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Research paper

Polymorphism and desolvation of flupirtine maleate

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Abstract

Crystallizates of the analgesic agent flupirtine maleate (Katadolon®; ASTA Medica, Dresden, Germany) obtained from isopropanol are examined by X-ray diffractometry, polarization microscopy and thermoanalysis. Depending on the crystallizing conditions, the modifications A and B as well as an isopropanol solvate are observed. The inversion temperature A → B of the enantiotropic modifications is 164°C (differential scanning calorimetry (DSC) onset). During thermal desolvation, modification B is formed well below the inversion temperature. In concentrated isopropanol suspensions, the solvate and modification B are rapidly transformed into modification A. It is shown how phase-pure products consisting of modification A, which is better wettable with water and stable at room temperature, can be obtained.

Keywords: Flupirtine maleate; Polymorphism; Modification; Desolvation; X-ray diffractometry; Polarization microscopy; Thermoanalysis

1. Introduction

Flupirtine maleate (Fig. 1) is 2-amino-3-carbethoxyamino-6-(4-fluorobenzylamino)pyridine maleate (1). This compound, developed by ASTA Medica, represents a novel structure with central analgesic activity. As a moderately potent analgesic without dependence and tolerance potential, it differs markedly from peripheral analgesics and does not bind to the opiate receptor. Flupirtine maleate is marketed under the trade name Katadolon®.

The synthesis of flupirtine maleate starts from 2-amino-6-(4-fluorobenzylamino)-3-nitropyridine. After catalytic hydrogenation of the nitro group with Raney nickel and hydrogen, the intermediate triamino compound is converted with ethyl chloroformate into the urethane and the formed flupirtine base is isolated. The active substance flupirtine maleate is obtained by reaction of maleic acid with the flupirtine base.

Experiments on the optimization of the synthetic procedure, precipitation or recrystallization of flupirtine maleate in isopropanol resulted, depending on the experimental conditions (water content, temperature, agitating time), in products differing with regard to the consistence of the crystallized products, the wettability of the crystals with water and to various bands of the IR spectrum [1].

The following phase-analytical studies show that these differences are to be attributed to the polymorphic behaviour of the substance.

2. Material and methods

2.1. Materials

Two specimens of flupirtine maleate from ASTA Medica's test production (no. 2860 and no. 2861), which differed as to their wettability with water, served as original samples for the phase-analytical examination and for various experiments on phase transformation. For the precipitation experiments, specimens of flupirtine base and of maleic acid

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coming from the test production were used. Solvents were isopropanol (analytical grade) and distilled water.

2.2. Experiments

To follow the phase transformations occurring on heating, the samples were stored at defined temperatures in a drying oven (±2.5 K). For the direct observation of phase transformations by X-ray diffractometry, the samples were heated in the sample holder of the diffractometer (T-controlled diffractometry).

For examination of the transformation behaviour of metastable phases, concentrated multiple-phase suspensions were stirred at different temperatures (Table 1). At certain intervals of time, from these suspensions samples were taken, pressed on filter paper and, in somewhat wet condition, examined by X-ray diffractometry. Thereafter, further records of various drying conditions were prepared.

To study primary phase formation, crystallizations under various cooling and precipitation conditions were carried out (Table 1). For this purpose, clear solutions of flupirtine maleate obtained by heating as well as of flupirtine and maleic acid were used. Prior to addition, seed crystals were dispersed in a small amount of the solvent. Cooling occurred with stirring (paddle agitator) in the water bath of a thermostat. In this case, too, at first the somewhat wet crystals were studied by X-ray diffractometry.

2.3. Analytical methods

2.3.1. X-ray diffractometry

The diffractograms were recorded with a powder diffractometer D5000 (Siemens, Karlsruhe, Germany) under the following conditions: Cu anode, accelerating voltage 40 kV, tube current 30 mA, variable (ϑ-dependent) antiscatter and divergence slit, graphite secondary monochromator and

Table 1
Crystallization conditions and phase formation

H_2O (%)	Crystallization (°C)	Seeding (%A)	Exp. no.	Phases			Stirring (°C)	Stirring (min)	Exp. no.	Phases		
Crystallization by precipitation (flupirtine base + maleic acid)												
0	50		5	BBb	SSSS	a	50	15	1			A
0	45		3	BBB	SS		45	60	1	B		a
0	40		3	BBB	SSs		40	40	1			A
							40	30	1	B		a
								60				A
0	50	2	2		SS		50	15	2			AA
0	50	5	1		S		50	30	1			A
0	40	1	1	B	S							
0	40	2	3		SSS	a	40	15	2			AA
0	40	5	1		S							
Crystallization by cooling (flupirtine maleate solution)												
0	60–35 l		1	B		a						
0	60–20 l		3		SSS	aa	20	120	1			A
							35	10	1		S	A
								75				A
0	60–20 r		2	b	SS							
0	60–35 l	5	1			A						
0	60–20 l	5	1		S	a						
5	60–20 r				S		20	130	1			A
30	60–35 l		1	B		A	RT	10 d*	1			A
30	60–20 r		1	B	s		RT	10 d*	1			A
90	60–20 r		1	B			20	70		B		
90	60–20 r	5	1	B		a						
Recrystallization by stirring of specimen 2861 (about 90% Mod. B + 10% Mod. A)												
0							60	30	1	B		A
0							25	70	1	B		A
							50	30				A
0							35	40	1	B		A
								70				A
0							20	70	1	B		A
								130				A
0							5	70	1	B		A
								140		b		A

A, B, modifications; S, solvate; BBb, modification B appeared in two experiments as essential component and in one experiment as accessory component; l and r, slow and rapid cooling, respectively. *Ten days at room temperature (RT) without stirring.

scintillation counter. For the temperature-controlled diffractometry, the low-temperature kit TTK (Siemens, Karlsruhe, Germany) with automatic temperature control (±0.1 K) and Ni filter as monochromator was used.

