J Therm Anal Calorim (2010) 99:325–335
DOI 10.1007/s10973-009-0186-1

Thermodynamic properties of polymorphic forms of theophylline. Part I: DSC, TG, X-ray study

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Received: 13 March 2009 / Accepted: 22 April 2009 / Published online: 24 June 2009
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Abstract The physicochemical properties of theophylline hydrate and anhydrous polymorphic forms I and II were evaluated using crystallographic and calorimetric method. This study has been carried out with the following techniques: differential scanning calorimetry (DSC), thermogravimetric analysis (TG) and X-ray diffractometry. The X-ray patterns on powder for investigated compounds are presented.

Keywords DSC · Diffractometry · Physico-chemistry properties · Polymorphism · TG · Thermal analysis · X-ray

Introduction

Many drugs exhibit polymorphism, which is defined as the ability of a substance to exist in the solid-state in different molecular arrangements or conformations, giving rise to more than one crystalline form [1]. Different polymorphs exhibit different physicochemical properties such as solubility, dissolution rate, bioavailability and chemical and physical stabilities [2].

The probability that a particular drug substance can exist in different solid forms is high [3]. So, polymorphism is an important problem in the pharmaceutical industry. Characterization of polymorphic forms constitutes an important aspect of pharmaceutical research and development [4].

The physicochemical properties of active pharmaceutical ingredients (API) are of great importance because they can affect the formulation characteristics and even the therapeutic effect (bioavailability). All these properties depend strongly on the polymorphic form. Therefore, it is necessary to know the physicochemical data, the thermodynamic stability and the phase relationship of all crystal modifications [5]. In order to avoid undesired changes during the production process or during the product lifetime, it is of the utmost importance to identify and control the polymorphic behaviour of any drug [3].

The results of the study of physico-chemical parameters of different polymorphic forms of certain substance enable us to predict and explain different behaviour of substances during the technological processing [6]. Different strategies for a systematic study of polymorphism can be applied. They usually involve a combination of techniques such as DSC, TG, thermomicroscopy, and X-ray diffraction [6–8].

In literature, there are many examples treated with the application of thermal methods of analysis, especially DSC, DTA, TG and DTG, in the studies of thermal properties of polymorphic forms of compounds used in medicine. In recent years, the studies on norfloxacin [2], indomethacin [4], chlorpropamide [9], paracetamol [10], prilocaine hydrochloride [11], tulobuterol [12], ambroxol [13] and other ones were done.

The subject of the study reported here is theophylline (3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione, 1,3-dimethylxanthine), which the main therapeutic uses are:

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chronic obstructive diseases of the airways, chronic obstructive pulmonary disease (COPD) and bronchial asthma [14, 15].

Methylxanthines are applied widely for many years in medicine versus numerous diseases, both temporarily and for treatment of chronically sick patients. Great significance of methylxanthines in the medicine and pharmacy is the reason for studies of the physico-chemical and thermal properties of these substances [16].

Theophylline forms a monohydrate that readily dehydrates in a dry atmosphere or elevated temperatures to anhydrous theophylline. Anhydrous theophylline has two polymorphic forms, i.e., I and II [17]. The identification of hydrated form and anhydrous forms of pharmaceutical substances as theophylline is of great importance in pharmaceutical science and industry. Thus, its polymorphic properties should be entirely known.

In order to get a better understanding of the behaviour of solid theophylline and determination properties forms I, II and monohydrate, a thermodynamic study has been carried out. The thermochemical properties and thermal behaviour were studied using: calorimetric measurements, differential scanning calorimetry (DSC), thermogravimetric analysis (TG), powder X-ray diffraction. The chemical structure of anhydrous form of theophylline is presented in Fig. 1.

The objectives of this work were (a) to develop procedures of obtaining pure polymorphs of theophylline; (b) to find conditions, under which a particular polymorph transforms into another one; (c) to determine the thermodynamics parameters (temperature, the enthalpy, Gibbs energy, entropy) characterizing these phase transition; (d) to verify the polymorphic relations between polymorphic form I and II; (e) to detail analysis and determination of the physicochemical characteristics of monohydrate and polymorphs of theophylline.

The essence this work was obtained thermodynamic data by DSC, TG and X-ray diffraction which can be useful in the accurate distinguish and identification of polymorphic forms of theophylline in pharmaceutical industry.

Undertake determination of the thermochemical, X-ray diffraction data arose due to verification accessible literature data for polymorphic forms I and II.

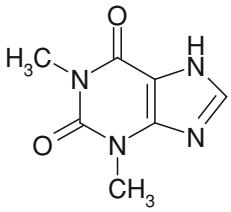

Fig. 1 Chemical structure of anhydrous form of theophylline

Experimental

Materials

The present paper shows the results of thermochemical studies on polymorphic forms of theophylline.

The compounds studied are (a) theophylline (powder, commercial product, France), from a storage bottle, (b) theophylline monohydrate and anhydrous polymorphic forms I and II.

The all substances studied were obtained at the laboratory "Chimie-Physique Minérale et Bioinorganique "Matériaux et Santé", Faculté de Pharmacie Université Paris XI" in Châtenay-Malabry, France [18]. All the experiments were performed at the Faculty of Pharmacy.

