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Polymorphism without IR- and Raman-spectroscopic differences: tiaprofenic acid, three modifications

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Two new polymorphic modifications of tiaprofenic acid (mod. II and mod. III) were found. Modification I (mod. I) is thermodynamically stable at any temperature below its melting point of 94 to 96 °C. Both, mod. II (m.p. 90 to 92 °C) and mod. III (m.p. 84 to 85 °C) melt inhomogeneously forming mod. I. The modifications can only be distinguished thermoanalytically and by means of powder X-ray diffraction. Surprisingly, IR- and Raman spectroscopy failed for the distinction of all the three modifications. The solubility of the non-hygroscopic modifications depending on temperature, on the pH-value and on the addition of polysorbate 80 were investigated. The thermodynamic relationships are depicted in a semischematic energy/temperature diagram. Mod. I is monotropically related to mod. II and mod. III. Between mod. II and mod. III an enantiotropic relationship exists.

1. Introduction

Tiaprofenic acid, (±)-5-benzoyl-α-methyl-2-thiophenacetic acid, Acidum tiaprofenicum INN ($C_{14}H_{12}O_3S$, M_r 260.31, Surgam®), a 2-arylpropionic acid, is used as a nonsteroidal anti-inflammatory drug. From the literature neither data on polymorphism nor on physico-chemical investigations of tiaprofenic acid are known. Since some 2-arylpropionic acids are either polymorphic [1–3] or form liquid crystals (lyotropic and/or thermotropic mesophases) [4, 5] tiaprofenic acid was investigated referring to these properties.

2. Investigations and results

Mod. I crystallizes e.g. from chloroform, methanol or acetone, mostly together with a few percent of mod. II and III. Pure mod. I can be obtained by stirring the crystal-mixtures in water or n-hexane. Mod. II crystallizes by fast evaporation from toluene. Mod. III can be obtained by precipitation with acetone and water at 60 °C or by stirring the melt in water, cooling down from 95 to 40 °C.
The melting points and other characteristical physical data of the modifications are summarized in Table 1. Mod. I melts on the thermomicroscope without sublimation. At 70 °C the slowly cooled melt crystallizes, mainly induced by scratching as mod. III (needles). Annealing the melt at 60 °C leads to mod. II (rods) and III (spherolithes). Both modifications melt inhomogeneously under transformation to mod. I.

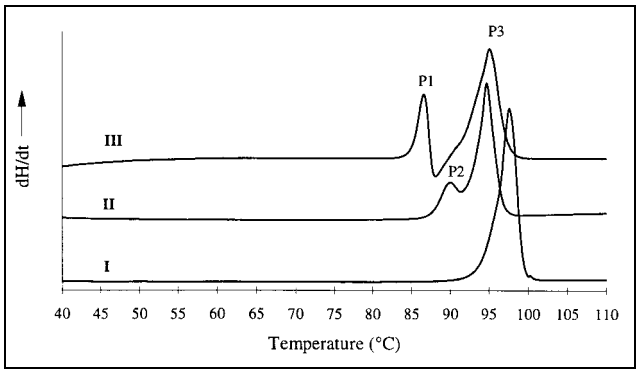

Fig. 1: DSC-curves of the tiaprofenic acid modifications (I, II and III); P1 and P2 inhomogeneous melting of III and II, P3 melting of I; heating rate 5 K · min^{-1}

DSC-investigations (Fig. 1) show the inhomogeneous melting of mod. III, that of mod. II is not obvious, because the melting peaks of mod. II and I are not separated. These are the reasons why the heat of fusion ΔH_f of both modifications (II and III) cannot be determined. Furthermore, the heats of transformation of mod. II and III could not be registrated, although investigations, both with low heating rates (0.5 and 1 K min^{-1}) and with an addition of mod. I (to force the transformation), were done. Thus, no solid-solid-transformation of both modifications was recognized.
The modifications were investigated with FTIR- and FT-Raman spectroscopy. It was astonishing that all three modifications are not distinguishable with both spectroscopic methods. In any case, mod. I, II and III can clearly be distinguished with powder X-ray diffractometry (Fig. 2).
The true densities of the modifications are listed in Table 1. Referring to mod. II, the form with the lowest true density, mod. III is havier by 0.44% and mod. I by 0.95%. The relative difference between the densities of mod. II

