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Dissolution kinetics of piroxicam in solid dispersions with polyethylene glycol 4000

M. Fernández, M.V. Margarit, I.C. Rodríguez and A. Cerezo

Department of Pharmacy and Pharmaceutical Technology, School of Medicine, University of Granada, E-18071 Granada (Spain)

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Summary

Solid dispersions were used to increase the solubility of active ingredients, with the ultimate goal of optimizing their bioavailability when incorporated into pharmaceuticals. The studies described were designed to improve the dissolution kinetics of piroxicam by using solid dispersions in polyethylene glycol 4000 and investigating the pharmaceutical availability of the solid dispersions in powdered form and in rigid gelatin capsules. Solid dispersions (melting-solvent method) and physical mixtures were prepared at drug:carrier proportions ranging from 10:90 to 80:20; gelatin capsules were also prepared in our laboratory. The dissolution assay was performed in artificial gastric juice without pepsin at 37°C. The results showed that PEG 4000 increased the amount of piroxicam dissolved in both physical mixtures and solid dispersions. The percentage of the drug dissolved after 5 min was 47.84% for powdered piroxicam, whereas the amount available in solid dispersions reached 83.33 to 96.54% of the drug in solution. The $t_{75\%}$ of powdered piroxicam (19.9 min) decreased to 0.3–2.5 min when PEG was included in a solid dispersion. Preparation of the solid dispersion in capsule form increased the dissolution $t_{75\%}$ from 2.6 to 8.9 min. We conclude that formulations of piroxicam in solid dispersions improve the availability of the drug, both in powdered form and in capsules, the most efficient release occurring at a proportion of drug to polyethylene glycol 4000 of 30:70.

Introduction

The absorption of drugs that are poorly soluble in water is limited by their degree and rate of dissolution in organic fluids, which in turn are a function of the surface area of the solid. It is therefore unsurprising that decreasing particle size is the most widely used method of increasing surface contact between the drug and the solvent, and hence, of improving solubility.

Solid dispersions have been used in this connection since they were first proposed in 1961 (Sekiguchi and Obi, 1961). These mixtures were subsequently studied in detail (Chiou and Riegelman, 1971), and their development and importance have been documented in a number of reports of their efficacy (Hajratwal, 1971; Puisieux and Henry, 1981; Lefebvre et al., 1985; Ford, 1986).

The present study was designed to compare the dissolution kinetics of solid dispersions of

Correspondence to: M.V. Margarit, Depto. de Farmacia y Tecnología Farmaceútica, Facultad de Farmacia, Universidad de Granada, E-18071 Granada, Spain.

piroxicam in polyethylene glycol 4000 with the kinetics in physical mixtures and in piroxicam alone, in search of possible increases in solubility and dissolution rate of the active principle. We also analyzed the pharmaceutical availability of the drug in capsules prepared with solid dispersions. The physical-chemical characteristics of the solid dispersions investigated were reported in another study (Fernández et al., 1992).

Materials and Methods

Materials

Piroxicam (Medichem), polyethylene glycol 4000 (PEG 4000) (Unichem Ibérica) and analytical grade hydrochloric acid and sodium chloride (Panreac) were used. Solid dispersions of piroxicam in PEG 4000 were prepared at the following proportions (%): 10:90, 20:80, 30:70, 40:60, 50:50 and 80:20 with the melting-solvent method. The solid dispersions and physical mixtures were prepared as described by Fernández et al. (1993). Briefly, piroxicam was dissolved in chloroform, and PEG 4000 was melted and mixed with the chloroform solution. The solvent was then evaporated until a constant weight was obtained. The sample was pulverized, and the 0.15–0.20 mm particle size fraction was obtained by sieving (mean particle diameter 0.175 mm). Physical mixtures were prepared by homogenizing the two components.

Capsules containing 10 mg piroxicam in lactose as a solid solvent were prepared with both solid dispersions and physical mixtures.

