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IDENTIFICATION OF AN ENANTIOTROPIC SYSTEM WITH HINDERED MULTIPHASE TRANSITIONS
Reexamination of polymorphism in carbamazepine

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A determination of the enthalpy increments for single phases of polymorphs through exact calorimetric measurements of respective heat capacities in stable and metastable regions, determination of the enthalpy increments for the liquid phase through dynamic measurements in the glassy state and separate measurements of the heat of fusion of polymorphs created precise data base which permitted to use the heat-of-fusion rule in a rigorous way and to verify univocally that the polymorphs III and I in carbamazepine form an enantiotropic system. The approach elaborated in the present study can be used in identification of all difficult polymorphic systems, where the solid-solid transitions have a complicated nature, are kinetically driven or hindered by other constraints.

Keywords: *carbamazepine, heat-of-fusion rule, hindered transitions, metastable phases, polymorphism*

Introduction

Polymorphism is an important problem in pharmaceutical industry. Once multiple phases in a solid substance have been identified, the principal task becomes the determination of the manner by which the phases are related. Enantiotropically related phases must have an equilibrium transition point on the temperature scale or an equilibrium transition line on the (p,T) diagram. On passing the transition point or the transition line by heating, the enantiotropic transition is always endothermic. In an ideal enantiotropic system each phase has its own (p,T) region of thermodynamic stability and the transition between them is reversible. When the phases are monotropically related, there is no equilibrium transition point, nor an equilibrium line, at least in the region of thermodynamic stability. The only transition which is possible here is that from the less stable phase to the stable phase. Such a transition is always exothermic and is not reversible.

The identification of the relationship between polymorphs is not always simple. It can happen that even in an enantiotropic system the solid-solid transitions have a complicated nature, are kinetically driven or hindered by other constraints. In such a case the shape of DSC traces can depend on the heating rate and/or on other variables of the experiment and thus the identification of the relationship between forms becomes difficult or even impossible. On the other hand in the literature there are a number of criteria which can help to distinguish or determine the polymorphism relationship [1]. One of them is the heat-of-fusion rule, which states that if the higher melting form has the lower heat of fusion, the two forms are enantiotropically related, otherwise they are monotropic [1]. Behme and Brook [2] have applied this rule to investigation of the polymorphic relation between the low melting form III and the higher melting form I in carbamazepine. However, the authors have observed a complicated dependence of the solid-solid transition on the heating rate. For this reason, they have derived the heat of fusion of form III from the sum of thermal effects associated with the solid-solid transition and the fusion of form I. In this previous work, the authors have assumed that the variations of the heat capacities with temperature of the two phases are sufficiently similar to be neglected, so the graphs of enthalpy *vs*. temperature are parallel. Besides, their values for the enthalpy of III/I transition and for the enthalpy of fusion of form I are significantly higher than the respective values from previous studies of Kala *et al.* [3] and of Krahn and Mielk [4].

The aim of the present study is to elaborate a rigorous application of the heat-of-fusion rule to identification of an enantiotropic polymorphic system in the case of hindered multiphase transitions and to verify the polymorphic relation between carbamazepine forms I and III. A scheme of the proposed approach is presented graphically in Fig. 1. The solid line presents an ideal equilibrium transformation from a low melting form A at the reference temperature T_{ref} up to the liquid phase. The dashed line presents a possible non-equilibrium transformation of the low melting form A directly to the

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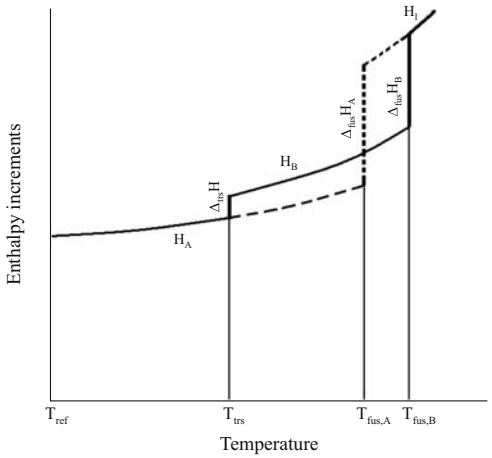

Fig. 1 A model presentation of phase transitions in an enantiotropic polymorphic system: full lines: equilibrium transitions and stable phases; dashed line: non-equilibrium transitions and metastable phases

liquid phase. This non-equilibrium transformation can be observed when working in non-equilibrium conditions, i.e. with high heating rates. In the present study an attempt will be made to measure separately the two enthalpies of fusion, as well as the enthalpy increments for the homogenous phases H_A and H_B and for the liquid phase H_l as functions of temperature. This will provide the means to apply rigorously the heat-of-fusion rule and to derive the proper value of the enthalpy of the solid-solid transition $\Delta_{trs}H$ that is of importance in accurate determination of the type of polymorphism in such systems.

