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Solid-state investigation of piroxicam benzoate

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Solid-state properties of piroxicam benzoate, an ester prodrug of piroxicam, were investigated. Samples were prepared by recrystallization from various organic solvents (toluene, ethanol, methanol, ethyl acetate and acetone). Recrystallized samples were characterized by means of FTIR, DSC, TGA, SEM and XRPD. DSC, TGA and XRPD methods confirmed that piroxicam benzoate crystallized in two pseudopolymorphic forms, A and B. Pseudopolymorphic form A was obtained by recrystallization from ethanol and methanol by slow cooling at room temperature and by rapid cooling in an ice-cold bath, and also from toluene by rapid cooling in an ice-cold bath. Pseudopolymorphic form B was obtained by recrystallization from toluene by slow cooling at room temperature.

Keywords: piroxicam benzoate, pseudopolymorphism, FTIR, thermal analysis, XRPD, SEM

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Piroxicam [*N*-(2-pyridyl)-2-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1--dioxide] is a well known analgesic and non-steroidal anti-inflammatory drug (1). In the continuing search for improved anti-inflammatory agents, a series of acyl piroxicam derivatives has been synthesized (2, 3) and pharmacologically evaluated (2). These compounds are useful in alleviating inflammatory conditions after oral, parenteral or topical administration. Piroxicam blood levels obtained after topical administration of acyl piroxicam derivatives were much higher than when piroxicam itself was administered at a higher concentration under the same conditions. Piroxicam benzoate is an ester prodrug of increased lipophilicity, which showed remarkable activity in the standard carrageenin--induced rat foot edema test (2). In our previous paper, the kinetic study of piroxicam benzoate hydrolysis and validation of the HPLC method for piroxicam benzoate determination was reported (4).

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Piroxicam is known to exist in different polymorphic forms and as a monohydrate (5–8) with specific solubility and stability parameters. The ester of piroxicam with pivalic acid exists in two polymorphic forms as well (9, 10). A conventional preformulation study was therefore undertaken in order to check whether polymorphs or pseudopolymorphs (solvates) of piroxicam benzoate could be identified. In this paper, polymorphism and pseudopolymorphism of piroxicam benzoate were studied on samples prepared by recrystallization from various organic solvents using two different ways of cooling. For solid-state characterization, analytical techniques such as DSC and TGA, FTIR, X-ray powder diffraction and SEM were used.

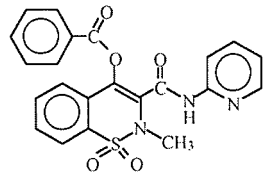

Fig. 1. The chemical structure of piroxicam benzoate.

EXPERIMENTAL

Preparation of piroxicam benzoate crystal forms

Piroxicam benzoate (**1**) (Fig. 1) was synthesized from piroxicam and benzoyl chloride following the procedure previously published (4). Compound **1** was recrystallized from solvents of various polarities (methanol, ethanol, ethyl acetate, acetone and toluene) by slow cooling at room temperature or by rapid cooling in an ice-cold bath (11). Products **1a-j** prepared in the way mentioned above are shown in Table I.

Table I. DSC thermal characteristics of piroxicam benzoate products ***1a–j***[a]

Compound No.	Crystallization solvent	Desolvation (°C)	Melting endotherm (°C)
1a	Acetone	–	146.67
1b	Ethyl acetate	–	144.01
1c	Methanol	108.42	144.51
1d	Ethanol	101.27	147.93
1e	Toluene	86.02	138.23
1f	Acetone	–	148.81
1g	Ethyl acetate	–	143.15
1h	Methanol	98.06	148.99
1i	Ethanol	98.01	147.11
1j	Toluene	79.75	145.08

[a] Products **1a-e** were prepared by slow crystallization at room temperature and **1f-j** by rapid cooling in an ice-cold bath.