Methods

Dissolution kinetics of samples in the form of powder and rigid gelatin capsules were studied in an automated, closed circuit system. The dissolution medium consisted of 900 ml TS artificial gastric juice without pepsin, pH 1.2 (USP XXII, 1990), maintained at 37 ± 0.5°C. The medium was pumped through the system at a rate of 790 ml/min. Part of the circuit passed through the continuous flow chamber of a Perkin Elmer 124 spectrophotometer, which was set at 333 nm to measure the cumulative absorption/time curves of the sample. Pulverized samples were tested with the dispersed amounts method (Kim et al., 1985) by placing 10 mg piroxicam or its equivalent in solid dispersion or physical mixture on the surface of the dissolution medium, and using a cut-off point of 30 min. With capsules, the cut-off point was extended to 60 min in accordance with the dissolution conditions of USP XXII (1990) (dissolution $t_{75\%}$ of 45 min).

Dissolution kinetics were determined from the mean of five determinations by fitting the experimental data to first order and logarithmic, Weibull, and cube root functions, to obtain straight line plots of the dissolution rates.

Results and Discussion

Pulverized samples

Fig. 1a–f shows the dissolution curves of solid dispersions and their corresponding physical mixtures of the same composition, plotted against piroxicam. The plots illustrate the cumulative percent concentrations of piroxicam dissolved, ± standard deviations. PEG 4000 enhanced solubility and the dissolution rate of piroxicam; these increases were, in general, greater in solid dispersions than in physical mixtures. This finding seems logical, given the solubilizing effect of the soluble carrier, which dissolves completely and rapidly, and affects the diffusion layer surrounding the particle of active substance, thus favoring the wettability, and hence dissolution, of piroxicam. In the 20:80 sample (Fig. 1b), percent dissolution was greater in the physical mixture than in the solid dispersion after 5 min.

The proportion of drug to polymer in the different samples had a significant effect on the dissolution rate. At lower concentrations of piroxicam, dissolution rates were higher. In the 10:90 and 30:70 solid dispersions, dissolution was almost instantaneous, 82.72 and 94.52% of the drug having dissolved within the first minute.

The decrease in solubility during the final minutes of the assay in the 30:70 solid dispersion (Fig. 1c) may have been due to oversaturation of the dissolution medium, leading to the recrystallization of the drug after its rapid dissolution.

