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THERMAL DECOMPOSITION OF METHYLXANTHINES
Interpretation of the results by PCA

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The thermal decomposition of theophylline, theobromine, caffeine, diprophylline and aminophylline were evaluated by calorimetrical, thermoanalytical and computational methods. Calorimetrical studies have been performed with aid of a heat flux Mettler Toledo DSC system. 10 mg samples were encapsulated in a 40 μL flat-bottomed aluminium pans. Measurements in the temperature range form 20 to 400°C were carried out at a heating rate of 10 and 20°C min^{-1} under an air stream. It has been established that the values of melting points, heat of transitions and enthalpy for methylxanthines under study varied with the increasing of heating rate.

Thermoanalytical studies have been followed by using of a derivatograph. 50, 100 and 200 mg samples of the studied compounds were heated in a static air atmosphere at a heating rate of 3, 5, 10 and 15°C min^{-1} up to the final temperature of 800°C. By DTA, TG and DTG methods the influence of heating rate and sample size on thermal destruction of the studied methylxanthines has been determined. For chemometric evaluation of thermoanalytical results the principal component analysis (PCA) was applied. This method revealed that first of all the heating rate influences on the results of thermal decomposition. The most advantageous results can be obtained taking into account sample masses and heating rates located in the central part of the two-dimensional PCA graph. As a result, similar data could be obtained for 100 mg samples heated at 10°C·min^{-1} and for 200 mg samples heated at 5°C min^{-1}.

Keywords: *DSC-DTA-TG-DTG, methylxanthines, principal component analysis (PCA), thermal decomposition*

Introduction

Methylxanthines are applied widely for many years in medicine *vs*. numerous diseases, both temporarily and for treatment of chronically sick patients [1, 2]. Theophylline, diprophylline and aminophylline have found their application in the treatment of diseases connected with cramps of smooth muscles in bronchis, theobromine acts diuretically and as the spasmolytic agent, whereas caffeine is used in complex preparations for the headache relief.

Great significance of methylxanthines in the medicine and pharmacy is the reason for studies of the physico-chemical and thermal properties of these substances. For instance, calorimetric and computational studies of dehydration of theophylline monohydrate indicated that the monohydrate–anhydrate transition of this compound is energetically reversible [3]. On the other hand, heat of hydration and hydration kinetics of theophylline anhydrate, evaluated by three different methods showed that the values estimated by microcalorimetry, heat conduction microcalorimetry and DSC agreed approximately with one another [4]. Dehydration and thermal properties of theophylline and its sodium salt were also analyzed by DSC, DTA, TG and thermomicroscopy [5, 6]. The results showed that the water loss was found to be a single or a two-step process, depending on the temperature of an isothermal examination. Similar studies performed for caffeine revealed that the hydrous form of this substance is not a monohydrate but contains about 4/5 mole of water per mole of caffeine hydrate [7–9].

Interesting studies were also followed on the polymorphic behaviour of xanthine derivatives, which showed that several forms may appear and that thermodynamic and kinetic aspects have to be taken into consideration [10–12]. Quantitative determination of polymorphs or amorphous form may be performed by using several techniques, mainly microcalorimetry. Furthermore, 8-substitued bis-xanthine derivatives with various substituents were investigated by DSC and TG [13, 14]. By this way the influence of non-cyclic and cyclic substituents on the thermal and thermo-oxidative behaviours has been evaluated.

Regarding above, for the study of physicochemical and thermal properties of xanthine derivatives several analytical techniques were applied, from which the most frequently DSC, DTA and TG were used. Skilled use of these techniques causes that they deliver in a relatively short time great sets of the measurement data, which describe compounds under study. Correct interpretation of these data is frequently difficult to

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do. Because of this, the objective of this work was to use one of so-called pattern recognition methods as the supporting element for the interpretation of the thermoanalytical data which characterize the studied methylxanthines. From the group of pattern recognition methods principal component analysis (PCA) was applied [15, 16]. With the aid of this advanced statistical method the influence of sample mass and heating rate on the course of thermal decomposition of the studied methylxanthines was evaluated. The valuable feature of PCA consists of a fact that this method is capable of doing the correct interpretation of the measurement data set and to obtain the maximum useful information from them [17–20].

