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Importance of heat capacity determination in homogeneous nucleation: application to progesterone

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Abstract

Progesterone is known to exist under different crystallographic forms in the solid state. The thermodynamic stable form (I), melts at 129.2 °C (402.35 K) under atmospheric pressure. After melting and cooling a metastable form (II) can be obtained which melts at 122 °C (395.15 K). This uncommon behaviour can be explained with the theory of nucleation, only if heat capacity of the different forms are known.

Keywords: Progesterone; Polymorphism; Heat capacity; Nucleation

1. Introduction

Study of polymorphism of drugs is of prime importance, because the bio-availability depends on the rate and duration of the dissolution of the drug. The enthalpy of dissolution can be expressed by the following equation deduced from the first law of the thermodynamic:

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

The first term is relative to the heat capacity at constant pressure for the liquid and the solid. The difference between C_p^{s} and C_p^{l} is generally very small, $\Delta_{\mathrm{fus}}H$ is the enthalpy of fusion, $\Delta_{\mathrm{mix}}H$ is positive or negative and corresponds to the heat of mixing between the solvent and the undercooled liquid. This term is always the same and is independent of the different solid forms. If two polymorphic forms exist, their enthalpy of fusion will be different, and the enthalpy of dissolution depends essentially on this term. The duration of the dissolution is proportional to the heat of dissolution [1]. This is the reason why it is necessary to obtain with precision the enthalpy of fusion of each form. The phase rule imposes that only one form is stable at one fixed temperature and pressure. If a metastable phase appears, it may transform in a stable phase. It is necessary to know the conditions of stability of each phase.

The comportment of progesterone has been observed by different authors [2–5] and two crystallographic forms are described [6,7]. We are sure that it exists at least two forms because their crystal structures are known. Form (I) is the stable one under a pressure of 1 bar. The thermal behaviour has been studied by differential scanning calorimetry (DSC) and the identification of the phases was done by X-ray

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diffraction. Thermomicroscopy was used to determine the nature of the peaks observed by DSC (melting point or solid–solid transition).

2. Experimental results

2.1. Thermal analysis

Thermal analysis has been performed with a DSC-7 Perkin-Elmer under nitrogen flow. Samples are introduced in pans with holes in order to avoid uncontrolled variation of pressure. Calibration has been performed with indium and tin of quality 5N (99.999 at.%) for heating rates of 1 K/min and 20 K/min. If the rate of cooling is not programmed, the cooling rate is 200 K/min. Four samples were submitted to a first heating ramp (20 K/min) followed by fast cooling (200 K/min) and re-heating (20 K/min). The results of the three successive ramps are presented in Tables 1 and 2.

The average value for the melting temperature of form I is 129.2 °C (402.35 K). It is 1 K lower than the proposed value of [4] and the heat of fusion is 83.2 J/g (excluding the third value). It is higher than the proposed value of [4] which is 77.7 J/g. As shown by the differences observed between the values of enthalpy of crystallisation (Table 1), after melting and cooling, the progesterone seems to be only partially crystallised. The temperature of crystallisation during the second run is at around 50 °C (323.15 K), and the heat of crystallisation is significantly lower than the heat of fusion. The peaks of crystallisation during heating are in several parts and it seems that two forms crystallise. This is verified by the presence of different peaks of fusion. A first endothermic peak at 105 °C (378.15 K) is observed, with a small and variable heat of transition, from one run to another. A thermomicroscopic observation has shown that at this temperature some drops of liquid appeared.

Table 1
DSC results of progesterone (first heating, four samples)

T_{fus} (°C)	$\Delta_{\text{fus}}H$ (J/g)
128.85	82.4
128.96	83.3
129.27	87.7
129.67	84.0

The second endothermic peak at 122 °C (395.15 K) with a high variation of enthalpy is attributed to the melting of form II, the values proposed by [4] were 67.79 and 68.73 J/g. They are in agreement with our results.