Experimental

Materials

Carbamazepine anhydrate (form III) was obtained from Ciba–Geigy Laboratories (Huningue, France). Polymorph I was obtained by heating form III between the transition temperature and its melting point, as described in the literature [2].

Methods

Powder X-ray diffraction

A Philips 1050 diffractometer and a Philips 1729 X-ray generator with a CuK_{α_1} anode (λ=1.54051 Å) were used. The apparatus was calibrated with silicium. The data were processed with the programs 'Gonio' and 'Rayon' [5].

Thermogravivetric analysis

The analyser was a Perkin-Elmer TGA 7. The samples of 5 to 10 mg were heated at a rate of 10 K min^{-1} when purging with nitrogen at 20 mL min^{-1}.

Calorimetry

Two DSC apparatus were used: a Q1000 from TA Instruments and a DSC 7 from PerkinElmer. The temperature scales of the instruments have been calibrated at a heating rate of 20 K min^{-1} with the melting point of indium (429.784 K) [6] and the melting point of tin (505.118 K) [6]. A correction was made for the other heating rates (varying from 5 to 100 K min^{-1}) considering the difference between the theoretical melting point of indium and its measured melting point at a given rate. The energy scales have been calibrated with the heat of fusion of indium (28.45 J g^{-1}) [7]. Non-hermetic aluminium based alloy pans were used under dry nitrogen flow (20 mL min^{-1}) when working with the DSC 7. The obtained results were confirmed with the Q1000 apparatus. Hermetic (to avoid possible pollution) aluminium based alloy pans were used under dry nitrogen flow (20 mL min^{-1}). A C80 Setaram calorimeter and a Setaram C_p program 'Setsoft' were used for the heat capacity measurements. The samples of investigated substances (near one gram) were introduced in a Pyrex glass cell located in a stainless steel vessel. The apparatus was calibrated (temperature and energy scales) with the melting points and enthalpies of fusion of indium and tin with parameters as mentioned above for the DSC calibration.

Thermomicroscopy

The equipment was composed of a hot stage from Mettler (FP5 and FP52) and an Olympus BH-2 microscope.

Results and discussion

Powder X-ray diffraction

Diffractometric analysis were used to confirm the form of the considered samples. X-ray diffraction pattern obtained for the commercial sample was characteristic of the form III of carbamazepine [8]. X-ray diffraction pattern of the polymorph obtained by heating the commercial sample above the transition temperature was characteristic of the form I of carbamazepine [8].

Thermogravimetric analysis

TG measurements revealed no mass loss in the temperature range 300 to 430 K, meaning that both samples were anhydrate forms.

DSC measurements

Results obtained are listed in Table 1. The full solid-state conversion from form III into form I was observed only at rates of 5, 10 and 20 K min^{-1} with an endotherm between 438 and 446 K; it was noticed that the onset temperature increased with the heating rate, but a slight decrease of the heat of transition with the heating rate was observed. The value T_{trs}=438.0±0.1 K and $\Delta_{trs}H_{III/I}$=12.2±0.7 J g^{-1} obtained at the low heating rate of 5 K min^{-1} were taken as the most probable temperature of transition and enthalpy of transition from form III to form I. This transition was followed by an endotherm associated with the fusion of form I at $T_{fus,I}$=463.7±0.2 K and $\Delta_{fus}H_I$= 111.3±2.7 J g^{-1} obtained at a heating rate of 5 K min^{-1}. At 40 and 60 K min^{-1} DSC traces showed only melting of form III overlapping with partial crystallization into form I followed by partial melting of form I. At higher heating rates, 80 and 100 K min^{-1}, only a single endotherm of fusion of metastable form III was observed with a suggestion that there was insufficient time for partial interphase events. The mean value of the onset temperature is $T_{fus,III}$=452.4±0.6 K and of the enthalpy of fusion $\Delta_{fus}H_{III}$=115.0±3.3 J g^{-1} (average of 6 measurements).

Thermomicroscopy was used to interpret the events observed by DSC.