Thermal analysis

DSC thermograms were recorded using a Perkin-Elmer DSC-Pyris 1 instrument (USA). The instrument was calibrated with indium and zinc prior to analyzing the samples under nitrogen purge of 35 mL min^{-1}. Samples (5–10 mg) were weighed in aluminum pans, closed and scanned at heating rates of 1 and 10 °C min^{-1} over the temperature range of 30 °C to 220 °C. Samples were also scanned in open pans at the heating rate of 5 °C min^{-1} over the same temperature range.

TGA curves were obtained from an approximately 5 mg sample using the Perkin--Elmer TGA 7 with a helium flow of 35 mL min^{-1}, heating rate of 10 °C min^{-1} in the range from 30 to 700 °C. The instrument was calibrated by scanning nickel (Ni) and iron (Fe) in magnetic field to check Curie point, before analyzing the samples. The data were analyzed using the software package »Pyris for Windows« (version 3.81).

Fourier transform infrared spectroscopy

FTIR spectra were obtained after grinding and mixing samples in dried KBr (about 1%) and then compressing them into discs at a pressure of 10 kN. Spectra were recorded using Perkin-Elmer Spectrum GX spectrometer over the 4000–370 cm^{-1} region. For each sample, 16 scans were collected at a 4 cm^{-1} resolution.

X-ray powder diffraction

The X-ray diffraction patterns were recorded using a Philips 3710 automatic powder diffractometer (Philips, the Netherlands) at 30 mA, 50 kV, with monochromatized Cu$K\alpha$ radiation using the X'Pert software suite (12). The samples were scanned at a temperature of 20 °C at the diffraction angle 2θ, increasing at 0.02 ° s^{-1} over the range of 5–40°. For background correction and elimination, the $K\alpha_2$ intensities from diffraction patterns were determined using the X'Pert Plus software (13).

Scanning electron microscopy

SEM photomicrographs of the samples were taken using the JSM-5800 scanning microscope (JEOL, Japan) after sputtering the selected crystals with gold film (S150 sputter coater, Edwards, UK).

RESULTS AND DISCUSSION

Products **1a-j** were studied by SEM microscopy, DSC and TGA analysis, FTIR-spectrometry, and X-ray powder diffraction. Visual inspection of the obtained crystal forms revealed differences in morphology. The differences were confirmed by studying the shape of crystal forms with a scanning electron microscope (Fig. 2). SEM photomicrographs of the basic sample and the products obtained by recrystallization from acetone, ethyl acetate, ethanol, methanol and toluene showed differences in the crystal shape and size. The way of cooling (slow or fast) had no influence on the crystal shape, except in recrystallization with toluene.

