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Research paper

Polymorphism and preformulation studies of lifibrol ☆

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Abstract

Three polymorphic modifications of lifibrol, a novel cholesterol-lowering drug substance, were detected and thoroughly investigated and characterized by thermomicroscopy, DSC, IR-spectroscopy and X-ray powder diffractometry. Mod. I (m.p. 142°C) and mod. II (m.p. 135°C) are stable. Furthermore, true densities, solubilities as function of temperature and pH-value as well as the behavior of the crystal forms under the influence of humid air were determined. The three modifications show distinct differences by IR-spectroscopy, through which a distinction even is possible. The density of mod. I is lower than that of mod. II. The transition of mod. II into mod. I corresponds to an endothermic reaction; from this it follows, that between mod. I and mod. II enantiotropism exists. Mod. II is at 20°C by about 44% less soluble as mod. I. Mod. III, which only can be produced by crystallizing the glassy solidified melt, has a negative heat of transition. That means that mod. III behaves monotropic with regard to both enantiotropic modifications I and II. Mod. I exists in form of small lamellae, mostly of irregular forms. Mod. II consists of rhombohedron grains. Because of this difference in habit, for mod. II one can predict the best properties in case of pressing tablets.

Keywords: Hypocholesterolaemic agent; Thermoanalysis; Solubility; Tabletting properties; Energy/Temperature diagram

1. Introduction

Lifibrol is 4-{4-[4–(1,1–dimethlethyl)–phenyl]-2-hydroxybutoxy}benzoic acid (Fig. 1). It deals with an inodorous and tasteless hypocholesterolemic substance with surface active properties. Its single daily oral dose is 200 to 800 mg [1–3].

The properties and the quality of drugs - and above all their physical stability - is closely connected with the crystal characteristics of the drug substance, especially if there is a need for a drug forming in high dosage [4].

Because it was already known from the synthesis that there are at least two different crystal forms of this drug, the existence of further crystal forms was to be studied and also the characteristics of all crystal forms were to be explored in detail. Among other things these studies of preformulations should be relevant for the selection of the modification being manufactured.

2. Materials and methods

2.1. Materials

Analytical grade solvents for crystallisation experiments and buffer substances of Merck (Darmstadt, Germany) were used. Buffer solutions were prepared according to [5].

2.2. Hot-stage microscopy

A polarized light hot-stage microscope Thermovar® (Reichert, Vienna, Austria) was used.

2.3. Differential scanning calorimetry (DSC)

A DSC-2 (Perkin–Elmer, Norwalk, Ct., USA) was used. The samples, mass about 1–6 mg for quantitative analysis exactly on ± 0.0005 mg (ultramicro-balance UM3 Mettler, CH-Greifensee), were scanned in capsules of aluminium, either closely sealed or equipped with a pore. Analytical grade nitrogen was used as purge gas (30 ml/min). Heating rate was chosen between 0.62 and 20 K/min. Registration of DSC-signals was done by a recorder. The calibration of the abscissa (temperature axis) was carried out by means of the organic calibration substances which are also used for thermomicroscopy. The ordinate (DSC-signal) was calibrated by tinfoil p.a. (Merck, D-Darmstadt).

☆ Dedicated to Prof. Dr. Maria Kuhnert-Brandstätter on the occasion of her birthday.

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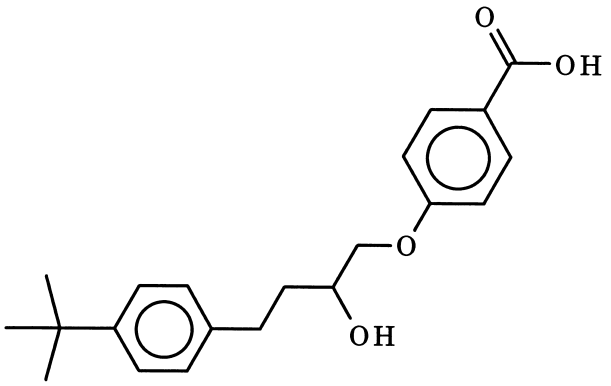

Fig. 1. Lifibrol INN.

2.4. IR-spectroscopy

The infrared spectra were recorded by a Beckman spectrophotometer 4220 (Beckman Instruments, USA-Fullerton, CA) using a scan speed of 300 cm^{-1} min^{-1}, KBr-technique and samples of approx. 2.0 mg for 300 mg KBr.

