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COMMUNICATION

Examination of the Polymorphism of Piroxicam in Connection with the Preparation of a New ''Soft-Patch'' Type Pharmaceutical Dosage Form

G. Csóka, E. Balogh, S. Marton, E. Farkas, and I. Rácz

Semmelweis University of Medical Sciences, Pharmaceutical Institute, Högyes E. str. 7, H-1092 Budapest, Hungary

ABSTRACT

The influence of different solvents (propylene glycol, glycerol, ethanol), as well as different technological procedures (melting, rapid and slow cooling), on the formation of polymorphous piroxicam modifications was examined in the course of the elaboration of a ''soft-patch'' type of semisolid pharmaceutical dosage form. The thermodynamical behavior, some physicochemical properties (such as melting point, dissolution rate), and infrared (IR) spectrum of the formed (needle and cubic) crystal modifications were studied, and the possibilities of their formation and their avoidance were examined.

INTRODUCTION

In the case of topical formulations like ointments and gels, the applied solvents, carrier systems, technological processes (melting, heating, and/or cooling) may encourage the formation of polymorphic modifications. Many papers have been published on the polymorphism of piroxicam (1–5).

A clinical requirement exists to formulate transdermal preparations like TTS adhesive plasters (6–8). The soft patch is a formulation containing a unit dose of the active substance and consists of thin flexible plates that are fixed to the skin by an adhesive film layer.

The authors studied gel systems suitable for the preparation of a new soft-patch transdermal preparation containing piroxicam with special respect to the effect of the applied conditions on the eventual formation of the crystal modifications.

MATERIALS AND METHODS

Materials

Piroxicam (Welding GmbH, Germany), ethanol, glycerol, propylene glycol, and sodium hydroxide (USP

XXII) were used. The solvents with different permittivities and other chemicals were analytical grade.

Methods

Preparation of the Piroxicam Modifications

The active substance was added at 75°C to the following solvents and mixtures: ethanol, glycerol, propylene glycol, a 1:1 mixture of glycerol and propylene glycol, and a 50.0:48.7:1.3 mixture of glycerol, propylene glycol, and a 10.7% solution of sodium hydroxide in water in a proportion of 1% by weight, but only saturated solutions were examined. The crystallization was performed by one of the following methods:

1. Cooling of the solution was performed slowly at room temperature and quickly in a freezing chamber at −20°C.
2. Adding cold water dropwise to the solution until it began to opalize and cooling it afterward slowly at room temperature and quickly in a freezing chamber at −20°C.

The crystals were separated, washed, and then dried in a drying chamber at 35°C.

Test Methods

Scanning Electron Microscopic Observations

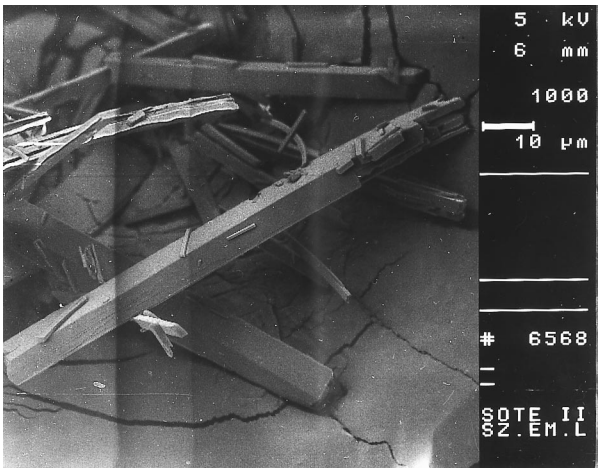
The scanning electron microscopic observations were made with the aid of an OPTON 940 DSM type instrument (see condition in Fig. 1).

