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Transitiometric analysis of solid II/solid I transition in anhydrous theophylline

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Abstract

For the first time, with the use of a high sensitivity, low heating rate, scanning transitiometry, it was possible to distinguish and characterise the polymorphic equilibrium transition between forms II and I in anhydrous theophylline. In this manner it was univocally proved, that forms II and I in theophylline are enantiotropically related. The temperature and enthalpy for that transition are as follows: T_{trs}(II/I) = 536.8 ± 2.2 K; $\Delta_{trs}H$(II/I) = 1.99 ± 0.09 kJ/mol. Making use of advantages of very slow heating rate and of a high energetic sensitivity of the transitiometer it was possible to observe in detail the polymorphic transition followed by melting of high temperature form I and to stop the solid I–liquid transition at a desired point of equilibrium. Such a solid I–liquid equilibrium could be stabilised and then displaced back to the crystallisation of form I with an adequate use of a precise temperature programming. In such a way a pure single phase of form I of theophylline was prepared. This fact was confirmed by X-ray powder diffraction patterns and calorimetric traces of fusion of the crystallised product. The temperature and enthalpy of the form I–liquid transition are as follows: T_{fus}(I) = 546.5 ± 0.2 K and $\Delta_{fus}H$(I) = 29.37 ± 0.29 kJ/mol.

Keywords: Polymorphism; Theophylline; Transitiometry

1. Introduction

Theophylline ($C_7H_8N_4O_2$: 3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione) is widely used in a variety of antiasthmatic drugs, thus its polymorphic properties should be entirely known. In reality there is still an important lack of knowledge with this respect. Suzuki et al. (1989) prepared independently and separately two polymorphic forms of theophylline and made their careful thermochemical analysis. Fig. 1 presents their DSC traces obtained at a heating rate of 16.7 mK/s (1 K/min) in closed vessels. On the basis of the DSC results presented in Fig. 1 the following data have been determined: for form I, T_{fus}(I) = 546.6 ± 1.0 K and $\Delta_{fus}H$(I) = 26.4 ± 0.3 kJ/mol; for form II, T_{fus}(II) = 542.3 ± 0.4 K and $\Delta_{fus}H$(II) = 28.2 ± 1.1 kJ/mol. From the above data and taking into account the rules governing the relations between the polymorphic phases (Burger and Ramberger, 1979), one can find that the polymorphs I and II in the anhydrous theophylline form an enantiotropic system. The heat of fusion rule states that, if the higher melting form has the lower heat of fusion, the two forms are enantiotropically related, otherwise they are monotropic (Burger and Ramberger, 1979). Thus, taking into consideration this rule and the above data, the following enthalpy for the polymorphic transition in theophylline should be observed $\Delta_{trs}H$(II/I) ≅ 1.8 ± 1.4 kJ/mol (difference between the fusion enthalpies of the two forms). However, when the polymorphic phases are enantiotropically related, there should be an equilibrium point determined by the transition temperature T_{trs}(II/I). But, as one can see from Fig. 1, such a transition was never observed, despite the efforts of the investigators. On the basis of the above data and taking into consideration the general thermodynamic rules for the polymorphism (Burger and Ramberger, 1979), Griesser et al. (1999) have estimated that the transition point should lie in the temperature range 468–504 K. Griesser et al. (1999) have also made measurements of the sublimation pressures of the two phases of theophylline and from the intersection of the two sublimation pressure curves suggested the transition point T_{trs}(II/I) = 505 K. The differences in both the sublimation pressures and their slopes versus temperature

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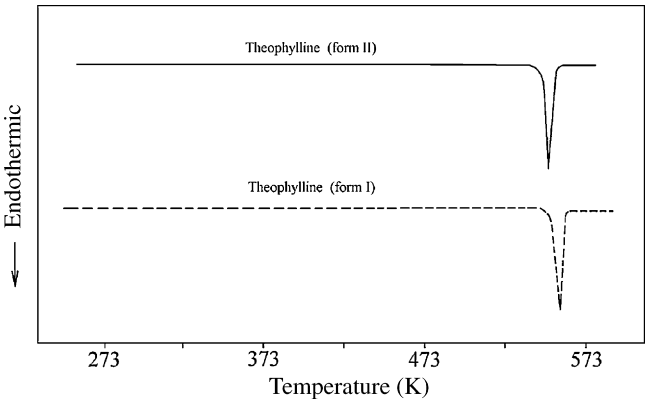