2.5. Powder X-ray-diffraction

X-ray powder diffraction patterns were taken from samples with a grain size up to 10 μm, investigation of the form before and after taking the diffractogram by thermomicroscope and IR-spectroscopy. A Siemens X-ray diffractometer D-500 was used (Diffrac/AT, Cu K_α Ni-filter, accelerative-voltage 40 kV, mains-power 20 mA, scintillation counter, angle interval 2–35° (2Θ)).

2.6. Determination of density

The volume of the different crystal forms was determined by an air comparison pycnometer (Beckman, model 930, Beckman Instruments, USA-Fullerton, CA). The sample volume was at least 10 cm^3. The mean of three parallel determinations (repeated evacuation, flow-gas helium) was taken at least of two different sample masses of the sample, which was dried to a constant mass immediately before.

2.7. Preparation of the climatic conditions

For determination of hygroscopicity in dependence on relative humidity, the samples were predryed to constant weight and were stored in desiccators over saturated aqueous salt solutions [6] or pure water (for 100% relative humidity) at 24°C. The water contents were measured after one, three and eight weeks, respectively. Desorption processes were also monitored. Measurements and control of the relative humidity were carried out by humidity-measuring instruments DLTM-100 (Reinhardt System- und Meβelektronic, D-Diessen-Obermühlhausen) or by calibrated Durotherm®-hygrometers (G. Lufft, D-Stuttgart). To ensure prompt restoration of humidity after opening the holder with 100% relative humidity, the desiccator was equipped with a motor-driven screw, and the water was additionally stirred with a magnetic stirrer.

2.8. Determination of water content

Determination of water content of the various crystal forms was carried out by titration according to Karl Fischer using pyridine-free reagents and the dead stop method (Karl Fischer titrator E 551, Multidosimat 645 and hand burette E 485 for presentation of solvent, Methrom AG, CH-Herisau). Analytical grade disodium tartrate dihydrate (15.65% water content) and oxalic acid dihydrate (28.85% water content) were used as Karl Fischer standards. The 95%-confidence interval with this method is below ±1% (relative) and ±0.10% (absolute) water content, respectively. The sample sizes ranged from 50 to 150 mg for both of the standards.

2.9. Determination of solubility

About 100 mg mod. I or mod. II of Lifibrol were suspended in approx. 200 ml buffer solution and stirred at constant temperature (±0.05 K) in tightly closed 250-ml-Erlenmeyer-flasks with a magnetic stirrer (900 rev./min). The samples were drawn with volumetric pipettes supplied with membrane filters HAWPO 1200 (pore diameter 0.45 μm) and filter holders SX000 1300 (diameter 13 mm, grind off in front) (Millipore GmbH, D-Neu Isenburg) at established time intervals until saturation was reached. About 2 ml of the first filtrate were put away. After dilution of 2.5 ml sample with the flow solvent in 5 ml-volumetric flasks, the concentration was measured immediately.

Because of the low solubility concentration measurements were done by HPLC using a Perkin–Elmer HPLC Series-3 (injection volumes 20, respectively, 100 μl, flow rate 1.0 ml/min, pressure about 75 bar) equipped with a Detector Knauer (wavelength: 302, 254 nm) and using a reversed phase-C_8 column (particle size 5 μm) from Synchrom Inc., USA-Linden, Indiana, of 25 cm length (internal diameter 4.6 mm). The HPLC was connected with an integrator (Hewlett Packard 3390 A, respectively, 3396 A). The linear calibration was carried out by means of a dilution series between 0 and 14.6 μmol/l; an external standard was used (concentration 1.17 μmol/l). The measurements were done by peak-height method; the retention time was about 4.2 min. The flow solvent was methanol for chromatography (55 parts) and aqueous potassium dihydrogen phosphate solution (0.005 mol/l, 45 parts), the pH-value of 2.5 was standardized with phosphoric acid; purge-gas was helium 4.0.

For the solubility in dependence on the pH various values of pH were gained by addition of drops of sodium hydroxide solution ($c = 0.1$ mol/l) 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 hydrogenphthalate and a phos-

