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COMMUNICATION

Enhancement of Dissolution and Bioavailability of Piroxicam in Solid Dispersion Systems

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ABSTRACT

Solid dispersion systems of water-insoluble piroxicam in polyethylene glycol (PEG) 4000 and in urea were prepared by fusion and solvent methods and were characterized in this study. The in vitro dissolution studies showed that the dispersion systems containing piroxicam and PEG4000 or urea gave faster dissolution than the corresponding simple mixtures. The differential scanning calorimetry (DSC) study indicated that the piroxicam-PEG system prepared by the fusion method is a solid dispersion, while the piroxicam-urea system prepared by the solvent method is likely to be a solid solution of piroxicam in urea. The storage testings showed that all dispersions were stable, except that uptake of water during storage may occur in the PEG system. A single-dose study with rabbits showed that the dispersion systems provided statistically significant to a higher extent and rate of bioavailability than the corresponding physical mixture ($p < 0.05$).

Key Words: *Dispersion; Dissolution; Pharmacokinetics; Piroxicam; Stability.*

INTRODUCTION

Piroxicam is a nonsteroidal anti-inflammatory agent with analgesic and antipyretic activities (1,2). The purpose of this study was to develop simple methods for the preparation of stable dosage forms with finely divided piroxicam for consistent drug release that may lead to faster initial drug absorption following oral dosing. The dissolution characteristics of solid dispersions of piroxicam in polyethylene glycol (PEG) 4000 and in urea, as well as the physical mixtures of piroxicam with PEG and with urea were compared in this study. The in vitro stabil-

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ity testing and the in vivo animal studies were also performed.

MATERIALS AND METHODS

Piroxicam and all other materials used in this study were either pharmaceutical or reagent grade. All particles used in this study were sieved and selected to be at 149–177 μm (80–100 mesh).

Preparation of the Physical Mixtures

Piroxicam and PEG4000 or urea were weighed accurately in different proportions (1:1, 1:2, 1:3). The two ingredients were mixed well in each sample.

Preparation of the Solid Dispersions

Solid dispersions containing piroxicam and carrier in different weight ratios (1:1, 1:2, and 1:3) were prepared by the fusion or solvent method as described below, and the resulting samples were stored in tightly closed containers until use.

Fusion Method

Each mixture was stirred and melted at 200°C in an oil bath. When the solid was completely dissolved, the hot liquid was moved to a water bath with continued stirring. It was subsequently cooled to 25°C.

Solvent Method

The solid dispersions with urea were also prepared by dissolving, with the aid of a minimal volume of ethanol, the mixture of piroxicam and the carrier at the weight ratios of 1:1, 1:2, and 1:3. The alcohol was removed by evaporation under reduced pressure.

Differential Scanning Calorimetry Study

All solid dispersions and physical mixtures were carried out on a Du Pont model 912 differential scanning calorimeter (DSC) (Du Pont, Wilmington, DE) under nitrogen gas flow of 30 ml/min and a heating rate of 10°C/min.

Dissolution Study

All dissolution studies were determined by the basket method (USP 23) at 37°C in 900 ml of simulated gastric fluid (pH 1.2) or simulated intestinal fluid (pH 7.4) at 100 rpm. Samples equivalent to 10 mg of piroxicam were subject to the testing.

Stability Test

Solid dispersions and physical mixtures containing the 1:2 weight ratio of piroxicam and PEG4000 or urea were stored at 25°C and 37°C for 10 weeks. Drug contents in the samples were measured once a week up to 10 weeks.

Assay of Piroxicam in Samples for the In Vitro Studies

The sample solution was analyzed by high-performance liquid chromatography (HPLC) (4). The analytical column for piroxicam was Aquapore RP-300 (Applied Systems, Santa Clara, CA). The mobile phase was a mixture of $CH_3CN:H_2O:CH_3COOH$ (46:50:4 v/v, pH 3.0). Samples were monitored at 365 nm at a flow rate of 1.0 ml/min.

Drug Absorption Study in Rabbits

Six male white New Zealand rabbits were used in each dosing experiment. Before the treatment, each rabbit was subjected to a stomach-emptying procedure. In the two-way crossover study, the 6 rabbits were divided into two balanced groups, and each rabbit was given 15 mg of the piroxicam-carrier physical mixture (1:2) and the piroxicam-carrier solid dispersion (1:2) in different dosing periods. The actual dose of piroxicam was 5 mg in all cases. The oral doses were administered in gelatin capsules. The washout period between the two dosing periods was 7 days. Blood samples were collected, and each plasma fraction was separated immediately and stored at −30°C before use.