By the dissolution of form I in ethanol at 40 °C (313.15 K) and drying at 50 °C (323.15 K), form II is obtained. The heat of fusion measured is 68.1 J/g. After cooling down to room temperature with a cooling rate of −200 K/min, a glassy form is obtained. When it is heated again at 20 K/min, two peaks of crystallisation appear. The first one is at 56 °C (329.15 K) and the second at 72 °C (345.15 K). This means that a mixture of two forms (II and another one named III) is present. They melt at 104.0 °C (377.15 K) with $\Delta_{\text{fus}}H = 40.5$ J/g and 119.5 °C (392.65 K) with $\Delta_{\text{fus}}H = 14.3$ J/g, respectively. It means that in this mixture, 21.03% of form II is present; we may deduce that the heat of fusion of form III is equal to: $\Delta_{\text{fus}}H = (40.5/(1 - 0.2103))$, $\Delta_{\text{fus}}H = 51.3$ J/g. It is possible to summarise the thermodynamic data for the three forms in the Table 3.

2.2. Calorimetric measurements

In order to determine the heat content and the heat capacity of the solid phases, form I and form II (form III has not been isolated) and the liquid phase, a C 80

Table 2
DSC results of progesterone (second heating, four samples)

Crystallisation		First peak of fusion		Second peak of fusion		Third peak of fusion	
T (°C)	$\Delta_{\text{cr}}H$ (J/g)	T (°C)	$\Delta_{\text{fus}}H$ (J/g)	T (°C)	$\Delta_{\text{fus}}H$ (J/g)	T (°C)	$\Delta_{\text{fus}}H$ (J/g)
50	−32.0	105.8	10.7	122.22	61.6	128.85	6.3
47	−20.6	104	11.7	122.12	65.2		
50	−57.2	106	4.0	122.22	70.0	128.96	3.9
50	−47.7	106.41	3.1	122.43	74.4		

Table 3
Thermodynamic data of the forms I, II and III of progesterone

	T_{fus} (°C)	T_{fus} (K)	$\Delta_{\text{fus}}H$ (J/g)	$\Delta_{\text{fus}}S$ (J/g K)
Form I	129.2	402.4	83.2	0.2068
Form II	122.2	395.4	68.1	0.1722
Form III	104.0	377	51.3	0.1362

calorimeter (Setaram) has been used. The materials were introduced in a Pyrex glass ampoule which itself was located in a stainless cell. Calibration was performed in temperature and energy with the measurement of the temperature and enthalpy of fusion of In and Sn (5N) for a heating rate of 0.2 K/min.

The forms I and II were analysed between 35 and 85 °C (308 and 358 K) and the liquid phase between 94 and 133 °C (367 and 406 K). After DSC analysis, showing that form I was pure, calorimetric analysis was performed up to 85 °C (358.15 K), then the product was melted and cooled, a new analysis was performed in order to be sure that only form II was present. Then form II was analysed. When the liquid phase was obtained, after melting, the sample was cooled in the calorimeter down to 94 °C (367.15 K) and heated up to 133 °C (406.15 K); these two limits where selected because under 94 °C (367.15 K) the formation of a glass is suspected, and over 133 °C (406.15 K) the vapour pressure cannot be neglected. In order to perform thermodynamic calculations, these values were extrapolated down to 25 °C (298.15 K) and up to the 133 °C (406.15 K).

The data are treated with the Setaram C_p program which gives the following polynomial expansion for the analytical description of C_p:

$$C_p = A_0 + A_1T + A_2T^2 + A_nT^n \tag{2}$$

with C_p in J/g K, and T in K. The coefficients of the above function for the different forms are given in Table 4.

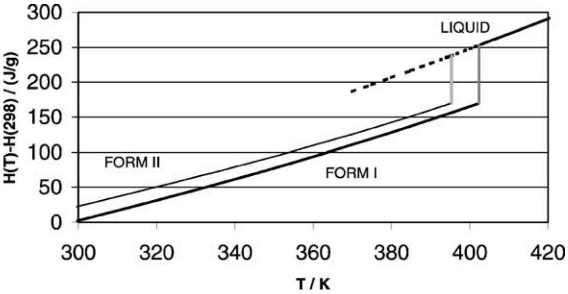

Fig. 1. Heat content vs. temperature for form I, form II and liquid phase.