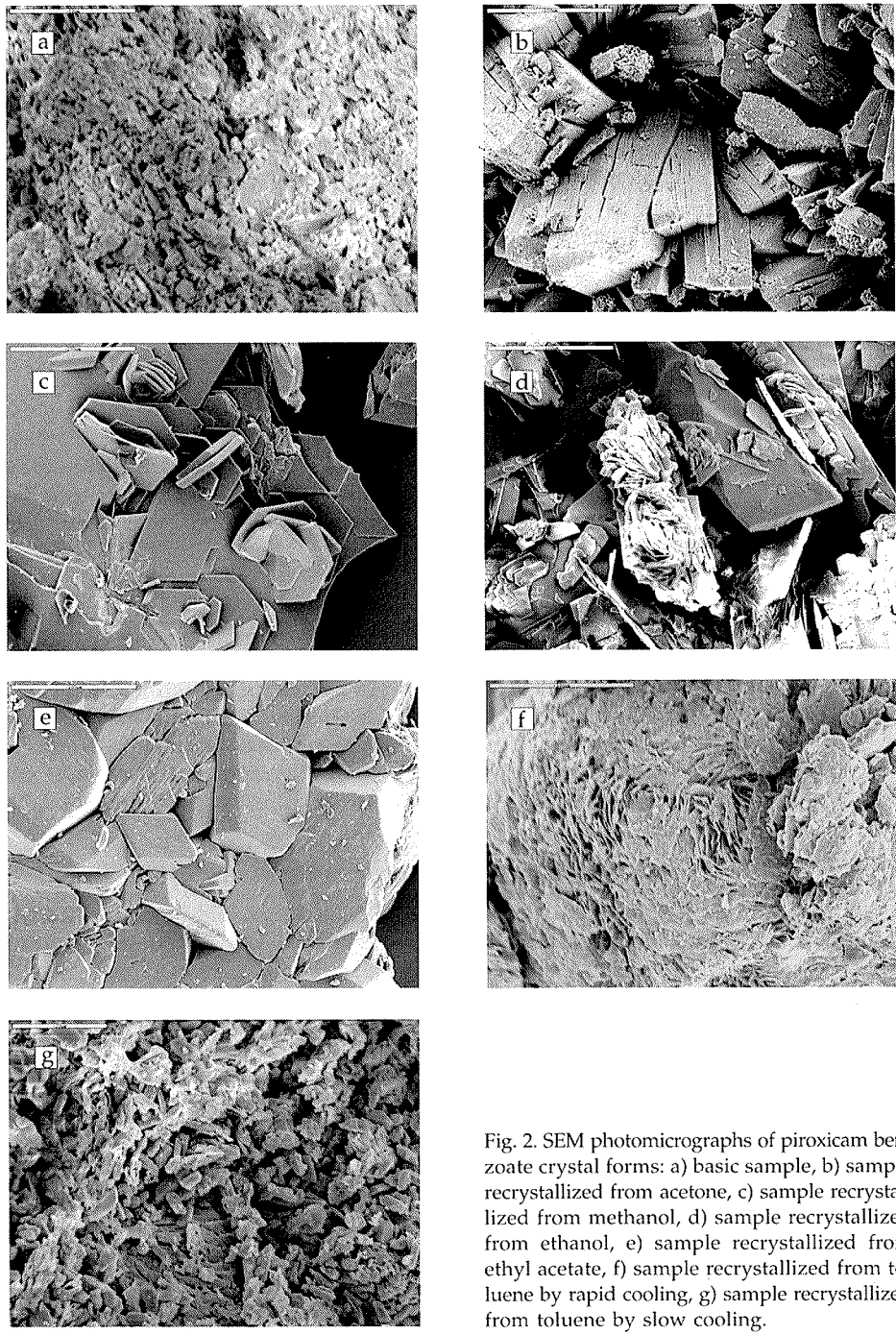

Fig. 2. SEM photomicrographs of piroxicam benzoate crystal forms: a) basic sample, b) sample recrystallized from acetone, c) sample recrystallized from methanol, d) sample recrystallized from ethanol, e) sample recrystallized from ethyl acetate, f) sample recrystallized from toluene by rapid cooling, g) sample recrystallized from toluene by slow cooling.