If possible, the samples were examined at first in their original condition and subsequently following careful, microscopically controlled comminution and texture-poor preparation. Comminution was terminated when the diameter of the largest crystals or crystal fragments was below 100 μm. To prevent texturation, the surface of the preparations was roughened.

2.3.2. Thermomicroscopy

For the microscopic examinations a polarizing microscope Jenapol interphako (Carl Zeiss, Jena, Germany) equipped with a heating stage with double refraction-free lens system (Linkam, Waterfield, UK) was available.

2.3.3. Thermogravimetry

The thermogravimetric measurements were performed with the system TGA-7 (Perkin-Elmer, Norwalk, USA) using a platinum crucible as sample container and nitrogen (99.999% N_2) as purge gas, at a heating rate of 10 K min^{-1}.

2.3.4. Differential scanning calorimetry

A differential scanning calorimeter (DSC-7; Perkin-Elmer, Norwalk, CT, USA) was used. Samples of several milligrams weighed on an ultramicro balance (±0.006 mg) were encapsulated in perforated aluminium. The temperature of the cooling block was 20°C and 5°C, respectively. Nitrogen (99.999% N_2) served as purge gas. The heating rate was 10 K/min. Indium 99.999% was used as calibration substance.

3. Results

3.1. Demonstration of chemical identity and purity of the original specimens

All original specimens were synthesized according to ASTA Medica's manufacturing specification for the preparation of flupirtine maleate (1) and were shown to have a thin-layer chromatographic purity of more than 99%. Only the final precipitations of the flupirtine base with maleic acid to form flupirtine maleate were modified, in order to obtain highest possible portions of the different modifications A and B.

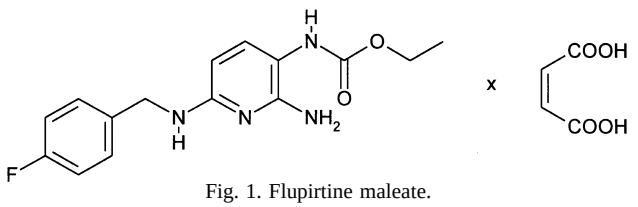

Fig. 1. Flupirtine maleate.

3.2. Phase analysis of the original specimens, detection of the modifications A and B

A comparison of the diffractograms (Fig. 2) reveals the existence of at least two different crystalline phases in the original specimen (2860 and 2861). In the diffractogram of specimen 2860 (curve a) the strongest reflex observed with sample 2861 (curve e) is not detectable. Conversely, in the diffractogram of specimen 2861 weak reflexes are observed at the positions of the strong reflexes of specimen 2860. Thus, assuming a two-phase system, specimen 2860 is made up of the one phase termed A in pure form, whereas specimen 2861, in addition of a small amount of phase A, consists of the phase termed B. Since the chemical purity of the specimens has been demonstrated and, moreover, the thermogravimetric curves below the temperature of homogeneous melting do not indicate any weight change, both phases represent two crystal modifications of flupirtine maleate.

This interpretation complies with the microscopic appearance of both specimens. While specimen 2860 consists of needle-shaped crystals of relatively uniform size (Fig. 3a), in specimen 2861 two fractions of needle-shaped crystals distinguishable by size can be observed (Fig. 3b), the crystallite size of the quantitatively minor, coarser fraction corresponding more or less to specimen 2860. Thus, specimen 2861 comprises, in addition to small crystals of modification B, minor amounts of greater crystals of modification A. Either modification shows a straight or almost straight extinction, the more weakly refracted ray (n_1) oscillating parallel to the needle axis (L-). At the same time, however, n_{1A} is near to the refractive index of the immersion fluid (1.48), whereas n_{1B} is clearly greater.

3.3. Thermal modification transformation A → B

Between 160 and 170°C the DSC curve of modification A (specimen 2860) shows a weak and between 180 and 190°C a strong endothermic effect (Fig. 4(a), Table 2). Microscopically, between 160 and 170°C alteration of double refraction and above 180°C melting of the specimen is observed. Even after heating up to 150°C for 20 min, the refractive index n_1 lies clearly above the refractive index of the immersion fluid (approximation to n_{1B}). A sample heated up to 170°C in the oven of the DSC apparatus shows on reheating only the strong endothermic effect between 180 and 190°C.

With specimen 2861 (modification B with a small portion of modification A), at first only the strong endothermic effect between 180 and 190°C is observed (Fig. 4(b)). Only at high sensitivity (1 W/g), a weak endothermic effect shifted to lower temperatures can be detected below the melting effect (Table 2). The alteration of double refraction described above is only observed with the greater crystals assigned to modification A. Above 180°C all crystals melt.

