted samples were assayed spectrophotometrically at 251.4 nm (12).

Statistical Analysis

The data for solubility studies were analyzed with the Statgraphic software program (Statgraphic v. 6.0, Los Angeles, CA, 1992).

RESULTS AND DISCUSSION

The infrared spectra for pure piz-M and PVP and for the SDs and PMs (from 10 : 90 to 70 : 30 w/w percentage

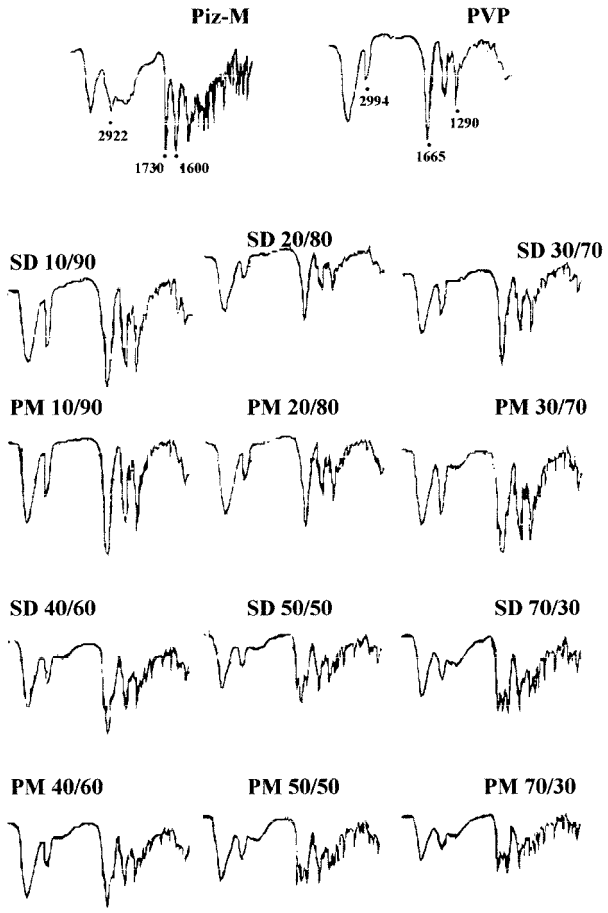

Figure 1. Infrared spectrograms of pizotifen malate and povidone as pure chemicals, solid dispersions, and physical mixtures.

drug : polymer content) are shown in Fig. 1. Both SDs and PMs reflected the characteristics of the main component present. Absorbance of piz-M predominated up to a drug content of 30%. The spectra for mixes containing 30% or more drug had characteristics of both crystalline piz-M and amorphous PVP.

At a proportion of piz-M of 10% or 20%, stretching vibration of the C═O group in PVP masked the absorption bands for piz-M (1730 and 1600 cm^{-1}; Table 2). The spectra contained a large band that overlapped the stretching vibration of the C═O and C═C groups in the drug. At a proportion of piz-M of 30% or higher, vibration bands for the drug appeared and became stronger as the proportion of drug increased.

The X-ray diffraction spectra for pure piz-M and PVP and for the SDs and PMs are shown in Fig. 2 for drug

Table 2

Infrared Assignment of Pizotifen Malate and Povidone Spectra

	Assignment	Wavenumber (cm^{-1})
Pizotifen malate	O—H	2922
	C═O	1730
	C═C	1600
	C—H	1435
		1375
		1300
		1100
	C—N	1180
Povidone	C—H	2994
		1495
		1463
		1423
		1387
	C═O	1665
	C—N	1290

concentrations up to 50%. The results for SDs and PMs showed an elevation of the baseline and characteristic diffraction peaks for piz-M. Both effects indicated the presence of two species, an amorphous one (PVP) and a crystalline one (piz-M).

Because of the low concentration of drug and coprecipitation of the two main components, the diffractogram for the 10 : 90 SD indicated that piz-M existed as microcrystals trapped in the carrier. No characteristic diffraction peaks were seen for the drug. Baseline elevation was less pronounced in the SD than in the pure polymer, indicating increased crystallinity. In contrast, in the 10 : 90 PM, the carrier appeared as an elevated baseline, and the drug produced characteristic diffraction peaks.

