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Characterization of piroxicam crystal modifications

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Abstract

Piroxicam polymorphism was extensively studied in the past. The objective of the present work was to evaluate polymorphism of piroxicam once again and to characterize the obtained crystal forms. Three polymorphic forms and one monohydrate form were obtained by crystallization from saturated solutions in various solvents. Polarity of solvents and crystallization rate defined by temperature of crystallization were found to be critical parameters in determining the polymorphic form. A new polymorphic form designated as form III was obtained by forced crystallization using dry ice. Only form I with the highest melting point was found to be stable under mechanical and thermal stress. Differences in IR spectra were attributed mainly to the differences in number and positions of H-bonds in the piroxicam crystal forms. Slow crystallization of piroxicam from absolute ethanol solution resulted in a mixture of form II and monohydrate. Crystal structure analysis proved that form II represents form α_2 already proposed in the literature. Differences in dissolution rates among crystal forms of piroxicam were attributed to differences in their wettability, where highest wettability was obtained for monohydrate and the lowest for form III.

Keywords: Piroxicam; Polymorphism; Characterization

1. Introduction

Expertise on polymorphism of drug substances and excipients is very important in pharmaceutical industry. Polymorphism has been extensively investigated due to its possible impact on quality and efficacy of pharmaceutical products.

Polymorphism of piroxicam was extensively investigated in the past 20 years (Vrečer et al., 1991), whereat the first report on piroxicam polymorphism was published in 1982 (Mihalić et al., 1982). Two polymorphic modifications (designated as cubic and needle form) and one monohydrate form, obtained by crystallization from solvents, were known at that time. Thermal crystallization of melted piroxicam in DTA cell resulted in three modifications designated as I, II and III (Kuhnert-Brandstätter and Völlenklee, 1985). Reck et al. (1988) introduced a new designation for cubic and needle polymorphic modifications. Cubic form was designated as β and needle form as α. New polymorph structure designated as α_2 was proposed by the X-ray diffraction studies by Reck (Reck and Laban, 1990) and the already known needle form (α) was designated as α_1. Only minor crystallographic differences were proposed between α_1 and α_2 forms (Reck and Laban, 1990). Fast cooling of piroxicam melt in the DSC cell resulted in an amorphous solid, which was converted into the mixture of polymorphs upon new heating cycle (Vrečer et al., 1991). New polymorph, designated as IV was detected in the mixture.

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Polymorphic modifications and monohydrate were extensively characterized using methods, which were available at that time (Kozjek et al., 1985; Mihalić et al., 1986). On the other hand melting point and melting enthalpy were known for modifications III and IV. Studies showed that only modification I (cubic, β) is physically stable in solid state upon thermal (Vrečer et al., 1991) and mechanical (Ghan and Lalla, 1992) stress.

Polarity of solvents (Vrečer et al., 1991; Janik et al., 1991) and crystallization rate (Mihalić et al., 1986) were assumed to be critical parameters for crystallization of modification I (cubic, β) and II (needle, α).

Piroxicam is known for forming intra- and intermolecular hydrogen bonds (Kojić-Prodić and Ružić-Toroš, 1982; Bordner et al., 1984; Reck et al., 1988; Reck and Laban, 1990). Examination of the literature confirmed the inconsistent designations of piroxicam polymorphic modifications.

The aim of the present study was to characterize piroxicam crystal modifications obtained by crystallization from various solvents using modern analytical techniques.

2. Materials and methods

2.1. Materials

Piroxicam was obtained from Esteve Quimica (Spain), solvents used for crystallization studies were of analytical grade and used as received. Solid carbon dioxide (CO_2) and liquid nitrogen were obtained from Messer (Slovenia).

2.2. Methods

Thermal analysis (DSC) was performed on Perkin-Elmer DSC 7 (dynamic N_2 atmosphere, heating rate 10 °C/min). Thermal effects were evaluated using Pyris software.

Thermogravimetric analysis (TG) were performed on Perkin-Elmer TGA-7 instrument (dynamic N_2 atmosphere, heating rate 10 °C/min).

FT-IR spectra of samples of piroxicam crystal modifications were obtained by Perkin-Elmer FT-IR Spectrometer 1720X using compressed KBr disc technique.

Near Infrared analysis was performed using Perkin-Elmer GX Custom System.

Raman spectra were recorded on FT Raman spectrometer Perkin-Elmer GX Custom System.

^{13}C solid state NMR spectra were recorded on Varian 300 MHz spectrometer at 75.43 MHz using CP-MAS technique at 18.1 kHz.

X-ray powder diffractograms were obtained by Phillips PW 1710 diffractometer (Cu Kα radiation, $2 \leq 2\theta \leq 37°$).

X-ray structure determination was performed on single crystal of the dimensions 0.25 mm × 0.2 mm × 0.15 mm using Nonius Kappa CCD diffractometer and Nonius Collect Software (Collect, 1998). Indexing and scaling of the data were performed using DENZO and SCALEPACK (Otwinowski and Minor, 1997).

True densities were determined with AccuPyc 1330 helium pycnometer; five measurements were performed on each sample. The results represent average value calculated from repetitions.

Contact angle was determined using Wilhelmy disc method on Tensiometer Krüss K12 at 20 ± 0.2 °C (water and artificial gastric juice were used as a liquid).

Solubility was determined USP XXIII method (apparatus II (paddle), 100 rpm). 100 mg of piroxicam was added to 500 ml of artificial gastric juice (pH = 1.2 ± 0.1) kept at chosen temperature (19, 25, 30, 37 and 45 ± 0.5 °C). Piroxicam concentrations in dissolution medium were determined at preselected time intervals "on line" using UV-Vis diode array spectrophotometer Hewlett-Packard HP 89550A and automatic sampling system (Multicell transport system).