Theophylline monohydrate, ($C_7H_8N_4O_2 \cdot H_2O$) was obtained by placing in an exsiccator a few grams of theophylline (commercial product) together with a flat open vessel filled with distilled water. The substance was kept at room temperature for a few days in order to prepare a hydrate.

Theophylline form I was prepared from hydrate by heating at (117.0 °C + vacuum) and recrystallization in methanol. Whereas theophylline form II was prepared from hydrate by heating in a glass tube for 14 h at 110.0 °C under vacuum of near 0.02 Pa.

Molar masses anhydrous and monohydrate theophylline are 180.166 and 198.182 g/mol, respectively.

Methods

Powder X-ray diffraction

Diffraction analysis was used to confirm the form of the considered samples. Identification of investigated substances has been carried out on a Philips 1050 diffractometer and a Philips 1729 X-ray generator with a CuK_α anode ($\lambda = 0.154051$ nm). The apparatus was calibrated with silicium. The data were processed with the programs "Gonio" and "Rayon" [19]. Measurements were performed at room temperature. The samples were pressed on a holder before measurements, in order to minimize possible orientations effects.

Thermogravimetric analyzer

Thermal behaviour of investigated compounds was investigated by a thermobalance TGA 7 (Perkin-Elmer). The calibration was performed at different temperatures using Curie magnetic transition temperatures for the recommended alloys i.e., alumel (163.0 °C), nickel (354.0 °C),

these temperature are given by Perkin Elmer. Calibration was performed using a standard mass of 100 mg. All the experiments were performed under dry nitrogen, with a flow of 6×10^{-2} L min^{-1}. The samples of 2–5 mg were heated at a rate of 5 °C and 20 °C min^{-1}.

Calorimetry

DSC scans of investigated substance were carried out with a DSC 7 (Perkin-Elmer) and a Q 1000 (TA Instruments).

Calibration of calorimeter DSC 7 was performed by determining the heat of fusion of indium, tin and bismuth. Indium and tin are considered as fixed point (EIT-90), In: $T_{fus} = 156.6$ °C, Sn: $T_{fus} = 231.9$ °C. Bismuth is not a fixed point $T_{fus} = 271.4$ °C (NIST—National Institute of Standard and Technology-reference).

The heat of fusion for indium (NIST), tin (Koch—Light) and bismuth (Fluka) were 28.5, 59.5, 53.2 J g^{-1}, respectively, as recommended by the American Society for Materials ASM and Editor Bull [20].

Non-hermetic aluminium based alloy pans were used under dry nitrogen flow (2×10^{-2} L min^{-1}) when working with the DSC 7. For analysis the amount of the sample used is in a range 2–3 mg.

The obtained results were confirmed with the Q 1000 apparatus. Calibration of calorimeter a Q 1000: was performed by determining the heat of fusion of indium (NIST—National Institute of Standard and Technology), melting point of indium was 156.5 °C, $\Delta_{fus}H = 28.3$ J g^{-1}. Hermetic aluminium based alloy pans were used under dry nitrogen flow (2×10^{-2} L min^{-1}). Samples size of 2–3 mg were used.

A C 80 Setaram calorimeter and a Setaram C_P program "Setsoft" were used for the heat capacity measurements. The samples of investigated substances were introduced in a Pyrex glass cell located in a stainless steel vessel. The apparatus was calibrated with the melting points and enthalpies of fusion of indium and tin with parameters as mentioned above for the DSC calibration. The C_P has been measured using the continuous method presented in paper [4].

The obtained data are treated with the Setaram C_P program which gives the following polynomial expression for the analytical description of C_P:

$$C_P = A_0 + A_1T + A_2T^2 + A_3T^3 \quad (1)$$

with C_P in J K^{-1} g^{-1} and T in K.

Also, a C 80 calorimeter has been used for the determination of enthalpy of solution ($T = 25$ °C) in water of polymorphic form II and monohydrate of theophylline. The experimental error was ±2%. For analysis purposes the amount of the sample used is in a range 3–4 mg. The volume used water was 2.5 cm^3.

Results and discussion

Powder X-ray diffraction

Before starting calorimetric experiments, the pure forms were prepared and verified by X-ray diffraction.

The obtained X-ray patterns for investigated substances are illustrated in Fig. 2a–d. The X-ray patterns present structural differences between investigated polymorph I, II and theophylline monohydrate.

X-ray diffraction pattern obtained for the commercial product (Fig. 2a) was characteristic of the form II of theophylline. Thus, it is possible to conclude that despite some small differences in the intensities, the starting material (theophylline, commercial product) for prepared polymorphic form was form II of anhydrous theophylline.

The results of the X-ray patterns (the positions, spacings and relative intensities) of polymorphs I, II and monohydrate of theophylline are listed in Tables 1 and 2. The our crystallographic data were compared with structural data of JCPDS (Joint Committee Powder Diffraction Standards). For comparison were used files for orthorhombic (27-1977) [21] and monoclinic (24-1946) [22] form.

X-ray powder diffractograms (Fig. 2b, c) show distinct differences in the positions and relative intensities of reflection (Table 1), clearly indicating different polymorphs I and II.

The obtained X-ray results indicate that anhydrous and monohydrate belong to the orthorhombic and monoclinic crystal system, respectively.