In the 20 : 80 SD and PM and samples containing greater proportions of the drug, increasing crystallinity led to the appearance of characteristic diffraction peaks for piz-M. The peaks became more defined as the proportion of drug increased.

Figure 3 shows characteristic thermograms for pure piz-M and PVP and binary mixtures. A characteristic fusion endotherm appeared for the drug, with a peak melting point at 197.8°C.

Because of the amorphous structure of the polymer, no peak melting point was seen in the thermograms. In scanning differential calorimetry analyses, no fusion endotherm was seen for SDs or PMs below a drug content

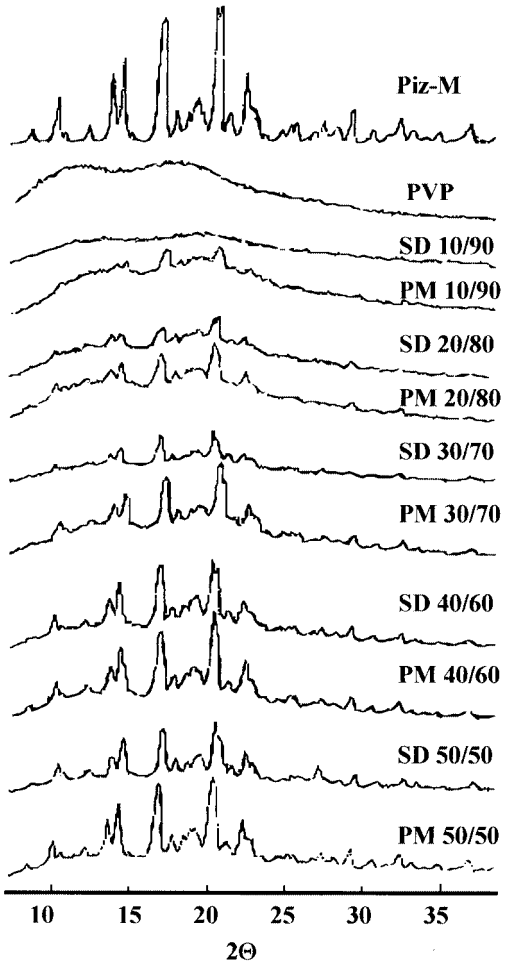

Figure 2. X-ray diffraction data for pizotifen malate and povidone as pure chemicals, solid dispersions, and physical mixtures.

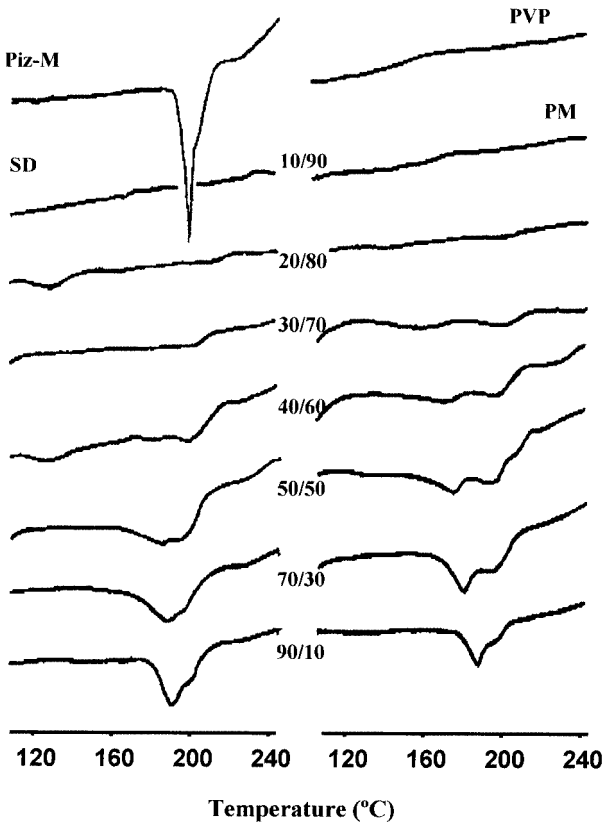

Figure 3. Differential scanning calorimetric data for pizotifen malate and povidone as pure chemicals, solid dispersions, and physical mixtures.

of 40%. This may reflect dissolution of the drug in the polymer during heating and the formation of a eutectic mixture. Consequently, the thermogram was more similar to that of the pure carrier. As the percentage of drug in the sample increased, the peak melting point for both components became better defined and more closely resembled the peak for pure drug (Table 1).