Assuming that the stable form of progesterone at $P = 1$ bar is form I and setting the reference for the enthalpy at 0 J/g at $T = 298.15$ K, it is then possible to calculate, from Eq. (2), the heat content for each phase

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

For form I, $\Delta H_{298.15}^{T}$ is calculated from 298.15 K to the melting temperature, then the enthalpy of fusion is added, and the heat content of the liquid is introduced. At the melting temperature of form II, the enthalpy of fusion is deduced from the enthalpy of the liquid, and from that point the heat content of form II is calculated. As it is possible to observe in Fig. 1, the heat content of form II is higher than that of form I. At this stage, we can only deduce from the liquid the value of the heat content of form III at its melting temperature.

2.3. X-ray diffraction

When using powder, analyses were performed using a Philips 1050 diffractometer and a 1729 Philips X-ray generator. A computer, which controls the program of measurement and analysis, completes this equipment. We used the programs “Gonio” and “Rayon” [7]. The anode used is Cu Kα ($\lambda = 1.54051$ Å).

Table 4
Coefficients of the function $C_p = f(T)$ for form I, II and liquid progesterone

	A_0	A_1	A_2
Form I	2.721528	−1.149855E−002	2.375431E−005
Form II	6.051572	−3.149199E−002	5.293451E−005
Liquid	−2.100634E+001	1.154067E−001	−1.441612E−004

Table 5
Comparison of X-ray diffraction patterns obtained for form I with the corresponding JCPDS files

This work		*h k l*	JCPDS 37-1690	
d spacing (Å)	I/I_0 (%)		*d* spacing (Å)	I/I_0 (%)
9.3706	4	1 1 0	9.29043	2
8.3231	31	0 1 1	8.26839	37
		1 0 1	8.00005	2
6.9479	62	1 1 1	6.90544	64
		2 0 0	6.28131	1
6.0826	22	1 2 0	6.05082	22
5.7711	22	0 2 1	5.73906	26
		2 0 1	5.36622	6
5.2387	100	1 2 1	5.22187	100
		0 0 2	5.17348	74
5.0178	5	2 1 1	4.99984	7
4.8728	17	0 1 2	4.84283	27
4.6620	9	2 2 0	4.64197	9
4.5391	8	1 1 2	4.51567	8
		1 3 0	4.31584	1
4.2407	8	2 2 1	4.23445	8
4.1524	11	0 2 2	4.13700	13
4.1390	9	1 3 1	3.98670	17
3.9447	20	1 2 2	3.93101	23
		3 0 1	3.88024	3
		2 1 2	3.83404	3
3.7215	5	2 3 0	3.71106	3
		2 3 1	3.49320	6
3.4634	11	2 2 2	3.45326	11
		0 3 2	3.43754	9
		3 2 1	3.38115	9
3.3494	17	0 1 3	3.34378	22
		1 3 2	3.31449	12
3.2522	3	0 4 1	3.27153	3
		1 1 3	3.23200	3
3.1728	4	3 1 2	3.16678	3
		4 0 0	3.14058	1
3.0973	3	0 2 3	3.08324	2
3.0183	5	2 3 2	3.01404	4
		1 2 3	2.99429	7
		3 3 1	2.96517	1
		2 1 3	2.95177	1
		4 1 1	2.93662	1
2.9172	4	2 4 1	2.90128	4
		0 4 2	2.87039	1
2.8030	6	1 4 2	2.79694	6
2.7725	6	2 2 3	2.76664	5
2.7633	6	4 2 1	2.75504	7
2.6977	5	1 5 0	2.69380	5
		3 3 2	2.65657	1
		4 1 2	2.63384	1
2.6136	3	3 1 3	2.61004	3
		4 3 0	2.59394	1
2.5314	2	2 5 0	2.52604	1
		4 3 1	2.51509	1
		2 5 1	2.453499	1
		5 0 1	2.43984	1
		0 2 4	2.42081	2
		5 1 1	2.40334	1
2.4000	3	1 4 3	2.39102	4
		3 4 2	2.36678	1
		5 2 0	2.36081	1
2.3206	4	4 3 2	2.31754	4
		3 3 3	2.30273	2
		4 1 3	2.28924	1
2.2684	4	4 4 1	2.26603	4