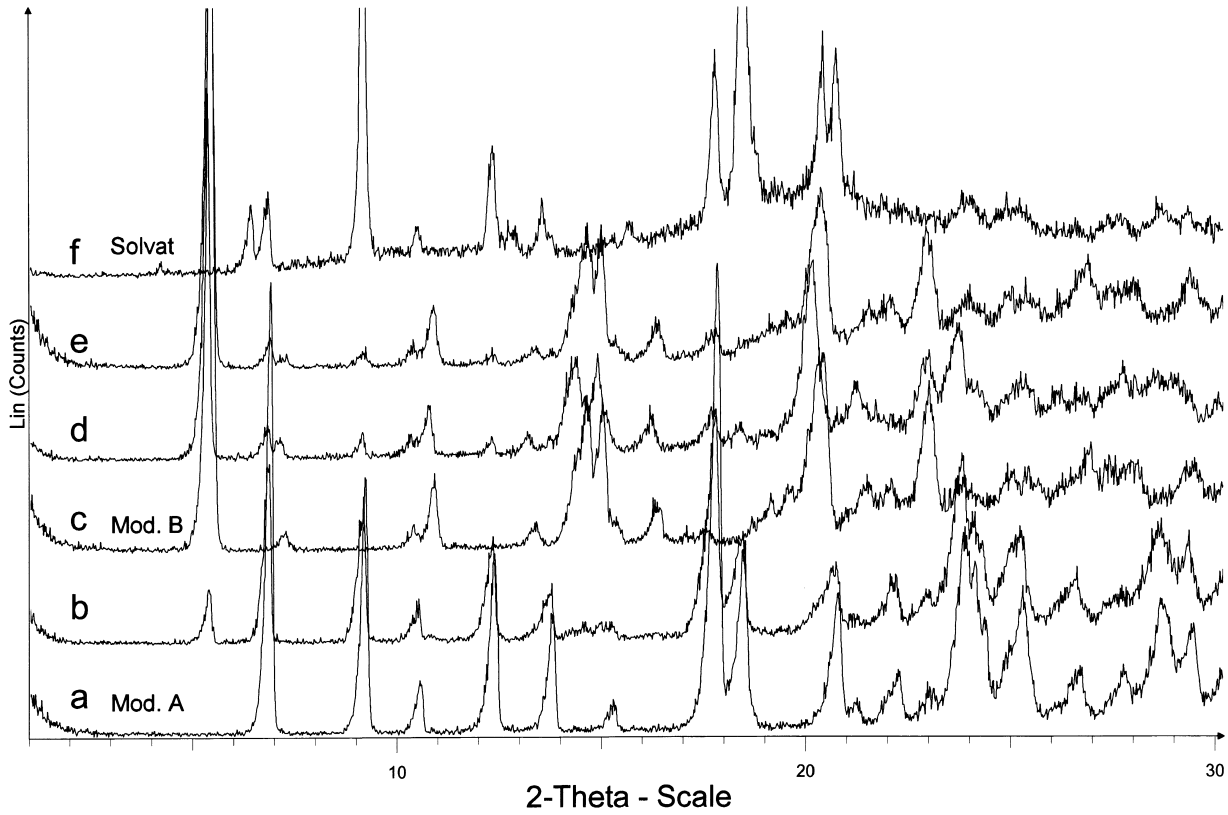

Fig. 2. X-ray diffractograms of the three phases A, B and S as well as of mixtures of both modifications. (a) Modification A (specimen 2860). (b) 90% Mod. A + 10% Mod. B. (c) Modification B (specimen 2861 heated). (d) 10% Mod. A + 90% Mod. B. (e) Specimen 2861 (about 10% Mod. A + 90% Mod. B). (f) Solvate.

According to these observations, between 160 and 170°C modification A is transformed into modification B, which melts between 180 and 190°C.

With T-controlled X-ray diffractometry, the lattice transformation starting above 160°C can directly be demonstrated (Fig. 5).

3.4. X-ray diffractometric detection limits of both modifications

Specimen 2860 is used as standard for modification A (Fig. 2(a), Table 3). Because modification B is obviously metastable at room temperature, the observed modification transformation offers the possibility of preparing a phase-pure specimen of this modification. For this purpose, specimen 2861, predominantly consisting of modification B anyhow, was heated up to 165°C for 10 min. Thereafter no A reflexes could be observed any more (Fig. 2(c), Table 3).

A comparison of the diffractograms of mixtures consisting of 90% of standard A and 10% of standard B (Fig. 2(b)) as well as of 90% of standard B and 10% of standard A (Fig. 2(d)) with the diffractograms of the pure modifications shows that the X-ray diffractometric detection limit of either modification in binary mixtures is below 10%. Moreover, a comparison of the corresponding curves shows that the original specimen 2861 (curve e) consists of approximately 10% modification A and, correspondingly, 90% of modification B.

3.5. Phase analysis of crystallizates, detection of a crystallized solvate

In case of both the precipitation and the cooling crystallization of flupirtine maleate from clear solutions, in the fresh, undried crystallizates characteristic reflexes of a third crystallized phase S are observed in addition to the reflexes of both modifications (Fig. 2(f), Table 3), which the thermogravimetric examinations (3.6.) revealed to be an isopropanol solvate of flupirtine maleate.