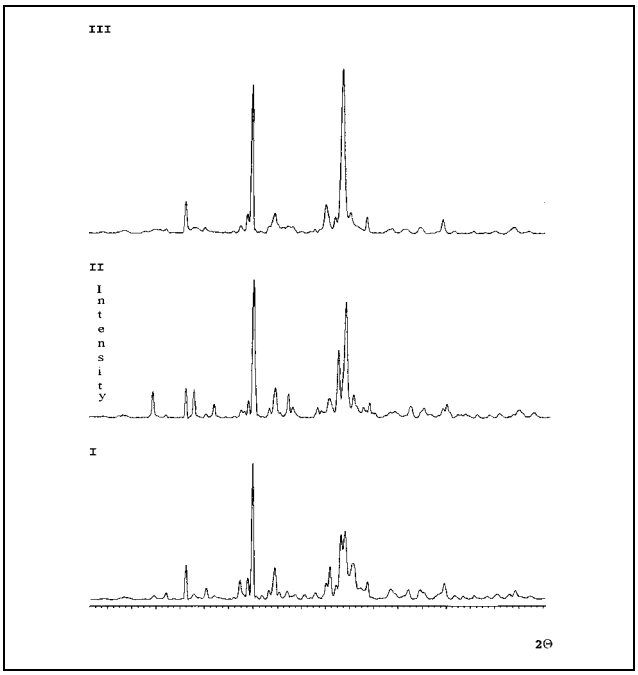

Fig. 2: Powder X-ray diffraction patterns of the tiaprofenic acid modifications I, II and III

Table 1: Characteristic physical data of the tiaprofenic acid modifications and a comparison with data known from the literature

Modification	I	II	III
Preparation (e.g.)	Crystallization from methanol etc.	Evaporation from toluene solutions	Precipitation from an aceton solution with water
Habit	microcrystalline	microcrystalline	microcrystalline, prismatic
Melting point (°C)			
Thermomicroscopy	94 to 96	90 to 92	84 to 85
DSC (heating rate 2.5 $K \cdot min^{-1}$	95.5 96 [6] 96 to 99 [7]	89 to 91	84 to 85
Heat of Fusion ΔH_f ($kJ\ mol^{-1}$)	27.4 ± 0.10[a]		
Solubility C_s (at pH 1.5)			
at 20 °C ($mmol\ l^{-1}$), relative	0.278, 0%	0.330, +19%	0.389, +40%
at 38 °C ($mmol\ l^{-1}$), relative	0.770, 0%	0.870, +13%	1.010, +31%
$pK_{a,2}$ (20 °C, 38 °C)	3.44, 3.56 3.0 [12][b]		
Heat of Solution ΔH_f ($kJ\ mol^{-1}$, 20 °C)	37.2	34.6	34.0
Entropy of Solution ΔS_s ($J\ mol^{-1}\ K^{-1}$, 20 °C)	127.0	118.0	116.1
Density ($g \cdot cm^{-3}$) ±95% c.i.	1.370 ± 0.001	1.357 ± 0.001	1.363 ± 0.001

[a] 95%-c.i.; [b] no further details given

and mod. I is not very large but significant for polymorphic modifications [8].

Mod. I, II and III thermogravimetrically proved non-hygroscopic even at a relative humidity of 98% during six weeks storage at 25 °C. But within this period mod. II and III transformed partly into mod. I. The transformation by magnetic stirring an aqueous suspension at 25 °C (38 °C) is considerably faster; mod. III transforms completely within 20 h (7 h) and II within 140 h (7 h) into I.

The saturation solubility depending on the temperature $C_s(T)$ was determined in a buffer solution of pH 1.5 (Table 2, Fig. 3). Eq. 1 was fitted to the data and the heats of solution ΔH_s as well as the entropies of solution ΔS_s were calculated [8–11].

$$\ln C_s = a + b \cdot T^{-1} + c \cdot \ln T \qquad (1)$$

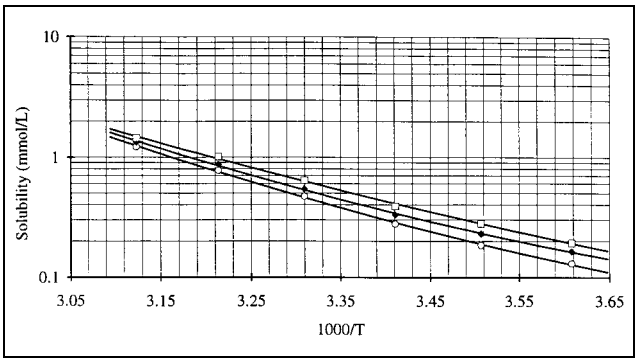

Fig. 3: Solubility of the tiaprofenic acid modifications (○ I, ◆ II, □ III) depending on temperature at pH 1.5

The difference between the calculated ΔH_s of mod. II and III (Table 1) is not significant. For such reasons, these data are useless for predicting the thermodynamic relationship between mod. II and III. Whereas a monotropic relationship between mod. I and II as well as mod. I and III can be predicted.