Crystallographic structure of orthorhombic form was solved by Wang [21]. The parameters of unit cell are following: $a = 8.500$ Å; $b = 24.640$ Å; $c = 3.830$; $Z = 4$; Space group: *Pmnb*; density $D_x = 1.492$ mg·m^{-3}. The parameters of unit cell, also were presented by Ebisuzaki et al. [23]. The parameters of unit cell are: $a = 8.501$ Å; $b = 24.644$ Å; $c = 3.8302$; $Z = 4$; $V = 801.4$ $Å^3$; density $D_x = 1.493$ mg m^{-3}.

Crystallographic structure of the monoclinic form has been reported by Li [22]. The parameters of unit cell are following: $a = 13.280$ Å; $b = 15.440$ Å; $c = 4.490$; $\beta = 98.53°$; $Z = 4$; Space group: $P2_1$; density $D_x = 1.314$ mg m^{-3}. The parameters of unit cell of monohydrate, also presented Sutor [24]. The parameters of unit cell are: $a = 13.300$ Å; $b = 15.300$ Å; $c = 4.500$; $\beta = 99.50°$; $Z = 4$; Space group: $P2_1$; density $D_x = 1.456$ mg m^{-3}.

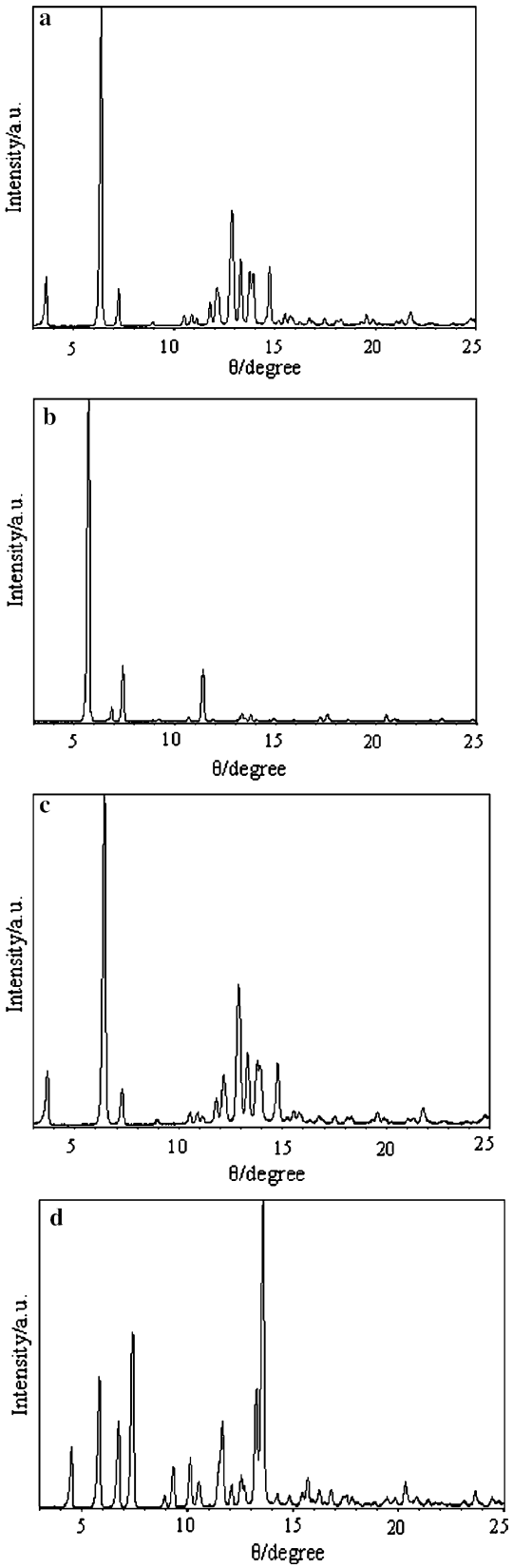

Fig. 2 **a** X-ray pattern for theophylline (commercial product). **b** X-ray pattern for theophylline form I. **c** X-ray pattern for theophylline form II. **d** X-ray pattern for theophylline monohydrate

Comparison between available structural data from literature for anhydrous form I and form II determined by Otsuka et al. [25] with experimental values obtained for anhydrous theophylline form I and II are presented in Table 3. The data determined by Otsuka et al. [25] for form II are similar to values presented in this work.

At the laboratory also carried out X-ray pattern for sample of theophylline (commercial product), which was kept several days in air.

In the case of this sample, we can observe decrease intensity. In X-ray pattern for theophylline, which was kept a few days in air, an additional peak is visible (theta 12.0900, intensity 10.67). It is similar as in the case of theophylline hydrate (theta 12.1200, intensity 8.25, Table 2). It indicates that at room temperature theophylline anhydrate incorporates water into lattice and slowly transforms to monohydrate.

Thermogravimetric analysis

Thermogravimetric measurements for theophylline form I and II confirm anhydrate form. The thermogravimetric analyse did not show mass losses between 40.0 and 200.0 °C for theophylline (commercial product), theophylline form I and II.

For theophylline monohydrate determinations were made in a temperature range from 40.0 to 150.0 °C at heat rate 5 and 20 °C min^{-1}.

In the case of theophylline hydrate, there was a visible loss of structural water in range of temperatures from 60.0 to 80.0 °C.