Based on the phase composition of the crystallizates obtained under different conditions (Table 1), the following tendencies can be seen. (1) After seeding with crystals of modification A, modification B can be observed only in case of too little seeding material (<2%) or in case of a low isopropanol proportion (10%). In any other case phase S or (to a low extent) modification A appears. (2) In the case of crystallizations without seeding, modification B is observed with lower isopropanol contents (70% and less). With a high isopropanol proportion, this phase appears in particular

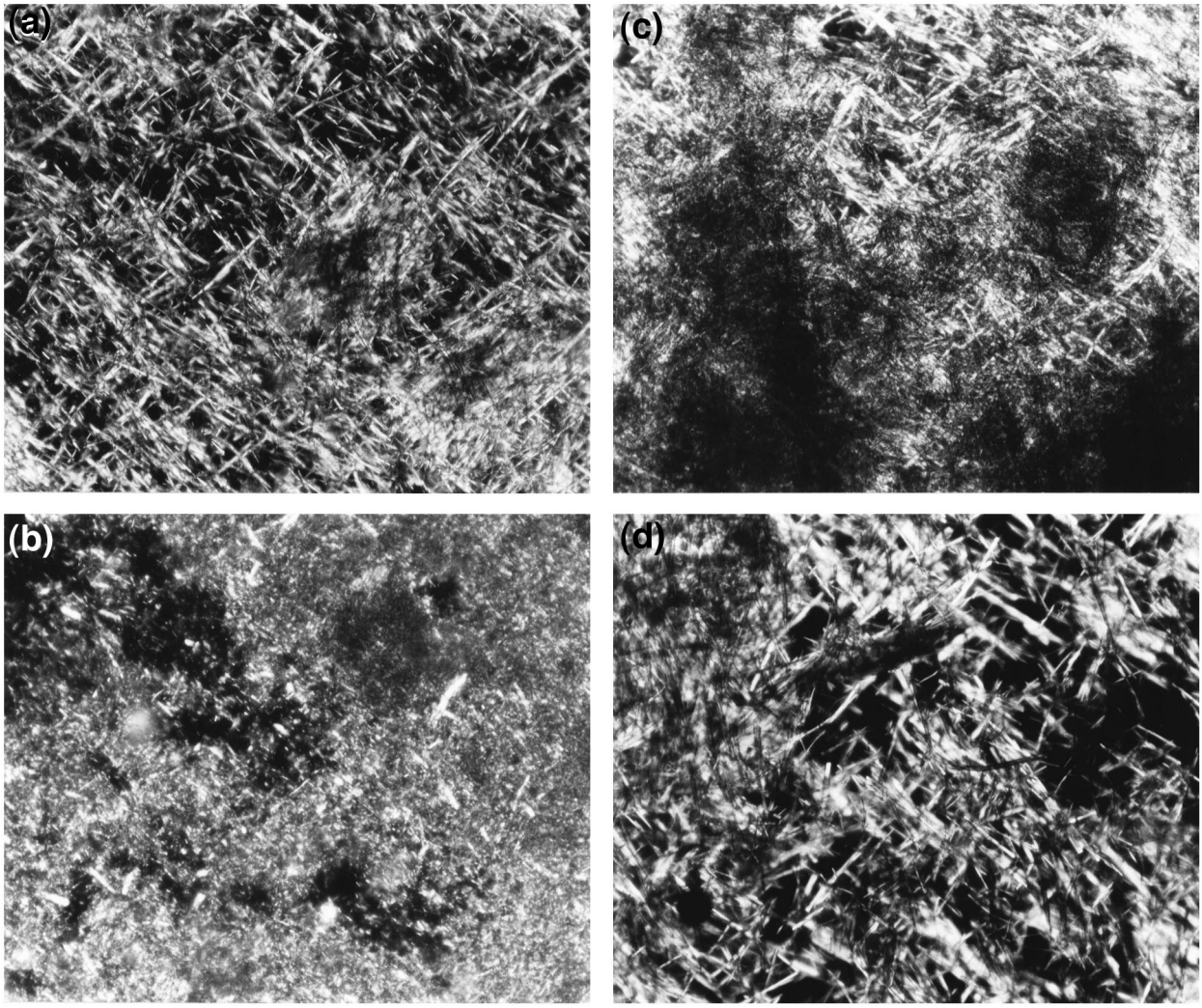

Fig. 3. Photomicrographs (longer picture edge about 900 μm, crossed polarises). (a) Modification A (specimen 2860). (b) Specimen 2861 (about 10% Mod. A + 90% Mod. B). (c) Specimen 2861 after stirring for 60 min in concentrated isopropanol suspension. (d) Specimen 2861 after stirring for 130 min.

at higher crystallization temperatures. Again, modification A appears only to a minor extent.

3.6. Thermal transformation of the solvate

As T-controlled X-ray diffractometry shows (Fig. 6), phase S observed in a fresh crystallizate obtained from isopropanol is stable only up to approximately 90°C.

Figs. 4(d,e) and 7(b,c) show the DSC and the TG curves of two samples of the same crystallizate, which were first heated up to 75 and 105°C in the TTK. With the sample heated to 75°C (reflexes of phase S), at about 100°C an endothermic effect (Table 2; Specimen 3031.33) and, at the same time, a distinct decrease in weight was observed, whereas the sample heated to 105°C (no S reflexes) behaved inert within this temperature range. Accordingly, phase S represents an isopropanol solvate of flupirtine maleate (flupirtine maleate with intracrystalline-bound isopropanol).

The desolvation is irreversible, i.e. on suspending in isopropanol no resolvation is observed with completely desolvated samples.

The transformation temperature of modification A is 164°C (Table 2; specimen 2860). On desolvation of the isopropanol solvate, modification B is formed well below the transformation point (Fig. 6), which cannot be observed if the solvate was transformed first by agitation of the suspension into modification A (Fig. 5).