The solubility as a function of the pH (Fig. 4), measured at 20.0 and 38.0 °C, is given by Eq. 2.

$$C_s = C_{s,0} \cdot (1 + 10^{pH - pK_{a,2}}) \qquad (2)$$

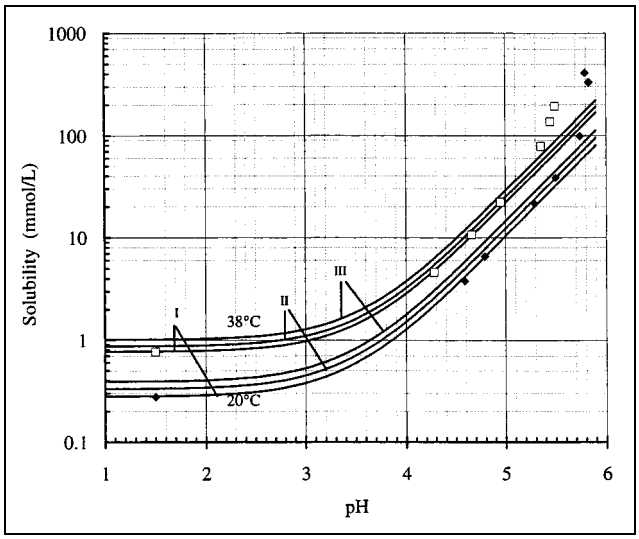

Fig. 4: Solubility of the tiaprofenic acid modifications at 20 °C (◆ I) and 38 °C (□ I) depending on the pH-value

Table 2: Measured (m.) and calculated (c.) solubility C_s ($mmol \cdot l^{-1}$) by Eq. 1 and its difference diff. (%) at pH 1.5

Form	I			II			III		
°C	m.	c.	Diff.	m.	c.	Diff.	m.	c.	Diff.
4.0	0.130	0.128	1.9	0.165	0.163	1.4	0.194	0.192	1.2
12.0	0.185	0.189	−2.2	0.230	0.233	−1.2	0.280	0.279	0.2
20.0	0.278	0.285	−2.4	0.330	0.340	−2.8	0.389	0.408	−4.8
29.0	0.470	0.459	2.4	0.540	0.531	1.8	0.640	0.628	1.9
38.0	0.770	0.751	2.5	0.870	0.845	3.0	1.010	0.967	4.4
47.0	1.220	1.244	−2.0	1.340	1.368	−2.0	1.452	1.492	−2.7

$C_{s,0}$ corresponds to the saturation solubility at pH 1.5 and can be calculated with Eq. 1 (Table 3), $pK_{a,2}$ the dissociation constant (Table 1) can be found by iteration. Investigations showed that measured data deviate from calculated data at pH-values higher than approx. 5. These extreme deviations (max. 555%) are caused by the formation of an oily phase, which was confirmed using a hot-stage microscope. Similar phases were found e.g. with ketoprofen [13].

Table 3: Regression coefficients for Eq. 1 and Eq. 3; solubility C_s (mmol · l^{-1})

Equation	Modification	a	b	c
1	I	−314.987	9957.820	49.248
1	II	−334.186	11078.791	51.986
1	III	−195.781	5069.939	31.262
3*	I	0.23	465.47	
3*	II	0.29	455.04	
3*	III	0.35	519.85	

* $Cs = a + b \cdot x$ (x = % polysorbate 80)

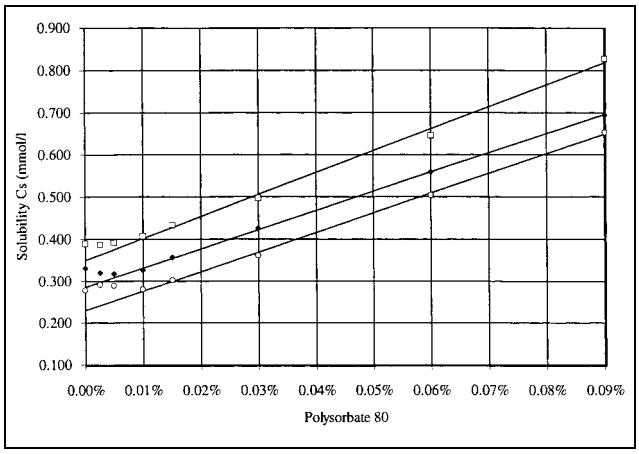

Fig. 5: Solubility of the tree tiaprofenic acid modifications (○ I, ◆ II and □ III) depending on concentration of polysorbate 80; at 20 °C and pH 1.5