Heat capacity and enthalpy increments for the single phase of form III

On the basis of measurements performed in a Setaram C80 calorimeter the following fitting equation was defined for the specific heat capacity (J K^{-1} g^{-1}) of form III valid over the temperature range from T_{ref}=298.15 K to $T_{fus,III}$= 452.4 K (melting from the metastable state)

$$C_{p,III} = -2.6749 + 1.09 \cdot 10^{-2} T + 6 \cdot 10^{-6} T^2 \quad (1)$$

By integrating Eq. (1) and setting the enthalpy of the single phase of form III at the reference temperature T_{ref}=298.15 K equal zero the following equation was obtained for the specific enthalpy increment (J g^{-1}) as a function of temperature

$$\Delta^{T}_{298.15}H_{III} = 260.05 - 2.6749T + 5.45 \cdot 10^{-3} T^2 + 2 \cdot 10^{-6} T^3 \quad (2)$$

valid over the temperature range from T_{ref}=298.15 K to $T_{fus,III}$= 452.4 K (melting from the metastable state).

Heat capacity and enthalpy increments for the single phase of form I

On the basis of measurements performed in a Setaram C80 calorimeter the following fitting equation was defined for the specific heat capacity (J K^{-1} g^{-1}) of form I valid over the temperature range from 360 K to $T_{fus,I}$= 463.7 K

$$C_{p,I} = -3.221 + 1.48 \cdot 10^{-2} T \quad (3)$$

By integrating Eq. (3) between T_{trs} and T and adding both the heat of transition $\Delta_{trs}H_{III/I}$ at the temperature of transition and the enthalpy increment defined from Eq. (2) for form III at the temperature of transition, the following equation was obtained for the enthalpy increment of form I valid over the temperature range from T_{trs}=438.0 K to $T_{fus,I}$=463.7 K, but which may be extrapolated with a reasonable precision down to 298.15 K

$$\Delta^{463.65}_{298.15}H_{I} = 305.4 - 3.221T + 7.4 \cdot 10^{-3} T^2 \quad (4)$$

Heat capacity and enthalpy increments for the liquid phase

Unfortunately, the heat capacity of the liquid phase could not be measured directly in a calorimeter, because of an evident decomposition of carbamazepine. For this reason an effort has been taken to determine the enthalpy function for the glassy state of carbamazepine on the basis of both calorimetric measurements of the heat of crystallization from the glassy state and the enthalpy function for form I from

Table 1 Results of DSC study for two samples of carbamazepine at different heating rates

Heating rate/ K min^{-1}	III/I transition		Fusion form III		Fusion form I	
	$T_{trs,III/I}$/K	$\Delta_{trs}H_{III/I}$/J g^{-1}	$T_{fus,III}$/K	$\Delta_{fus}H_{III}$/J g^{-1}	$T_{fus,I}$/K	$\Delta_{fus}H_I$/J g^{-1}
5	438.0±0.1	12.2±0.7			463.7±0.2	111.3±2.7
10	441.5±0.1	11.5±0.3			463.6±0.1	108.9±2.4
20	446.3±0.2	11.0±0.4			464.0±0.2	102.5±2.5
80			452.0±0.5	114.5±3.9		
100			452.8±0.2	115.4±3.3		

Eq. (4). The measurements were performed with a Perkin-Elmer DSC7. A given sample of carbamazepine was melted at a heating rate of 20 K min^{-1}, rapidly cooled at a rate of 200 K min^{-1} (maximum cooling rate authorised by the apparatus) to obtain a glassy state and then heated at different rates to re-crystallize. It was verified by diffractometry that the re-crystallized phase was always form I, which is metastable at $T<T_{trs}$. Both the temperature and the enthalpy of crystallization depended on the heating rate. For each temperature of crystallization a respective enthalpy increment was calculated from Eq. (4). By summing at each temperature the enthalpy of crystallization and the enthalpy increment of form I, the enthalpy of the glassy state could be determined. A set of such data obtained with various heating rates is listed in Table 2. Because the recrystallisation occurred above the glass-liquid transition temperature, data listed in Table 2 concern the metastable liquid and can be used for fitting the enthalpy function for the liquid phase.