The high-temperature phase formation obviously depends on the course of desolvation as well. In this way, on desolvation of a fresh, still wet crystallizate (Fig. 4(c) and Fig. 7(a)) the transformation effect is observed at 164°C (Table 2; specimen 2861.16). With a sample preheated up to 75°C (Figs. 4(d) and 7(b)), which releases the residual isopropanol only at somewhat higher temperature (Table 2; specimen 3031.33), the transformation coincides with the desolvation.

3.7. Phase transformations S → A and B → A

On stirring the concentrated crystal suspensions obtained

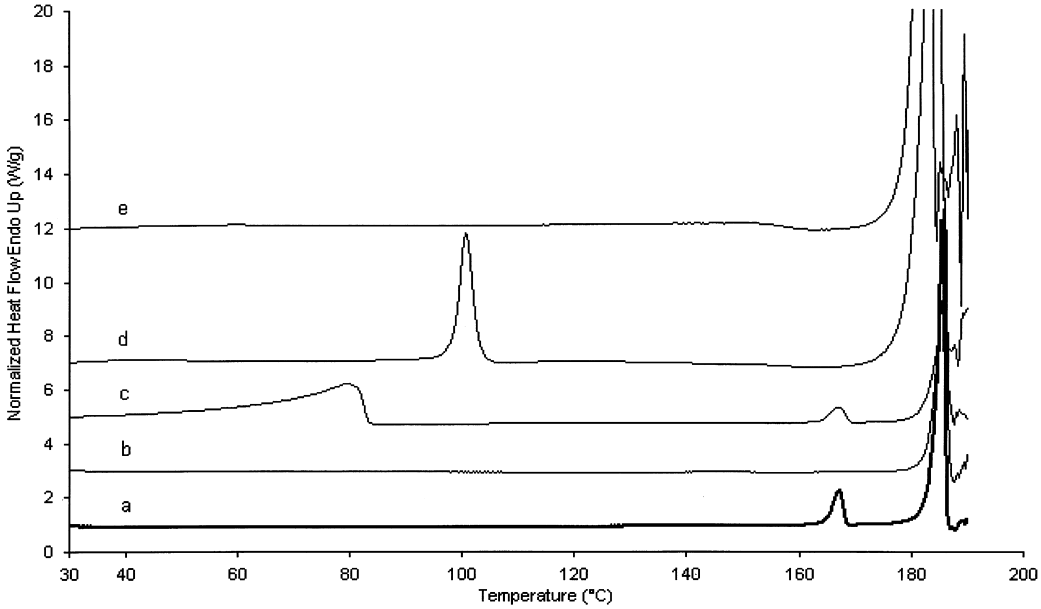

Fig. 4. DSC curves of the modifications as well as of differently pretreated solvate. (a) Modification A (specimen 2860). (b) Specimen 2861 (about 10% Mod. A + 90% Mod. B). (c) Wet solvate. (d) Solvate preheated up to 75°C. (e) Solvate preheated up to 105°C.

by precipitation or cooling crystallization, phase transformations solvate → modification A and modification B → modification A are observed (Table 1), the transformation of the solvate proceeding more rapidly. Both transformations are also observed if the suspensions are just allowed to stand; they are, however, slower in this case. Fig. 8 shows some of the diffractograms recorded during such transformations. The curves (a), (b), and (c) were recorded during the transformation of the specimen 2861, initially consisting of 90% of modification B, after stirring for 10, 40 and 70 min respectively, at 35°C. The curve recorded after 70 min (c) corresponds to the pattern of modification A. The curves (d) and (e) demonstrate the transformation of a crystalline product obtained by precipitation of flupirtine maleate at 40°C without seeding. After stirring for 60 min at 40°C, the crystallizate initially consisting mainly of modification B was completely transformed into modification A (curve e). Curves (f) and (g) show the transformation of a crystallizate precipitated with addition of 2% of modification A at 40°C. The solvate appearing first (curve f) was transformed into modification A just after 15 min of stirring (curve g).

The progressive transformation of specimen initially consisting of 90% of modification B and 10% of modification A (2861) into modification A can be followed by microscopy as well (Fig. 3(b,d)).

4. Discussion

There is enantiotropism between both of the modifications A and B. Below the temperature T_U, (onset: 164°C

Table 2
DSC measured values

Specimen	Pretreatment	Dehydration			Transformation			Melting		
		Onset (°C)	Peak (°C)	Energy (J/g)	Onset (°C)	Peak (°C)	Energy (J/g)	Onset (°C)	Peak (°C)	Energy (J/g)
2860		–	–	–	164.5	166.8	16.9	183.8	185.1	122.7
2860		–	–	–	164.3	166.5	19.3	183.6	184.9	138.5
2860		–	–	–	164.7	166.9	17.6	183.6	185.2	125.7
2860		–	–	–	164.4	166.7	18.8	n.m.	n.m.	n.m.
2860	170°C	–	–	–	–	–	–	183.3	184.5	122.2
2861		–	–	–	135.6	145.7	1.3	184.1	185.3	130.8
2861		–	–	–	137.8	145.3	1.5	184.1	185.3	116.6
2861		–	–	–	142.3	145.4	0.6	183.8	185.5	124.7
2861.11	Wet	75.9	82.4	188.9	159.1	163.8	10.3	182.3	184.8	87.9
2861.16	Wet	61.6	79.4	160.5	163.8	166.8	10.8	183.2	185.3	65.5
3031.33	75°C	98.2	100.4	16.7	–	–	–	181.0	184.3	110.9
3031.33	105°C	–	–	–	–	–	–	180.6	182.7	119.1

n.m., not measured.