Fig. 1. DSC traces of two polymorphic forms of theophylline obtained at a temperature scanning rate of 16.7 mK/s (1 K/min)—after Suzuki et al. (1989).

are very small, thus the precision of such a determination of the transition point could not be high. Phadnis and Suryanarayanan (1997) have undertaken another study of that problem. By making DSC measurements at a higher heating rate of 0.17 K/s (10 K/min) under nitrogen purge, they also did not find any transition point by heating form II until it is melting. However, the authors made an observation that one of the phases in theophylline under investigation was not stable and suggested that the metastable new phase in theophylline forms a monotropic system with its form II, later confirmed by Suikho et al. (2001). From the above analysis it becomes clear that the transition between forms II and I in theophylline was never observed and investigated in a direct experiment and that the regions of thermodynamic stability of the two polymorphic modifications are not yet known, thus their estimated thermodynamic properties cannot be used as reliable data for the pharmaceutical practice.

When analysing carefully the above results one could conclude, that further investigations on the polymorphism in theophylline should rather focus on significantly lower heating rates, because it is very possible that form I of theophylline is thermodynamically stable only over a narrow temperature range. The low heating rate and the low enthalpy suggested above for the polymorphic transition would also require much higher energetic sensitivity than those available in known DSC instruments. Another observation would suggest to use closed vessels in order to investigate samples at constant mass and under near equilibrium conditions. All those requirements can be fulfilled by scanning transitiometry technique (Randzio, 1996). The aim of the present contribution is to analyse transitiometrically the polymorphism in anhydrous theophylline in order to specify irrevocably the type of the relation between polymorphic forms II and I and to identify the equilibrium transition point between them.

2. Materials and methods

2.1. Materials

Form II of theophylline, the starting material for all transitiometric experiments performed in this study, was prepared according to the following procedure. A few grams of theophylline was taken from a storage bottle and placed in an exsiccator together with a flat open vessel filled with distilled water. The whole assembly was kept at room temperature during a few days in order to prepare a hydrate. Then a sample of the hydrate placed in a glass tube was heated during 14 h at 383 K under vacuum of near 0.02 Pa. The product obtained was pure form II of theophylline confirmed by X-ray powder diffractometry, as it is presented in Fig. 2a, where the continuous line corresponds to the present experimental result and the vertical tick marks show the literature peak positions predicted for the orthorhombic unit cell: $a = 0.850$ nm; $b = 2.464$ nm; $c = 0.383$ nm (JCPDS 27, 1977; Ebisuzaki et al., 1997). *p*-Bromochlorobenzene and *p*-di-bromobenzene were from FLUKA (purity >99%), further purified by CHEMIPAN through crystallisations from various solvents (ethanol, methanol, *n*-hexane). The final purity determined by chromatography was 99.99% for both substances, and determined by the cryometric Skau method, 99.98% for *p*-bromochloro-benzene and 99.94% for *p*-di-bromobenzene. Benzoic acid (assay 100.3%) was from Sigma; indium (purity 99.999%) was from Aldrich; tin (purity 99.999%) and bismuth (purity 99.999%) were from Koch-Light, and were not further treated.

2.2. X-ray powder diffractometry

A Philips 1050 diffractometer and a Philips 1729 X-ray generator with a Cu $K\alpha_1$ anode ($\lambda = 0.154051$ nm) were used with the reflection method. The apparatus was calibrated with silicium provided by Philips. Powder was placed on a glass support in a cavity formed by a solution of HF. The surface of the powder was then smoothed out in order to be perfectly flat, and gently pressed using McCreery's procedure as described in X-ray diffraction procedures (Klug and Alexander, 1973).

2.3. Scanning transitiometry

A BGR TECH ST-VI scanning transitiometer was used. Detailed description of its construction and design can be found in the literature (Randzio, 1996; Randzio et al., 2003; Randzio and Orlowska, 2005), thus only a short remainder is given here, mainly with respect to the experimental vessels.