The similar DSC behaviors of SDs and PMs of the same composition indicated that there was no physical interaction between piz-M and PVP. These results were consistent with the findings obtained with infrared spectrophotometry and X-ray diffraction.

To determine the threshold proportion for the formation of a eutectic mixture, we measured the heat of fusion (14,15). A linear relation was found between heat of fusion and composition of the sample (Fig. 4), with a correlation coefficient approaching unity ($r = 0.9993$). The intersect of the straight line with the abscissa indicated that the miscibility threshold was reached at a drug proportion of 16%–17%.

In all samples tested, the polymer, because of its hydrophilic nature and amorphous structure, dissolved completely within the period of the assay; dissolution was faster than for the drug, which is hydrophobic and crystalline. However, complete dissolution occurred only when the proportion of polymer in the sample was below its solubility in water (100 mg · ml^{-1}) (16).

The results for solubility in equilibrium for PMs were subjected to analysis of variance and linear regression analysis. Solubility of piz-M was dependent on the amount of polymer in the sample ($p < .05$), although the direct linear relation between the two variables was weak. Solubility of the pure drug, SDs, and PMs was examined with multifactorial analysis of variance, which showed that solubility of the drug was dependent on the method of prepa-

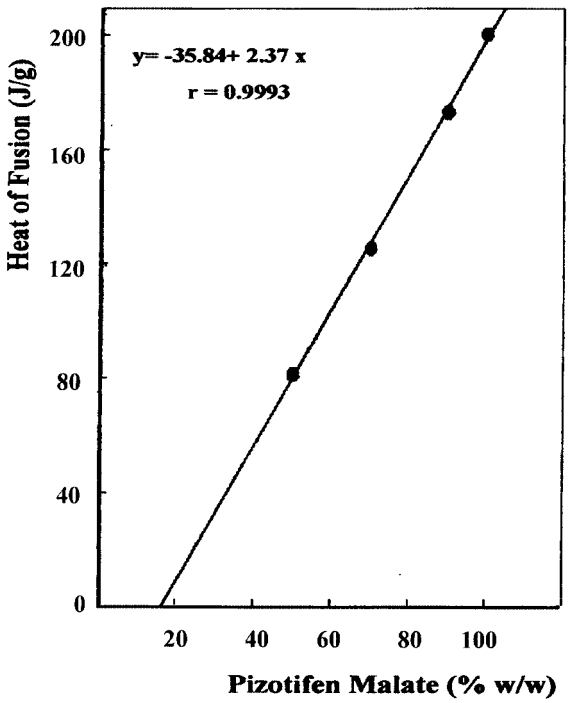

Figure 4. Relation between pizotifen malate concentration in solid dispersions and heat of fusion.

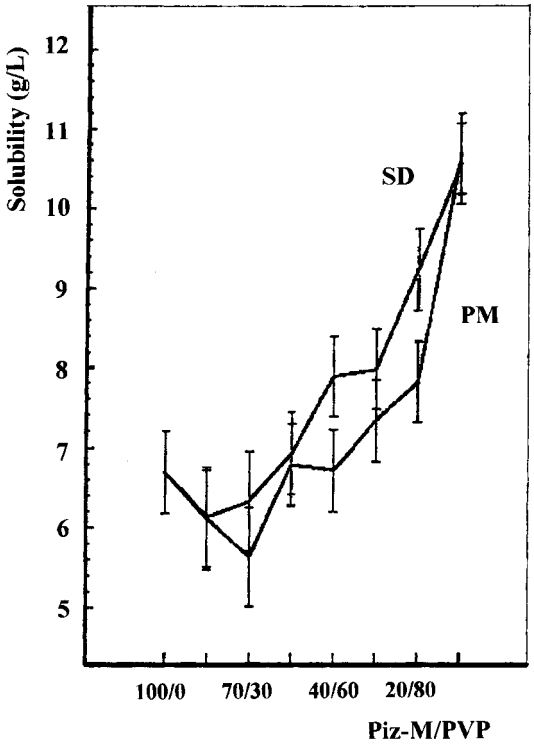

Figure 5. Equilibrium solubility of pizotifen malate as a pure chemical, solid dispersions, and physical mixtures. Each value represents the mean ± SD ($n = 3$).

ration of the sample, the amount of polymer present, and the interaction between these two factors ($p < .05$).