Analysis of Plasma Piroxicam

The plasma concentration of piroxicam was also determined by HPLC. The analytical column for piroxicam was a μ-Bondapak CN column (Waters, Milford, MA), and the mobile phase was a mixture of $CH_3CN:H_2O:CH_3COOH$ (pH 3.0). The chromatograms were monitored at 333 nm at a flow rate of 1.0 ml/min (3).

RESULTS AND DISCUSSION

Differential Scanning Calorimetry Studies

DSC scans were done for the PEG4000 solid dispersions prepared by the fusion method at different drug/carrier ratios. The endothermic peak showed up around the melting point of piroxicam (205°C) and supports that piroxicam still remains crystalline in the dispersion systems (4). When the DSC scans for the drug-urea system prepared by the solvent method were examined,

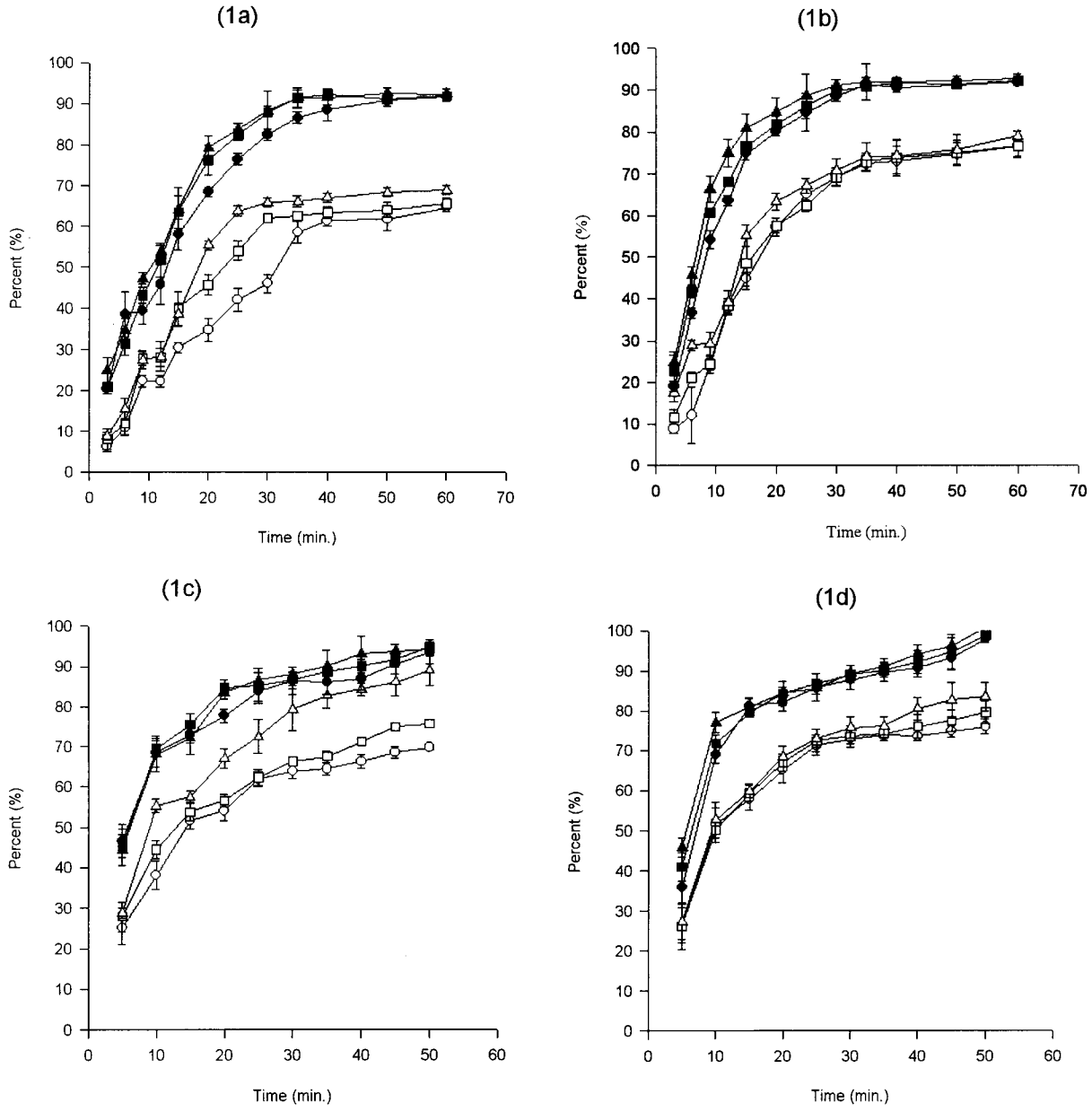

Figure 1. Dissolution rate profiles (mean ± SD) for piroxicam with PEG4000: (a) in simulated gastric juice (pH 1.2); (b) in simulated intestinal juice (pH 7.4); (c) with urea in simulated gastric juice (pH 1.2); and (d) in simulated intestinal juice (pH 7.4). ○, 1:1 physical mixture; □, 1:2 physical mixture; △, 1:3 physical mixture; ●, 1:1 solid dispersion; ■, 1:2 solid dispersion; ▲, 1:3 solid dispersion.

no piroxicam peak could be distinguished, which indicates the possible interaction between piroxicam and urea. A solid solution for the piroxicam-urea system is likely.

Dissolution Rates

Piroxicam-PEG4000 System

The dissolution of piroxicam was faster in simulated intestinal fluid than in simulated gastric fluid (Fig. 1). For piroxicam-PEG4000 systems in simulated gastric fluid, the percentages of piroxicam dissolved were 58% ± 4% for the 1:1 dispersion, 64% ± 4% for the 1:2 dispersion, and 64% ± 5% for the 1:3 dispersion. In contrast, the 1:1 physical mixture gave 31% ± 1% dissolution and 40% ± 4% for the 1:2 mixture, as well as 39% ± 3% for the 1:3 mixture (Fig. 1a). The intestinal fluid gave faster dissolution than gastric fluid, which is logical since piroxicam is a weak acid, with a pK_a of 6.3, and the degree of ionization is higher in a medium at a higher pH.

Piroxicam-Urea System

The piroxicam-urea dispersion systems were compared with their corresponding physical mixtures in simulated gastric and intestinal fluids. Figure 1 shows the comparative dissolution features. Faster drug release was observed for the dispersion systems, and the simulated intestinal fluid provided higher dissolution rates. This phenomenon is similar to that of the drug-PEG dispersions.