Calorimetric measurements

On the basis of measurements performed in a Seteram C80 calorimeter the following fitting equation was defined for the specific heat capacity (J K^{-1} g^{-1}) of theophylline (commercial product) valid over the temperature range from 40.0 to 230.0 °C

$$C_P = -4.83 + 3.80 \times 10^{-2}T - 7.548 \times 10^{-5}T^2 + 5.19 \times 10^{-8}T^3 \quad (2)$$

On the basis of measurements, also the following fitting equation was defined for the specific heat capacity (J K^{-1} g^{-1}) of theophylline (commercial product) valid over the temperature range from 55.0 to 114.0 °C

$$C_P = 57.20 + 4.72 \times 10^{-1}T + 1.31 \times 10^{-3}T^2 - 1.20 \times 10^{-6}T^3 \quad (3)$$

Data of X-ray diffraction shows orthorhombic cell and anhydrous form for theophylline (commercial product) after measurement C_P. Comparison DSC scans determined

Table 1 Comparison between the structural data from literature and experimental values obtained for anhydrous theophylline form I and form II

Orthorhombic [9]		Monoclinic [10]		Theophylline anhydrous form I			Theophylline anhydrous form II		
Distance (d)/Å)	Intensity (I/I_o)/%	Distance (d)/Å	Intensity (I/I_o)/%	Theta	Distance (d)/Å	Intensity (I/I_o)/%	Theta	Distance (d)/Å	Intensity (I/I_o)/%
12.400	25						3.670	12.0334	16.90
7.0100	100	7.7000	65	5.720	7.7283	100.00	6.420	6.8886	100.00
		6.6600	65	6.860	6.4487	4.62			
6.1800	10	6.0700	100	7.420	5.9644	17.54	7.250	6.1035	10.75
5.0100	1	4.9800	30	8.910	4.9731	0.56	8.980	4.9347	2.19
		4.8000	35	9.160	4.8385	0.57			
4.2500	2	4.2100	10	10.680	4.1563	1.51	10.560	4.2030	4.47
4.0200	2			10.980	4.0440	0.32	10.910	4.0697	4.27
3.6970	5	3.7100	15	11.410	3.8936	16.01	11.130	3.9902	3.10
				11.880	3.7416	0.63	11.810	3.7635	8.62
3.6570	5	3.5800	3				12.180	3.6508	15.77
3.4660	15						12.880	3.4555	42.90
				13.330	3.3408	2.56	13.330	3.3408	22.41
3.2530	8			13.760	3.2383	2.06	13.790	3.2314	19.87
3.2150	8						13.930	3.1996	18.54
				14.090	3.1640	0.55			
3.0410	8	3.0180	10	14.710	3.0334	0.46	14.750	3.0253	19.25
				14.900	2.9956	1.19			
2.9520	2						15.200	2.9378	2.89
2.8480	2	2.8670	3				15.520	2.8787	4.79
				15.890	2.8133	0.50			
							15.780	2.8324	4.31
2.7620	<1	2.7630	10				16.300	2.7444	2.18
2.6890	1	2.6750	5				16.720	2.6773	3.24
		2.5920	10	17.220	2.6018	1.43			
		2.5220	3	17.550	2.5544	1.94	17.510	2.5601	3.16
				17.960	2.4980	0.32			
2.4910	1	2.4950	3				18.100	2.4793	2.76
2.4660	2			18.240	2.4609	0.33	18.280	2.4557	2.90
				18.580	2.4174	0.55			
2.3090	2						19.310	2.3293	2.28
2.2750	<1	2.2810	1				19.580	2.2984	4.12
		2.2490	2				19.890	2.2640	2.72
		2.2220	2	20.510	2.1984	2.10			
2.1540	<1	2.1710	5	20.870	2.1621	0.84			
							21.000	2.1493	2.33
2.1320	<1			21.410	2.1101	0.44	21.280	2.1223	2.54
2.0870	2						21.760	2.0777	5.79
1.9980	<1			22.690	1.9968	0.53	22.730	1.9935	1.88
				22.860	1.9827	0.36			
				23.210	1.9545	0.85			
		1.9260	5	24.000	1.8937	0.26	23.800	1.9087	1.72
				24.760	1.8391	0.62	24.730	1.8412	3.20

for theophylline (commercial product) and for theophylline (commercial product) after measurement C_P in range of temperature from 55.0 to 114.0 °C shows changes in the temperatures of fusion. Theophylline after measurement C_P melts at a lower temperature (265.8 ± 0.5 °C) than theophylline (commercial product) (270.8 ± 0.8 °C). These

Table 2 Comparison between the structural data from literature and experimental values obtained for theophylline monohydrate

Monoclinic [10]		Theophylline monohydrate		
Distance (d)/Å	Intensity (I/I_o)/%	Theta	Distance (d)/Å	Intensity (I/I_o)/%
10.1000	80	4.520	9.7739	29.38
7.7000	65	5.820	7.5959	42.87
6.6600	65	6.740	6.5630	28.96
6.0700	100	7.390	5.9885	57.80
4.9800	30	8.910	4.9731	4.00
4.8000	35	9.330	4.7511	13.63
4.4200	5	10.160	4.3666	16.65
4.2100	10	10.540	4.2108	9.10
3.8300	20	11.600	3.8112	28.67
3.5800	3	12.120	3.6686	8.25
3.5200	4	12.550	3.5448	10.79
		12.710	3.5009	7.69
3.360	30	13.260	3.3581	38.89
3.3020	70	13.580	3.2804	100
		14.270	3.1249	4.86
		14.830	3.0094	4.33
2.8940	3	15.420	2.8969	5.42
2.8670	3	15.710	2.8447	10.40
		15.900	2.8116	3.25
2.7630	10	16.270	2.7493	6.20
2.6750	5	16.850	2.6573	6.63
2.5710	10	17.410	2.5743	4.25
		17.550	2.5544	4.80
2.5220	3	17.790	2.5211	3.71
		18.030	2.4886	2.30
		18.480	2.4300	1.99
2.3920	3	18.860	2.3828	2.35
		19.480	2.3098	4.01
2.2810	1	19.830	2.2706	4.06
2.2220	2	20.350	2.2149	9.01
2.1710	5	20.850	2.1641	4.37
		21.410	2.110	3.33
		21.790	2.0750	1.89
		22.050	2.0517	2.32
		23.070	1.9657	2.65
1.9260	5	23.660	1.9194	5.96
		24.450	1.8610	3.77
1.8410	1	24.790	1.8370	2.85