In general, the increase in solubility was greater in SDs than in PMs (Fig. 5). Maximum solubility, which almost doubled that of the pure drug, was seen in the 10:90 SD. Comparison of the solubility in equilibrium for SDs and PMs at the same drug:polymer proportion showed no significant differences ($p > .05$). This may have been because the piz-M:PVP ratio was optimal for the formation of a eutectic mixture (as shown by X-ray diffraction and DSC studies) and because of the hydrotropic effect of the polymer. The chemical structure of PVP allows it to form complexes via hydrogen bonds only with electron-negative substances (16). The presence of malate confers electron-negativity to pizotifen, thus facilitating the formation of complexes. In the present study, such complexes appeared at a molar ratio of 1 piz-M:1.5 PVP.

In the range of PMs tested, solubility was highest in the 10:90 mixture. The amount of polymer in this sample (148 mg · ml^{-1}) was above the solubility in water at saturation, so that the interaction between piz-M and PVP was more intense; in fact, solubility was twice that of the pure drug.

However, in SDs, the particle size of piz-M was smaller, and the rates of dissolution were probably faster than for PMs. In the former, the drug can be expected to dissolve almost instantaneously.

As the proportion of the drug in the samples increased (20:80), solubility decreased, although it remained significantly better in both SDs and PMs than for piz-M alone ($p < .05$). However, solubility of the SDs (dissolved drug:polymer molar ratio 1:1) was better than in the PMs (dissolved drug:polymer molar ratio 1:1.5). In addition to the hydrotropic effect of PVP in the former, piz-M existed in both crystalline form and as a eutectic mixture.

The lower solubility of the 20:80 SD and PM in comparison with the 10:90 samples can be explained by the fact that the amount of PVP was below the solubility of the polymer in water; thus, the hydrotropic effect of the polymer was less evident.

Solubility of the 30:70 and 40:60 SDs was also significantly better than for the pure drug ($p < .05$). In contrast, solubility of the PM at these proportions did not differ significantly from that of pure piz-M.

Although the dissolved drug:polymer molar ratio was 1:1 in all SDs at a range of ratios from 10:90 to 40:60, none of these samples appeared to reflect the hydrotropic effect of PVP. The greater solubility of the SDs was probably due to the presence of a small proportion of the drug as a eutectic mixture.

Solubility in samples containing higher proportions of piz-M (50:50, 70:30, and 90:10) did not differ significantly from each other or from that of the pure drug ($p > .05$). At these high concentrations, solubility tended to decrease in comparison with the pure drug, as noted by other authors (17,18), although the decrease was significant ($p < .05$) only for the 70:30 PM. Nevertheless, we assume dissolution is faster in SDs than in PMs.

In conclusion, the results of infrared spectrophotometry, X-ray diffraction analysis and differential scanning calorimetry indicated that polymorphic forms of piz-M were absent, and that the drug and carrier did not interact chemically. However, differential scanning calorimetry suggested that a eutectic mixture was formed when the proportion of drug was 16%–17%.

Solubility of piz-M was significantly increased in comparison with that of the pure drug ($p < .05$) in SDs prepared at a drug:polymer ratio of 40:60 or less. The increase appeared to result from the formation of a eutectic mixture (10:90, 20:80, 30:70, and 40:60 mixtures) in conjunction with the hydrotropic effect of PVP (10:90 and 20:80 mixtures only).

In PMs, solubility was significantly increased with respect to the pure drug only at drug:polymer ratios of 10:90 and 20:80. We attribute this effect to the hydrotropic effect of the polymer.

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