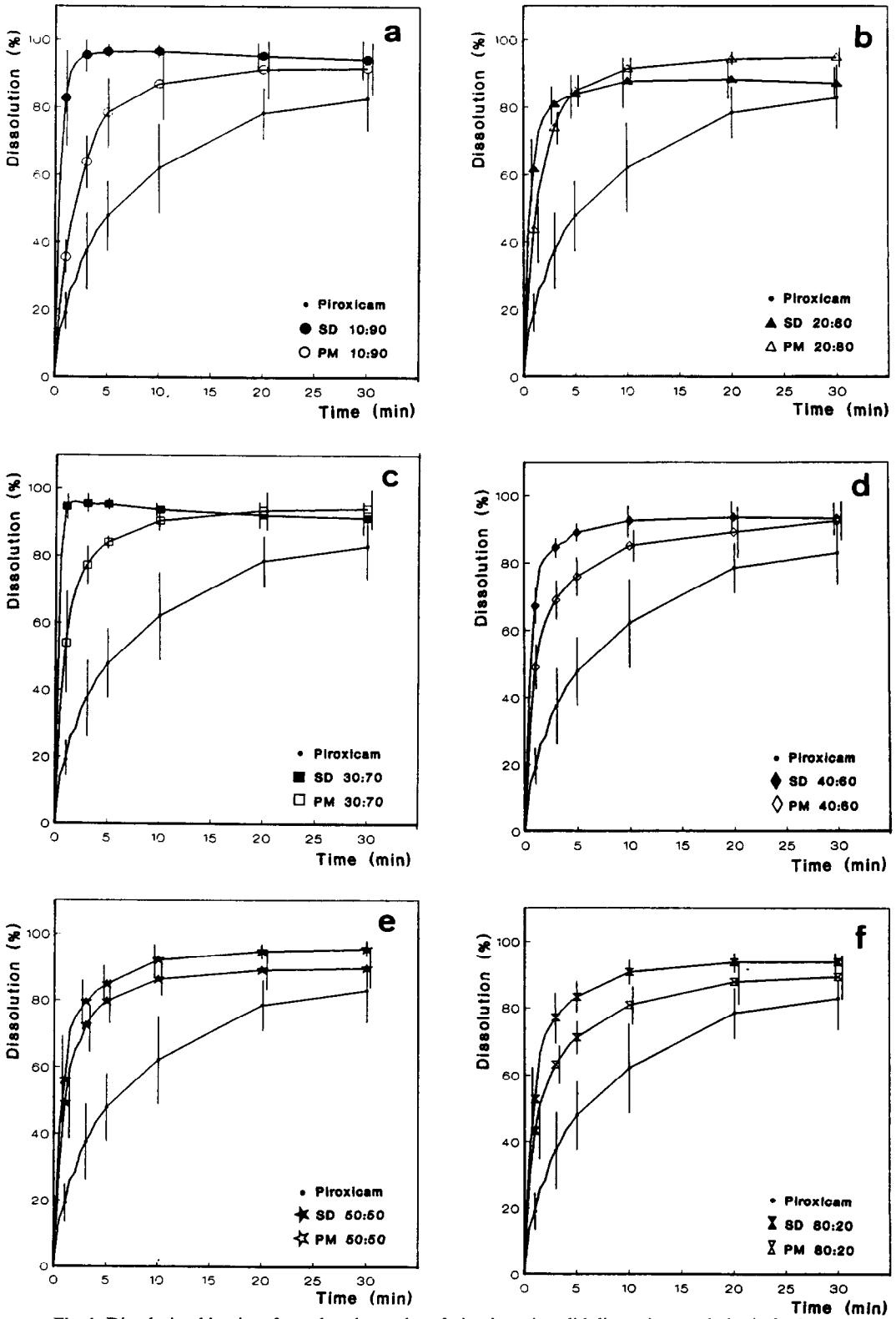

Fig. 1. Dissolution kinetics of powdered samples of piroxicam in solid dispersions and physical mixtures.

This phenomenon has been observed by other workers in solid dispersions of testosterone with PVP and PEG (Hoelgaard and Moller, 1975), as well as in other solid dispersions prepared with PEG 4000 (Kim et al., 1985).

At higher concentrations of piroxicam (> 40%), the dissolution rate was lower, probably because the PEG 4000, on dissolving, released an excess of fine, poorly soluble particles of the drug. Hence, dissolution was probably controlled by the active substance itself.

Our study of the dissolution kinetics of the solid dispersion and physical mixture was based on experimental data obtained during the first 20 min of the assay ($n = 13$). When the data were fitted to the functions used and subjected to linear regression analysis, the dissolution process was found to reflect first order kinetics, with significant correlation coefficients with $P < 0.05$ and $P < 0.01$ (Table 1). Because the 10:90 and 30:70 solid dispersions reached asymptotic concentrations after 2 min of assay time, we could not determine their dissolution kinetics.

Table 1 shows the specific dissolution rate constants (k), and the time (in min) needed for 75% of the dose to dissolve ($t_{75\%}$). Taking piroxicam as a reference, 82.84% of the drug added to the dissolution medium was solubilized (30 min). This rate was significantly different from that of the rest of the samples assayed at a specific dissolution rate constant of $k = 0.072\ \text{min}^{-1}$, and $t_{75\%} = 19.9$ min. The dissolution rates of physical mixture, which ranged from 0.090 to 0.133 min^{-1}, were faster than those of the pure drug. Of the solid dispersion, dissolution was virtually instantaneous in the 10:90 and 30:70 formulations, making these the proportions of choice in the manufacture of this dosage form.

An additional parameter of interest in studies of dissolution kinetics is the dissolution $t_{75\%}$ (45 min), as established by USP XXII (1990) for piroxicam capsules. This value was found, by interpolation between the dissolution concentration/time curves, to range from 0.3 to 2.5 min for DS, and from 2.9 to 5.4 min for physical mixture. Thus, the dissolution $t_{75\%}$ of the two types of preparation was clearly slower than that of the pure drug.