Powder dissolution profiles were obtained using USP XXIII method (apparatus II (paddle), 100 rpm); 20 mg sample of piroxicam was added to 500 ml artificial gastric juice (pH = 1.2 ± 0.1) at 37 ± 0.5 °C); piroxicam concentrations in dissolution medium were determined "on line" using UV-Vis diode array spectrophotometer Hewlett-Packard HP 89550A and automatic sampling system (Multicell transport system).

2.2.1. Intrinsic dissolution rate (IDR)

VanKel intrinsic dissolution apparatus was used: sample (100 mg) was put into the die cavity and compressed into a disc. The die with the disc was fixed into the holder, which was mounted through the shaft on to the dissolution tester. Holder was sunk into the dissolution medium (artificial gastric juice (pH = 1.2 ± 0.1) at 37 ± 0.5 °C) and rotated at 100 rpm; piroxicam

concentrations in dissolution medium were determined "on line" using UV-Vis diode array spectrophotometer Hewlett-Packard HP 89550A and automatic sampling system (Multicell transport system). Intrinsic dissolution rate was calculated according to Eq. (1) (VanKel, 1992).

$$\mathrm{IDR} = \frac{K}{S} \quad (1)$$

where K, slope of the "disc" dissolution profile (mg/min); S, surface area of the disc in contact with the dissolution medium (cm^2).

2.2.2. Preparation of polymorphic forms of piroxicam

Form I was obtained by crystallization from benzene saturated solution; form II (needles) was crystallized from saturated solution in absolute ethanol; form III was obtained by pouring the hot saturated piroxicam solution in absolute ethanol on dry ice or by spray drying of piroxicam solution in absolute ethanol in Büchi 190 Mini Spry Dryer using following parameters: air flow rate, 800 ml/min; inlet air temperature, 94 °C and outlet air temperature, 50–55 °C.

3. Results and discussion

3.1. Crystallization of piroxicam polymorphs

The study of piroxicam crystallization from polar and nonpolar solvents at different temperatures (crystallization rate) showed that three modifications designated as I, II and III, where form I has the highest melting point and form III the lowest, can be obtained by varying the type of solvent and crystallization rate (Table 1).

Pure modification I was obtained either by crystallization from saturated solution in benzyl alcohol and 1,2-dichlorethane or by crystallization from cooled benzene or chloroform solution. Crystallization from latter solvents at room temperature resulted in mixture of modifications I and II. Pure modification II in form of needles was obtained by crystallization from aliphatic alcohols at room temperature, while crystallization from the same solvents at lower temperatures (liquid nitrogen bath or pouring on to dry ice (solid CO_2)) resulted in mixture of both modifications. The exception is form III, which was obtained by pouring hot saturated solution in ethanol on to dry ice (Pretrišič, 2001). If the same procedure was repeated using liquid nitrogen, modification II was obtained.

Monohydrate form was obtained, as already known from the literature, by crystallization from water.

Table 1
Solvents and conditions used in crystallization of piroxicam crystal forms

Solvent	Form I	Form II	Form III	Hydrate
Ethanol				
RT		+		
Solid CO_2			+	
Liquid N_2		+		
Methanol				
RT		+		
Solid CO_2	+	+		
Liquid N_2	+	+		
Isopropanol				
RT		+		
Solid CO_2	+			
t-Butanol				
RT		+		
Solid CO_2	+	+		
Benzyl alcohol				
RT	+			
Solid CO_2	+			
Liquid N_2	+			
Chloroform				
RT	+	+		
Solid CO_2	+			
Liquid N_2	+			
Methylenechloride				
RT		+		
Solid CO_2	+	+		
1,2-Dichloroethane				
RT	+			
Benzene				
RT	+	+		
Ice bath	+			
Purified water				
RT				+

3.2. Characterization of piroxicam crystal forms

Infrared spectroscopy proved to be very useful in analyzing the polymorphism of piroxicam. Piroxicam polymorphs and hydrate exhibit very pronounced differences in FT-IR, Raman and NIR spectra (Figs. 1–3). FT-IR spectra of forms I and II are practically identical

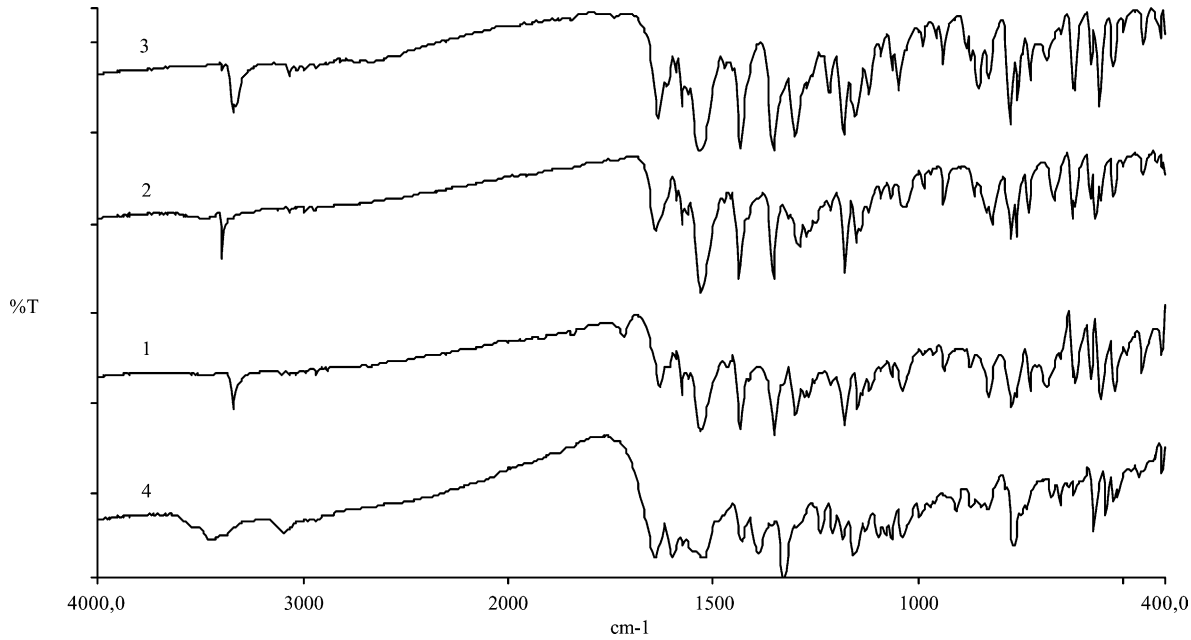

Fig. 1. FT-IR spectra of crystal forms of piroxicam: (1) form I; (2) form II; (3) form III; (4) monohydrate.