Table 6
Comparison of X-ray diffraction patterns obtained for form II with the corresponding JCPDS files

This work		*h k l*	JCPDS 37-1691	
d spacing (Å)	I/I_0 (%)		*d* spacing (Å)	I/I_0 (%)
		0 0 2	11.2484	1
8.2457	5	0 1 2	8.39354	9
6.3747	26	0 1 3	6.44507	59
5.9405	100	1 0 1	6.02626	100
		0 0 4	5.60910	8
5.4102	86	1 0 2	5.46479	96
5.1010	23	0 1 4	5.13188	37
4.9787	41	1 1 2	5.01104	61
4.7612	24	1 0 3	4.80126	38
		1 1 3	4.48406	36
4.4556	21	1 2 0	4.43967	6
		1 2 1	4.35351	1
4.1467	16	0 2 4	4.18709	22
		1 2 2	4.12561	7
3.9534	5	1 1 4	3.96912	5
		0 3 2	3.93445	2
3.7935	7	1 2 3	3.81781	11
3.639	4	0 3 3	3.65995	5
		0 1 6	3.59304	1
		1 1 5	3.50672	6
3.4647	13	1 3 0	3.48513	10
		1 3 1	3.44276	7
		1 3 2	3.32907	1
3.1996	4	0 2 6	3.21601	3
3.1432	9	1 3 3	3.15800	12
3.1057	11	1 1 6	3.11483	5
3.0763	12	2 0 1	3.09580	10
		0 3 5	3.06873	2
3.0005	19	2 0 2	3.01205	28
		1 3 4	2.96133	2
2.9228	7	2 1 2	2.92911	8
		2 0 3	2.88484	1

Table 6 (*Continued*)

This work		$h\ k\ l$	JCPDS 37-1691	
d spacing (Å)	I/I_0 (%)		d spacing (Å)	I/I_0 (%)
2.8500	4	1 2 6	2.86144	3
		2 1 3	2.81235	3
		2 2 0	2.79864	4
2.7809	6	1 4 1	2.78676	8
2.7542	4	1 3 5	2.75504	2
2.7485	4	0 4 4	2.74354	1
		1 4 2	2.72729	3
		2 2 2	2.71763	3
2.6405	5	2 1 4	2.67041	4
2.6255	5	1 4 3	2.63234	6
2.6144	5	2 2 3	2.62337	5
		1 2 7	2.60270	3
		0 4 5	2.57948	3
		0 2 8	2.56519	2
2.5523	3	1 3 6	2.55247	4
2.5000	4	2 1 5	2.51509	3
		2 3 1	2.49214	3
		0 5 2	2.45788	1
		2 3 2	2.44753	1
		0 4 6	2.41080	3
2.3871	4	0 5 3	2.38491	6
2.3593	5	2 1 6	2.35842	8

Results are presented in Table 5 for form I and in Table 6 for form II and compared with JCPDS files (37-1690) and (37-1691).

These two tables show that there is no doubt possible about the characterisation of form I and form II. The two forms crystallise in an orthorhombic system $P2_12_12_1$ with the following parameters (Å).

Form I: $a = 12.559$, $b = 13.798$, $c = 10.340$, $V = 1791.81\,\text{Å}^3$.

Form II: $a = 6.252$, $b = 12.592$, $c = 22.488$, $V = 1770.37\,\text{Å}^3$.

2.4. Interpretation of the results

As these experiments prove that at least three forms exist, the unary phase diagram of progesterone should present a monotropic case, but if after the sequence melting/cooling/re-heating, the second melting shows that the metastable phase crystallised, which is not normal; it is necessary to search the reason of this apparently strange behaviour.

3. Theory of nucleation

As at least two reactions are possible: liquid → solid (I) and liquid → solid (II), it means that a competition exists between them. The problem is relevant of the kinetic, and an approach of the estimation of the free energy of activation is necessary. The theory of nucleation may answer this question. It seems necessary to redraw the basis of this theory.

