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POLYMORPHIC AND THERMODYNAMIC STUDY OF INDOMETHACIN*

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Abstract

Indomethacin is known to exhibit polymorphism. As a consequence the various forms have different solubilities and may have different bioavailabilities. This study has been carried out with the following techniques: calorimetry, differential scanning calorimetry (DSC), thermogravimetric analysis (TG), X-ray diffraction and thermomicroscopy.

Two solid forms have been prepared and studied: their melting temperature and their enthalpy of fusion are determined. The heat capacity and heat content were measured *vs*. the temperature for these two solid forms and for the liquid phase. This is fundamental for the determination of the stable form. More of this, with a view to study phase diagrams of indomethacin with another compound (solvent or not), the knowledge of the C_p of the various forms is necessary for calculation of the liquidus curve, this allows to minimize the number of experiments.

Keywords: heat capacity, heat content, indomethacin, polymorphism

Introduction

Indomethacin is well known as anti-inflammatory, antipyretic and analgesic agent. Its formula is $C_{19}H_{16}ClNO_4$, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H indole-3-acetic acid (Fig. 1). It has been first described by [1] with three forms, by [2, 3] with two forms and [4] proposes four polymorphic forms but only three have been isolated named I, II and IV with the respective melting temperature proposed by [4]:160, 154, 134°C; form III with a melting point at 148°C has not been isolated. Solubility tests in water and in a hydrochloric acid (0.1 N), performed at 25°C on the three forms I, II and IV, showed large differences [4].

Characterization of polymorphic forms constitutes an important aspect of drug development. In order to get a better understanding of the behaviour of solid indomethacin and the possible evolution of a metastable form to a stable one, a thermodynamic study has been carried out. Different polymorphs of a drug may exhibit signifi-

* This publication is dedicated to the memory of Yves Feutelais

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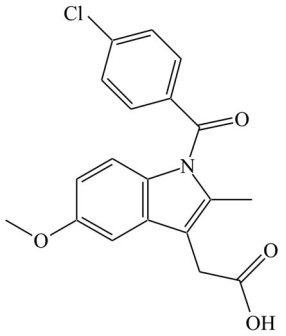

Fig. 1 Chemical structure of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H indole-3-acetic acid

cantly different biological activities due to their different solubility and dissolution rate as it has been shown by [5].

The rate and duration of dissolution depend on the enthalpy of dissolution, which in fact is the sum of three terms and can be expressed by the following equation deduced from the first law of thermodynamics:

$$\Delta_{sol}H(T_0)=\int_{T_0}^{T_{fus}}(C_p^s-C_p^l)\mathrm{d}T+\Delta_{fus}H(T_{fus})+\Delta_{mix}H(T_0) \quad (1)$$

The first term of the second part of this equation is generally slightly negative and is close to zero. The second term $\Delta_{fus}H$ is the enthalpy of fusion, this is always positive and differs for each crystallographic form. The third term $\Delta_{mix}H$ is the enthalpy of mixing between the solvent and the compound in the undercooled liquid state at T_0. It may be positive or negative, and does not depend on the crystallographic form, and so the most important term for the modification of the enthalpy of dissolution is the enthalpy of fusion. We can thus deduce that the bio-availability depends on the heat of fusion and that the study of the polymorphism is of paramount importance for the pharmacokinetics.

In a recent work devoted to the crystal growth of indomethacin polymorphs from glassy state, Andronis *et al.* [6] studied the rate of nucleation of the two forms I and II. They used the formula of Volner [7], obtained from the theory of the germination. This theory needs the knowledge on ΔG_v which is the difference of free energy between the Gibbs energy of the glass and that of the form I or II at the same temperature. As the C_p of the polymorphic form and the glass were unknown Andronis used the Hoffman equation [8]:

$$\Delta G_v=\Delta_{fus}H(T_m-T)\frac{T}{T_m^2}$$

This formula is an approximation.

The free energy of activation depends of ΔG_v. Andronis [6] admitted: 'The crystallization behaviour of the form I (γ), however, is not so clearly understood at this point'.