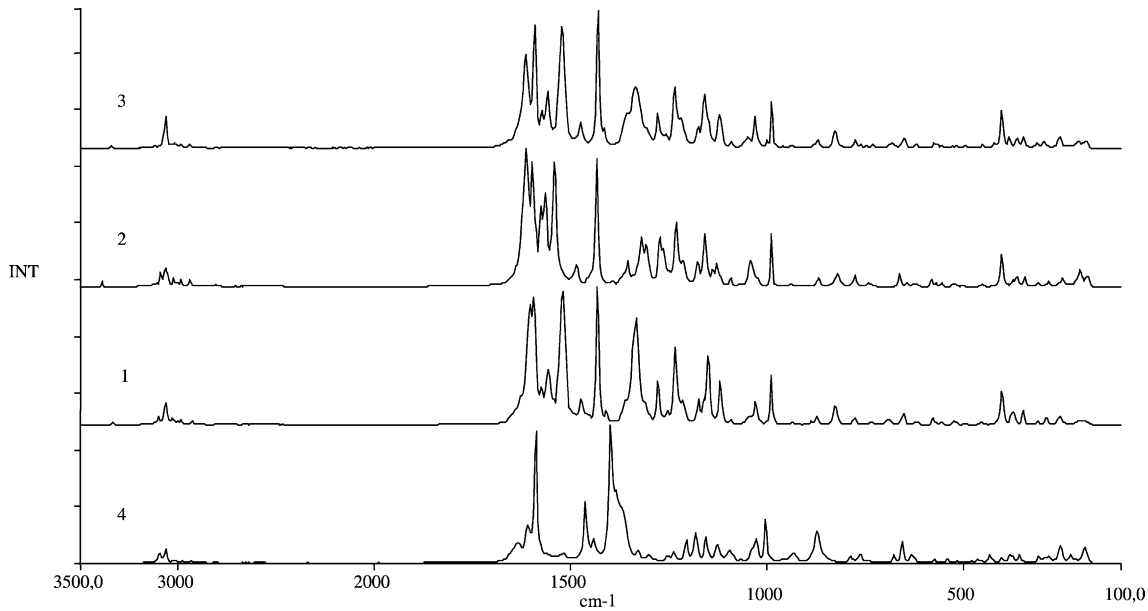

Fig. 2. Raman spectra of crystal forms of piroxicam: (1) form I; (2) form II; (3) form III; (4) monohydrate.

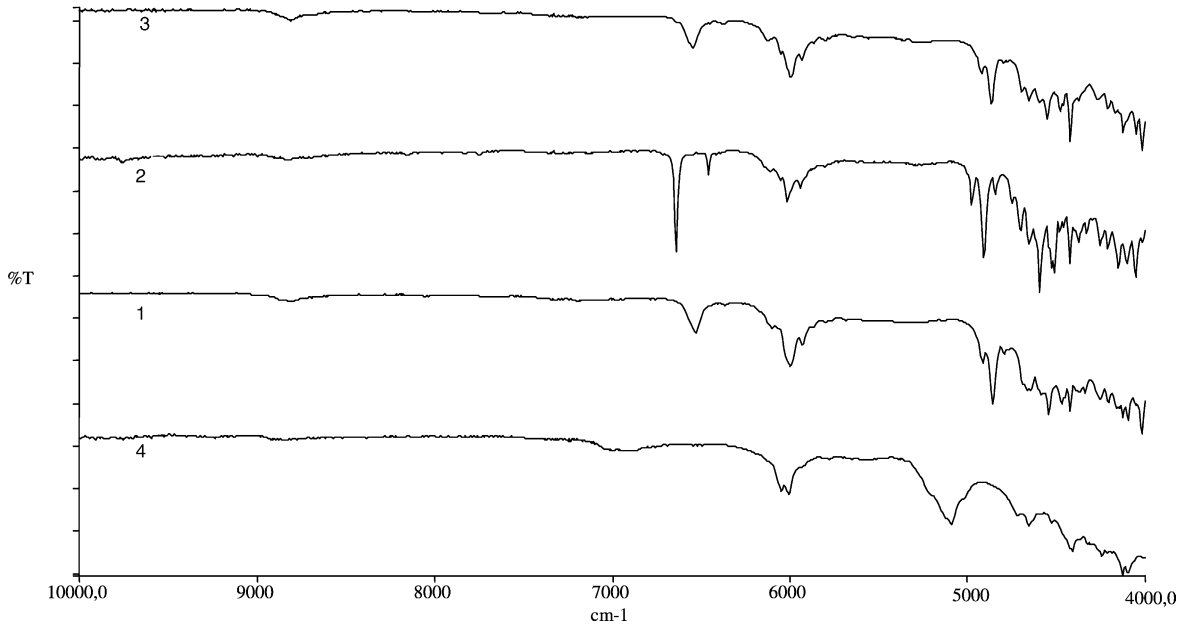

Fig. 3. NIR spectra of crystal forms of piroxicam: (1) form I; (2) form II; (3) form III; (4) monohydrate.