Experimental

Materials and methods

The five following methylxanthines were used in the studies (manufacturers are given in parenthesis): theophylline, 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dion, $C_5H_2O_2N_4(CH_3)_2$, (A.C.E.F., Fiorenzuola D'arda, Piacenza, Italy); theobromine, 3,7-dihydro-3,7-dimethyl-tetrahydro-1H-purine-2,6-dion, $C_5H_2O_2N_4(CH_3)_2$, (Pharma-Zentrale Gmbh, Germany); caffeine, 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dion, $C_5HO_2N_4(CH_3)_3$, (A.C.E.F., Fiorenzuola D'arda, Piacenza, Italy); diprophylline, 7-(2,3-dihydroxypropyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dion, $C_5HO_2N_4(CH_3)_2 \cdot C_3H_5(OH)_2$, (Polfa, Cracow, Poland) and aminophylline, dihydrate aethylenediamine 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dion, $C_5H_2O_2N_4(CH_3)_2 \cdot C_2H_8N_2 \cdot 2H_2O$, (Pharma-Zentrale Gmbh, Germany).

DSC scans of methylxanthines were carried out with a heat flux DSC, model 822^e (Mettler Toledo, Boston, USA), with a liquid nitrogen cooling system (Dewar vessel). Samples under study, approx. 10 mg were accurately weighed (±0.01 mg) and encapsulated in a 40 μL flat-bottomed aluminium pans with crimped-on lids. Measurements in the temperature range from 20 to 400°C were obtained at a heating rate of 10 and 20°C min^{-1} under a nitrogen stream at a flux rate 70 mL min^{-1}.

Calibration of calorimeter was performed by determining the heat of fusion of indium, melting point of indium was 156.60°C, ΔH_f=28.43 J g^{-1}. Each experiment was repeated at least three times. From DSC scans, the temperatures of onset (T_i), end (T_f), peak maximum (T_p) and peak extrapolated (T_e) as well as the temperature range of endothermic peak (ΔT), peak height (h) and peak width (w) were determined by using the STAR^e software.

DTA, TG and DTG curves of the thermal decomposition of the studied compounds were recorded using an OD-103 derivatograph (MOM, Hungary). 50, 100 and 200 mg samples were heated in an unsealed platinum crucible at a heating rate of 3, 5, 10 and 15°C min^{-1} up to the final temperature of 800°C. The α-Al_2O_3 was employed as a reference material.

From DTA curves, the temperatures of onset (T_i), end (T_f) and peak maximum (T_p) as well as the temperature ranges of endo- and exothermic peaks (ΔT) in the consecutive stages of thermal decomposition of the studied compounds were fixed. In the case of TG and DTG curves, the temperatures of onset (T_i) and end (T_f) of mass loss, the temperature range of reaction interval (ΔT) and mass loss (Δm) were calculated. Furthermore, the temperature of DTG peak maximum (T_p) was also determined.

Melting points of the examined compounds were measured by Boëtius device (Carl Zeiss, Jena, Germany).

PCA calculations

PCA was used for complex interpretation of the thermoanalytical data sets for studied compounds. In this method high number of variables can be reduced to two or three principal components which very often illustrate relations among objects in multidimensional space. In this way problems which are difficult to imagine or interpret become easy to present in clear two or three dimensional plots.

Starting point for PCA calculations is a matrix of the data X with dimensions n×p, where n is a number of objects (rows) and p is a number of variables (columns). In these studies five matrices were constructed for the studied compounds (theophylline, theobromine, caffeine, diprophylline and aminophylline). In each matrix three sample masses (50, 100 and 200 mg) heated at four heating rates (3, 5, 10 and 15°C min^{-1}) for each compound being decomposed were used as the rows (12 rows). Columns were the results of thermal decomposition of the studied compounds; from DTA curves – T_i, T_f, T_p and ΔT for the successive endothermic or exothermic peaks; from TG and DTG curves – T_i, T_f, ΔT and Δm for the loss in mass. The matrices comprised from 12 to 22 columns, depending on the compound under study.