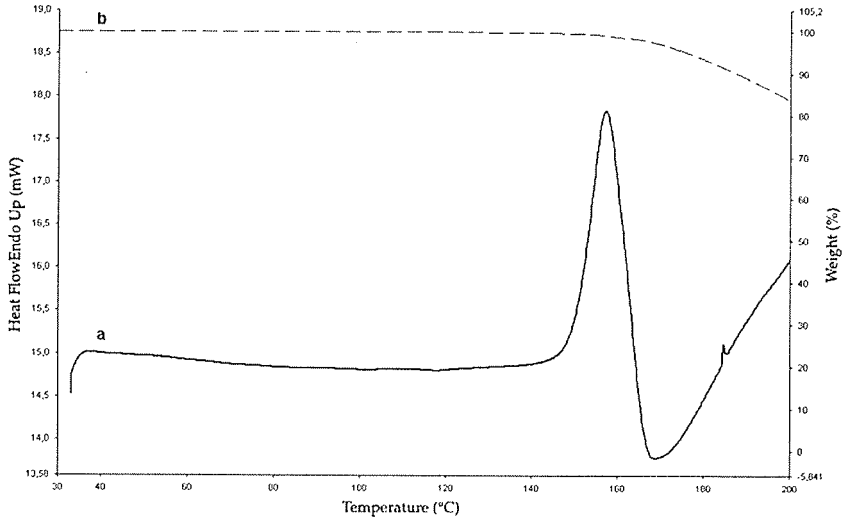

Fig. 3. DSC (a) and TGA (b) curves of piroxicam benzoate basic sample (sample mass 5 mg, heating rate 10 °C min^{-1}, gas flow 35 mL min^{-1}, DSC measurement performed in closed pan).

Thermal behaviors of the basic sample are shown in Fig. 3. DSC curve showed one endothermic event in the range from 141 to 163 °C, recognized as melting of the sample at onset temperature of 150 °C. Thermogravimetric data showed the first mass loss of 62.7% in the range from 132 to 319 °C which was ascribed to sample degradation. It was followed by the second mass loss of 19.8% indicating the completeness of degradation at 400 °C. Thermo analytical data indicated that a degradation process occurred after sample melting.

The products recrystallized from acetone (**1a**, **1f**) and ethyl acetate (**1b**, **1g**) showed the same endothermic event as the basic sample, endothermic peak from 144 to 163 °C, while those recrystallized from ethanol (**1d**, **1i**), methanol (**1c**, **1h**) and toluene (**1e**, **1j**) showed two endothermic peaks, the first from 79 to 108 °C, whose intensity and ΔH (3–7 J g^{-1}) depended on the solvent, and the second from 138 to 149 °C attributable to the melting of piroxicam benzoate (Table I). The products tested in open pans showed similar thermal behavior. After cooling and repeated heating, the samples showed no additional peak in the range from 75 to 100 °C, only the endothermic peak of piroxicam benzoate fusion.

TGA curves of the products showed different stages of mass loss, depending on the recrystallization solvent. According to DSC data, the products obtained from ethanol, methanol and toluene showed two steps of mass loss, the first from 60 to 130 °C due to the removal of crystallization solvent from the lattice and the second from 130 to 400 °C due to the degradation of piroxicam benzoate (Table II). The mass loss data determined in the desolvation process show no stoichiometric relation between piroxicam benzoate and solvent in the crystal lattice, indicating that the solvent has a space-filling role in lattice channels (14, 15).

Table II. TGA data of piroxicam benzoate solvate products mass loss

Crystallization solvent	Temperature range (°C)	Mass loss (%)	
		Slow cooling	Fast cooling
Methanol	70–150	1.2	1.5
Ethanol	60–145	3.5	2.5
Toluene	60–110	4.6	3.7

Results obtained by both methods, DSC and TGA, confirmed that the desolvation occurred in one step, followed by the melting and degradation of piroxicam benzoate. It has also shown that piroxicam benzoate crystallized from ethanol, methanol and toluene as a solvate in a non-stoichiometric relation.

FTIR spectra showed characteristic sharp bands at 3330 (NH), 1750 (ester C=O) and 1682 cm^{-1} (amide I), 1515 cm^{-1} (amide II), 1433 cm^{-1} (CH_3, Ar-C=C), 1063 cm^{-1} (SO_2N) and 703 or 707 cm^{-1} (phenyl). Only small differences between FTIR spectra in the fingerprint region (900–500 cm^{-1}) were found regardless of the experimental conditions and recrystallized products (Fig. 4). No significant differences between recrystallized products were evidenced by FTIR spectra, indicating the existance of the piroxicam benzoate solvate form.