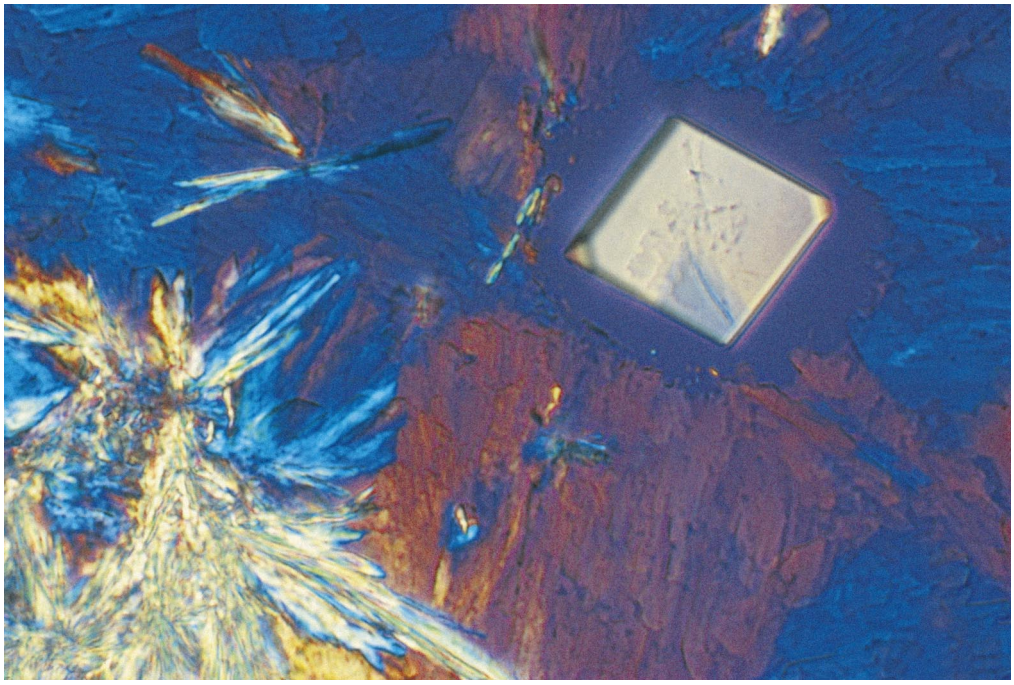

Fig. 2. Rhombohedron crystal of mod. II beside the crystal film of mod. I.

phate buffer solution at 20.0 and 38.0°C in accordance to DIN 19266.

For uninfluenced concentration measurements by HPLC both modifications were purified by suspending the crystals first in the solvent mixture and afterwards in bidestillated water and shaking the suspensions for about one hour, each. The identity of mod. I of all samplings was examined IR-spectroscopically and microscopically. The determination of solubility was carried out with two parallel experiments in each case.

3. Investigations and results

3.1. Preparation of different modifications and thermomicroscopy

An extensive screening for polymorphic modifications by different methods results in the detection of three modifications, which are designated as usual by roman numerals in the sequence of their melting points.

Mod. I is formed by common crystallization from acetone, chloroform, carbon tetrachloride, xylene or ethylacetate. Mod. I is also obtained by precipitation of alkaline solutions with acids or by precipitation with a miscible non-soluble medium such as petroleum ether from a benzolic solution. Mod. I exists of hexagonal structured small lamellae, mostly of irregular forms. The lamellae are about 5 to 30 μm and show indistinct interference colours in polarized light. When supercooling the melt slowly down to 90°C on the thermomicroscope mod. I crystallizes – mainly starting from nuclei on the edge of the melting drops – with a fast, radial front. During the slow crystallization one can recognize star-shaped aggregates, that form a mosaic of spherulites. When the molten sample is transferred directly from the hot stage to a cold block of metal, crystallization of all three modifications may take place. Addition of ethanol to the solidified melt or to the crystals of mod. I leads to the formation of the rhombohedron crystals of mod. II after some time (Fig. 2).

The preparation of **mod. II** takes place by stirring an aqueous or aqueous/alcoholic suspension of mod. I with magnetic-stirrer at room temperature. Mod. II is also formed by crystallization from methanol or ethanol or by slow precipitation of alcoholic solutions (ethanol, methanol) of the substance with water. In the microscope rhombohedron grains (approximately 10–25 μm), which show low interference colours in polarized light, can be recognized. When heating up mod. II at over than 125°C in the thermomicroscope the loss of interference colours due to the transformation of the crystals into mod. I can be detected. The melting occurs inhomogeneously at 135°C, respectively, from 139 to 141°C (m.p. of mod. I). Solving experiments with decan-1-ol at different temperatures at the thermomicroscope show, that the transition point between mod. I and II has to be within 70 and 85°C.