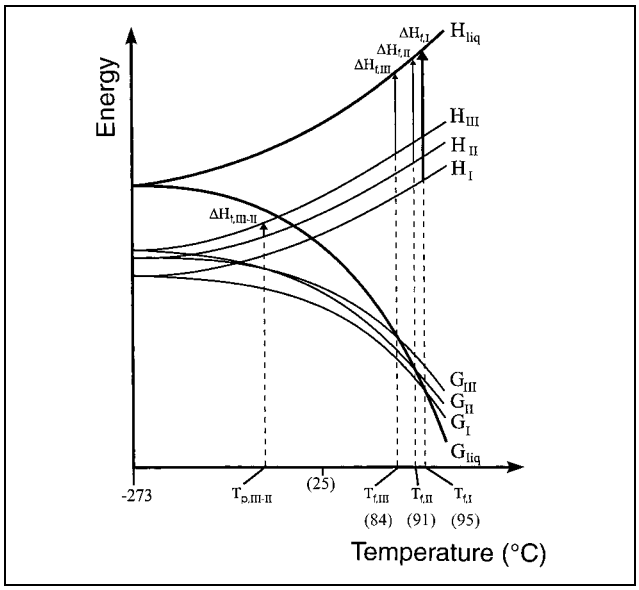

Fig. 6: Semi-schematic energy/temperature diagram of mod. I, II and III of tiaprofenic acid; H enthalpy, G Gibbs free energy, ΔH_f heat of fusion, ΔH_t heat of transition, T_p transition point, T_f melting point; vertical bold line corresponds to measured heat of fusion

The solubility depending on addition of polysorbate 80 shows nearly a linear increase of C_s with increasing polysorbate-80-concentrations (Table 3, Fig. 5). These additions have a similar influence on the solubility of the modifications (e.g. mod. I approx. 235%, II approx. 211% and III approx. 213% for 0.09% polysorbate-80-addition).

3. Discussion

The large surprise of the present investigations is the fact that spectroscopic methods (IR, Raman) are not suitable to characterize the modifications of tiaprofenic acid. This behaviour is relatively rare in connection with polymorphic modifications, although already described in the literature [14–17] and indicates that hydrogen bonds do not predominate in the different crystal structures of these modifications.

For these reasons, the Infrared Rule [8, 18] is useless, but in return, the Density Rule [8, 18] can be reliably respected. Due to the solubility order of the modifications (I < II < III) at room temperature and above and due to the Density Rule, mod. I relates monotropically to II and III, yet mod. II relates enantiotropically to III. This behaviour is shown in a semi-schematic energy/temperature diagram (Fig. 6).

Mod. II and III are not proper for drug formulation and application, because they are metastable.

Tiaprofenic acid forms high-entropy-phases at pH-values higher than approx. 5. Therefore the solubility highly increases (up to 555% from the theoretical value). Addition of 0.09% polysorbate 80 leads to an approx. 200% increase in solubility. Both effects could be useful for raising the bioavailability of semisolid formulations of topical application.

4. Experimental

4.1. Materials

Analytical grade solvents for crystallization experiments and buffer substances of Merck (Darmstadt, Germany) were used. Buffer solutions of pH 1.5 (hydrochloric acid – potassium chloride) as well as of pH 5.8 and 6.8 (potassium dihydrogen phosphate – sodium hydroxide) were prepared according to the literature [19].

4.2. Equipment

4.2.1. Thermomicroscopy

Kofler hot-stage Thermovar® (Reichert, Vienna, Austria). Additionally a Kofler hot bench was used for preparing crystal films (Reichert, Vienna, Austria).