Legendre *et al.* [9] have shown that in the study of the crystallization of progesterone from a glass, without the knowledge of the C_p, it was not possible to explain the behaviour during the crystallization. A competition exists between the two reactions:

$$\text{Glass} \rightarrow \text{Form I and Glass} \rightarrow \text{Form II}$$

The favoured reaction is the one for which the free enthalpy of activation is the lowest, the Hoffman equation is an approximation based on the equality of the C_p of the glassy form and the two solid forms; we have shown that for the progesterone, an inversion occurred for a determined temperature of crystallization.

A recent study by Carpentier *et al*. is devoted to the thermochemical behaviour of indometacin just above T_g The aim of this work is to determine if polymorphic transitions occur for this compound, and under which conditions the solid crystalline phase becomes stable from a thermodynamic point of view. The thermochemical behaviour was studied using: calorimetric measurement, differential scanning calorimetry (DSC), thermogravimetric analysis (TG), thermomicroscopic analysis and powder X-ray diffraction.

Experiments and apparatus

Differential scanning calorimetry

DSC 7 (Perkin Elmer): the apparatus was calibrated in temperature with the melting point of indium 5N (NIST – National Institute of Standard and Technology): 156.634°C and tin 5N (Koch–Light): (231.9681°C), for each heating rate. The enthalpy of fusion of indium and tin are respectively 28.44 and 59.22 J g^{-1}. These are recommended values by the American Society for Materials ASM [10] for the melting point temperature and by Editor Bull. [11] for the enthalpy of fusion of indium. The calibration was performed for each heating rate.

Pans are in aluminium based alloys and covered with caps. Holes are always used in order to remain at a constant pressure. All the experiments are performed under dry nitrogen gas atmosphere, with a flow of $2 \cdot 10^{-2}$ L min^{-1}.

Thermomicroscopic equipment composed of a Mettler FP5 and an Olympus BH-2 microscope was used for the interpretation of the phenomena observed by DSC.

Calorimetric measurement

A C80 calorimeter of Setaram (Calvet type) has been used either in an isothermal mode or with the variation of temperature. It is perfectly adapted for heat capacity (C_p) measurements, with a heating rate β=0.1 K min^{-1}. Calibration in temperature and power is performed with the melting of indium and tin as for the DSC. Samples are introduced in a glass cell which is itself in a stainless steel vessel. The amount of product is in a range of 500 mg.

The C_p has been measured using the continuous method:

$$C_p = \frac{1}{m}\left(\frac{\partial Q}{\partial T}\right)_p$$

in which m is the mass of the sample, Q is the heat (at constant pressure) and T the temperature.

In a Calvet calorimeter, a variation of heat flow (HF in J s^{-1}, t is the time in s) is measured,

$$HF = \left(\frac{\partial Q}{\partial t}\right)_p \text{ and } \left(\frac{\partial Q}{\partial T}\right)_p = \left(\frac{\partial Q}{\partial t}\right)\left(\frac{\partial t}{\partial T}\right);\ \frac{\partial t}{\partial T} = \frac{1}{\beta}$$

where β is the heating rate in K s^{-1}.

$$C_p = \frac{1}{m}\frac{1}{\beta}\left(\frac{\partial Q}{\partial t}\right)_p$$

For the heat flow corresponding to the C_p of the studied product the value of a blank obtained for empty cells and measured in the same conditions, must be subtracted from the heat flow measured for the full cells.

Thermogravimetric analyser

TGA 7 (Perkin Elmer) calibration was performed at different temperatures using Curie magnetic transition for the recommended alloys: Alumel (163°C), Nickel (354°C). The calibration of mass was performed using a standard mass of 100 mg. All the experiments were carried out under dry nitrogen atmosphere, with a flow of $6 \cdot 10^{-2}$ L min^{-1}.

The apparatus is coupled with an infrared spectrometer (Perkin Elmer FT-IR spectrum 2000), gases are transferred from the TG furnace to the heated spectroscopic cell by a line heated at 200°C.