to those published in the literature (Mihalić et al., 1986; Vrečer et al., 1991) for cubic and needle form. Kuhnert-Brandstätter (Kuhnert-Brandstätter and Völlenklee, 1985) published mid IR spectra for piroxicam forms I and II, but the published spectrum for form designated as II is very close to that designated in our study as III. Main differences in the mid IR spectra of piroxicam polymorphs can be observed from 3300 to 3400 cm^{-1}, where the band for OH and NH stretching can be found (Mihalić et al., 1986). Janik et al. (1991) have found that absorption bands at 3393 and 3341 cm^{-1} represent the vibrations of free NH and H-bonded NH group. According to their observations enol –OH absorption band can be found in FT-IR spectrum as broad peak with the maximum at 2800 cm^{-1} (Janik et al., 1991). From our spectra of forms I and II, the peaks of –NH stretching absorption bands for both polymorphs are at 3393 and 3334 cm^{-1}, what is in good agreement with the published data (Mihalić et al., 1986; Janik et al., 1991). Form III exhibit absorption band for amide NH stretching as double peak at 3323 and 3342 cm^{-1}. Different positions of the absorption band for NH (OH) in FT-IR spectra are attributed to the differences in H-bonding (inter- and intramolecular) at piroxicam forms (Mihalić et al., 1986; Janik et al., 1991). It is known from the literature that form I (β, cubic form) exists in form of dimers where two molecules of piroxicam are connected through an intermolecular H-bond between amide NH group and oxygen in sulfoxide group (Reck et al., 1988; Janik et al., 1991), on the other hand it is also known that form II (α, needle form) forms chains through intermolecular H-bond between enol OH group and oxygen from sulfoxide group (Reck et al., 1988; Janik et al., 1991). In both forms, a very stable intramolecular H-bond, connecting enol OH group with carbonyl oxygen forming a six member ring, was found (Janik et al., 1991). From the FT-IR spectrum of form III, it could be assumed that both groups that participates in H-bonding at forms I and II, i.e. enol OH and amide NH group, are free in form III. This would result in lower stability of form III due to absence of its stabilization by H-bonds.

According to the IRR rule, which was postulated by Burger (Burger and Ramberger, 1979), we can conclude, that form II has higher entropy than form I, what could result also in lower melting point of form II in comparison to form I.

Differences among crystal forms were obtained also by Raman and NIR spectrophotometry. High

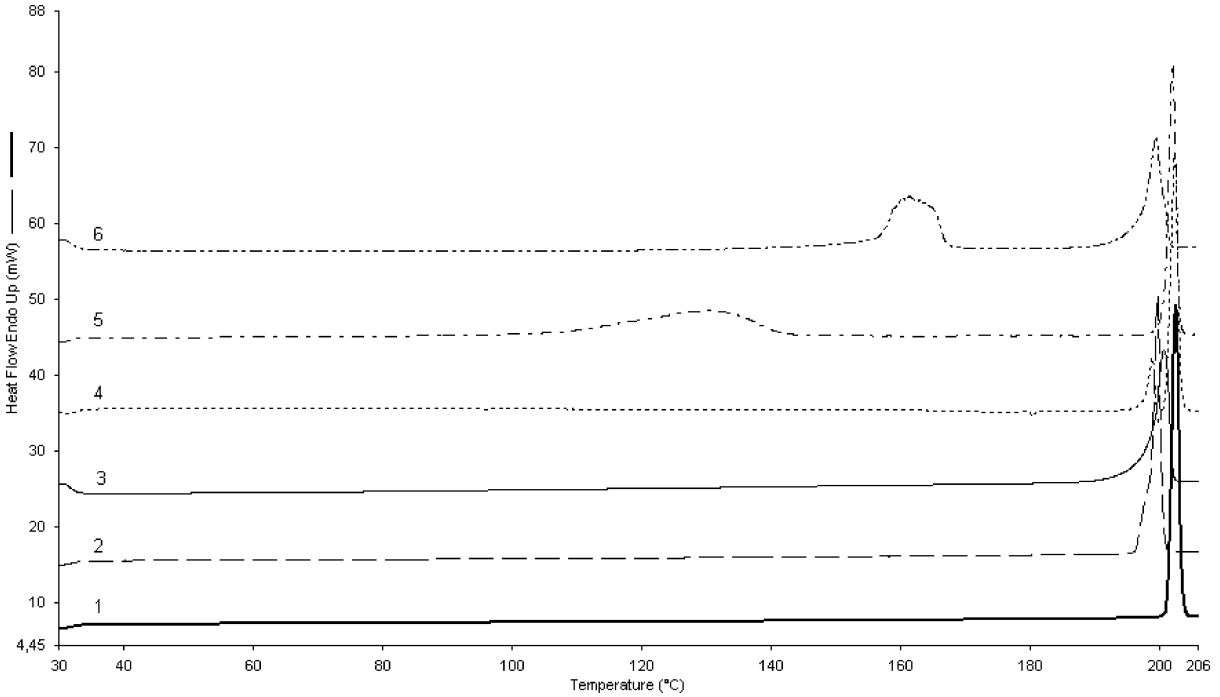

Fig. 4. DSC analysis of crystal forms of piroxicam: (1) form I; (2) form II (fast crystallization); (3) form II (slow crystallization); (4) form III; (5) monohydrate (fast crystallization); (6) monohydrate (slow crystallization).

similarity of Raman and NIR spectra of piroxicam forms I and III were observed, what was attributed to the conversion of unstable form III to stable form I during the preparation of the sample for recording spectra. On the other hand significant differences can be observed in NIR and Raman spectra of forms I and II.

Thermal analysis of samples prepared by crystallization proved the existence of three polymorphs (Fig. 4). Form III was, as it was predicted above from FT-IR spectrum, found to be thermally unstable and was converted to unstable form II that further crystallize to form I. DSC curve obtained for form II show broadened melting peak with a shoulder. This observation can be attributed to the presence of two different crystal species in the sample, with very small difference in melting point. As can be seen in Fig. 4, the shoulder in melting peak of form II crystals is not present in sample, which was obtained by slow crystallization at room temperature.