Melting Point Determination

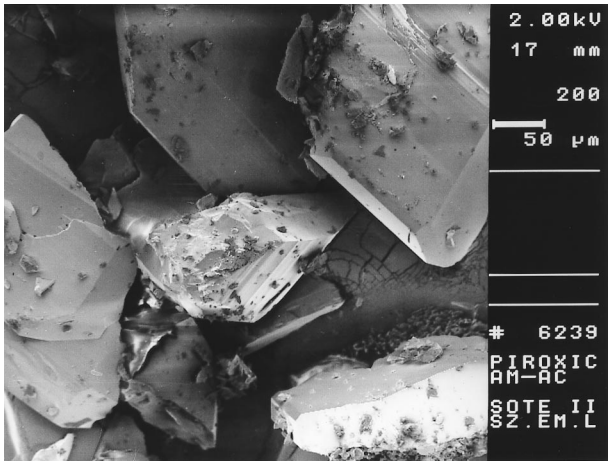
The melting point determinations were made in a DuPont 990 Thermal Analyzer System in argon atmosphere (see the parameters in Fig. 2.)

Determination of Dissolution Rate

For determination of dissolution rate, 100 mg of the crystals were weighed into 250 ml of distilled water at 25°C in a dissolution testing device according to USP XXII (Pharmatest PTW2 Dissolution Tester, Pharmatest Apparatebau GmbH, Hamburg, Germany). Rotation speed was 100 rpm. At regular intervals, samples were taken, and the volume was replaced. Concentrations were determined spectrophotometrically at 350 nm (UV-160A spectrophotometer, Shimadzu Co., Kyoto, Japan).



(A)



(B)

Figure 1. Scanning electron microscopic observation of two kinds of piroxicam crystals: (A) needle crystals; and (B) cubic crystals.

Infrared Spectra

For the infrared (IR) spectra, 1 mg of the prepared substances was compressed with 500 mg of spectroscopic quality anhydrous potassium bromide powder into disks. The disks were examined by a Perkin Elmer 1600 Fourier transform infrared (FTIR) instrument.

Mathematical Methods

The following mathematical model, the modified Nernst equation, was applied (9) to characterize the dissolution of different crystals.

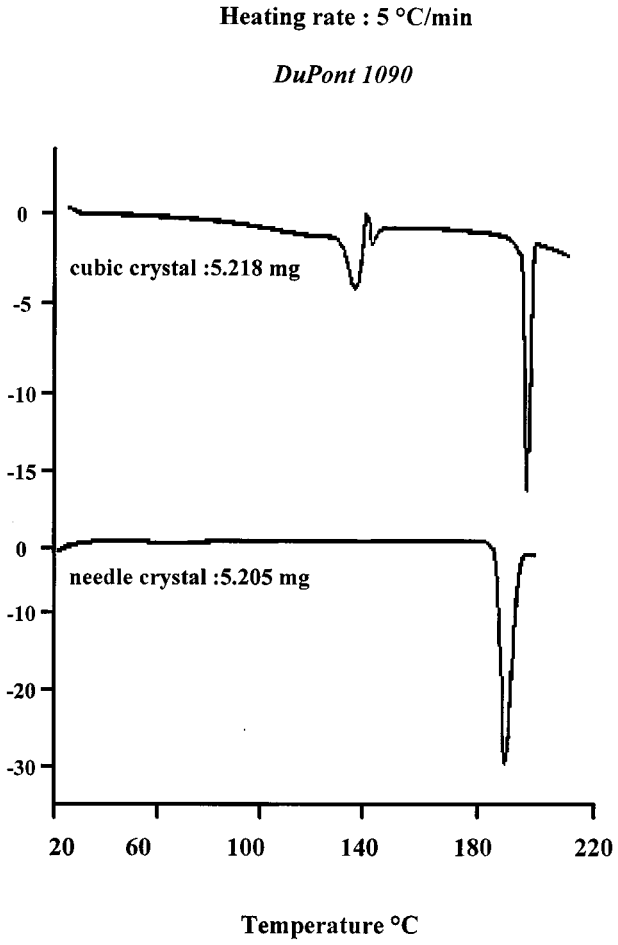


Figure 2. DSC curves of two kind of piroxicam crystals.

$$M_t/M_\infty = 1 - \exp[-a(Kt)^\alpha]$$

where K is the dissolution rate constant, M_t is the amount of drug released at time t, M_∞ is the amount of drug released at infinity, t is time, and a and α are constants that describe structural and geometric characteristics of the curve, respectively.