Piroxicam is a weak acid with low water solubility; it is probable that PEG and urea may increase the wettability of the solid and cause a local solubilization effect by the carrier at the diffusion layer. It is also considered that improvement of the dissolution rate of piroxicam might be due to the amorphous phase of piroxicam, and that particle size reduction resulted from the interaction of piroxicam-PEG4000 and piroxicam-urea (4–8).

Rabbit Study

The plasma concentration data obtained were treated by the noncompartmental method. Analysis of variance (ANOVA) was used to make statistical evaluations of these pharmacokinetic data. The pharmacokinetic parameters are listed in Table 1.

The peak concentration C_{max}, mean residence time (MRT), and peak times T_{max} were significantly different between the dispersion systems and their corresponding physical mixtures ($p < .05$). The faster initial dissolution of the dispersion systems (Fig. 2) could be the reason that higher plasma peak levels and shorter peak times were obtained. This is in accordance with the well-known pharmacokinetic principle. The terminal half-life for piroxicam-PEG and piroxicam-urea physical mixtures was longer than those of their dispersions, so the physical mixtures might assume a ''flip-flop'' phenomenon with slower drug release (9).

Storage Testing

For piroxicam-PEG systems, the dispersion provides slightly faster decline of the piroxicam potency than the physical mixture ($p < .05$, Table 2). For piroxicam-urea systems, good stability was found for the dispersions and the physical mixture. This indicates that the piroxicam-urea dispersion system was stable during aging.

Table 1

Pharmacokinetic Parameters for Different Piroxicam Systems

	PEG-M	PEG-S	UREA-M	UREA-S
AUC (mg*hr/L)	25.1 ± 5.5	21.9 ± 3.1	23.2 ± 4.8	19.5 ± 3.1
MRT (hr)	15.8 ± 1.6[a]	8.8 ± 0.9[a]	16.3 ± 2.2[a]	10.3 ± 0.5[a]
T_{max} (hr)	7.3 ± 1.0	2.0 ± 0.0	7.3 ± 1.0[a]	1.7 ± 0.3[a]
C_{max} (mg/L)	1.5 ± 0.3[a]	2.1 ± 0.2[a]	1.4 ± 0.2[a]	1.9 ± 0.2[a]
$T_{1/2}$ (hr)	8.2 ± 1.3[a]	5.4 ± 0.6[a]	8.5 ± 1.5[a]	6.3 ± 0.5[a]
Cl_p/F (l/hr)	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
V_d/F (L)	6.5 ± 1.1[a]	4.1 ± 0.5[a]	7.2 ± 1.3	5.4 ± 0.8

PEG-M = piroxicam–PEG 4000 physical mixture; PEG-S = piroxicam–PEG 4000 solid dispersion; UREA-M = piroxicam-urea physical mixture; UREA-S = piroxicam-urea solid dispersion.