The calorimetric vessels are made from 0.8 cm internal diameter 316 SS tubing and are fixed on a mounting table attached to the mobile stand. Only the measuring vessel is connected to the PV line. The reference vessel acts only as a thermal reference, a stainless steel bar of appropriate dimensions is placed in it to balance the baseline of the differential calorimetric signal. The tubing of both measuring and reference vessels are connected to reducers, placed inside the calorimeter when it is in the lowered (measuring) position. The connections from the reducers to the manifold are made with thin stainless steel capillaries in order to reduce heat losses to the environment. The vessels are closed with a cone plug fixed in place by an internally threaded cover, which also acts as a heat exchanger between the calorimetric vessel tubing and the calorimetric detector. Two sleeves are also fixed on the calorimetric vessel tubing below the cover in order to help the control of the heat exchange

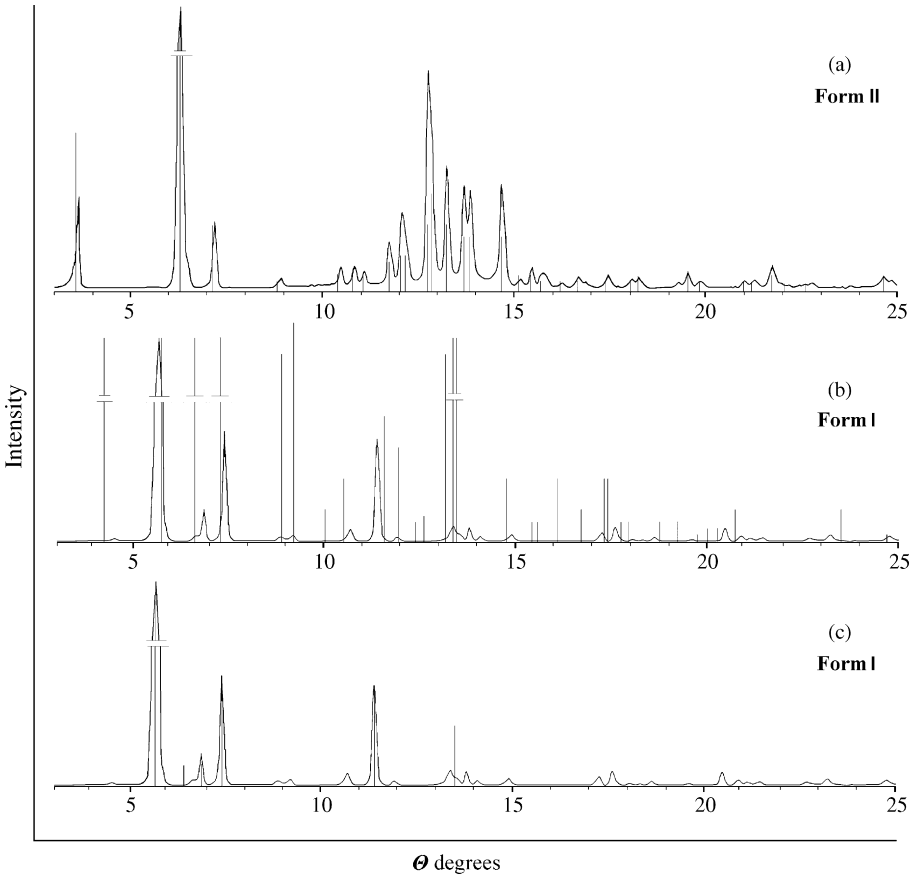

Fig. 2. X-ray powder diffraction patterns of form II of theophylline (a) prepared from a hydrate (see the text), the vertical tick marks show the literature peak positions predicted for the orthorhombic unit cell: $a = 0.850$ nm; $b = 2.464$ nm; $c = 0.383$ nm (JCPDS 27, 1977; Ebisuzaki et al., 1997) and of form I of theophylline prepared with procedures presented in Figs. 4 and 5 (see the text): (b) the vertical tick marks show the literature peak positions predicted for the monoclinic unit cell: $a = 1.328$ nm; $b = 1.544$ nm; $c = 0.449$ nm; $\beta = 98.53^\circ$ (JCPDS 24, 1946), (c) the vertical tick marks show the peak positions from the diffraction patterns of Suzuki et al. (1989).