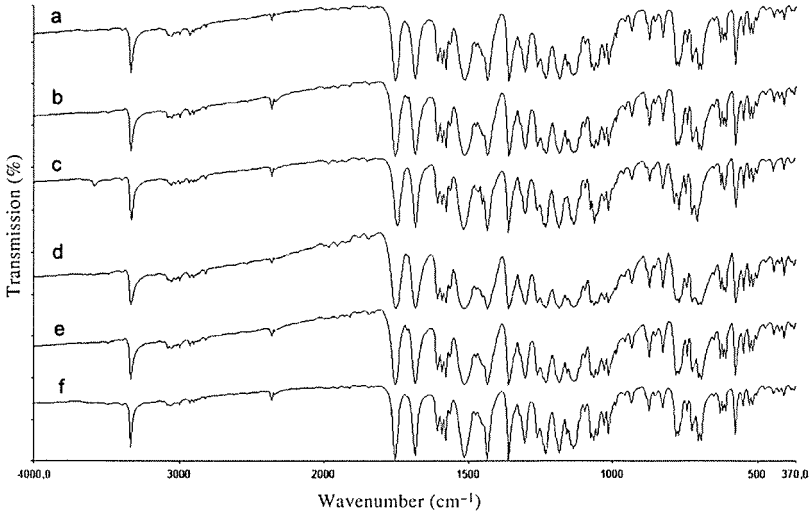

Fig. 4. FTIR spectra of piroxicam benzoate recrystallized by rapid cooling from various solvents: a) basic sample, b) sample recrystallized from acetone, c) sample recrystallized from methanol, d) sample recrystallized from ethanol, e) sample recrystallized from ethyl acetate, f) sample recrystallized from toluene.

It is known that XRPD is a powerful technique for identification of crystalline and non-crystalline phases. This technique was therefore used to establish the possible differences in the crystal form. Powder diffractograms of piroxicam benzoate and the recrystallized products are shown in Fig. 5. All recrystallized products demonstrate good crystallinity properties, well documented by sharp peaks within the 5–40° 2θ region. Powder diffractograms of crystal products obtained from acetone and ethyl acetate have the same peak position and shape as piroxicam benzoate before crystallization whereas the powder diffractograms of crystal products obtained from methanol and ethanol showed a strong peak at 6.86° in 2θ for ethanol and at 6.94° in 2θ for methanol, with several peaks in the range $10.50° < 2\theta < 13.00°$. These peaks did not exist in piroxicam benzoate before crystallization from methanol and ethanol. No significant differences in powder diffractograms for the products prepared by slow or rapid crystallization from acetone, ethyl acetate, ethanol and methanol were observed.

The powder diffractogram obtained for the product recrystallized from toluene by rapid crystallization in an ice-cold bath has the same peak position and peak shape as the products recrystallized from methanol and ethanol, with a strong peak at 7.00° in 2θ and several peaks in the range $10.50° < 2\theta < 13.00°$. The powder diffractogram for the product recrystallized from toluene by slow crystallization at room temperature has a