Matrix X is at first standardized, then matrix R is calculated according to it. After further calculations, new columns in matrices P and W were obtained, which were called principal components (PC's). New matrix P reflects main relations between objects and makes possible their classification as a result of the influence of sample mass and heating rate on thermal decomposition of methylxanthine under study. Matrix W illustrates main relations among variables and enables

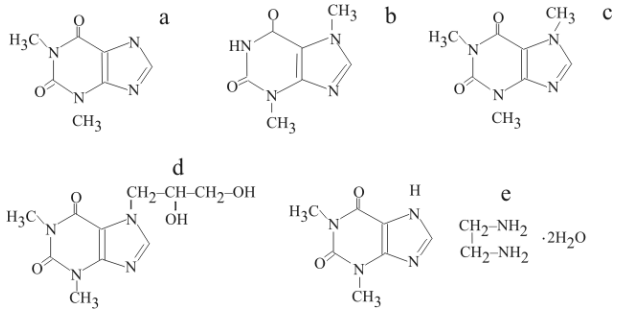

Fig. 1 Chemical formulas of the studied compounds: a – theophylline, b –theobromine, c – caffeine, d – diprophylline and e – aminophylline

selection of key thermoanalytical parameters, which make the best classification of the analyzed objects.

All statistical calculation was done by using of the Statistica 7.1 (Statsoft®, Cracow, Poland) software.

Results and discussion

Structural formulas of the methylxanthines under study are presented in Fig. 1. All the compounds are xanthine derivatives, which differ from each other by location of the methyl substituents and their quantity [21]. It is also necessary to mention that diprophylline contains additionally dihydroxypropyl substituent whereas aminophylline is referred to as a compound, a salt or a stable mixture of theophylline and ethylenediamine [6, 21].

DSC scans of methylxanthines are shown in Fig. 2, whereas DSC data registered at two different heating rates for these compounds are listed in the Table 1. As it has been shown, DSC scans of methylxanthines are characterized by similar course of thermal destruction. They have melting point at a heating rate of 10°C min^{-1} from 156.52°C in the case of diprophylline to 348.92°C in the case of theobromine. The melting heat is also specific for each compound, from 22.81 to 57.42 kJ mol^{-1} for theophylline and theobromine, respectively.

Analysis of the shape of DSC scans suggests that with exception of aminophylline, all of the compounds are in anhydrous forms. Furthermore, theophylline, theobromine and caffeine melt with decomposition whereas diprophylline after melting is relatively stable and evaporates with decomposition at higher temperatures. The small endothermic peak at 144°C on the DSC scan of caffeine can be due to the polymorphic transformation of this compound. According to the literature, a low-temperature β-modification of caffeine transforms to a high-temperature α-modification at 141±2°C [12]. Interesting is also the DSC scan of aminophylline, which differs from other xanthine derivatives. This stable mixture of theophylline and