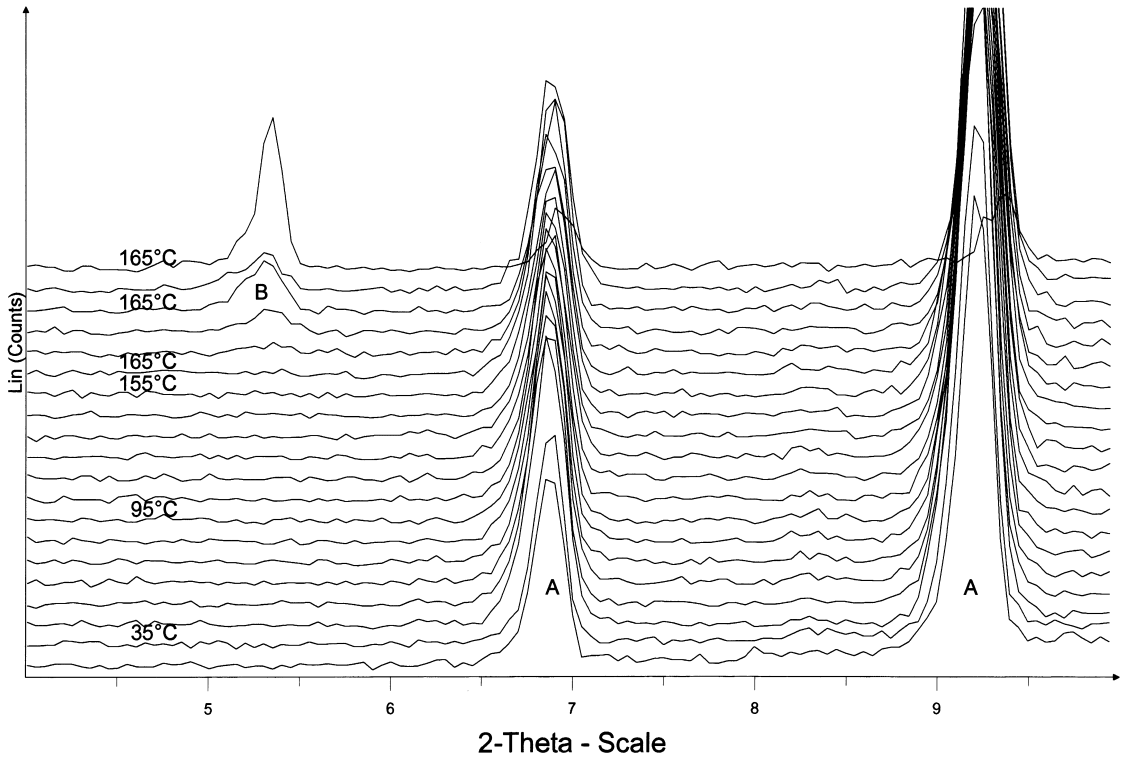

Fig. 5. T-controlled X-ray diffractometry of modification A.

Table 3
Lattice plane distances (d) and relative intensities (Int.)

Mod. A		Mod. B		Solvate		Mod. A		Mod. B		Solvate	
d (Å)	Int.	d (Å)	Int.	d (Å)	Int.	d (Å)	Int.	d (Å)	Int.	d (Å)	Int.
				21.0	3	4.18	5				
		16.2	100					4.13	6		
				13.7	16	4.05	5	4.02	5		
12.8	98			12.9	17	3.99	11				
		12.1	3			3.86	7	3.86	17		
9.58	55			9.62	100	3.72	40	3.73	2	3.70	4
8.36	11	8.48	3	8.42	6	3.68	32				
		8.10	10			3.64	20				
7.14	38			7.16	25	3.56	15	3.55	3	3.53	6
				6.92	5	3.51	27	3.49	4		
		6.59	3	6.53	13	3.34	9				
6.41	25							3.30	7		
		6.13	13					3.24	4	3.23	4
		6.04	20			3.21	10	3.19	5		
		5.89	20			3.11	23			3.11	6
5.78	7	5.75	2			3.03	18	3.03	3	3.04	7
				5.64	5			2.95	3		
		5.41	4			2.92	17			2.91	9
		5.04	1			2.90	21				
4.97	100			4.98	41			2.88	4		
4.79	39			4.80	87	2.80	2				
		4.74	3					2.78	4		
		4.63	5			2.71	5				
		4.53	6			2.68	9				
		4.42	13			2.56	8				
		4.36	24			2.51	13			2.51	4
		4.34	24	4.35	35	2.43	7			2.43	5
4.27	28			4.28	38	2.38	23			2.39	10