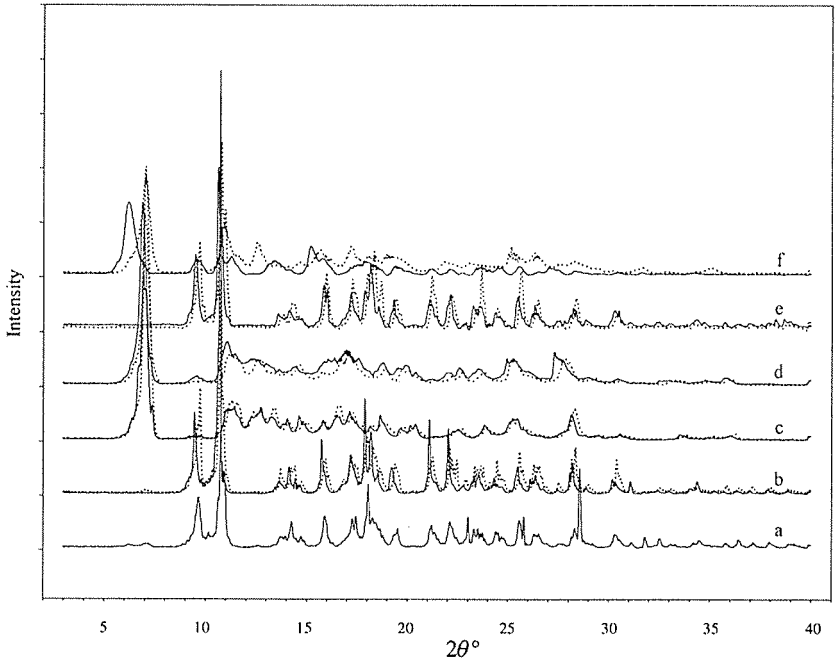

Fig. 5. XRPD patterns of piroxicam benzoate recrystallized from various solvents: a) basic sample, b) sample recrystallized from acetone, c) sample recrystallized from methanol, d) sample recrystallized from ethanol, e) sample recrystallized from ethyl acetate, f) sample recrystallized from toluene (— slow cooling, ···· rapid cooling).

strong peak at 6.25°, which is shifted by 0.75° with respect to the peak found in the powder diffractogram for the product obtained by rapid crystallization in an ice-cold bath.

The differences in the position of peaks between piroxicam benzoate and the products obtained after recrystallization from ethanol, methanol and toluene confirm that pseudopolymorphic modifications of piroxicam benzoate were obtained. Different conditions of crystallization in the case of toluene indicated the existance of two structurally different toluene solvates. One of these solvates, prepared by fast cooling, appears to be similar in structure to the solvates formed with ethanol and methanol.

CONCLUSIONS

Solid-state characteristics of piroxicam benzoate, a new synthesized prodrug of piroxicam, were investigated in order to extend the knowledge of the prodrug properties that might determine *in vivo* performance of dosage forms and point to the most stable form for further development.

The results of this study show that crystal modification of piroxicam benzoate changed during crystallization from various organic solvents and depended on the crystallization conditions, which was confirmed by different analytical methods. SEM microscopy showed differences in the crystal shape and size of the recrystallized products. Thermoanalytical methods (DSC and TGA) and XRPD analysis confirmed that piroxicam benzoate crystallized in two structurally different solvate forms, pseudopolymorphic forms A and B. Pseudopolymorphic form A recrystallized from ethanol and methanol by slow cooling at room temperature and by rapid cooling in an ice-cold bath, and also from toluene by rapid cooling in an ice-cold bath. Pseudopolymorphic form B recrystallized from toluene by slow cooling at room temperature. Solid-state stability of piroxicam benzoate pseudopolymorphic forms and their transformation to more stable are matters of further investigation.

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SAŽETAK

Istraživanje piroksikam benzoata u čvrstom obliku

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Istraživane su karakteristike čvrstog oblika piroksikam benzoata, potencijalnog prolijeka piroksikama. Uzorci su pripremljeni prekristalizacijom iz različitih organskih otapala (toluena, etanola, metanola, etil-acetata i acetona) na dva načina hlađenja. Prekristalizirani uzorci su karakterizirani metodama FTIR, DSC, TGA, SEM mikroskopijom i X-rentgenskom difrakcijom praha. Termoanalitičke metode i X-rentgenska difrakcija praha pokazale su da piroksikam benzoat kristalizira u dvije pseudopolimorfne forme, A i B. Pseudopolimorfna forma A dobivena je prekristalizacijom iz etanola i metanola sporim hlađenjem na sobnoj temperaturi i brzim hlađenjem na ledu, te iz toluena brzim hlađenjem na ledu. Pseudopolimorfna forma B dobivena je prekristalizacijom iz toluena sporim hlađenjem na sobnoj temperaturi.

Ključne riječi: piroksikam benzoat, pseudopolimorfizam, FTIR, termička analiza, XRPD, SEM mikroskopija

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