Mod. III is a rather metastable form. It can be produced by heating the solidified glassy melt up to 50–60°C at the hot stage microscope. Thereat small grainy aggregates crystallize, which show fine brown needles in the flimsy film. When heating up to 80–90°C transformation to mod. I takes place, whereby the growth of the star-shaped spherulites starts from a lot of nuclei. During a crystallization of mod. III, which was carried out very slow, fiber twisting [7]

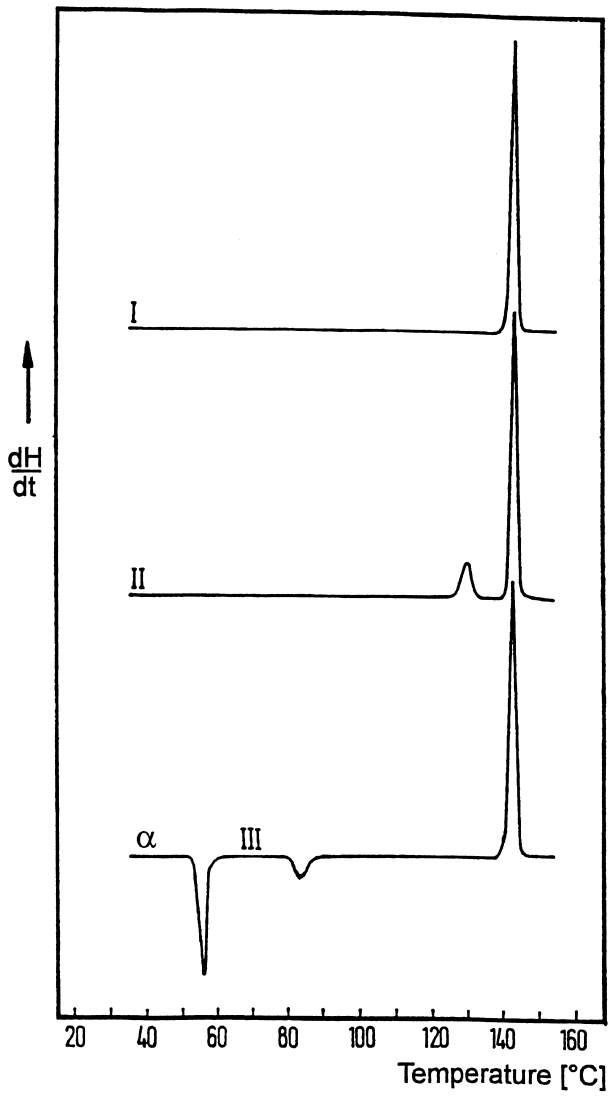

Fig. 3. DSC-curves of mod. I and II and the amorphous form α (crystallizing into mod. III) of Lifibrol.

occured. Both, the crystallization of mod. III by heating the supercooled melt, and the transformation into mod. I were duplicated on a KBr-pellet, thus they could been proved IR-spectroscopically.

3.2. DSC-investigations

In Fig. 3 some characteristic DSC-curves of the three modifications and the amorphous form, respectively, are depicted. Beside the heats of transition from mod. III and mod. II into mod. I also the heat of crystallization of mod. III by heating the glassy solidified melt and the heat of fusion of mod. I can be detected quantitatively by means of DSC. In some cases, depending from the properties of the crystals and the conditions of the DSC-experiment, inhomogenous melting of mod. II is recorded. The measured values can be found together with other data in Table 1.

3.3. IR-spectroscopy

The three modifications of Lifibrol are stable enough to get their IR-spectra by the KBr-method (Fig. 4). The spectrum of the amorphous form was taken by drawing up the molten sample on a clear KBr-pellet, before and after recording the spectrum the melt was examined for absence of mod. III. The characteristics of absorption of mod. I and III are quite similar; the most remarkable difference can be found at 1020–1040 cm^{-1}, where two sharp bands of mod. I appear, whereas mod. III only shows one wide peak. However, the spectrum of mod. II differs from the others; the first peak appears not before about 3300 cm^{-1}, the ν C = O-peak of the carboxylic acid around 1700 cm^{-1} is marked sharper and the δ-hydroxyl-peak at 1250 cm^{-1} is obviously displaced compared to the other forms. Furthermore there are differences at 1060, 960, 630 and 540 cm^{-1}.

3.4. Powder X-ray diffractometry

Mod. II shows the sharpest reflection peaks, while the X-ray diffraction powder diagrams of mod. I and mod. III indicate a lower degree of order. Mod. I is distinguished by a first sharp reflection peak with a high intensity of more than 50.000 cnts/s. In the diffractogram this reflection