The free energy of nucleation is given by the following formula:

$$\Delta_{\mathrm{f}}G = \tfrac{4}{3}\pi r^3(G_{\mathrm{v}}^{\mathrm{s}} - G_{\mathrm{v}}^{\mathrm{l}}) + 4\pi r^2\gamma - \Delta_{\mathrm{d}}G \qquad (3)$$

$\Delta_{\mathrm{f}}G$ is the free enthalpy change when a small volume of solid appears in the liquid. The first term of the second part, relative to the volume is negative if $T < T_{\mathrm{fus}}$. We suppose that the solid is a sphere of radius r, $G_{\mathrm{v}}^{\mathrm{s}}$ and $G_{\mathrm{v}}^{\mathrm{l}}$ are the free energy of the solid and the liquid phase per unit of volume. We are able to evaluate the difference of free energy per mole. An approximation is possible if we consider that the difference between the volumes of the liquid and the solid phases is negligible. The second term relative to the surface is positive, γ is the interfacial energy per unit of surface. The third term is necessary when the germination is the result of a solid–solid transition and is due to the elastic distortion. This formula is valuable only in the case of a homogeneous nucleation. In the case of a heterogeneous nucleation, it is necessary to take in account the angle θ of the tangency of the liquid with the solid surface. The formula is multiplied by $S(\theta)$ with

$$S(\theta) = \tfrac{1}{4}(2 + \cos\theta)(1 - \cos\theta)^2 \qquad (4)$$

In all cases, the variation of free energy for a heterogeneous nucleation is always lower than in a homogeneous case.

The maximum for the free energy of formation is given for $r = r^*$. This value is deduced from the derivation of Eq. (3):

$$r^* = -\frac{2\gamma}{G_{\mathrm{v}}^{\mathrm{s}} - G_{\mathrm{v}}^{\mathrm{l}}}$$

For this value of r, ΔG^* is the free energy of activation of the reaction liquid → solid:

$$\Delta G^* = \frac{16\pi\gamma^3}{3(G_{\mathrm{v}}^{\mathrm{s}} - G_{\mathrm{v}}^{\mathrm{l}})^2} \qquad (5)$$

The relation between $G^{\mathrm{s,l}}$ and $G_{\mathrm{V}}^{\mathrm{s,l}}$ is

$$G^{\mathrm{s,l}} = G_{\mathrm{V}}^{\mathrm{s,l}} \times V^{\mathrm{s,l}} \tag{6}$$

in which $G^{\mathrm{s,l}}$ is the molar energy of respectively the solid, and liquid and $V^{\mathrm{s,l}}$ is the molar volume of the considered phase. At the temperature of fusion of the solid phase, we have

$$G^{\mathrm{s}} - G^{\mathrm{l}} = \Delta_{\mathrm{fus}}H\left(\frac{T}{T_{\mathrm{fus}}} - 1\right) - \int_{T_{\mathrm{fus}}}^{T} (C_p^{\mathrm{l}} - C_p^{\mathrm{s}})\,\mathrm{d}T + T\int_{T_{\mathrm{fus}}}^{T} \left(\frac{C_p^{\mathrm{l}} - C_p^{\mathrm{s}}}{T}\right)\mathrm{d}T \tag{7}$$

with units J/mol or J/g according to the unit of $\Delta_{\mathrm{fus}}H$.

A widely used approximation is made that both enthalpy and entropy of melting are independent of temperature. If we assume that $\Delta_{\mathrm{fus}}H$ is temperature independent, then Eq. (7) reduces to

$$G^{\mathrm{s}} - G^{\mathrm{l}} = \Delta_{\mathrm{fus}}H\left(\frac{T}{T_{\mathrm{fus}}} - 1\right) \tag{8}$$