between the calorimetric vessel tubing and both the calorimeter block and the shield. For further information on the functioning of the instrument see http://www.transitiometry.com. In the present study the temperature is scanned at constant volume, while the calorimetric signal (the heat flow) and variations of pressure as dependent variable are simultaneously recorded. All the experiments were performed at the Faculty of Pharmacy. A sample of near 0.5 g of powder form II of theophylline was placed in the transitiometric vessel, immediately after preparation. Then the vessel was rapidly closed and moved into the calorimetric detector. After about 2 h of thermal equilibration a temperature scanning started at a rate of 2.5 mK/s (0.15 K/min). In the first experiment the beginning of the temperature scanning was at 303 K. However, over the low temperature region no transition was observed, thus in the next experiments the temperature scanning started always at 500 K. Both temperature and energetic calibrations of the calorimetric detector were performed with the following substances: *p*-bromochlorobenzene, $T_{fus} = 337.73$ K, $\Delta_{fus}H_m = 18.760$ kJ/mol; *p*-di-bromobenzene, $T_{fus} = 360.45$ K, $\Delta_{fus}H_m = 20.530$ kJ/mol; benzoic acid, $T_{fus} = 395.55$ K, $\Delta_{fus}H_m = 18.062$ kJ/mol; indium, $T_{fus} = 429.75$ K, $\Delta_{fus}H_m = 3.28$ kJ/mol; tin, $T_{fus} = 505.05$ K, $\Delta_{fus}H_m = 7.194$ kJ/mol; bismuth, $T_{fus} = 544.55$ K, $\Delta_{fus}H_m = 11.296$ kJ/mol. The calibration experiments were done by enclosing a calibration substance in a 60 mm long thin glass tube placed in the centre of the calorimetric vessel. The precision of the temperature scale is ±0.2 K. The energetic calibration constant k_c of the calorimetric detector depends on temperature and is described by relation (1):

$$k_c\,(\mathrm{WV^{-1}}) = 4.762 \times 10^{-2} - 1.0893 \times 10^{4} T\,(\mathrm{K}) + 1.6688 \times 10^{-7} T^2\,(\mathrm{K^2}) \quad (1)$$

The mean deviation between Eq. (1) and the calibration data is 1.4%. The reproducible resolution of the calorimetric detector at the selected sensitivity used in the present study varies from 3.2×10^{-5} W at 450 K to 3.8×10^{-5} W at 550 K. The real temperature T_R is related to the actual temperature readings T_A by relation (2):

$$T_R\,(\mathrm{K}) = 9.52 + 0.97315 T_A\,(\mathrm{K}) \quad (2)$$

3. Results

Because until the present study the solid II–solid I transition in theophylline was never observed in a direct experiment, the

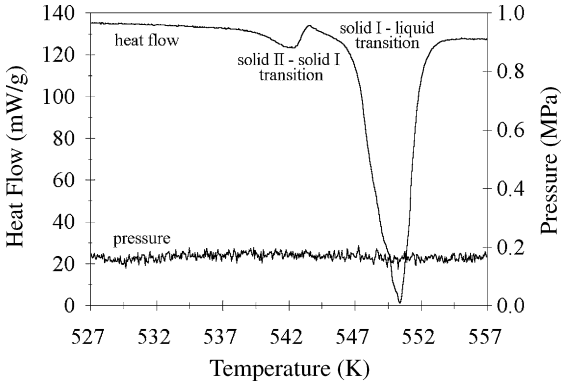

Fig. 3. Transitiometric traces of theophylline representing both the transformation of form II into form I and the melting of form I obtained by scanning temperature at a rate of 2.5 mK/s (0.15 K/min) in a closed vessel.

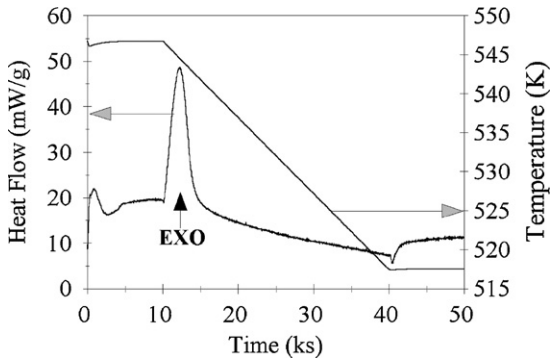

Fig. 5. A heat flow trace of re-crystallisation of form I of theophylline by cooling at a rate of −1 mK/s (0.06 K/min) from the solid-to-liquid ratio presented in Fig.4.