Table 1
Parameters of Lifibrol crystal forms

Modification	**I**	**II**	**III**
Melting point (°) (thermomicroscope)	142	135	
Stability (room-temperature)	<Mod. II	Stable	<Mod. I
Preparation	Crystallization from ethylacetate	Crystallization from methanol	Heating of the glassy melt
Crystal habit	Lamellae	Rhombohedron grains	
Heat of fusion (kJ/mol) ±95% c.i.	+38.11 ± 0.16	+49.11 (calculated)	
Heat of transition (kJ/mol) into mod. I ± 95% c.i.,		+11.00 ± 0.21	−4.20 ± 0.67
measured at (°C)		123–130	73–80
Heat of crystallization ±95% c.i. (kJ/mol),			−10.64 ± 1.35
measured at (°C):			47–51
Transition point (°C) (thermomicroscope)		70–85	
Density (kg/m^3) ±95% c.i.	1178 ± 3	1209 ± 4	
First peak in IR-spectrum (cm^{-1})	3463	3302	3450–3470

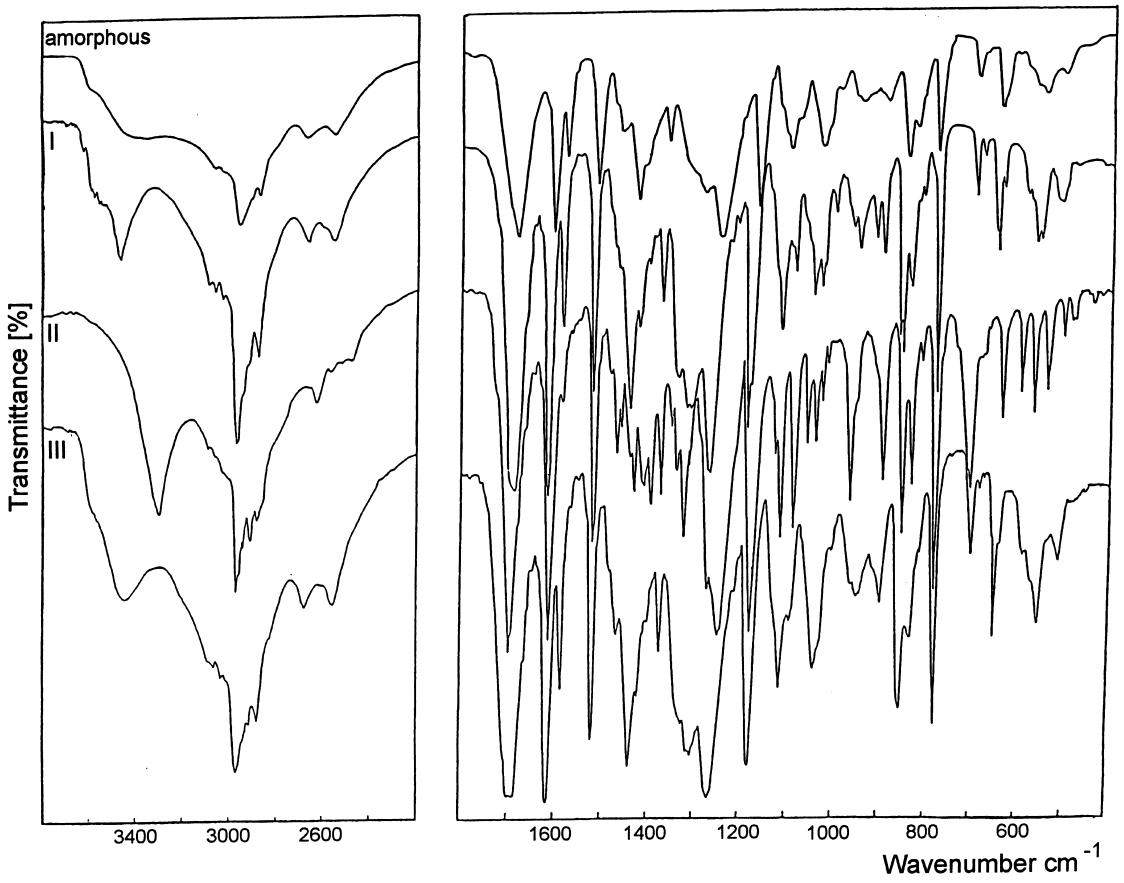

Fig. 4. IR-spectra of the amorphous form and of mod. I, II and III of Lifibrol, KBr-technique.

peak had to be cut in favour of the following bands of less intensity (Fig. 5). The typical d-spacings and the relative intensities are listed in Table 2. Because of the high electrostatic charge of the powder of mod. III - depending on the way of its preparation - the recording of a powder diffractogram was only possible as suspension in paraffin-oil. This explains the wavy background at 15 to 22Θ. When preparing the X-ray powder diffractogram of mod. III the absence of parts of mod. I within the powder sample must be certified by means of IR-spectroscopy.