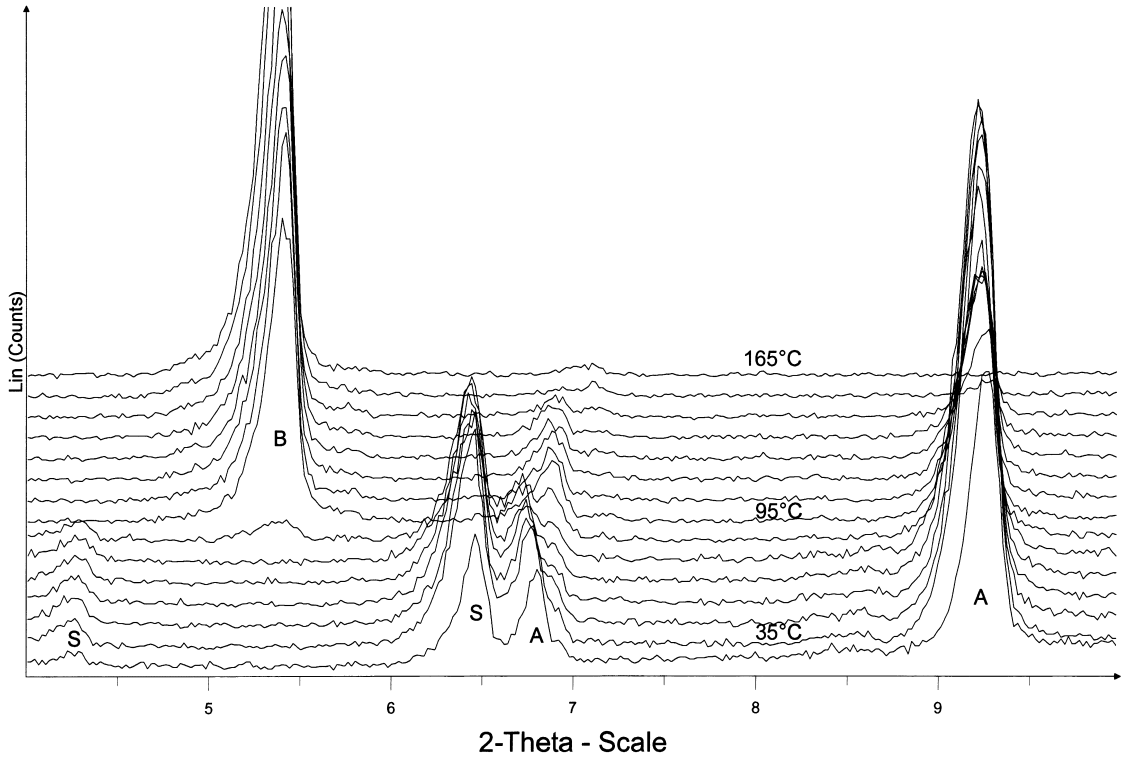

Fig. 6. T-controlled X-ray diffractometry of the solvate.

at 10 K/min), modification B shows higher vapour pressure (higher free enthalpy) and can, therefore, exist there only as a metastable phase. Above this temperature, this holds true for modification A. That is why modification A does not make it as far as the vapour pressure of the melt (virtual melting point of A), but is transformed into modification B prior to melting. According to the Oswald rule (gradual transition into the lowest-energy state [2]), if there are no

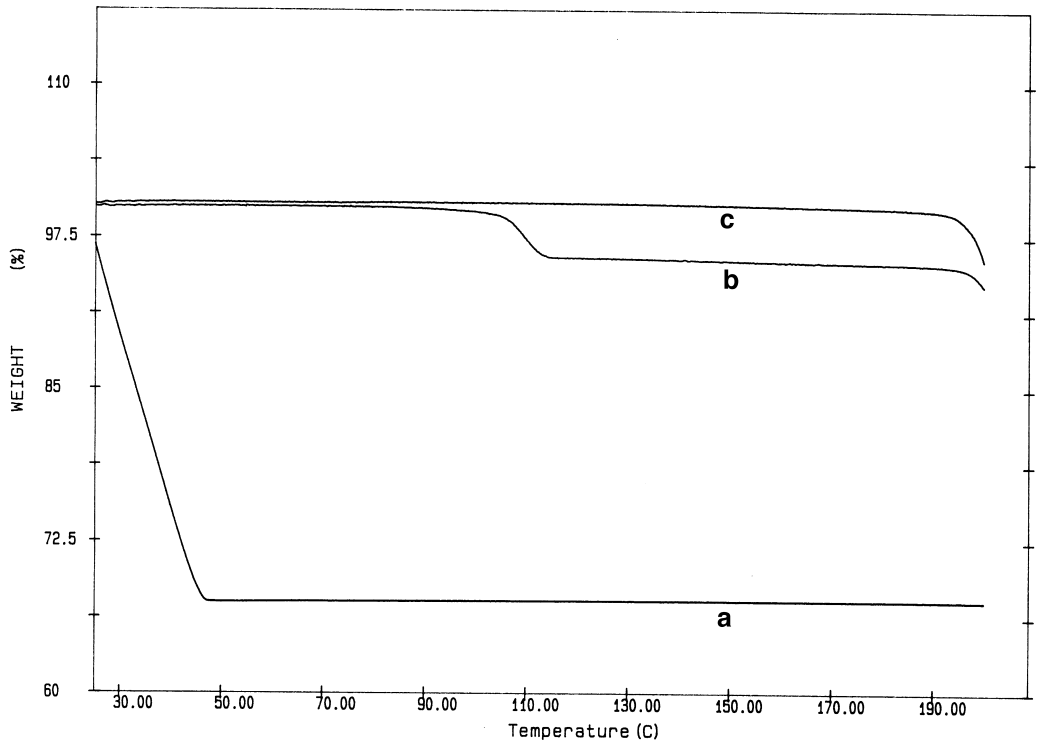

Fig. 7. TG curves of differently pretreated solvate. (a) Wet. (b) Preheated up to 75°C. (c) Preheated up to 105°C.