results suggest that theophylline (commercial product) in time measurement C_P undergoes polymorphic transformation.

The enthalpy of solution $\Delta_{sol}H_m^{\infty}$ in water at 25 °C has been measured with a C 80 Setaram calorimeter. The enthalpies of solution obtained from calorimetric determinations in water for theophylline (commercial product), form II and theophylline monohydrate are following: 19.64 and 25.23 kJ mol^{-1}.

The temperature of fusion T_{fus} and the enthalpy of fusion $\Delta_{fus}H$ of each polymorph were determined by calorimeter DSC 7 at rate 20 °C min^{-1}. The obtained values were confirmed using calorimetric investigations (Q 1000 T Instruments, hermetic pans, at rate 20 °C min^{-1}).

Table 3 Comparison between available the structural data from literature for anhydrous form I and form II [25] with selected experimental values obtained for anhydrous theophylline form I and II

Anhydrous form I [25]		Anhydrous form II [25]		Theophylline anhydrous form I		Theophylline anhydrous form II	
Distance (d)/Å	Intensity (I/I_o)/%	Distance (d)/Å	Intensity (I/I_o)/%	Distance (d)/Å	Intensity (I/I_o)/%	Distance (d)/Å	Intensity (I/I_o)/%
12.2773	100	12.2773	1	–	–	12.0334	16.90
–	–	–	–	7.7283	100	–	–
6.9700	63	6.9700	100	6.4487	4.62	6.8886	100.0
6.1508	67	6.1508	16	5.9644	17.54	6.1035	10.75
4.0953	15	4.0953	5	3.8936	16.01	4.0697	4.27
3.6776	10	3.6776	13	3.7416	0.63	3.6508	15.77
3.4796	10	3.4796	27	–	–	3.4555	42.90
3.3510	5	3.3510	16	3.3408	2.56	3.3408	22.41

Analysis of the shape of DSC scans suggests that with exception of monohydrate, all of the compounds are in anhydrous forms. In case monohydrate of theophylline, in a temperature range of from 30.0 to 80.0 °C a small peak is visible which indicate the elimination of water during heating.

The thermophysical data obtained for theophylline (commercial product), theophylline (commercial product), which was kept several days in air, theophylline monohydrate and theophylline (commercial product) after measurements C_P, polymorphic forms I and II are summarized in Table 4. The DSC analysis showed only one endothermic peak during the heating run. The purities were determined by calorimeter Q 1000 T Instruments for theophylline (commercial product), monohydrate, forms I and II were 99.99, 99.82, 99.98 and 99.84%, respectively.

The fusion entropies $\Delta_{fus}S$ of investigated substances were calculated by equation:

$$\Delta_{fus}S = \Delta_{fus}H/T_{fus} \quad (4)$$

where T_{fus} is fusion temperature.

The fusion temperature T_{fus} obtained in this work by DSC for form I (274.7 ± 1.0 °C) is close to temperature 273.4 ± 1.0 °C reported by Suzuki et al. [17]. The observed enthalpy of fusion $\Delta_{fus}H$ (155.5 ± 3.0 J g^{-1}) is in a good agreement with the reported value of 146.5 ± 1.6 J g^{-1} [17]. Whereas the fusion temperature T_{fus} (270.7 ± 0.6 °C) obtained in this work by DSC for form II is close to temperature 269.1 ± 0.4 °C reported by Suzuki et al. [17]. The observed enthalpy of fusion $\Delta_{fus}H$ (167.1 ± 2.2 J g^{-1}) is in a good agreement with the reported value of 156.5 ± 6.1 J g^{-1} [17].

The temperature of fusion T_{fus} of form II according to Griesser et al. [5] is equal 273.0 °C. Temperature of fusion T_{fus} of form I was reported first by Doser [26]: T_{fus} = 276.0 °C.

Phadnis et al. [27] reported a new metastable anhydrate I* which has not yet been reported. In the literature it appears to be related monotropically to form II. The temperature of fusion T_{fus} and the enthalpy of fusion $\Delta_{fus}H$ were 272 °C and 161.0 J g^{-1}, respectively.

The temperature of fusion and the enthalpy of fusion $\Delta_{fus}H$ for form II reported by Phadnis et al. [27] were as follows: 271.0 °C and 166.5 J g^{-1}. Whereas T_{fus} for monohydrate determined by Phadnis et al. [27] was equal 271.0 °C.