Rate of crystallization of piroxicam monohydrate influences the shape of dehydration peak (Fig. 4), where in case of slow crystallization much narrower peak at higher temperatures was obtained. On the other hand the melting peak was broadened and the melting point was lower. No changes in absorption band position were observed in FT-IR and NIR spectra in both hydrate samples.

X-ray powder diffraction data (Fig. 5) confirm existence of four distinct crystal modifications of piroxicam. Our X-ray powder diffraction data for form I and monohydrate form corresponds to those published in the literature for cubic (Mihalić et al., 1986) or β form (Reck et al., 1988) and monohydrate (Mihalić et al., 1986). Our powder diffraction data for form II does not correspond to those published in the literature. From the careful examination of literature data it was concluded that needle form described by Mihalić et al. (1986) corresponds to form α_1 described by Reck (Reck et al., 1988). From the powder X-ray diffraction of our form II and literature data (Reck et al., 1988) it was concluded that polymorphic form designated by us as form II actually represent form α_2 which was proposed in the literature (Reck et al., 1988). It is interesting, that IR spectroscopy can not distinguish

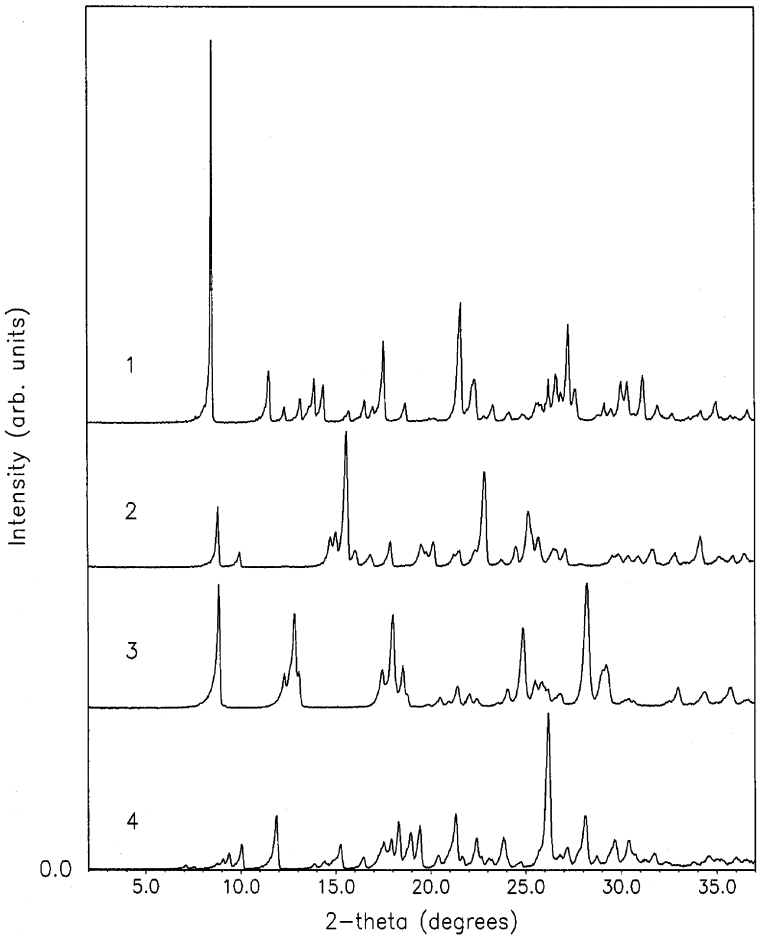

Fig. 5. Powder X-ray diffractograms of crystal forms of piroxicam: (1) form I; (2) form II; (3) form III; (4) monohydrate.

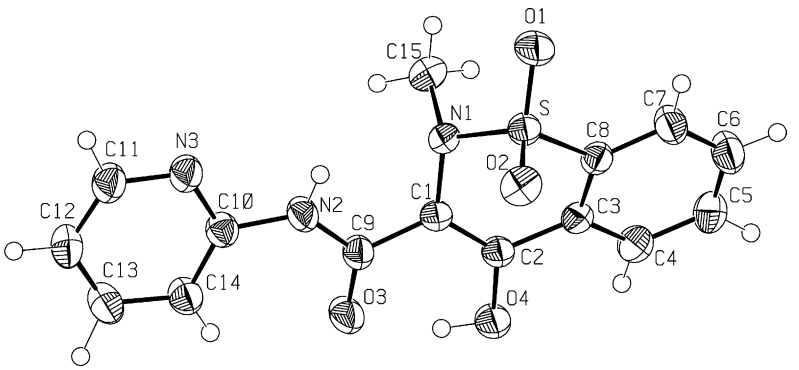

Fig. 6. The asymmetric unit (molecule) of the α_2 modification of piroxicam. Ellipsoids are plotted at 50% probability.

between form α_1 and α_2. Powder X-ray diffractogram of our form III reflects no similarities to diffractograms of already known piroxicam crystal forms. From the powder X-ray data for form III we can conclude, that it represents a new polymorphic form for which no crystallographic data have so far been published.

From the literature data (Reck et al., 1988) and our powder diffractograms we can confirm what was already proposed by Janik (Janik et al., 1991) that two H-bonds exist in form I (β) crystals, i.e. intramolecular and intermolecular.

The unit cell (Fig. 6) dimensions of the needles obtained by slow crystallization from ethanol (monoclinic, $a = 17.5858(4)$ Å, $b = 11.8594(2)$ Å, $c = 6.93940(10)$ Å, $b = 97.5612(8)$ Å, space group $P2_1/c$) were consistent with the α_2 modification of piroxicam proposed by Reck (Reck and Laban, 1990). An interesting fact is that this modification was previously only available in powder form and its structure was derived from the α_1 modification by molecular modeling and powder diffraction (Reck and Laban, 1990). A possibility of obtaining reliable single crystal experiment-based structural parameters of this form was a good motivation to proceed.