results are reported together with some details of the experimental procedures. The temperature of the main (bigger) transition presented in Fig. 3 is equal to 546.5 ± 0.2 K, thus according to Suzuki et al. (1989) this transition corresponds to the melting of form I. Because the starting material was form II, thus the smaller transition should correspond to the transition from solid forms II to I. To check whether these observations were correct, in the next experiments the temperature scanning was stopped in the course of the main transition and the solid–liquid equilibrium was established (Fig. 4). This was possible to realise, because in a transitiometric experiment the rate of temperature scanning is very low, the system can be stopped at any desired temperature and then isothermally equilibrated at that temperature. The intention of the situation presented in Fig. 4 was to stop the temperature scan at a given form I–liquid equilibrium ratio, established in the experimental vessel. Next, after the equilibration at the temperature, at which it was stopped (546.7 K), the system was cooled very slowly down to 517.5 K at a rate of 1 mK/s (0.06 K/min). As it can be seen in Fig. 5, first, at the beginning of cooling a re-crystallisation is observed (a strong exothermic effect) of that part of the sample (already form I), which melted before stopping the heating. Next, until the end of the cooling no transition was observed. It means that form I could not transform to form II during the time scale of the experiment. A similar kinetically hindered situation was previously observed in the polymorphic transition in caffeine, where the solid II–solid I transition could be observed only on heating (Defossemont et al., 2004), the transition from forms I to II being very slow (Lehto and Laine, 1998). After the cooling and thermal equilibration at 517.5 K the experimental vessel was removed from the calorimeter and cooled down to the room temperature. After opening the vessel a powder diffractometric analysis of the sample was performed. The continuous line in Fig. 2b shows the diffractometric traces obtained and the vertical tick marks show the literature peak positions predicted for the monoclinic unit cell: $a = 1.328$ nm; $b = 1.544$ nm; $c = 0.449$ nm; $\beta = 98.53°$ (JCPDS 24, 1946). Fig. 2c presents the same diffractometric traces, but compared this time with the vertical tick marks showing the peak positions from the diffraction patterns of Suzuki et al. (1989) for the form I of theophylline. The next experiment was performed exactly as the previous one, except that after cooling to 517.5 K and thermal equilibration at that temperature, the system was reheated to 575 K at a rate of 2.5 mK/s (0.15 K/min). The result obtained is shown in Fig. 6. This time there is only one transition at 546.5 ± 0.2 K, the equilibrium melting temperature of form I. Thus, the heat flow trace in Fig. 6 shows the melting of form I of theophylline. It can be concluded that both the diffraction patterns and the transitiometric analysis prove that the main transition in Fig. 3 is the melting of form I and thus the small transition in Fig. 3 is the polymorphic equilibrium transition

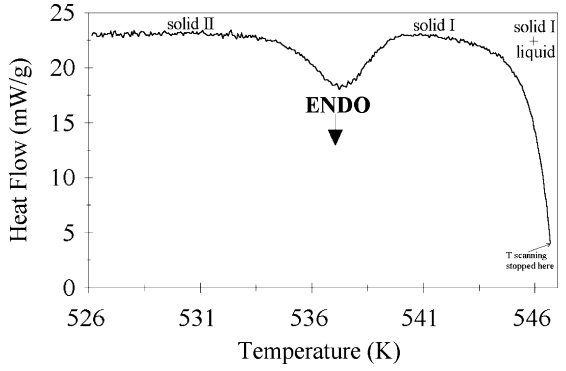

Fig. 4. A heat flow trace of the transition from form II of theophylline to form I and the subsequent melting of form I, which could be stopped at a given solid-to-liquid equilibrium ratio.

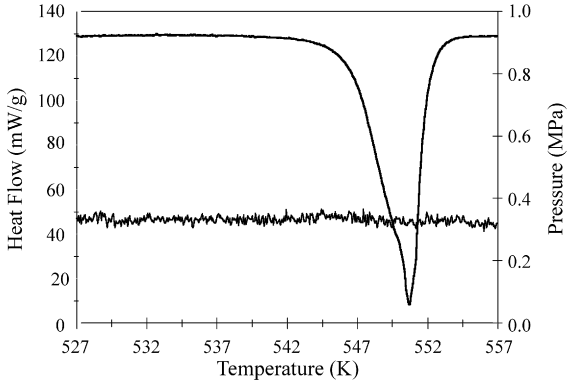

Fig. 6. Transitiometric traces of melting of form I of theophylline, prepared with procedures presented in Figs. 4 and 5, obtained by scanning temperature at a rate of 2.5 mK/s (0.15 K/min) at constant volume.