Capsules

The dissolution data for samples prepared in capsules are shown in Fig. 2a–f, which illustrate the dissolution curves for physical mixtures and solid dispersions, respectively, together with the reference curve for capsules containing piroxicam and lactose. Most capsules required a latency period of 2 min, except the 10:90 solid dispersion capsule, from which 4.48% of the drug had dissolved after this time. In capsules containing powdered piroxicam alone, 89.38% of the drug was dissolved by the end of the assay; this peak concentration (C_{max} was surpassed by capsules containing solid dispersions after 30 min (C_{max} from 90.23 to 100%) and physical mixtures prepared with 80, 70 and 50% carrier (C_{max} of 92.67, 97.86 and 91.74%, respectively). The asymptotic

TABLE 1

Data for the dissolution kinetics of powdered samples of piroxicam in solid dispersions and physical mixture

Composition (%) piroxicam : PEG 4000	Solid dispersions				Physical mixture			
	$y = a - bx$ ($n = 13$)				$y = a - bx$ ($n = 13$)			
	a	b	$r_{exp.}$	$t_{75\%}$ (min)	a	b	$r_{exp.}$	$t_{75\%}$ (min)
10:90	–	–	–	0.80	4.06	0.118	0.89	4.30
20:80	3.48	0.075	0.66	1.90	3.86	0.133	0.86	3.30
30:70	–	–	–	0.30	3.72	0.116	0.84	2.90
40:80	3.35	0.103	0.72	1.40	3.89	0.094	0.85	4.30
50:50	3.63	0.123	0.84	2.20	3.82	0.093	0.80	3.70
80:20	3.72	0.118	0.85	2.50	4.02	0.090	0.98	5.40

Piroxicam reference ($n = 13$): $y = 4.40 - 0.072x$, $r_{exp.} = 0.97$, $t_{75\%} = 19.90$ min.