Structure was solved by means of SIR92 (Altomare et al., 1994) while the refinement and plotting were done using Xtal3.4 (Hall et al., 1995) program package. The refinement was carried out on F by a full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically. All hydrogen atoms were readily found in the difference Fourier map and were subsequently refined isotropically. Regina (Wang and Robertson, 1985) weighting scheme was used in the final stage of the refinement. Refinement of 260 parameters using 2167 reflections converged with $R = 0.048$, $R_w = 0.041$, goodness of fit of 1.06, maximum shift/error of 0.008 and minimum and maximum residual electron densities of -0.40 and 0.41 e/Å^3, respectively. The molecule with the labels of atoms is presented in Fig. 6.

In general, it can be said that the structure does not differ significantly from the one mentioned above (Reck and Laban, 1990). There is, however, one significant difference regarding the position of the H4O hydrogen atom (enol OH group), involved in the hydrogen bonding. Reck and Laban (1990) of course did not have a possibility to determine the hydrogen positions so that they assumed that the H4O is pointing out of the plane of C2–O4–O3 toward the sulfoxide O2 in the neighboring molecule, thus forming a weak intermolecular hydrogen bond (the O4–O2 distance in the case of found by Reck and Laban (1990) is 3.01 and 3.00 Å in our case). They were not discussing any intramolecular hydrogen bonds. Our data, however, show unambiguously that H4O is positioned in the plane of C2–O4–O3, pointing toward O3 and thus forming a strong intramolecular hydrogen bond with the O4–O3 distance of 2.57 Å and the O4–H4O–O3 angle of 148°. It may be stated that the hydrogen bond on the H4O is bifurcated, but it is clear that the

Table 2
Chemical shifts (ppm) of piroxicam carbon atoms in solution and in solid state

Carbon atom's numbering	$CDCl_3$	Florey	Form I	Form II	Form III	Hydrate
C1	111.5	117.7	112.6	113.2	113.1	109.3
C2	158.7	159.3	158.6	156.2	158.6	–
C3	128.3	128.8	130.4	130.0	131.4	132.1
C4	126.6	126.6	127.5	128.6	128.0	132.1
C5	132.5	132.9	133.4	132.9	133.8	135.0
C6	133.0	133.3	133.4	132.9	133.8	135.0
C7	124.8	124.2	124.1	124.0	128.0	126.0
C8	134.6	135.2	133.4	135.5	138.4	135.0
C9	166.9	167.2	167.1	166.3	167.5	168.8
C10	150.1	150.5	150.5	148.4	150.2	149.0
C11	114.3	115.8	119.0	121.4	121.9	116.6
C12	138.4	139.0	143.8	148.4	142.0	149.0
C13	120.6	120.4	119.7	121.4	121.9	122.9
C14	148.2	147.2	143.8	148.4	150.2	149.0
C15	39.9	39.2	40.2	41.69	39.0	42.2

intermolecular hydrogen bond O4–H4O···O2 with the distance of 3.00 Å and O4–H4O–O3 angle of 112° is in any case inferior to the intramolecular one.

Although it can be seen from the data in Reck and Laban (1990) that another intramolecular N2–H2···N1 hydrogen bond may exist, the authors did not discuss it. But the details can be seen from our data: the distance N2–N1 and the angle N2–H2–N1 are 2.73 Å and 119°, respectively.

As piroxicam crystal forms differ among them also in number and positions of H-bonds, we expected that this fact would result also in differences in the solid