X-ray crystallographic analysis on powder

Identification of phases have been carried out on a PW 1729 (Philips) X-ray diffractometer equipped with a goniometer driven by a software developed by [12]. The anode used is CuK_α (λ=1.54051 Å). Measurements were performed at room temperature.

Chemical product

We used indomethacin from Sigma company. This commercial product is composed mainly of form I (99.5%) and form II (0.5%), DSC analysis shows two peaks corresponding to the fusion of the two forms. The percentage of each form is deduced by comparing the peak area to the peak of the pure form I or II, this is confirmed by X-ray crystallography. Evaporation of a solution of the commercial product in water led to pure form I, while acetonitrile or ethanol were used to obtain pure form II.

Results and discussion

Dissolution results

For the different experiments, crystallization from various solvents have been studied.

By dissolution in distilled water, then evaporation, only the form I is obtained. The same form is obtained with pure methanol.

The DSC analysis showed only one endothermic peak during the heating run. To know the significance of this peak, it is necessary to observe the same sample with a thermomicroscopic apparatus. At the same temperature, the peak observed corresponds to the fusion of the product.

The measured values with a heating rate of 20°C min^{-1} for the fusion were:

$$T_{fus}=159.1\pm0.5°C$$

$$\Delta_{fus}H=103\pm1\ J\ g^{-1}$$

This form is usually named form I.

Crystallographic structure of the form I has been solved by [13] on a single crystal. The parameters of the triclinic cell ($P\bar{1}$, Z=4) are:

a=9.295 Ĺ b=10.969 Ĺ c=9.742 Ĺ

α=69.38° β=110.79° γ=92.78°

The JCPDS (Joint Committee Powder Diffraction Standards) file is (31–1733).

Our crystallographic data are presented in Table 1 for the comparison with the selected data of JCPDS.

Table 1 Comparison of X-ray diffraction patterns obtained for forms I and II with the corresponding JCPDS files

Form I; *m.p.*=159.1°C				Form II; *m.p.*=153.0°C			
This work		JCPDS: 40–1710		This work		JCPDS: 39–1883	
d/Å	I/I_0/%	*d*/Å	I/I_0/%	*d*/Å	I/I_0/%	*d*/Å	
8.7203	19.32	8.701	30	12.7812	30.24	12.6277	31
7.6648	64.59	7.609	100	10.4427	68.58	10.4023	100
6.9916	16.59	6.916	15	8.6018	21.98	8.58813	23
5.6342	4.79	5.619	2	7.7249	34.81	7.69453	29
5.3342	73.83	5.315	50	7.4461	67.55	7.43677	92
5.2279	33.24	5.203	50	6.3884	61.80	6.37091	50
5.1465	36.86	5.111	30	6.2449	65.78	6.21521	66
5.1347	37.53			6.1077	77.58	6.10861	86
4.7970	16.31	4.773	10	5.9764	31.12	5.94551	29
4.5844	34.69	4.587	25	5.5225	29.50	5.50496	24
4.5391	46.33	4.513	50	5.2448	27.73	5.21550	16