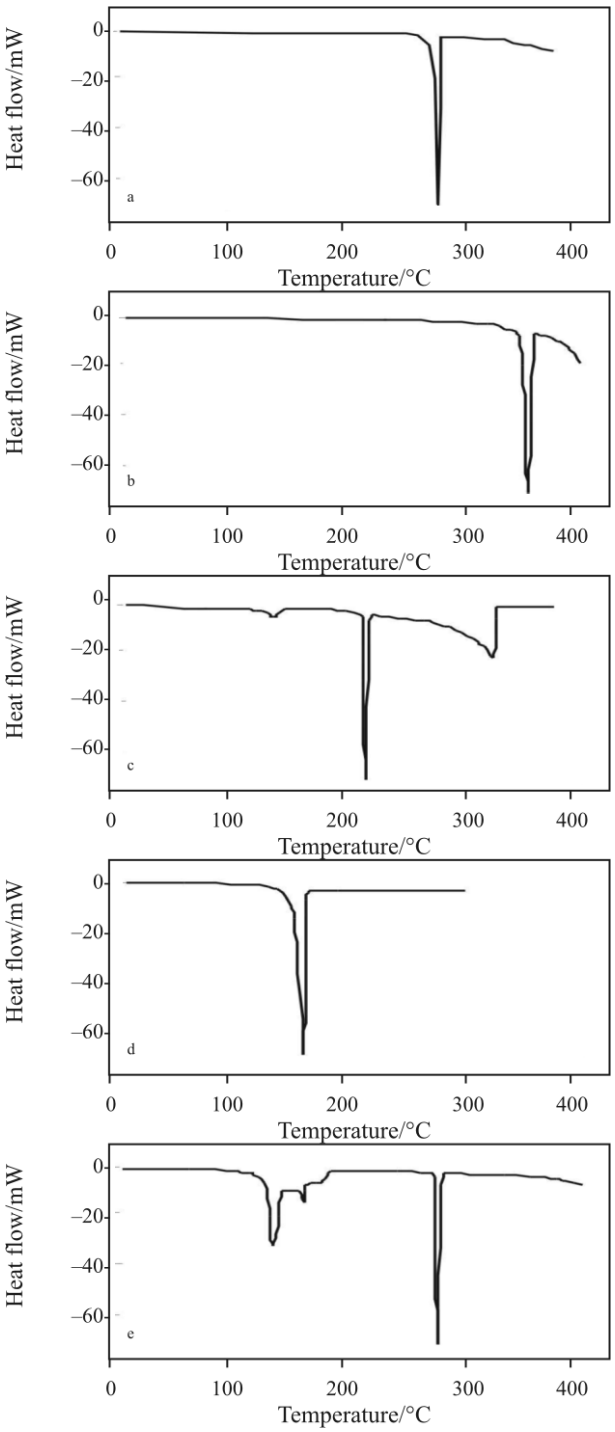

Fig. 2 DSC scans of the studied compounds: a – theophylline, b – theobromine, c – caffeine, d – diprophylline and e – aminophylline. 10 mg samples were heated at a rate of 10°C min^{-1}

ethylenediamine decomposes at low temperatures with dehydration of two molecules of crystallization water and evaporation of one molecule of ethylenediamine. Free theophylline melts with decomposition at higher temperatures.

Table 1 Results of the DSC analysis of the studied compounds heated in air at different heating rates

No.	Methylxanthine	Sample mass, heating rate	Melting point/°C	Peak width/°C	Peak height/mW	Transition heat/J g^{-1}	Enthalpy/ kJ mol^{-1}
1.	Theophylline	10.10 mg 10°C min^{-1}	271.28	3.61	62.88	–159.92	22.81
		9.75 mg 20°C min^{-1}	272.74	5.21	96.87	–190.87	34.39
2.	Theobromine	9.75 mg 10°C min^{-1}	348.92	4.81	73.79	–318.70	57.42
		10.15 mg 20°C min^{-1}	349.88	6.45	108.29	–213.75	38.51
3.	Caffeine	11.15 mg 10°C min^{-1}	235.84	2.90	65.36	–118.36	22.98
		9.80 mg 20°C min^{-1}	237.60	4.14	77.09	–107.89	20.95
4.	Diprophylline	11.75 mg 10°C min^{-1}	156.52	4.61	39.35	–165.29	42.02
		9.60 mg 20°C min^{-1}	157.37	5.84	51.75	–142.72	36.29
5.	Aminophylline	10.40 mg 10°C min^{-1}	271.78	2.81	69.37	–141.85	25.56
		10.10 mg 20°C min^{-1}	272.54	3.81	95.04	–151.49	27.29

Based on the above results, it can be concluded that the values of melting points of methylxanthines under study are in good accordance with those found in the literature [21, 22] and measured by Boëtius device. Furthermore, it should be also mentioned, that the heating rate has significant influence on the shape of DSC scans. Along with heating rate to be on the increase, the width and height of the peak and the temperature in which the peak occurs, become distinctly shifted into the higher values.

Results of DTA, TG and DTG analyses of all tested compounds at the extreme values of sample masses and heating rates are compiled in the Table 2. As it has been shown, thermal decomposition of caffeine and diprophylline occurs in three stages, whereas decomposition of theophylline, theobromine and aminophylline can be described as two-stage process.