Other two data points, very suitable for such fitting, can be obtained: 1) at $T_{fus,I}$=463.7 K by summing the enthalpy increment calculated with Eq. (4) for that temperature ($\Delta^{463.65}_{298.15}H_I$=402.8 J g^{-1}) and the enthalpy of fusion $\Delta_{fus}H_I$=111.3 J g^{-1}, what gives $\Delta^{463.65}_{298.15}H_I$=514.1 J g^{-1}; 2) at $T_{fus,III}$=452.4 K, the same can be applied for form III giving $\Delta^{463.65}_{298.15}H_I$=465.4 J g^{-1}. Adding these two data points to the data listed in Table 2 and fitting, the following equation was derived for the specific enthalpy increments for the liquid phase of carbamazepine valid over the temperature range from 367.7 to 463.7 K, but which reasonably well extrapolates to 298.15 K at lower temperatures and to 498 K at higher temperatures.

$$\Delta^{T}_{298.15}H_I = 56.34 - 2.1067T + 0.0067T^2 \quad (5)$$

Table 2 Data for the determination of the enthalpy increments for the liquid phase of carbamazepine $\Delta^{T}_{298.15}H_I = \Delta_{cryst}H_I + \Delta^{T}_{298.15}H_I$

Cooling rate/K min^{-1}	$T_{cryst,I}$/ K	$\Delta_{cryst}H_I$/ J g^{-1}	$\Delta^{T}_{298.15}H_I$/ J g^{-1}	$\Delta T^{T}_{298.15}H_I$/ J g^{-1}
1	367.7	62.3	121.6	183.9
2	371.7	62.3	130.6	192.9
3	372.0	65.0	131.3	196.3
4	374.3	65.1	136.5	201.6
5	378.3	67.6	145.9	213.6
10	381.0	71.9	153.5	225.4
20	387.0	68.2	167.2	235.4
40	395.7	75.4	189.5	264.9
60	402.8	79.8	208.5	288.3
80	404.0	86.4	211.9	298.3

By differentiating Eq. (5) with respect to temperature the following equation was obtained for the specific heat capacity function of the liquid phase of carbamazepine

$$C_{p,l} = -2.107 + 1.34\cdot10^{-2}T \quad (6)$$

A rigorous treatment of the heat-of-fusion rule

Based on a study of Burger and Ramberger [1], the following equation can be written for an exact definition of the heat-of-fusion rule which can be used for verification of the polymorphic relation between form III and form I in carbamazepine or for identification of such a relation in any similar polymorphic system

$$\Delta_{trs}H(T_{trs}) = \Delta_{fus}H_{III} - \Delta_{fus}H_I + \Delta^{T_{fus,III}}_{T_{trs}}H_{III} - \Delta^{T_{fus,I}}_{T_{trs}}H_I + \Delta^{T_{fus,I}}_{T_{fus,III}}H_I \quad (7)$$

Taking the enthalpies of fusion presented above and calculating the enthalpy increments of the particular single phases with Eqs (2), (4) and (5) respectively one gets a value which is equal to the experimental result obtained at a low heating rate.

$$\Delta_{trs}H(T_{trs}) = 115.0 - 111.3 + 48.5 - 88.7 + 48.7 = 12.2 \text{ J g}^{-1} \quad (8)$$

A graphic presentation of the results obtained in the present study for stable and unstable regions is given in Fig. 2.

The results obtained in the present study create a consistent system of data which explicitly proves that the polymorphic relation between form III and form I in carbamazepine is univocally of enantiotropic nature. The exact data provided can be useful in further scientific and industrial procedures, especially in analysis and treatment of various metastable situations. A comparison of selected data points from the

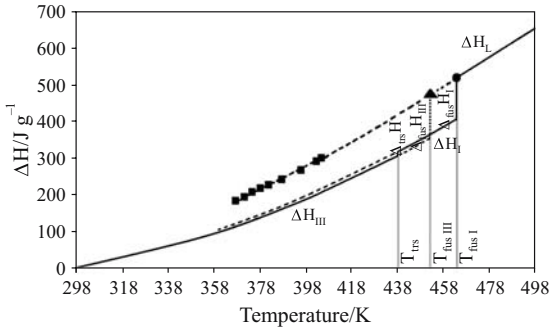

Fig. 2 Enthalpy diagram for carbamazepine as results of the present study; full line: equilibrium transitions and stable phases; dashed line: non-equilibrium transitions and metastable phases; ■ – from calorimetric data on re-crystallization from glass to metastable form I and enthalpy of form I (Table 2); ● – from enthalpy of form I and its enthalpy of fusion (see the text); ▲ – from enthalpy of form III and its enthalpy of fusion (see the text)

Table 3 A comparison of data from this study with available data from the literature for solid-solid and solid-liquid transitions in carbamazepine