Table 1 Continued

Form I; *m.p.*=159.1°C				Form II; *m.p.*=153.0°C			
This work		JCPDS: 40–1710		This work		JCPDS: 39–1883	
d/Å	I/I_0/%	*d*/Å	I/I_0/%	*d*/Å	I/I_0/%	*d*/Å	
4.3687	14.42	4.357	5	5.0391	42.92	5.06760	1
4.2801	8.30	4.254	5	4.9211	70.21	4.92794	41
4.0798	100.00	4.068	75	4.8073	63.42		
3.8893	20.27	3.887	15	4.5587	55.31		
3.8421	20.66	3.832	15	4.5105	63.13	4.50636	48
3.7116	19.04	3.696	15	4.4041	44.54		
3.4921	16.76	3.473	10	4.2914	62.83	4.29086	30
3.3921	16.98	3.390	10	4.2367	45.13		
3.3538	66.43			4.2158	38.20		
3.3188	22.72	3.299	10	4.0241	98.53	4.03112	57
3.2482	14.53	3.236	10	3.9215	89.09	3.91714	27
3.1541	15.37	3.149	10	3.8064	64.60	3.80955	9
3.1036	12.81	3.103	5	3.7062	48.38	3.70023	9
3.0994	12.75			3.6266	70.65	3.63328	35
3.0491	24.61	3.037	20	3.5658	39.82	3.56173	9
2.9430	19.32	2.935	20	3.5282	59.29		
2.9084	10.86	2.905	5	3.3606	48.67	3.40126	13
2.8363	6.24	2.827	5	3.2704	29.65	3.27844	9
2.7456	11.69	2.739	5	3.1728	51.62		
2.7196	8.46	2.710	3	3.1438	62.83	3.14259	20
2.6719	10.47	2.656	5	3.1147	39.68		
2.6311	12.75	2.62	3	3.0263	28.17		
2.6274	12.86			3.0158	28.17		
2.5704	9.52			2.9843	29.06		
2.5401	6.40			2.8791	48.23	2.88469	22
2.5108	5.23			2.8456	45.48		
2.4783	4.40			2.7949	19.47		
2.4505	5.46			2.7456	25.22		
2.4021	16.37			2.7068	15.93		
2.3389	5.12			2.6692	34.81		
2.3052	7.07			2.6489	22.27		
2.2783	6.74			2.6129	17.70		

The influence of the solvent on the morphology of the γ-polymorph of indomethacin has been described recently by [14].

By dissolution in ethanol (96 GL Rectapur from Merck), followed by an evaporation of the solvent, a mixture of two forms is obtained. As the enthalpies of fusion of the pure forms I and II are known, it is easy to determine the proportion of the two forms, because with a heating rate of 20°C min^{-1}, the liquid does not recrystallize and the two peaks of fusion do not overlap: form I (10%) and another form named form II (90%). By a second operation of dissolution and crystallization in the same solvent the pure form II is obtained.

The measured values for the fusion were:

$$T_{fus}=153.0\pm0.5°C$$

$$\Delta_{fus}H=92\pm1\ J\ g^{-1}$$

The parameters of the monoclinic cell reported by [6] are:

a=5.462 Å	b=25.310 Å	c=18.152 Å
α=90°	β=94.38°	γ=90°

Even in a case of a slow cooling rate (=–0.2°C min^{-1}), no crystallization was observed for the two forms. A glass is formed, and if the sample is heated again the recrystallization is not observed.

Thus the DSC analysis showed in each case only one peak, and the enthalpy of fusion of the form I is higher than the one for the form II. In this case the form I is the stable one (for the pressure of 1 bar) and form II is metastable: it is a case of monotropy.

This second form has been studied by X-ray diffraction, and the difference between the two forms is confirmed.

Results of X-ray diffraction are presented in Table 1 and compared to the JCPDS files.

Thermodynamic results

Recently, Marini *et al.* 16 show that the knowledge of the entalpy of fusion for indomethacin was important for drug - excipient compatibility. Before carrying out the heat capacity C_p measurements, a thermogravimetric study has been performed on form I and form II from room temperature to 165°C. No mass loss has been observed. This result is important because it ensures that these forms are not solvated. Forms I and II after isolation and verification have been studied in a C80 calorimeter, equipped with the 'set soft program' provided by Setaram. The following method has been used: a blank has been recorded between 50 and 140°C (323 and 413 K) with first an isotherm of one hour at 50°C followed by a linear heating to 140°C with a rate of 0.1°C min^{-1}, then the two samples have been submitted to the same treatment.

For the liquid, the treatment is different, the solid phase (form I) is heated at few degrees over the melting point, then cooled to 150°C, and annealed at this temperature for one hour (no crystallization occurred during this step), then it is heated up

to 160°C with a heating rate of 0.1°C min^{-1}. The measurement of the C_p is performed on the undercooled liquid. A blank is recorded in the same conditions.