4.2.2. Differential scanning calorimetry

DSC-7 (Perkin-Elmer, Norwalk, Ct., USA); aluminium sample-pans; sample mass for qualitative analyses approx. 1 to 5 mg, for quantitative analyses at precisely $\pm 5 \times 10^{-4}$ mg (ultramicrobalance UM 3, Mettler, Greifensee, Switzerland); nitrogen p.a. as purge gas (30 ml · min^{-1}); registration of the DSC-signal by means of EDP (7 Series/UNIX DSC-7 Lab system, Perkin-Elmer). Calibration of the temperature axis (abscissa) was carried out with caffeine (m.p. 236.2 °C, tight closed sample capsule) and with benzophenone (m.p. 48.0 °C, perforated sample capsule). The calibration of the DSC-signal (ordinate) was done with indium 99.999% (Perkin-Elmer, Norwalk, Ct., USA).

4.2.3. Thermogravimetry

TGA-7 thermogravimetric system (Perkin-Elmer, Norwalk, Ct., USA), sample mass 1 to 4 mg, aluminium sample-pan in platinum pan, nitrogen p.a. as purge gas (20 ml · min^{-1}), heating rate 10 K · min^{-1}. Temperature calibration with calibrate thermocouple instrument; mass calibration with a 100-mg-calibration mass (Perkin-Elmer).

4.2.4. FTIR-microscopy

Bruker IFS 25 FTIR-Spectrometer (Bruker Analytische Meßtechnik GmbH, Karlsruhe, Germany), Bruker FTIR-Microscope (15 × Cassegrain-objektive and visible polarization). Samples were rolled on zinc selenide windows (13 × 2 mm). Crystal films were prepared between two zinc selenide windows on a Kofler hot bench. To record spectra at higher temperatures a Bruker heatable sample stage with an external temperature control unit was used. Spectra were measured in transmission mode in the spectral range from 4000 to 600 cm^{-1} (resolution: 4 cm^{-1}, microscope, 100 interferograms) or from 4000 to 400 cm^{-1} (resolution: 2 cm^{-1}, spectrometer, 50 interferograms).

4.2.5. FT-Raman-spectroscopy

FT Raman Bruker IFS 88, Raman module FRA 106, with 100 mW Nd-YAG Laser at 1064 nm. One hundred scans at 4 cm^{-1} resolution over the range 3500 to 80 cm^{-1} were recorded.

4.2.6. Pycnometry

Air comparison pycnometer (Ultrapycnometer 1000, Quantachrome Corp., Syosset, N.Y., USA) provided with a small sample cell; sample weights 3 to 4 g. The sample was purged with helium for 15 min, calibration was carried out with a steel-sphere.

4.2.7. Powder X-ray diffraction

Siemens D-5000 X-ray diffractometer equipped with θ/θ-Goniometer (Siemens AG, Karlsruhe, Germany) using monochromatic CuKα radiation from 2 to 40° 2θ at a rate of 0.01° 2θ/s. The diffractometer was fitted with a low temperature camera (Anton Paar KG, Graz, Austria), which allowed diffraction data to be collected from sample heated to temperatures up to 100 °C.

4.3. Determination of solubility

A suspension of each modification was stirred at a constant temperature (± 0.1 K) in a lockable, cylindrical glass vessel (∅ 5 and 2.5 cm) with a magnetic stirrer (900 rpm) in approx. 15 ml solvent. The taking of samples was done with volumetric pipettes supplied with membrane filters HAWP 1200 (pore diameter 0.45 µm) and filter holders SX000 1300 (diameter 13 mm, grind off in front) (Millipore GmbH, D-Neu Isenburg). The samples were diluted with the HCl/KCl buffer solution (pH 1.5) and measured at 307.2 nm ($\varepsilon = 15357 \pm 0.99\%\, l \cdot mol^{-1} \cdot cm^{-1}$ 95% − VB%) against HCl/KCl buffer solution as a blank (UV-spectrophotometer Shimadzu UV 160 A, Shimadzu Corp., Kyoto, Japan). For determination of the solubility depending on temperature (HCl/KCl buffer solution, pH 1.5) at each temperature three samples were withdrawn every 1 to 2 min. For the solubility depending on detergent addition samples were withdrawn (20 °C) every 1 to 2 min and 20 min, respectively.

Different pH-values were gained by a dropwise addition of sodium hydroxide solution ($c = 0.1\ mol \cdot l^{-1}$) to the chosen buffer solution. After 30 min at each pH-value three samples were withdrawn for evaluation; pH-values were measured with a pH-meter Φ71 (Beckman) connected with a combined glass electrode. The two-point calibration of the pH-meter was made with potassium tetraoxalate, potassium hydrogen phthalate and a phosphate buffer solution at 20.0 and 38.0 °C in accordance to DIN 19266.

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