The temperatures of fusion T_{fus} determined for theophylline (commercial product) and form II are very similar:

Table 4 Thermodynamic data of the DSC measurements for theophylline

Compound	T_{fus}/°C	T_{fus}/K	$\Delta_{fus}H$/J g^{-1}	$\Delta_{fus}S$/J g^{-1} K^{-1}
Theophylline (commercial product)	270.8 ± 0.8	544.0	169.0 ± 3.0	0.310
Theophylline (commercial product) which was kept several days in air	267.1 ± 1.0	540.2	163.1 ± 2.8	0.302
Theophylline (commercial product) after measurement $C_{P\ (328-387\ K)}$	265.8 ± 0.5	539.0	167.0 ± 2.5	0.310
Theophylline (commercial product) after measurement $C_{P\ (312-501\ K)}$	267.3 ± 0.5	540.5	164.0 ± 2.7	0.303
Theophylline form I	274.7 ± 1.0	548.0	155.5 ± 3.0	0.284
Theophylline form II	270.7 ± 0.6	544.0	167.1 ± 2.2	0.307
Theophylline monohydrate	269.7 ± 1.0	543.0	159.4 ± 3.2	0.294

270.8 ± 0.8 °C and 270.7 ± 0.6 °C which confirm that theophylline (commercial product) exists in the orthorhombic unit cell of anhydrous form II.

On the base data obtained by DSC measurements and according to the rules of the polymorphic relation of Burger and Ramberger [28] it appears that the polymorphs I and II in anhydrous theophylline form are related in 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 [28].

Melting of polymorph II is accompanied with the transformation into polymorph I. Enthalpy measured in the experiment consists of two contributions, enthalpy of polymorph transition and the enthalpy of fusion of polymorph I.

For polymorph II, we have

$$\Delta_{\mathrm{fus}}H_{\mathrm{II}} = \Delta_{\mathrm{trs}}H_{(\mathrm{II}\rightarrow\mathrm{I})} + \Delta_{\mathrm{fus}}H_{\mathrm{I}} \tag{5}$$

Using the measured values of enthalpy of fusion for polymorph I and II, we can calculate the enthalpy of the polymorph transition in theophylline: $\Delta_{\mathrm{trs}}H_{(\mathrm{II}\rightarrow\mathrm{I})} = (167.1 \pm 2.2) - (155.5 \pm 3.0)\mathrm{J\ g^{-1}} = (11.6 \pm 3.7)\mathrm{J\ g^{-1}}$. Similarly is the value of the enthalpy of transition for data obtained by Suzuki: $\Delta_{\mathrm{trs}}H_{(\mathrm{II}\rightarrow\mathrm{I})} = (156.5 \pm 6.1) - (146.5 \pm 1.6)\mathrm{J\ g^{-1}} = (10.0 \pm 6.3)\mathrm{J\ g^{-1}}$.

Based on obtained experimental data on the enthalpy of fusion $\Delta_{\mathrm{fus}}H$ and the melting temperature T_{fus} of crystals polymorphs of theophylline, the temperature of phase transition $T_{\mathrm{trs(II\rightarrow I)}}$ was estimated, using the Eq. 6 [10]:

$$\mathrm{T_{trs}} = \frac{(\Delta_{\mathrm{fus}}H_{\mathrm{II}} - \Delta_{\mathrm{fus}}H_{\mathrm{I}})}{\frac{\Delta_{\mathrm{fus}}H_{\mathrm{II}}}{T_{\mathrm{fus,II}}} - \frac{\Delta_{\mathrm{fus}}H_{\mathrm{I}}}{T_{\mathrm{fus,I}}}} \tag{6}$$

The transition temperature $T_{\mathrm{trs(II\rightarrow I)}}$ was also estimated from melting data by the following equation derived by Yu [29]:

$$\mathrm{T_{trs}} = \frac{\Delta H_{\mathrm{II}\rightarrow\mathrm{I}}}{\Delta S_{\mathrm{II}\rightarrow\mathrm{I}}} = \frac{\Delta_{\mathrm{fus}}H_{\mathrm{II}} - \Delta_{\mathrm{fus}}H_{\mathrm{I}} + k\cdot\Delta_{\mathrm{fus}}H_{\mathrm{I}}\cdot(T_{\mathrm{fus,I}} - T_{\mathrm{fus,II}})}{\frac{\Delta_{\mathrm{fus}}H_{\mathrm{II}}}{T_{\mathrm{fus,II}}} - \frac{\Delta_{\mathrm{fus}}H_{\mathrm{I}}}{T_{\mathrm{fus,I}}} + k\cdot\Delta_{\mathrm{fus}}H_{\mathrm{I}}\cdot\ln(\frac{T_{\mathrm{fus,I}}}{T_{\mathrm{fus,II}}})} \tag{7}$$

A value of 0.003 was used for the factor k, which was empirically determined and allows a good approximation of the heat capacity differences in the majority of cases [2, 29].

The values of the temperature of phase transition $T_{\mathrm{trs(II\rightarrow I)}}$ calculated from the Eqs. 6 and 7 were 226.6 and 231.6 °C, respectively.