The result is expressed in a polynomial form as $C_p=a+bT+cT^2+dT^{-2}+\ldots$

For the two solid forms and the liquid, two coefficients are needed to obtain the best polynomial fit. C_p is expressed in J K^{-1} g^{-1} and T in Kelvin (K).

The results are:

$$\text{Form I } C_p=0.5467068+0.00327189T$$

$$\text{Form II } C_p=-0.1406643+0.00428942T$$

$$\text{Liquid } C_p=10.01719-0.01894227T$$

These factors have too large numbers of significant figures. They have been used as mathematical tools.

It is now possible to calculate the heat content for the three phases.

If the enthalpy of the form I is taken as 0 J g^{-1} for 298.15 K, the variation of enthalpy for the form I between 298.15 K and its melting temperature will be:

$$\Delta H_{298.15}^{T_{fus}} = \int_{298.15}^{T_{fus}} C_p \mathrm{d}T$$

By integration between 298.15 K and T it is possible to determine the coefficients of the function $\Delta H_{298.15}^{T_{fus}} = f(T)$.

The measured melting temperature of this phase is: T_{fus}=432.25 K, and the enthalpy of fusion is $\Delta_{fus}H$=103 J g^{-1}. The enthalpy of the liquid phase at 425.25 K is obtained by adding the enthalpy of fusion of the form I to the enthalpy of this form at the melting temperature. Then by integration, it is possible to determine the coefficients of the function corresponding to the variation of enthalpy of the liquid phase, *vs.* the temperature. In order to determine the function corresponding to the variation of enthalpy of the form II, we must calculate the enthalpy of the form II at its temperature of fusion, starting from the enthalpy of the liquid at the melting temperature of the form II (426.15 K), the enthalpy of fusion (92.05 J g^{-1}) is subtracted from this value, then the integration is performed.

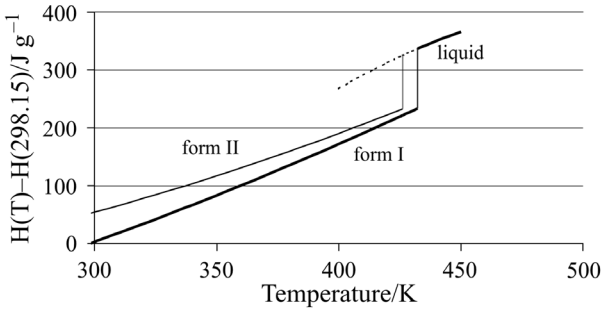

Fig. 2 Heat content *vs*. temperature for form I, form II and liquid phase

For the three phases the difference between the enthalpy at T[$H(T)$] and that of form I at 298.15 K [H(298.15)] may be presented by a polynomial function with three coefficients given in Table 2.

$$H(T)–H(298.15)=\Delta H^{T}_{298.15}=A_0+A_1T+A_2T^2$$

Using these functions, $\Delta H^{T}_{298.15}$ *vs*. temperature for the three phases are presented in Fig. 2.

As we can see, the heat content of the metastable form II is higher than the one of the stable form I at 298.15 K, and the representation of these functions is typically representative of a monotropy.

Table 2 Coefficients of the function $A_0+A_1T+A_2T^2$ for indomethacin in forms I, II and liquid

	A_0	A_1	A_2
Form I	–308.425382	0.5467068	0.001636
Form II	–96.556468	–0.140664	0.002145
Liquid	–2223.794224	10.017190	–0.009471

Conclusions

Thermodynamic quantities of forms I and II were determined from heat capacity and DSC measurements. The comparison between the temperature and enthalpy of melting of the two forms clearly shows that the form I is stable at atmospheric pressure while form II is metastable. This result suggests that the pressure–temperature diagram for these two forms is a monotropic one. The existence of metastable form of indomethacin at room temperature and atmospheric pressure may lead to difficulties in formulation, particularly in creams, ointments and suspensions. The differences and relation between the stable and metastable forms described in this work appear then to be of primary importance in a pharmaceutical point of view. From dissolution experiments carried out in different solvents several solvates were obtained. They will be described and characterized in a forthcoming publication.

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