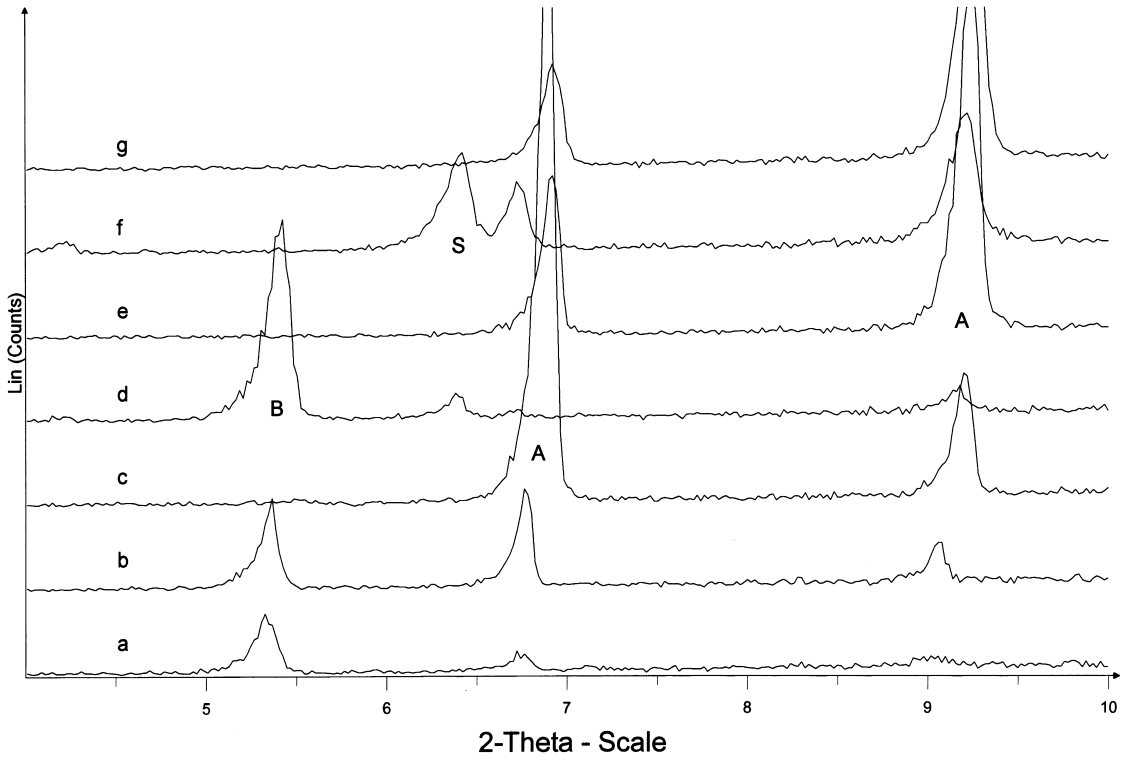

Fig. 8. X-Ray diffractograms of the crystallization and stirring experiments. (a–c) Specimen 2861 (about 10% Mod. A + 90% Mod. B) after stirring for 10, 40, and 70 min in concentrated isopropanol suspension. (d,e) Crystallizate obtained by precipitation without seeding, original and after stirring for 60 min. (f,g) Crystallizate precipitated with addition of 2% of Mod. A, original and after stirring for 15 min.

or too little A nuclei, preferential occurrence of modification B should be taken into consideration. On contact with the stable phase (stirring in concentrated suspension), modification B is transformed into the stable modification A.

In the case of primary crystallization (formation of nuclei) of modification A, obviously isopropanol molecules are at first inserted into the lattice. The solvate structure can be converted into the isopropanol-free structure of modification A even in the presence of the solvent.

On rapid heating of the solvate (Fig. 6), reorganization of the lattice strongly deformed by abrupt desolvation results in the formation of modification B. In this case, deformation with the predried specimen (trapped solvate regions) will be greater than with the wet specimen (continuous solvent evaporation).

Meanwhile, we could observe the dependence of the high-temperature phase formation on the progression of desolvation (slow, continuous desolvation → solvent-free low-temperature phase; rapid, abrupt desolvation → high-temperature phase) also with other organic active substances.

Contrary to primary crystallization, with the transformation B → A in suspension no intermediary solvate phase can be observed.

In view of the X-ray diffractometric determination of the described phases it should be taken into account that the same phase, depending on the type of formation (primary crystallization from the solution, transformation in the presence of a solvent, thermal transformation) and the conditions thereof, may exist in various structural conditions, which may possibly have a considerable impact on the reflex intensities of both modifications. As corresponding intensity measurements on specimens of different origin have indicated, the detection limits of both modifications mentioned above (Section 3.4.) apply to unfavourable cases (relatively well crystallized phase in the calibration mixture, relatively poorly crystallized phase in the analytical sample) as well.

In the synthesis of the active substance, phase-pure products consisting of modification A, which is more wettable with water and stable at room temperature, are aimed at. This can be obtained by seeding with modification A and/or stirring of the crystallizate in concentrated suspension at temperatures to up to 60°C. Under these conditions, crystallization of modification B is suppressed and the solvate possibly formed is rapidly transformed into modification A, so that, on subsequent drying at temperatures below the transformation point A → B, modification B cannot be formed.

References

[1] W.V. Bebenburg, S. Pauluhn, 2-Amino-3-carbethoxyamino-6-(p-fluor-benzylamino)-pyridin-maleat, patent DE 3133519 C2, 1989.
[2] K. Meyer, Physikalisch-chemische Kristallographie, VEB Deutscher Verlag für Grundstoffindustrie, Leipzig, 1968.