The first stage of thermal destruction includes the range of temperatures in which any processes connected with the change of chemical structure in analyzed compound do not take place. It is exemplified by lack of mass loss in the TG and DTG curves. The high, narrow and sharp-topped DTA peaks occurred in this stage are connected with the phase transformations, such as polymorphic change in the case of caffeine or melting in the case of diprophylline. In the second stage of decomposition, the compounds under study melt. Despite fact that melting process does not include the change of mass, very often a small decrease of mass connected with vaporization of the liquid phase is observed. In this situation the DTA curve shows the second, lower and wider endothermic peak related to a heat of evaporation. The process of evaporation occurs frequently with decomposition of the melted compound. In the third stage, as a result of further increase of temperature, the products of decomposition are subject to final destruction combined with complete deflagration of the carbonated remains.

Reactions of thermal decomposition in solid and liquid phase very often have multistage course [23–25]. Decomposition of the same compound can proceed in various ways, depending on the properties of sample investigated, for instance mass of sample, grain size, thermal conductivity and capacity, degree of crystallinity and influence of dilution by inactive substance, as well as depending on the experimental conditions, for instance speed of sample heating. In order to assess the influence of sample masses and of heating rates on the thermal decomposition of methylxanthines, 50, 100 and 200 mg samples were heated at the increasing heating rates 3, 5, 10 and 15°C min^{-1}.

DTA, TG and DTG curves which exemplified the influence of a sample mass on the thermal decomposition of theophylline are shown in Fig. 3. Based on these results it can be concluded, that along with the increase of sample mass with the same heating rate, the height of peaks and their area enlarge proportionally to the value of heat being exchanged by a sample with environment. Simultaneously a slight displacement of the temperature of peak maximum

Table 2 Results of the DTA, TG and DTG analysis of the studied compounds heated in air at different heating rates and sample masses

No.	Methylxanthine	Sample mass, heating rate	Decomposition stage		
			Temperature range of DTA peak, ΔT/°C; temperature of DTA peak, °C Temperature range of decomposition stage, ΔT°C; temperature of DTG peak, T_p°C; mass loss in *TG* Δ_m(%)		
			I	II	III
1.	Theophylline	50 mg 3°C min^{-1}		250–270, 260[a]; 270–345, 315[a]; 345–390, 360[a] 195–520, 330; 100%	570–805, 630[a]
		200 mg 15°C min^{-1}		245–330, 255[a]; 330–485, 415[a]; 485–570, 495[a] 195–665, 410; 100%	570–805, 630[a]
2.	Theobromine	50 mg 3°C min^{-1}		300–335, 310[a]; 335–365, 360[a] 195–395, 325; 100%	435–525, 475[a]
		200 mg 15°C min^{-1}		315–425, 385[a]; 425–545, 465[a] 215–550, 395; 100%	545–735, 610[a]
3.	Caffeine	50 mg 3°C min^{-1}	130–160, 150[a]	225–300, 285[a] 140–325, 290; 100%	415–480, 455[a]
		200 mg 15°C min^{-1}	115–175, 145[a]	205–420, 345[a] 145–485, 365; 100%	420–730, 550[a]
4.	Diprophylline	50 mg 3°C min^{-1}	110–150, 130[a]	345–380, 365[a] 180–510, 340; 100%	380–515, 495[b]
		200 mg 15°C min^{-1}	105–210, 140[a]	310–510, 480[a] 210–770, 440; 100%	510–800, 570[b]
5.	Aminophylline	50 mg 3°C min^{-1}		65–135, 95[a]; 245–265, 225[a]; 330–380, 360[a] 70–130, 105; 19%; 190–370, 320; 81%	405–505, 455[a]
		200 mg 15°C min^{-1}		60–235, 115[a]; 235–320, 260[a]; 320–550, 460[a] 60–210, 145; 17.5%; 230–525, 415; 82.5%	560–710, 630[a]