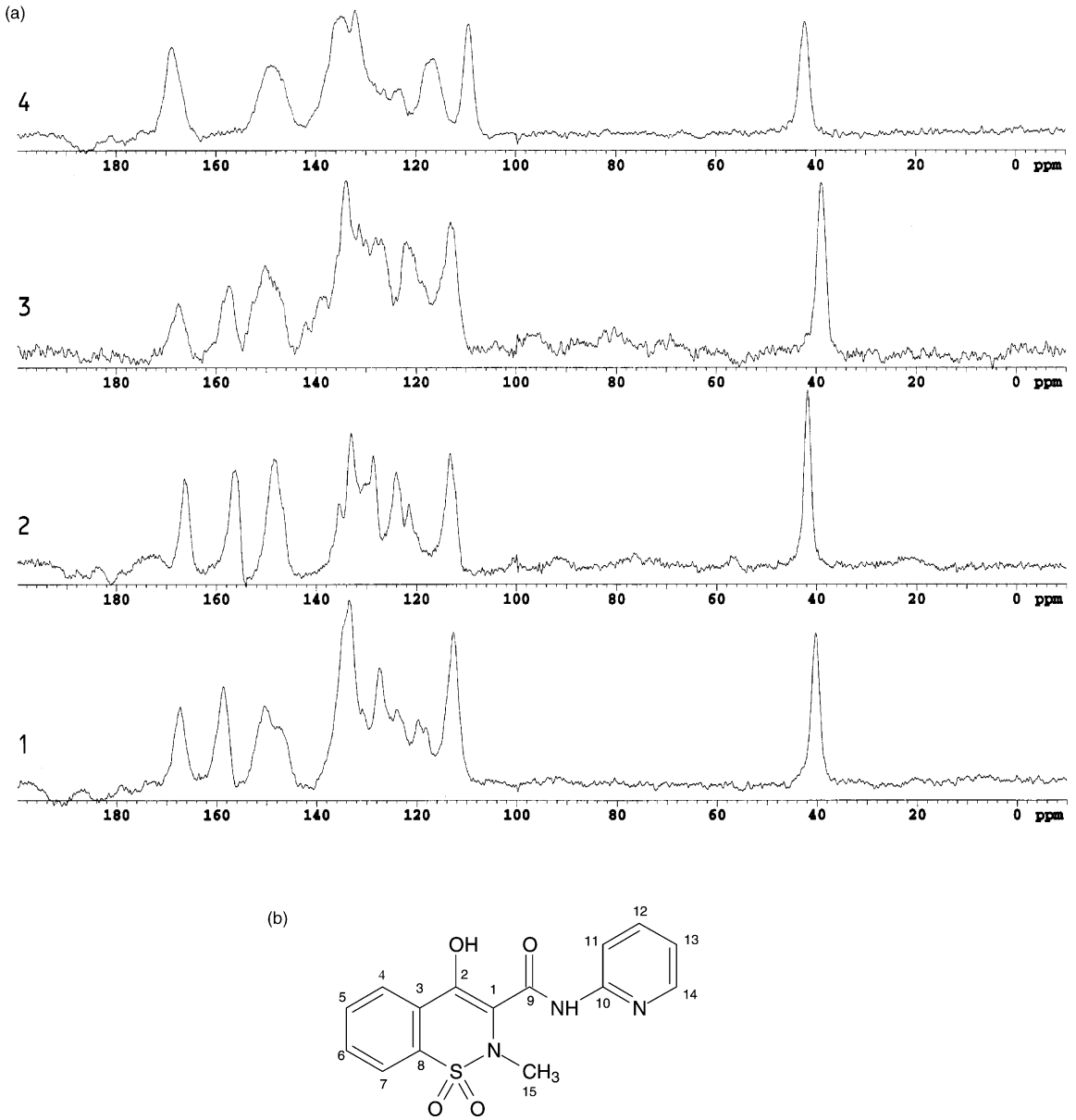

Fig. 7. (a) Solid state ^{13}C NMR spectra of crystal forms of piroxicam: (1) form I; (2) form II; (3) form III; (4) monohydrate; (b) structure formula of piroxicam with numbering of carbon atoms.

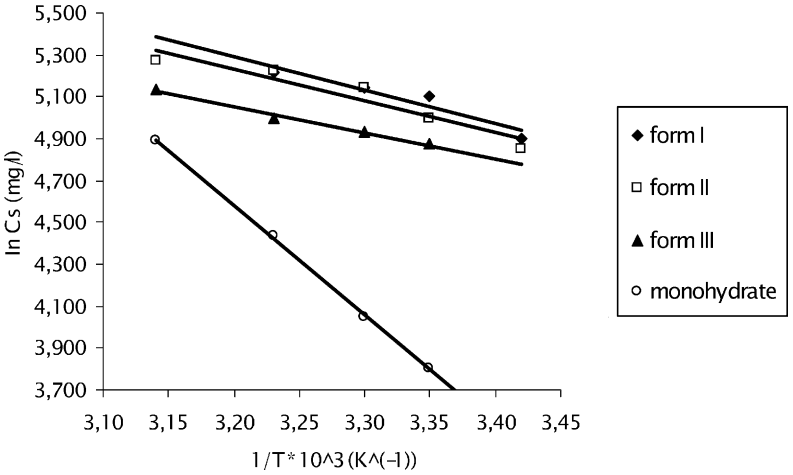

Fig. 8. Van't Hoff solubility diagram for piroxicam crystal forms.

state ^{13}C NMR spectra. As can be seen in Fig. 7a and Table 2, some differences actually exist. Nonetheless chemical shifts of some carbon atoms, which are considered to be in neighborhood of center participating in forming H-bonds, differ only slightly among crystal forms. It is known, that enol hydroxyl group on C2, carbonyl group on C9, amide NH and sulfoxide group participate in H-bonds formation, so it was expected that chemical shifts obtained for carbon atoms C2, C9, C10, and C8 should have the biggest differences at different crystal modifications. As can be seen in Table 2, the largest difference can be observed in NMR spectrum of the monohydrate form. Spectra of forms I and II differ in chemical shifts of carbon atoms on positions 2, 8, 10, 11, 12, 13, 14 and 15. Differences in chemical shifts of carbon atoms in benzothiazine ring demonstrate that there could be differences in H-bonding of enol OH and sulfoxide group between both modifications. Differences in chemical shifts of pyridine carbon atoms can be attributed to the differences in intermolecular van der Waals bonding. On the other hand differences in chemical shifts for carbon atoms on positions 7, 8, 11, 12, 13, 14 and 15 can be observed in NMR spectrum of form III in comparison to form I. It was proposed that there are differences in chemical environment of sulfoxide group between both modifications.

True densities of the polymorphic forms differ only slightly (Table 4). The results show that form II has the highest density, what means closer packaging of piroxicam molecules in crystal, while forms I and III have very similar densities.

Piroxicam is known to have very low solubility, which is, due to its acidic properties, pH dependent (Herzfeldt and Kummel, 1983). Precipitation of monohydrate form from the supersaturated solution was observed during solubility tests of forms I, II and III. Maximal piroxicam concentrations obtained during the solubility testing were used as solubility of forms I, II and III, due to the observed precipitation of monohydrate form. Unexpected lower solubility of form III in comparison to forms I and II was attributed to higher precipitation rate observed at form III. As expected, monohydrate shows the lowest solubility among all tested piroxicam crystal forms. All piroxicam crystal forms shows the increase of the solubility with the rise of temperature (Fig. 8) what is contradictory to the data published by Kozjek et al. (1985), who found decrease in solubility of needle form (form II) with rising temperature of the dissolution medium.