RESULTS AND DISCUSSION

Unexpectedly and contrary to previous data in the literature (1–4), the rate of cooling had no effect on the crystal habit of the product. Independently from the used solvent and the cooling rate applied, white needle crystals were obtained applying alcohols only, without a precipitating agent (water). Equally independent of the solvent and the cooling rate, yellow cubic crystals formed when a precipitating agent (water) was used. The characteristic crystal habit of the two crystal modifications can be seen in Fig. 1.

Practically no precipitation occurred from the binary solvent mixture, which can be explained by a shift in the permittivity of the medium. No precipitate was formed in the case of the ternary solvent mixture. Aqueous sodium hydroxide solution not only increases the solubility of piroxicam, but regardless of the rate of cooling, it also prevents precipitation.

By comparing the thermodynamic properties of the two kinds of piroxicam crystals, it could be stated that the endothermic peaks at about 200°C indicate that the crystal melting differs for each crystal. The needle crystal melted at 197°C–198°C, while the cubic crystal melted at 202°–203°C (Fig. 2).

A difference could be observed in the –NH– and –OH absorption bands of the IR spectra of the two crystal modifications, too. That of the needles was at 3392 cm^{-1}, while that of the cubes was at 3337 cm^{-1}.

The dissolution rates of the two crystal modifications were calculated using a modified Nernst's equation (9). The small differences in dissolution rate values of samples taken at different time intervals indicate that the rate constants are independent of the sampling time, and the equation is well suited for the description of the dissolution kinetics of piroxicam crystals. The so-called shape factor α characterizing the form of the curve can be calculated using the same equation. It can be seen that no greater difference for these parameters can be stated (Table 1).

Table 1

Dissolved Amounts and Dissolution Rate Constants of Piroxicam Crystals

	M Measured (%)		Dissolution Rate Constants (K) (1/min)	
Time (min)	Cubic	Needle	Cubic	Needle
30	13	9.7	$4.0\ 10^{-2}$	$2.0\ 10^{-2}$
60	16	17	$3.2\ 10^{-2}$	$2.6\ 10^{-2}$
120	22	24	$3.4\ 10^{-2}$	$2.7\ 10^{-2}$
180	25	27	$3.3\ 10^{-2}$	$2.6\ 10^{-2}$
240	28	29	$3.2\ 10^{-2}$	$2.4\ 10^{-2}$
300	30	31	$3.4\ 10^{-2}$	$2.4\ 10^{-2}$
$K_{average}$			$3.3\ 10^{-2}$	$2.4\ 10^{-2}$
SD			$8.7\ 10^{-4}$	$2.6\ 10^{-3}$
RSD (%)			2.631	10.61
α			0.41	0.48

CONCLUSION

In the course of soft-patch-type preparations containing piroxicam, it is appropriate to keep in mind that two kinds of crystalline piroxicam may be formed, depending on the nature of the solvents and the different proportions of mixtures used, as well as the procedures (melting, congealing) applied.

Under the examined crystallization conditions (ethanol, glycerol, propylene glycol as solvents, as well as their binary and ternary mixtures; water as precipitating agent; and rapid or slow cooling), needle and cubic piroxicam crystals were formed. Contrary to the data in the literature, it was found that, independent of the cooling rate, exclusively white needles separated from the alcoholic solutions, while yellow cubic crystals precipitated whenever water was added to the alcoholic systems.

According to thermoanalytical measurements, the crystal modifications so formed have different melting points (needles 198°C, cubes 203°C). The endothermic peak at 140°C indicates that the cubic crystal is a monohydrate form.

The NH and OH absorption bands of the IR spectra of the two crystal modifications are also different. The two kinds of crystals, however, show no substantial differences in their dissolution rates in water.

In the formulation of soft-patch-type gel systems, it is preeminent to prepare matrix systems with active ingredients completely homogeneously distributed in them. Our experiments have shown that, independent of the applied solvent and cooling rate, both requirements can be met by increasing the pH value of the gel system. Well suited for this purpose are stearate gel, which, even at a piroxicam content of 1%, proves complete homogeneity and safely prevents the precipitation of crystals.

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