The entropy of transition $\Delta_{\mathrm{trs}}S_{(\mathrm{II}\rightarrow\mathrm{I})}$ at temperature of transition ($T_{\mathrm{trs}} = 231.6$ K) can be estimated according to the Eq. 8:

$$\Delta_{\mathrm{trs}}S_{(\mathrm{II}\rightarrow\mathrm{I})} = \Delta_{\mathrm{trs}}H_{(\mathrm{II}\rightarrow\mathrm{I})}/T_{\mathrm{trs}} \tag{8}$$

The obtained value 0.023 J $\mathrm{g^{-1}\ K^{-1}}$ is good agreement with the value received on the basis the entropies of fusion for polymorph I and II (Table 4).

The Gibbs energy of transition $\Delta_{\mathrm{trs}}G_{(\mathrm{II}\rightarrow\mathrm{I})}$ can be estimated on the base following equation:

$$\Delta_{\mathrm{trs}}G_{(\mathrm{II}\rightarrow\mathrm{I})} = \Delta_{\mathrm{trs}}H_{(\mathrm{II}\rightarrow\mathrm{I})} - \Delta_{\mathrm{trs}}S_{(\mathrm{II}\rightarrow\mathrm{I})}\cdot T_{\mathrm{trs}} \tag{9}$$

The obtained value is 6.30 J $\mathrm{g^{-1}}$.

The estimated value $T_{\mathrm{trs(II\rightarrow I)}} = 231.6$ °C is consistent with those given by Griesser et al. (232.0 °C) [5]. Griesser et al. [5] have made measurements of the sublimation pressures of the polymorphs of theophylline and from the intersection of the sublimation pressures curves suggested the value $T_{\mathrm{trs(II\rightarrow I)}}$. Also, Griesser et al. [5] estimated the value $T_{\mathrm{trs(II\rightarrow I)}} = 195.0$–231.0 °C from the enthalpies of fusion and the melting points, based on the data of Burger and Ramberger [30].

The temperature and enthalpy of transition were determined by Legendre and Randzio, using transitiometric analysis for solid II/solid I transition in anhydrous theophylline [18]. $T_{\mathrm{trs(II\rightarrow I)}}$ was equal 263.6 °C, whereas $\Delta_{\mathrm{trs}}H_{(\mathrm{II}\rightarrow\mathrm{I})}$ was equal 11.1 ± 0.5 J $\mathrm{g^{-1}}$. Measurements for the values of the temperature of fusion and the enthalpy of fusion for polymorphic forms I and II are as follows: $T_{\mathrm{fus(I)}} = 273.3$ °C, $\Delta_{\mathrm{fus}}H_{\mathrm{I}} = 163.0 \pm 1.6$ J $\mathrm{g^{-1}}$, $\Delta_{\mathrm{fus}}H_{\mathrm{II}} = 174.1 \pm 2.1$ J $\mathrm{g^{-1}}$.

These above results are consistent and are in accordance with the rules of Burgers and Ramberger [28] about an enantiotropic transition.

In order to give a full description of investigated compound, the samples of theophylline (commercial product) were submitted for DSC analyse at a heating rate of 20 °C $\mathrm{min^{-1}}$ and a different cooling rates of 80, 40, 20, 10, 5, 2 °C $\mathrm{min^{-1}}$. The samples were heated in a temperature range from 30 to 320 °C and next cooled to 30 °C. Results of DSC study at different cooling rates are presented in Table 5. As we can see in each case only one peak appears during the heating run.

For a cycle (heating and cooling rates of 20 °C $\mathrm{min^{-1}}$) the DSC scan shows during cooling one big 257.0–253.6 °C and two small exothermic peaks of crystallization at 249.3–246.7 °C and 251.0–249.5 °C. The peaks of crystallization during cooling are in several parts and it seems that two forms crystallize. Figure 3 shows DSC scans at heating and cooling rate of 20 °C $\mathrm{min^{-1}}$.

Two similar small peaks were obtained in the case of DSC measurement at cooling rate 5 °C $\mathrm{min^{-1}}$ in the range of temperatures from 248.6 to 247.5 °C and from 249.6 to 249.0 °C.

Figure 4 shows the DSC cooling scan of theophylline (commercial product). Sample was heated from 30.0 to

Table 5 DSC measurements for theophylline (commercial product)

Number of measurement	*T* onset/°C	*T* end/°C	*T* peak/°C	$\Delta_{fus}H$/J g^{-1}
1	*Step 1: Heat from 30 to 320 °C at 20 °C/min*			
	272.8	277.0	274.7	165.0
	Step 2: Cool from 320 to 30 °C at 80 °C/min			
	257.4	245.0	251.7	−147.3
2	*Step 1: Heat from 30 to 320 °C at 20 °C/min*			
	269.3	275.8	272.1	158.0
	Step 2: Cool from 282 to 200 °C at 40 °C/min			
	248.0	241.1	245.6	−125.3
3	*Step 1: Heat from 30 to 320 °C at 20 °C/min*			
	272.5	277.1	274.3	158.7
	Step 2: Cool from 320 to 30 °C at 20 °C/min			
	256.9	253.6	255.6	−123.7
4	*Step 1: Heat from 30 to 320 °C at 20 °C/min*			
	272.6	277.5	274.7	163.0
	Step 2: Cool from 320 to 30 °C at 10 °C/min			
	255.0	252.7	254.2	−125.6
5	*Step 1: Heat from 30 to 320 °C at 20 °C/min*			
	270.2	277.3	273.1	155.5
	Step 2: Cool from 320 to 30 °C at 5 °C/min			
	252.1	251.0	251.7	−127.0
6	*Step 1: Heat from 30 to 320 °C at 20 °C/min*			
	272.7	277.3	274.7	169.0
	Step 2: Cool from 320 to 30 °C at 2 °C/min			
	255.2	254.9	255.1	−75.3