3.5. True density

The true density of mod. I is by 2.6% lower than that of mod. II (Table 1). This is a significant difference [8,9]. Because mod. III is quite unstable and large amounts proved difficult to prepare, no measurement of true density was made of this modification.

3.6. Stability and influence of humidity

Mod. I and II could only be drained to a water content of about 0.2% (0.04 mol water per mol Lifibrol). After about three weeks storage at 24.0°C and 100% relative humidity the three modifications reached a water content of 0.4–0.5%. According to this results the three crystal forms of

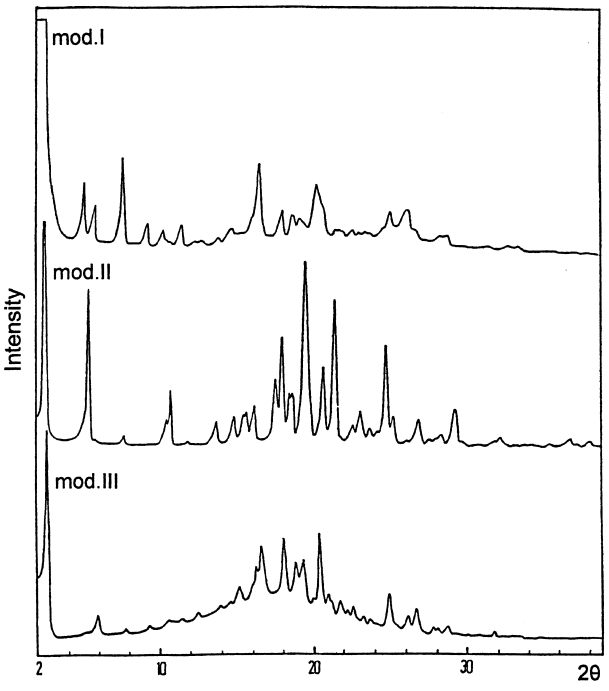

Fig. 5. X-ray powder diffraction patterns of mod. I, II and III of Lifibrol.

Table 2
d (Å) and relative intensities I (%) of characteristic X-ray diffraction bands of the three modifications

Mod. I		**Mod. II**		**Mod. III**	
d	*I* (%)	*d*	*I* (%)	*d*	*I* (%)
34.79	100.0	34.80	100.0	33.10	100.0
17.39	2.6	16.56	35.3	14.10	17.1
15.36	4.6	8.48	6.6	11.47	11.4
11.60	3.0	8.25	12.6	9.49	12.6
9.60	1.9	6.47	6.5	7.09	18.6
8.54	1.8	5.96	7.5	5.84	30.8
7.75	1.9	5.67	8.4	5.45	39.4
6.43	1.7	5.49	10.3	5.34	48.4
6.07	2.6	5.04	15.3	4.89	52.4
5.39	9.8	4.91	24.4	4.70	41.0
4.94	5.1	4.80	12.2	4.58	42.4
4.74	4.7	4.75	12.1	4.34	54.8
4.64	4.8	4.53	39.3	4.23	26.4
4.39	7.8	4.27	17.6	4.08	23.7
4.29	5.6	4.12	32.5	3.93	20.8
3.93	3.0	3.84	8.5	3.56	25.9
3.56	4.2	3.58	23.0	3.40	16.5
3.42	3.4	3.31	6.9	3.34	19.6
		3.04	9.2	3.10	11.7

Lifibrol are completely inhygroscopic. Even when storing mod. I and II for the same time at 40.0°C and 100% relative humidity the water content reaches only 0.5%. But at these conditions within a few days mod. III – with a water content of 0.5% – transforms into mod. I.

3.7. Dissolution behaviour

Solubility experiments have been made with the practically relevant mod. I and mod. II.

3.7.1. The effect of temperature on solubility

The measurements of the saturation solubility dependent on temperature were made in hydrochloric acid ($c \approx 0.1$ mol/l) with admixture of potassium hydrogenephosphate ($c = 0.005$ mol/l) standardized at pH = 1.2. Fig. 6 shows the solubility of mod. I and II in the van't Hoff diagram [10].

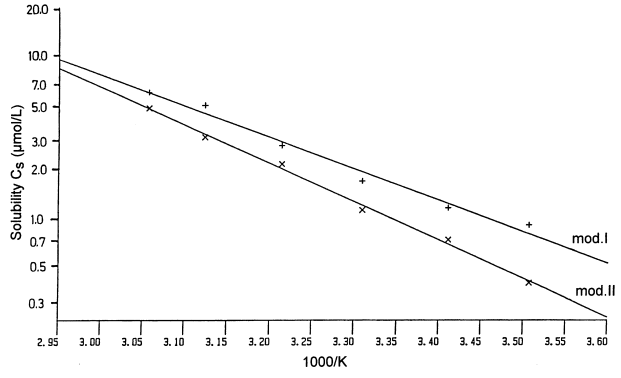

Fig. 6. Lifibrol, calculated and measured solubility of mod. I and II at pH 1.2 in the van't Hoff diagram.