Contrary to the results of solubility, the dissolution rate study showed very high dissolution rate of monohydrate in comparison to other crystal forms. Comparison of dissolution rate constants calculated from dissolution profiles in time interval 0–30 min of piroxicam crystal forms in artificial gastric juice at 37 °C using 100 mg dose (supersaturation, Table 3) showed the highest value for monohydrate, followed by form II, form III and form I. As can be seen in Fig. 9, form II and monohydrate form exhibit higher

Table 3
Some physical characteristics of piroxicam crystal modifications

Parameter	Form I	Form II	Form III	Monohydrate
Melting point (°C)	202.6	199.7	–	202.01
Melting enthalpy (J/g)	110.28	112.96	–	104.75
Solubility in artificial gastric juice pH 1.2, 37 °C (mg/l)	184.9	186.3	147.7	84.5
Dissolution rate constant $\times 10^{-2}$ (artificial gastric juice pH 1.2, 37 °C) (min^{-1})	4.97 ± 2.17	8.90 ± 1.65	5.71 ± 1.76	15.17 ± 1.64

dissolution profiles also at 20 mg dose (normal dose of piroxicam in a capsule) in comparison to form I and III. Reversed order in dissolution rate between from II and monohydrate was attributed to the influence of lower solubility (Table 3) of later when using 100 mg dose.

Intrinsic dissolution rate (IDR) study (Fig. 10) was performed only with forms I, II and monohydrate due to the instability of form III under mechanical stress (compaction of sample into discs). Only minor transition of form II to I was observed during preparation of discs for the study. Calculated values for IDR of form I, form II and monohydrate are 2.27×10^{-2}, 2.79×10^{-2} and 1.97×10^{-2} mg/min/cm^2. From the IDR values it can be clearly seen, that the more stable form shows lower IDR values in comparison to form with lower melting point. This observation is in accordance with literature data (Brittain and Grant, 1999). The lowest IDR was obtained for monohydrate. This finding is not in agreement with powder dissolution rates, where dissolution rate of monohydrate was higher than that obtained for form I. This difference could be attributed to the influence of the solubility on the dissolution kinetic from the disc.

Wettability of crystal forms of piroxicam with artificial gastric juice and water was evaluated (Table 4) using contact angle measurements. Monohydrate form has lowest contact angle and consequently highest wettability. On the other hand form III has highest contact angle and lowest wettability. The results of contact angle measurements support the data of dissolution rate studies, where higher wettability of piroxicam monohydrate results in faster dissolution and higher dissolution rate constant.

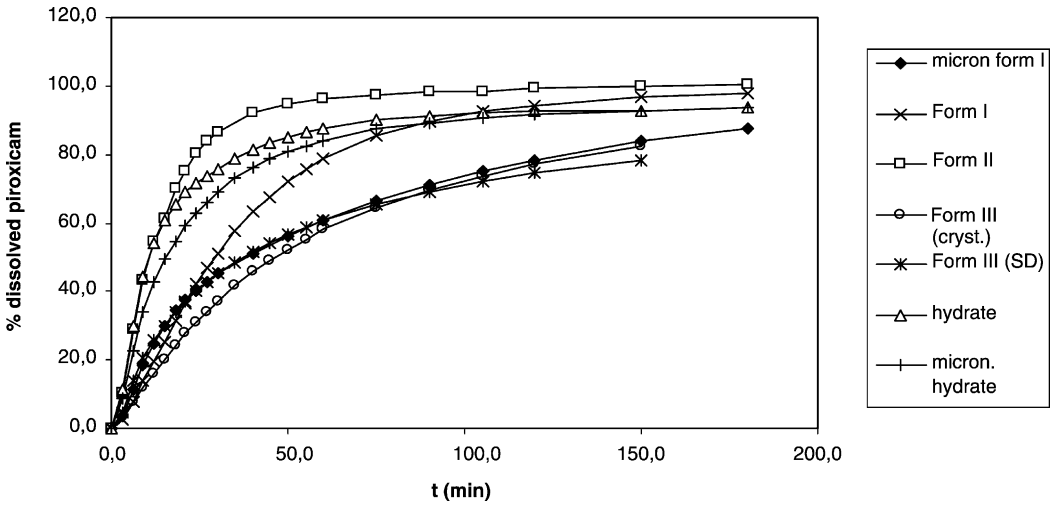

Fig. 9. Dissolution profiles of piroxicam crystal forms in artificial gastric juice using 20 mg dose of drug.

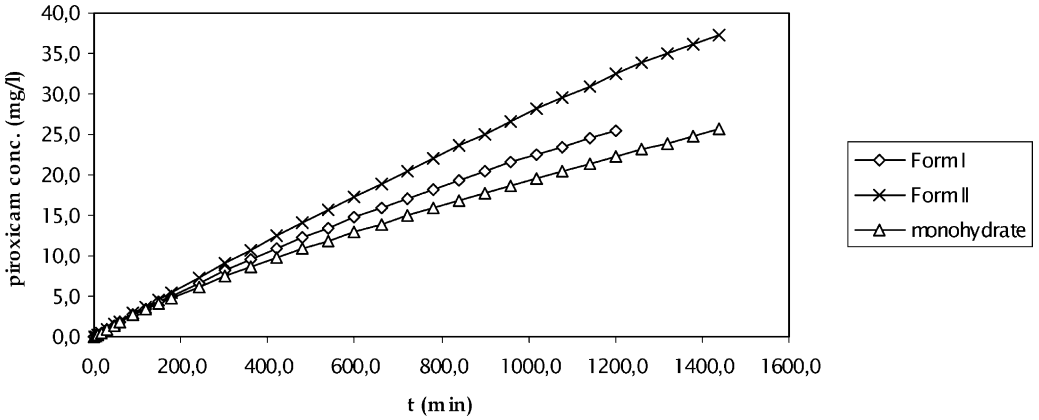

Fig. 10. Intrinsic dissolution rates of piroxicam crystal forms.

Table 4
True densities and contact angles of piroxicam crystal forms

Sample	True density (g/cm^3)	Contact angle	
		Water (°)	Artificial gastric juice (°)
Micronized form I	1.4732 ± 0.0022	76	72
Form I	1.4710 ± 0.0005	75	69
Form II	1.5294 ± 0.0034	74	70
Form III (crystallized)	1.4739 ± 0.0018	83	77
Form III (SD)	n.d.	n.d.	75
Monohydrate	1.5101 ± 0.0064	73	62
Micronized monohydrate	1.5062 ± 0.0010	71	61

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