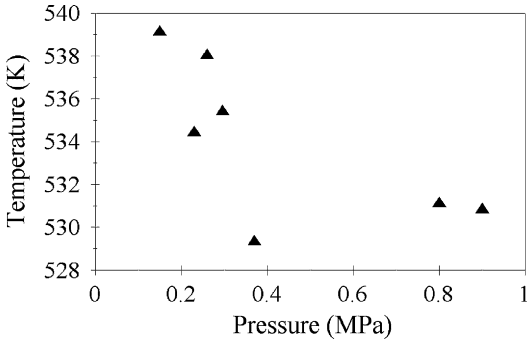

Fig. 7. Temperature of the polymorphic transition from forms II to I of theophylline as a function of the water vapour pressure investigated in a closed vessel.

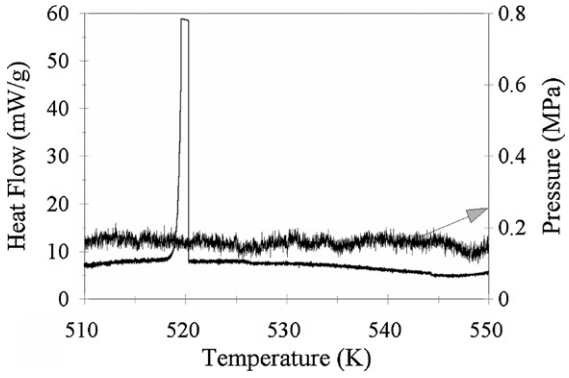

Fig. 8. Crystallisation of form II of theophylline from a completely melted state by cooling down at a rate of 1 mK/s (0.06 K/min).

between forms II and I of theophylline. The preparation of form I of theophylline, for which the very existence was contested by some researchers (Bruns et al., 1984), by a direct crystallisation from the liquid phase was performed for the first time in the present study and was possible because in the liquid–solid system there were only seeds of form I. The form II transformed completely into form I at the transition point.

On the basis of the experiments performed in the present study it was found that the mean values for the thermodynamic parameters of phase transitions in theophylline are as follows: T_{trs}(II/I) = 536.8 ± 2.2 K and $\Delta_{trs}H_m$(II/I) = 1.99 ± 0.09 kJ/mol; T_{fus}(I) = 546.5 ± 0.2 K and $\Delta_{fus}H_m$(I) = 29.37 ± 0.29 kJ/mol.

One can notice that the error in the polymorphic transition point ±2.2 K is much higher than the accuracy of temperature measurements in this study (±0.2 K). This is caused by unexplained problems with water, which is bounded in theophylline even after when its hydrate was heated at 383 K under vacuum of 0.02 Pa during at least 14 h. This was observed for samples of form II prepared from hydrates which remained in the exsiccator more than 3 days, the water vapour pressure in the closed transitiometric vessel raised considerably during heating above 500 K. This vapour pressure influenced significantly the temperature of the transition forms II–I. Fig. 7 presents the polymorphic transition temperatures obtained in all performed measurements as a function of water vapour pressure measured in the closed transitiometric vessel. Only the first four points, where the vapour pressure did not exceed 0.3 MPa, were taken into consideration in the determination of the transition temperature, presented above. It is possible that in the future it will be necessary to perform detailed transitiometric measurements with samples dried differently (Suikho et al., 1997; Airaksinen et al., 2004). Maybe it could help in a more precise determination of the polymorphic transition temperature.

It is also interesting to add that when the investigated sample was heated until the complete melting (see Fig. 3) and then cooled slowly down, much below the transition temperature T_{trs}(II/I), only a sudden crystallisation was observed at 520.3 K. An example of such a situation is presented in Fig. 8. A powder diffraction pattern of the crystallised product showed that this time it was a pure form II of theophylline. This experimental fact can be explained as follows: in the liquid state there were no seeds of any crystalline modification and according to the present results the observed temperature of crystallisation (520.3 K) lies in the region of thermodynamic stability of form II, thus crystallisation of this form was favourable from the thermodynamic point of view.