Table 3
Measured (m.) and with Eqs. (2) and (3) calculated (c.) solubility C_s (µmol/l) at pH 1.2 and its difference Q (%)

°C	Mod. I		Mod. II		Q
	C_s (m.)	C_s (c.)	C_s (m.)	C_s (c.)	
12.0	0.86	0.76	0.38	0.39	97
20.0	1.11	1.18	0.70	0.66	79
29.0	1.64	1.87	1.07	1.15	62
38.0	2.74	2.88	2.09	1.95	48
47.0	4.89	4.34	3.08	3.21	35
54.0	5.90	5.87	4.69	4.65	26

The straight lines based on the van't Hoff reaction isobare (Eq. (1)) were fitted to the measured data of both modifications by the method of least squares.

$$c_s = B \exp\left(-\Delta H_L R^{-1} T^{-1}\right) \quad (1)$$

where c_s is the saturation solubility (µmol/l), B is a constant, ΔH_L is the last molar heat of solution, R is the gas constant, T is the temperature (Kelvin).

The determined relations for the solubilities of mod. I and II in µmol/l depending on temperature are given in its logarithmic form (Eqs. (2) and (3)).

$$\ln c_{s,I} = 15.622 - 4531.54\ T^{-1} \quad (2)$$

$$\ln c_{s,II} = 18.399 - 5516.73\ T^{-1} \quad (3)$$

The measured and calculated values are listed also in Table 3. Subtracting Eq. (3) from Eq. (2) and introducing the abbreviation $Q_s = c_{s,I}/c_{s,II}$ yields Eq. (4).

$$\ln Q_s = -2.777 + 985.19\ T^{-1} \quad (4)$$

For comparison, in Table 3 also is given the relative solubility difference Q between mod. I and II in percent, where

$$Q = 100[\exp(\ln Q_s) - 1] \quad (5)$$

The measured values of mod. I deviate more than those of mod. II of the calculated lines. The reason therefore is likely the lamella-formed crystal habit and the resulting more lipophil behaviour of the crystals of mod. I.

3.7.2. pH-dependent solubility

The saturation solubility of mod. II was measured in dependence on the pH-value in phosphate buffer solutions ($c \approx 0.01$ mol/l) at 20.0 and 38.0°C. Afterwards, Eq. (6) was adapted iterative to the measured values. The equation describes the solubility C_s of a weak acid of low solubility in dependence on the pH-value for a given temperature [10].

$$C_s = C_{s,0}\left(1 + 10^{pH - pK_{a,2}}\right) \quad (6)$$

$C_{s,0}$ is the concentration of non-ionized molecules in the saturated solution. $C_{s,0}$ is also named basal solubility and

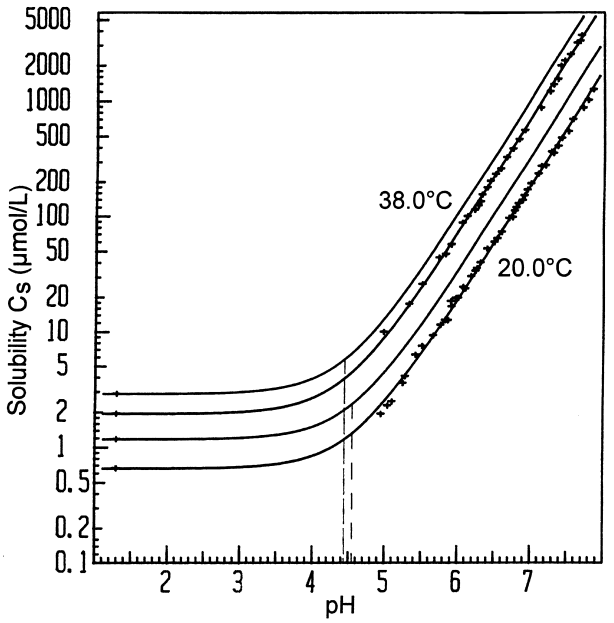

Fig. 7. Lifibrol, calculated and measured solubility of mod. I and mod. II at 20.0 and 38.0°C dependent on pH; the dotted vertical lines represent the dissociation constants at 20.0 and 38.0°C.

was calculated following to Eq. (3) for 20.0 and 38.0°C (see Table 3). $pK_{a,2}$ is the dissociation constant, which was determined by iterative adaptation with 4.55 (20.0°C) and 4.44 (38.0°C).