[a] Significant difference between physical mixture and solid dispersion ($p < .05$).

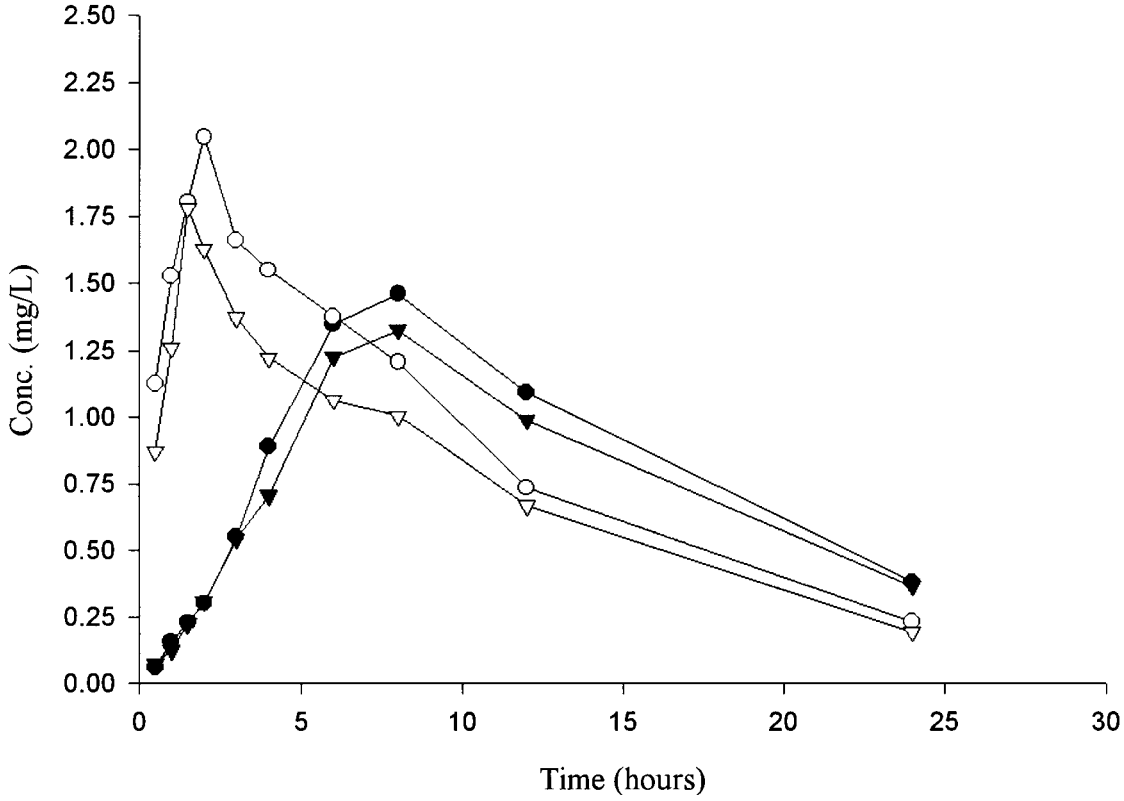

Figure 2. Mean plasma levels of piroxicam following oral administration at a dose of 5 mg to rabbits. ■, Physical mixture (PEG4000); ○, solid dispersion (PEG4000); ▼, physical mixture (urea); ▽ solid dispersion (urea).