4. Discussion

When comparing the experimental diffractometric result with the tick marks presenting the literature peak positions predicted for the orthorhombic unit cell of anhydrous theophylline (Fig. 2a) it is possible to conclude that despite some small differences in the intensities, the prepared starting material for all transitiometric experiments performed in the present study was form II of anhydrous theophylline. A similar comparison for form I is not so evident. Although a comparison of the present diffractometric data with the data of Suzuki et al. (1989) (Fig. 2c) shows a reasonable agreement, the diffraction patterns of Suzuki et al. (1989) are of low resolution and thus cannot be taken as a reliable reference. On the other hand there are important differences in intensities between the present data and the literature tick marks (Fig. 2b), although there is a reasonable agreement in the peak positions. In order to verify the situation two independent experiments have been performed. First, a sample of form I of anhydrous theophylline was prepared in a C80 Setaram calorimeter, but with the use of the procedure described above. Next, a diffractometric analysis of the obtained form was performed and the absolute results (counts) have been presented as a function of 2Θ. The results are presented in Fig. 9, where the continuous line shows the diffractometric traces and the vertical tick marks show the literature peak positions predicted for the monoclinic unit cell (JCPDS 24, 1946). It can be seen that there is a reasonable agreement in the peak positions, but still noticeable differences exist between the amplitudes of the measured and calculated peaks. These differences can be caused by the morphology of the prepared crystalline form, which can depend on the conditions of crystallisation. In the present study the crystallisation of the form I was always performed near thermodynamic equilibrium, but the XRPD analysis was performed at room temperature, where form I is in a metastable state.

When analysing the results obtained in the present study, one can notice that there is an excellent agreement between

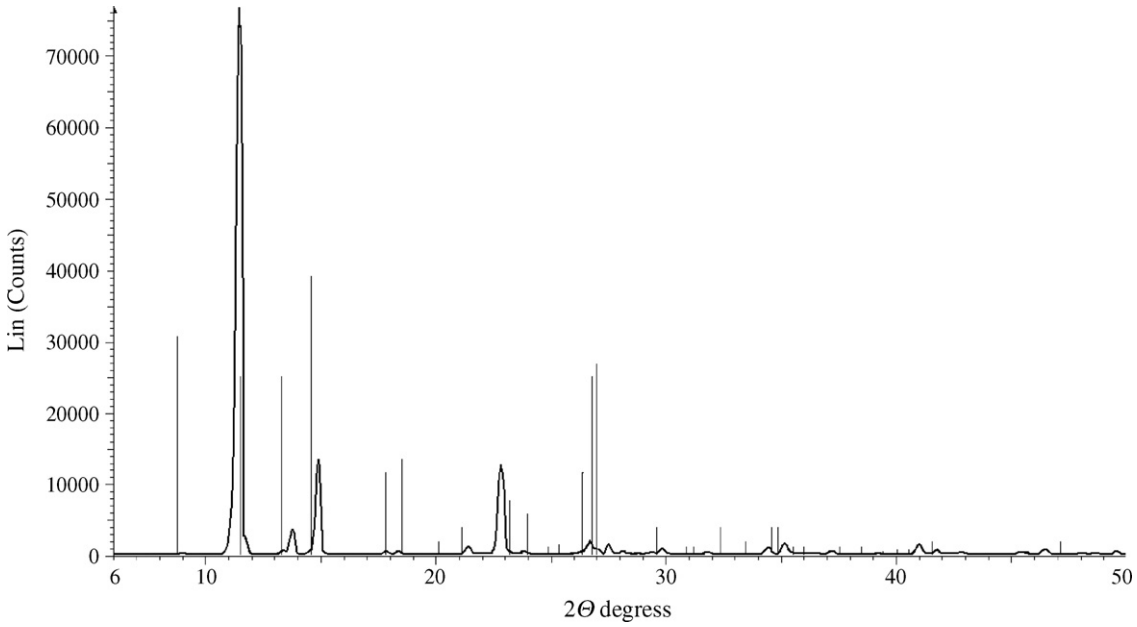

Fig. 9. X-ray powder diffraction patterns of form I of theophylline prepared independently in a C80 Setaram calorimeter with procedures presented in Figs. 4 and 5 (see the text), the vertical tick marks show the literature peak positions predicted for the monoclinic unit cell: $a = 1.328$ nm; $b = 1.544$ nm; $c = 0.449$ nm; $\beta = 98.53^\circ$ (JCPDS 24, 1946).