The volumes of the crystallographic cells are 1791.81 Å^3 for form I and 1770.37 Å^3 for form II. The difference between both volumes is only 1% and the molar volume of the liquid as well as the coefficients of dilatometry are unknown. Assuming that the molar volume of the liquid in the studied temperature range is identical to the molar volumes of form I and II ($V^{I} = V^{II} = V^{l} = V$), the free energy of activation can be simplified to

$$\Delta G^{*} = \frac{16\pi\gamma^{3}V^{2}}{3(G^{\mathrm{s}} - G^{\mathrm{l}})^{2}} \tag{9}$$

Thus, the free energy of activation is written as

$$\Delta G^{*} = \frac{\kappa}{(G^{\mathrm{s}} - G^{\mathrm{l}})^{2}} \tag{10}$$

It is now possible to compare the quantity $\mathrm{d}G^{*} = \Delta G^{*}/\kappa$ for the two reactions:

(I) L → form I: $\mathrm{d}G_{\mathrm{I}}^{*}$;
(II) L → form II: $\mathrm{d}G_{\mathrm{II}}^{*}$.

We give in Fig. 2 the variation of the difference $\mathrm{d}G_{\mathrm{I}}^{*} - \mathrm{d}G_{\mathrm{II}}^{*}$ versus temperature according to Eq. (7) (full line) and Eq. (8) (dashed line). When $G^{\mathrm{s}} - G^{\mathrm{l}}$ is calculated after Eq. (7), $\mathrm{d}G_{\mathrm{I}}^{*} - \mathrm{d}G_{\mathrm{II}}^{*}$ is first negative and changes sign for $T \approx 328$ K (55 °C). Moreover, the calculated difference appears very small in this range of temperature. That means, when cooling, competition between crystallisation of form I and II occurs. If the cooling rate is low, form I crystallises first. But since during this process the temperature of the furnace is still decreasing, after some time crystallisation of form II can occur. This may explain why we got the two forms. On the contrary, if the cooling rate is high, the system directly reaches the range of crystallisation of form II and the system is almost constituted of the metastable form.

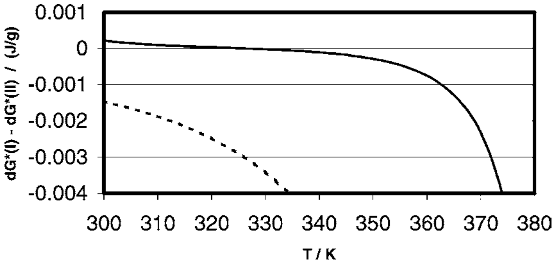

Fig. 2. The variation of the difference $\mathrm{d}G_{\mathrm{I}}^{*} - \mathrm{d}G_{\mathrm{II}}^{*}$ vs. temperature according to Eq. (7) (full line) and Eq. (8) (dashed line).

If we consider the same calculation according to Eq. (8), $\mathrm{d}G_{\mathrm{I}}^{*} - \mathrm{d}G_{\mathrm{II}}^{*}$ is always negative and the difference is larger than in the previous calculation. It does not allow to explain the presence of form II. Coming back to Eq. (7), that means that the heat capacity of the liquid, form I and form II cannot be considered as identical and the assumption, generally made in the homogeneous germination theory, is here no more valid.

Some simplifications have been introduced in the calculation, especially the variation of volume versus temperature, which has been neglected. What is more, when the fusion is performed in a DSC, with a pan of small volume, the influence of the surface of the pan is more important than when the fusion is realised in a great cell. In this case, the nucleation must be considered as partially heterogeneous. In these conditions, it is difficult to observe a perfect reproduction of the phenomenon. The amount of each form may change from one experiment to another.

4. Conclusions

Temperature and enthalpy of melting were determined for the three forms I, II and III from DSC measurements. A classical treatment of theory of germination does not allow to explain the thermal behaviour of progesterone. The presence of metastable form at room temperature could be explained only after experimental heat capacity determination of the liquid and the two solid forms I and II. The comparison between the temperature and enthalpy of melting of the three forms clearly shows that form I is stable at atmospheric pressure while form II and III are metastable. The existence of metastable form of progesterone 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. Considering only forms I and II, the obtained results suggest that the pressure–temperature diagram for these two forms is a monotropic one. A calorimetric investigation under pressure is worked on in order to confirm this result and to reach the thermo-mechanical coefficients.

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