Table 2

Stability Data of the Piroxicam in Different Systems

Day	25°C, PM (%)	25°C, PS (%)	37°C, PM (%)	37°C, PS (%)	25°C, UM (%)	25°C, US (%)	37°C, UM (%)	37°C, US (%)
7	99.7 ± 0.9[a]	99.3 ± 1.1[a]	100.8 ± 1.5[a]	99.3 ± 0.2[a]	102.4 ± 3.5[a]	99.3 ± 1.3	98.7 ± 1.2	98.8 ± 0.6
14	98.4 ± 1.0	98.7 ± 0.3	99.4 ± 1.0	98.3 ± 0.6	97.7 ± 1.1	98.7 ± 0.9	100.9 ± 1.8	99.3 ± 1.9
21	98.6 ± 1.0	98.5 ± 0.6	99.4 ± 0.5	98.4 ± 0.4	99.3 ± 1.1	98.7 ± 1.0	98.7 ± 2.1	98.9 ± 2.2
28	99.7 ± 0.9	98.9 ± 1.2	98.3 ± 0.4	98.5 ± 1.2	97.7 ± 3.4	99.1 ± 0.2	98.5 ± 2.4	99.2 ± 0.4
35	98.2 ± 1.1	98.3 ± 1.2	99.0 ± 1.1	98.8 ± .13	98.7 ± 0.8	99.1 ± 0.8	99.0 ± 0.6	98.5 ± 0.8
42	98.8 ± 0.4	98.0 ± 0.7	98.6 ± 0.8	97.6 ± 2.3	100.3 ± 0.6	98.5 ± 0.3	97.8 ± 0.4	98.9 ± 0.9
49	98.6 ± 1.8	98.1 ± 1.3	98.8 ± 2.8	97.5 ± 2.1	100.0 ± 1.3	99.5 ± 1.0	99.3 ± 0.9	99.2 ± 0.5
56	97.6 ± 0.7	97.6 ± 0.6	98.6 ± 0.5	96.9 ± 1.7	99.9 ± 0.7	98.1 ± 1.4	100.3 ± 1.2	100.4 ± 0.8
63	99.0 ± 0.8	97.5 ± 1.0	98.7 ± 0.3	95.7 ± 1.9	99.1 ± 0.9	98.4 ± 0.7	98.7 ± 0.7	98.3 ± 0.9
70	98.4 ± 0.1[a]	97.2 ± 0.5[a]	98.2 ± 0.8[a]	95.1 ± 2.3[a]	97.5 ± 0.9[a]	98.7 ± 0.9	97.9 ± 0.7	98.6 ± 1.4

PM = piroxicam–PEG 4000 mixture; PS = piroxicam–PEG 4000 solid dispersion; UM = piroxicam-urea mixture; US = piroxicam-urea solid dispersion.

[a] Significant difference between 7 and 70 days ($p < .05$).

The mechanism leading to the decline of the piroxicam potency in the piroxicam-PEG dispersions is still unknown. It is assumed that the piroxicam-PEG dispersion absorbed moisture during storage, which increased the weight of the sample and reduced the percentage of piroxicam when the weight of the sample was not corrected for the moisture uptake. The result of the Karl Fischer water content determination supports the above prediction. It was concluded that the piroxicam-urea dispersion system prepared by the fusion method could be used for the formulation of a stable fast-release piroxicam preparation with good stability.

REFERENCES

1. E. H. Wiseman and D. C. Hobbs, Review of pharmacokinetic studies with piroxicam, Am. J. Med., 9, (February 16, 1982).
2. R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery, Piroxicam, a reappraisal of its pharmacology and therapeutic efficacy, Drugs, 28, 292 (1984).
3. T. M. Twomey, S. R. Bartoluci, and D. C. Hobbs, Analysis of piroxicam in plasma by high-performance liquid chromatography, J. Chromatogr., 183, 104 (1980).
4. M. T. Sheu, C. M. Yeh, and T. D. Sokoloski, Characterization and dissolution of fenofibrate solid dispersion systems, Int. J. Pharm., 103, 137 (1994).
5. K. Sekiguchi and N. Obi, Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man, Chem. Pharm. Bull., 9, 866 (1961).
6. W. L. Chiou and S. Riegelman, Pharmaceutical application of solid dispersion systems, J. Pharm. Sci., 60, 1281 (1971).
7. P. Mura, A. Manderioli, G. Bramanti, and L. Ceccarelli, Properties of solid dispersions of naproxen in various polyethylene glycols, Drug Dev. Ind. Pharm., 22, 909 (1996).
8. D. Q. M. Craig and J. M. Newton, The dissolution of nortriptyline HCl from polyethylene glycol solid dispersions, Int. J. Pharm., 78, 175 (1992).
9. L. Shargel and A. B. C. Yu, *Applied Biopharmaceutics and Pharmacokinetics*, 3rd ed., Prentice-Hall, London, 1996, pp. 177–179.