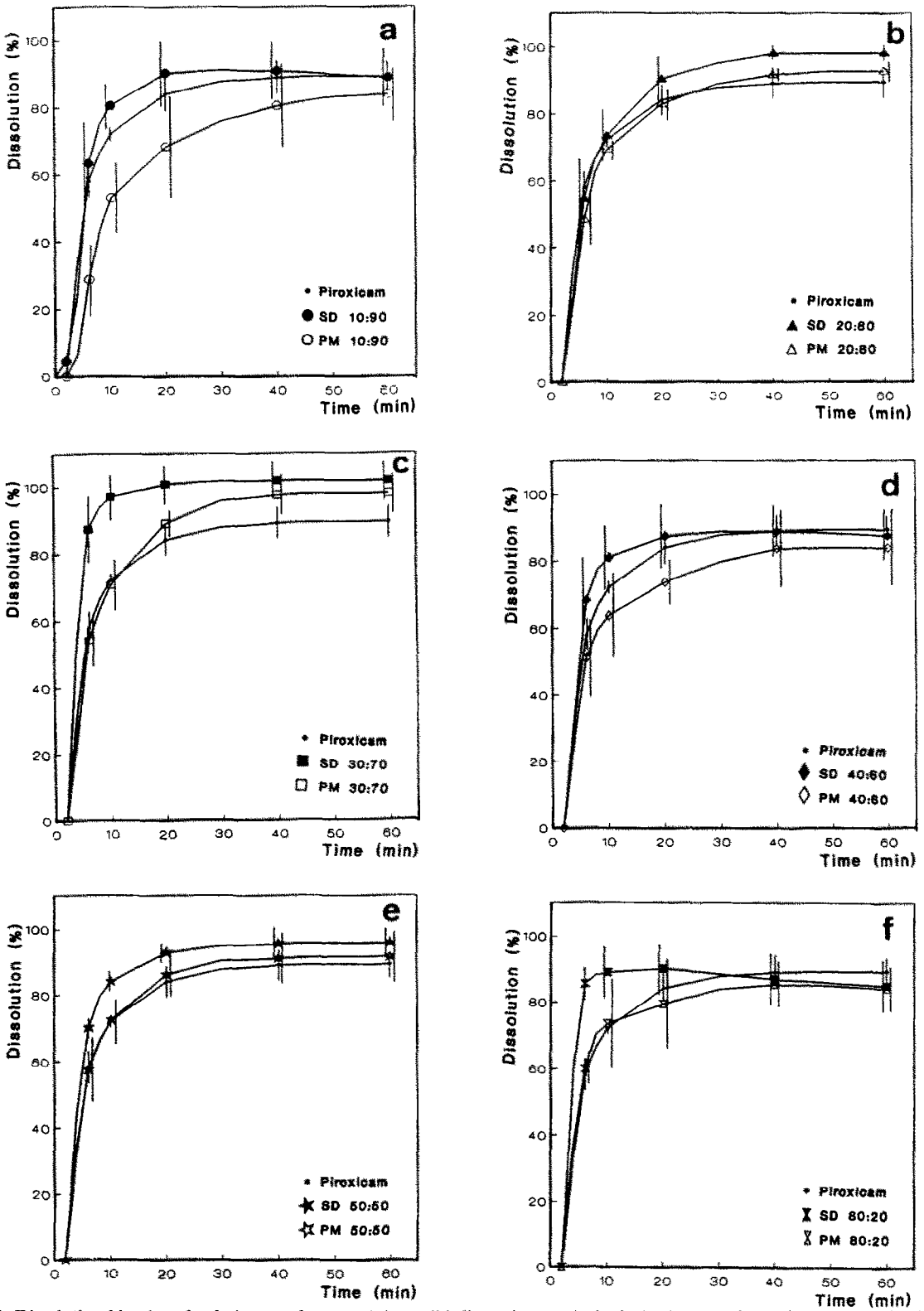

Fig. 2. Dissolution kinetics of gelatin capsules containing solid dispersions and physical mixtures of piroxicam with polyethylene glycol 4000.

TABLE 2

Data for the dissolution kinetics of gelatin capsules of piroxicam in solid dispersions and physical mixture

Composition (%) piroxicam : PEG 4000	Solid dispersions				Physical mixtures			
	$y = a - bx$ ($n = 7$)				$y = a - bx$ ($n = 7$)			
	a	b	$r_{exp.}$	$t_{75\%}$ (min)	a	b	$r_{exp.}$	$t_{75\%}$ (min)
10:90	4.34	0.088	0.91	7.90	4.47	0.051	0.96	26.60
20:80	4.33	0.106	0.98	8.90	4.31	0.075	0.96	12.40
30:70 [a]	3.88	0.247	0.92	3.20	4.39	0.103	0.98	13.00
40:60	3.96	0.069	0.84	5.50	4.23	0.050	0.91	20.40
50:50	3.97	0.098	0.92	5.00	4.20	0.078	0.95	9.50
80:20 [a]	3.69	0.106	0.73	2.60	4.07	0.055	0.86	9.00

[a] $n = 6$.

Capsule piroxicam reference ($n = 7$): $y = 4.16 - 0.069x$, $r_{exp.} = 0.92$, $t_{75\%} = 10.40$ min.

segment of the curve began at 30 min for solid dispersions, and at 40 min for physical mixtures and the reference capsule. The kinetic assays were therefore performed with the concentrations reached after 30 min, except for the 30:70 and 80:20 solid dispersions, which were studied during the first 20 min, the time needed to reach their asymptotic concentrations.

As with the pulverized samples, the statistical analyses showed that piroxicam followed first order kinetics according to the equations given in Table 2 with a significant correlation coefficient at the level of $P < 0.01$.

Our overall analysis of the dissolution behavior of capsules containing piroxicam alone, as a solid dispersion and as a physical mixture, suggests that availability is greater from capsules composed of solid dispersion, piroxicam and PEG 4000 than from capsules prepared with physical mixture and piroxicam. The availability from capsules containing physical mixture did not suggest any improvement in the dissolution rate of the drug; the 30:70 combination was the only one to display a dissolution rate 1.5-times faster than that of the reference capsule.

All capsules assayed fulfilled the requirements of USP XXII (1990), with $t_{75\%} = 2.6$ at 8.9 min for solid dispersions, 10.4 min for piroxicam alone, and 9–26.6 min for physical mixtures.

PEG 4000 can be considered a good carrier for the preparation of solid dispersions of piroxicam with improved dissolution characteristics. The most efficient mixtures tested in this series of assays were solid dispersions of piroxicam and PEG 4000 in proportions of 10:90 and 30:70, prepared as powder, and the 30:70 composition in capsule form. Our findings indicate the 30:70 solid dispersion as the optimum formulation for the preparation of pharmaceuticals.

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