To describe the pH-dependent solubility of the metastable mod. I as extensive experiments as with mod. II are not required, because the dissociation constant does not depend on the crystal lattice and consequently is identical with both forms. The $C_{s,0}$-values can be determined using Eq. (2) and are given in Table 3.

Fig. 7 shows the measured values and the calculated curves of pH-dependent saturation solubility of both forms at 20.0 and 38.0°C in a semi-logarithmic diagram.

4. Discussion

Because of the measured data the thermodynamic behaviour of the three modifications of Lifibrol can be shown in a semischematic energy/temperature-diagram (Fig. 8) [11,12]. The enantiotropism between mod. I and mod. II is in agreement with the measured densities (density-rule) and the position of the first peaks in the IR-spectra (IR-rule) [8,9]. However, mod. III, which shows a certain resemblance to mod. I due to its spectral characteristics, behaves monotropic with regard to both enantiotropic forms. That means that mod. III is in a metastable condition at each temperature. The X-ray powder diffractogram of this modification does not show a lot of sharp reflections signifying a high extent of disorder.

The multiplication of the negative slope of the adjusted straight lines (Eqs. (2) and (3)) with the gas constant R (8.314 J/mol K) results as heat of solution for mod. I with 37.6 kJ/mol and for mod. II with 45.9 kJ/mol. The comparison of the differences of heat of solution (8.3 kJ/mol) with the calorimetric measured heat of transition of 11 kJ/mol (Table 1) for the endothermic transformation of mod. II into mod. I shows an agreement with regard to the enthalpy difference between both modifications. The remaining difference of about 2.7 kJ/mol is not only to be explained by the deviation of the measured values, but mainly by the relative far distance between the two measuring temperatures. The point of intersection of the straight lines of Eqs. (2) and (3) is approximately at 82°C. At this temperature both modifications have the same extrapolated solubility-value, which certainly comes up to the conditions of the transformation point; yet, one must not identify these two points, because the effected extrapolation is still important. After all there is a good agreement between this extrapolated temperature of 82°C and the transformation range found thermomicroscopically (70–85°C).

The examinations suggest the formulation of mod. II, which is stable at room and body temperature. In regard to the crystal habit of mod. II the filtration behaviour and the tabletting properties of this modification could be determined to be essentially better than those of mod. I [13,14]. Nevertheless the use of the metastable mod. I – after examination of the pharmacocinetic behaviour – should still be

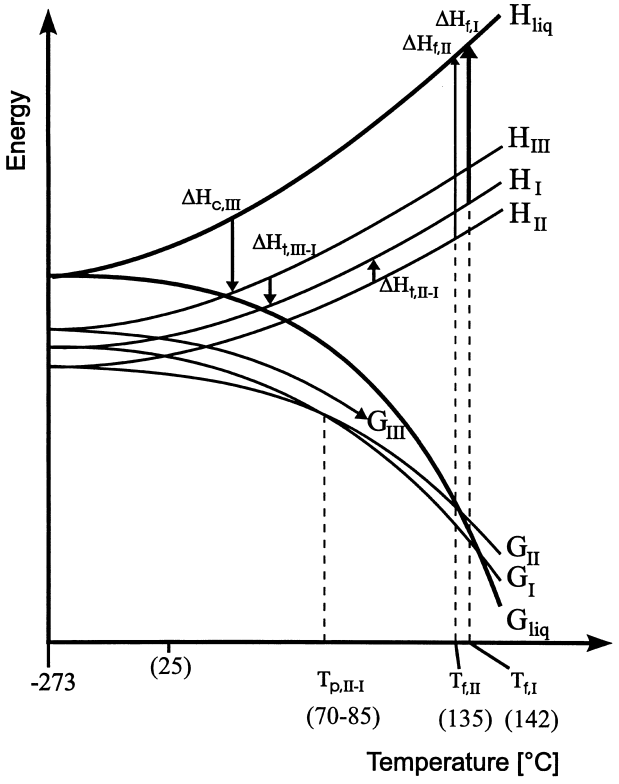

Fig. 8. Semischematic energy/temperature-diagram of the three modifications I, II and III and the melt (liq.) of Lifibrol; H molar enthalpy, G molar free enthalpy, ΔH_f heat of fusion, ΔH_c heat of crystallization, $T_{p,II-I}$ transition point between mod. I and II, T_f melting point.

considered because of its higher solubility. Mod. III is only of analytical importance.

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