the present study and the results of Suzuki et al. (1989) as far as it is concerned with the temperature of fusion of form I of theophylline. On the other hand the enthalpy of fusion of form I obtained in the present study is 11% higher than the value reported by Suzuki et al. (1989). On the basis of thermodynamic rules valid for polymorphism (Burger and Ramberger, 1979), the enthalpy of fusion of metastable form II determined from the present results would be equal to $\Delta_{fus}H_m(II) = (29.37 \pm 0.29 + 1.99 \pm 0.09)$ kJ/mol $= 31.36 \pm 0.38$ kJ/mol. This value is also higher by 11% with respect to the data of Suzuki et al. (1989). It is very likely that the reason of that discrepancy is the calibration performed by Suzuki et al. (1989). The highest temperature calibration point in their study was obtained with tin ($T_{fus} = 505.08$ K), while the fusion of form I of theophylline is 546.5 K. By making approximation over 41 K temperature interval, the authors could have made an error of 11% on the calibration constant of their instrument, and then on the values of the respective enthalpies of fusion.

In the near equilibrium conditions of the transitiometric measurements performed in the present study it was not possible to investigate fusion of form II of theophylline from the metastable state, because before that form II transformed into stable form I. However, when a sample of theophylline taken from the storage bottle was left in air during a few days, and then was analysed in a transitiometer, an interesting result was obtained, which is presented in Fig. 10. One can see that this time there is no polymorphic transition at the transition point determined above. Instead, near the fusion temperature of form II (according to Suzuki et al., 1989), a small endothermic effect appears and then is immediately followed by an exothermic effect, and in turn an important endothermic effect ends the process. According to the data given in the result section of the present study, the complicated trace presented in Fig. 10 can be explained as follows. Because of an unknown yet reason, in that sample there is no polymorphic transition at the transition point. When approaching the fusion temperature of metastable form II, it started to melt, but at this temperature only solid form I is stable and because of the low heating rate the unstable liquid phase had enough time to crystallise into stable solid form I (exothermic effect). When the temperature reached slowly the value of 546.5 K, form I started to melt. Thus, the heat flow trace given in Fig. 10 presents the transformation of form II into form I by intermediary of the liquid state and the melting of form I ends the process.

Now, it also becomes clear why Suzuki et al. (1989) could prepare form I of theophylline by heating its form II at the temperature of near 540 K. This temperature lies inside of the thermodynamic stability region of form I determined by $T_{fus}(I) = 546.5 \pm 0.2$ K and $T_{trs}(II/I) = 536.8 \pm 2.2$ K, established in the present study.

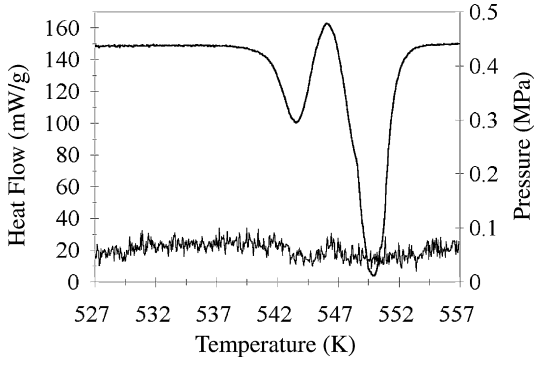

Fig. 10. Transitiometric traces of aerated theophylline exhibiting melting of form II together with its immediate crystallisation from a metastable liquid to stable form I followed by melting of form I.

5. Conclusions

For the first time, with the use of a high sensitivity, low heating rate scanning transitiometer, it was possible to distinguish and characterise the polymorphic equilibrium transition between forms II and I in theophylline. In this manner it was univocally proved, that the polymorphic phases in theophylline are enantiotropically related. The temperature and enthalpy for that transition are as follows: $T_{trs}(II/I) = 536.8 \pm 2.2$ K; $\Delta_{trs}H(II/I) = 1.99 \pm 0.09$ kJ/mol. Making use of advantages of very slow heating rate and high energetic sensitivity of the transitiometer it was possible to observe in detail the polymorphic transition followed by melting of high temperature form I and to stop the solid–liquid transition at a desired solid-to-liquid equilibrium ratio. This solid–liquid equilibrium could be stabilised and then displaced back to the crystallisation of form I with an adequate use of a precise temperature programming. In such a way a pure single phase of form I of theophylline was prepared. This fact was confirmed by X-ray powder diffraction patterns and calorimetric traces of fusion of the crystallised product. The temperature and enthalpy of the form I–liquid transition are as follows: $T_{fus}(I) = 546.5 \pm 0.2$ K and $\Delta_{fus}H_m(I) = 29.37 \pm 0.29$ kJ/mol.

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