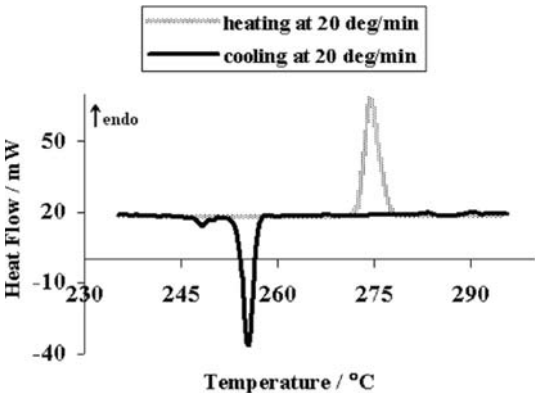

Fig. 3 The DSC heating and cooling scans of theophylline (commercial product). Sample was heated from 30.0 to 320.0 °C at 20 °C and cooled from 320.0 to 30.0 °C at 20 °C

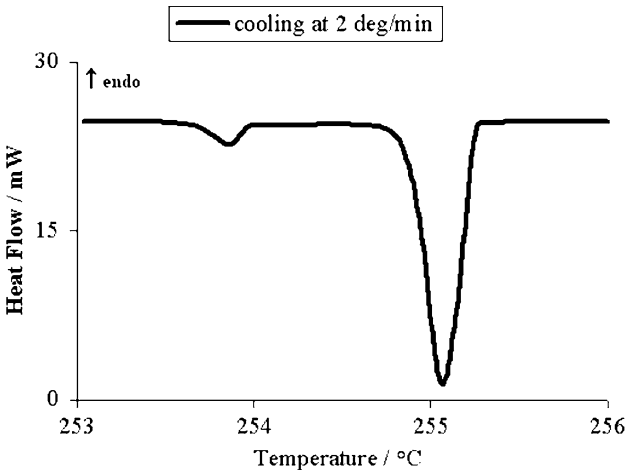

Fig. 4 The DSC cooling scan of theophylline (commercial product). Sample was heated from 30.0 to 320.0 °C at 20 °C and cooled from 320.0 to 30.0 °C at 2 °C

330.0 °C at a rate 20 °C min^{-1} and cooled from 330 to 30 °C at a rate 2.0 °C min^{-1}. When sample is cooled at a rate of 2.0 °C min^{-1}, two peaks of crystallization appear. The first one is at 255.3–254.9 °C and the second, which is smaller at 254.1–253.5 °C. This means that a polymorphic form crystallizes.

Conclusions

In the present study, the polymorphism of theophylline has been examined. The physicochemical characterization of polymorphic forms of theophylline I, II and theophylline

monohydrate by means of varied techniques of analysis (X-rays, DSC, TG) showed differences in structural parameters and temperatures of fusion between polymorphic forms I and II. The structure of polymorph I differs significantly from the structure of polymorph II.

Such a combination of experimental techniques yields the information very useful for the characterization of polymorphs of theophylline and pharmaceutical process.

The present study was undertaken to carrying detailed analysis, receive reliable data and differences between polymorphs I, II and monohydrate. The aim this work was also verification literature data.

When comparing the experimental DSC, diffractometric results it is possible to conclude that despite some small differences in the intensities, the starting material (theophylline, commercial product) for prepared polymorphic form was form II of anhydrous theophylline.

The diffractograms of polymorphs I, II and monohydrate of theophylline are very different and allow a clear and fast identification of the polymorphs.

In this work collected and compared data for polymorphic forms of theophylline are presented. Review of the literature shows that different values exist. The literature lacks such detailed comparison.

The comparison between the temperature and enthalpy of fusion of the two forms shows that the form II is stable at room temperature and atmospheric pressure, while form I is stable at a higher temperature and atmospheric pressure.

The enthalpy of polymorph transition was estimated after measurements of the heat effects of a melting. Furthermore, the Gibbs energy and entropy of polymorphic transition were estimated.

On the basis of data obtained by DSC measurements, transitiometric analysis [18] and according to rules of the polymorphic relation of Burger and Ramberger [28] we can observe that the polymorphs I and II in anhydrous theophylline form are related in 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 [28].

It is important to conclude that if the theophylline (commercial product) is kept in air for a few days the metastable fusion is observed at 267.1 ± 1.0 °C with an enthalpy of 163.1 ± 2.8 J g^{-1}. This confirms that the transition is enantiotropic. During storage, the anhydrous form is expected to transform to the monohydrate.

The essence this work was obtained and verification X-ray diffraction data of polymorphic forms of theophylline.

The obtained values together with other thermodynamic results obtained by DSC, TG and X-ray diffraction can be use for accurate distinguish and identification polymorphic forms of theophylline in pharmaceutical industry.

The enthalpies of solution and solvation for polymorphic forms I and II have been measured and the results and analysis will be presented in a forthcoming publication.

Acknowledgements The authors are grateful to Prof. S. L. Randzio for the preparation of investigated compounds. The author Piotr Szterner would like to thank the Centre of Excellence TALES (Thermodynamic Laboratory for Environmental Purposes) for the support.

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