Reference	III/I transition		Fusion form III		Fusion form I	
	$T_{trs,III/I}$/K	$\Delta_{trs}H$/J g^{-1}	$T_{fus,III}$/K	$\Delta_{fus}H_{III}$/J g^{-1}	$T_{fus,I}$/K	$\Delta_{fus}H_{I}$/J g^{-1}
3	449	11.0			463.7	102.4
4	423–433	8.0	453		462.1±1.4	103.6
2	423–443	14.0	447–449	125.7	464.2	111.7
Present study	438.0±01	12.2±0.7	452.4±0.4	115.0±3.6	463.7±0.2	111.3±1.6

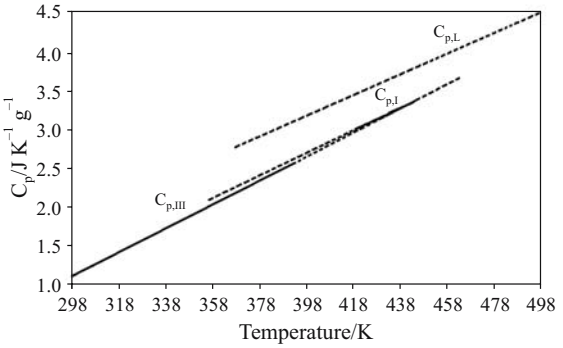

Fig. 3 Specific heat capacity diagram for carbamazepine as results of the present study

present study with similar data available in the literature is given in Table 3. One can see that the present enthalpic data for the solid-solid transition and for the fusion of form III are slightly higher than the respective data of Kala *et al.* [3] and of Krahn and Mielk [4] and significantly lower than the data of Behme and Brooke [2]. The latter data have been obtained under two assumptions: 1) that the integration of thermal events from the solid-solid transition to the fusion of form I provides the heat of fusion of the form III and 2) that the variations of the heat capacities with temperature of the two phases are similar, so the graphs of enthalpy of the two phases *vs*. temperature are parallel. The use of a calorimeter with sample mass of near 1 g in the present study permitted the collection of the heat capacity data (see also Fig. 3) much more precisely than by the method of O'Neill [9] realized in a DSC (Behme and Brooke) [2]. It results from the present study that the C_p difference between form I and form III is not constant. A slight decrease of this difference with temperature over the temperature range under investigation is described by the following equation

$$C_{p,III} - C_{p,I} = 0.546 - 3.9 \cdot 10^{-3} T + 6 \cdot 10^{-6} T^2 \qquad (9)$$

This difference is not very important with respect to the large values of the enthalpies of fusion, but can be of importance with respect to the heat of transition (Eq. (7)).

Conclusions

A determination of the enthalpy increments for single phases of polymorphs through fitting of calorimetric measurements to obtain respective heat capacities, determination of the enthalpy increments for the liquid phase through dynamic measurements in the glassy state and separate measurements of the heat of fusion of polymorphs created precise data base which permitted to use the heat-of-fusion rule in a rigorous way and to verify univocally that the polymorphs III and I in carbamazepine form an enantiotropic system. The approach elaborated in the present study can be used in identification of difficult polymorphic systems, where the solid-solid transitions have a complicated nature, are kinetically driven or hindered by other constraints.

References

1 A. Burger and R. Ramberger, Mikrochim. Acta [Wien], II (1979) 259.
2 R. J. Behme and D. J. Brooke, Pharm. Sci., 80 (1991) 986.
3 H. Kala, U. Haack, P. Pollandt and G. Brezesinski, Acta Pharm. Technol., 32 (1986) 72.
4 F. U. Krahn and J. B. Mielk, Pharm. Acta Helv., 62 (1987) 247.
5 B. Fraisse, PhD Thesis, Université des Sciences et Techniques du Languedoc, Montpellier, France (1995).
6 Bulletin of Alloy Phase Diagrams, 7 (6) (1986) 602.
7 R. Hulgren, P. D. Desai, D. T. Hawkins, M. Gleiser, K. K. Kelley and D. D. Wagman, Selected Values of the Thermodynamic Properties of the Elements, American Society for Metals, Metals Park, OH 44073 (1973).
8 C. Rustichelli, G. Gamberini, V. Ferioli, M. C. Gamberini, R. Ficarra and S. J. Tommasini, Pharm. Biomed. Anal., 23 (2000) 41.
9 M. J. O'Neill, J. Anal. Chem., 38 (1966) 1331.

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