The peak: [a]endothermic, [b]exothermic

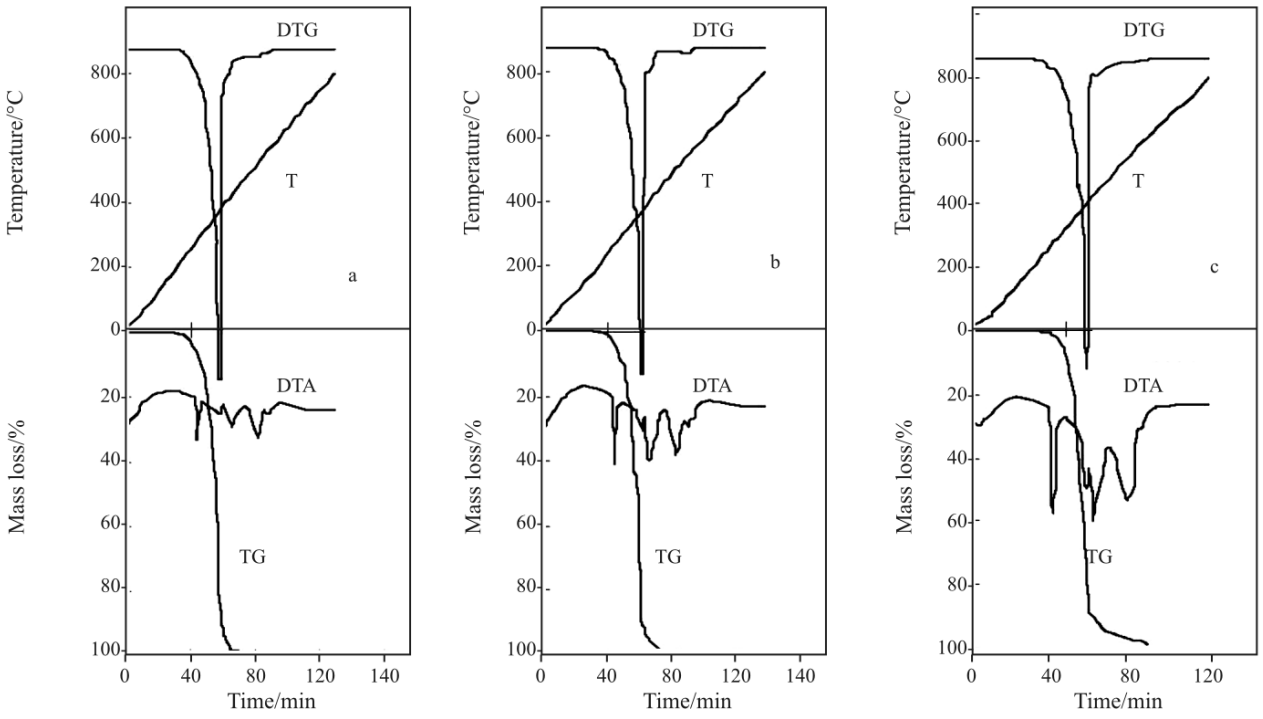

Fig. 3 DTA, TG and DTG curves of the thermal decomposition of theophylline for the sample sizes: a – 50, b – 100 and c – 200 mg. Samples were heated at a rate of 5°C min^{-1}

Table 3 Results of PCA calculations for the DTA, TG and DTG data sets of the studied compounds

No.	Methylxanthine	Dimension of matrix n×p	Number of principal component					
			PC1		PC2		PC3	
			Variance/%	Eigenvalue	Variance (cumulative variance)/%	Eigenvalue	Variance (cumulative variance)/%	Eigenvalue
1.	Theophylline	12×12	64.0	7.7	21.9 (85.9)	2.6	5.0 (90.9)	0.6
2.	Theobromine	12×17	66.7	11.3	14.1 (80.8)	2.4	8.9 (89.7)	1.5
3.	Caffeine	12×17	60.2	10.2	26.7 (86.9)	4.5	5.9 (92.8)	1.0
4.	Diprophylline	12×20	70.0	14.0	17.2 (87.2)	3.4	4.5 (91.7)	0.9
5.	Aminophylline	12×22	70.2	15.4	15.4 (85.6)	3.4	5.0 (90.6)	1.1

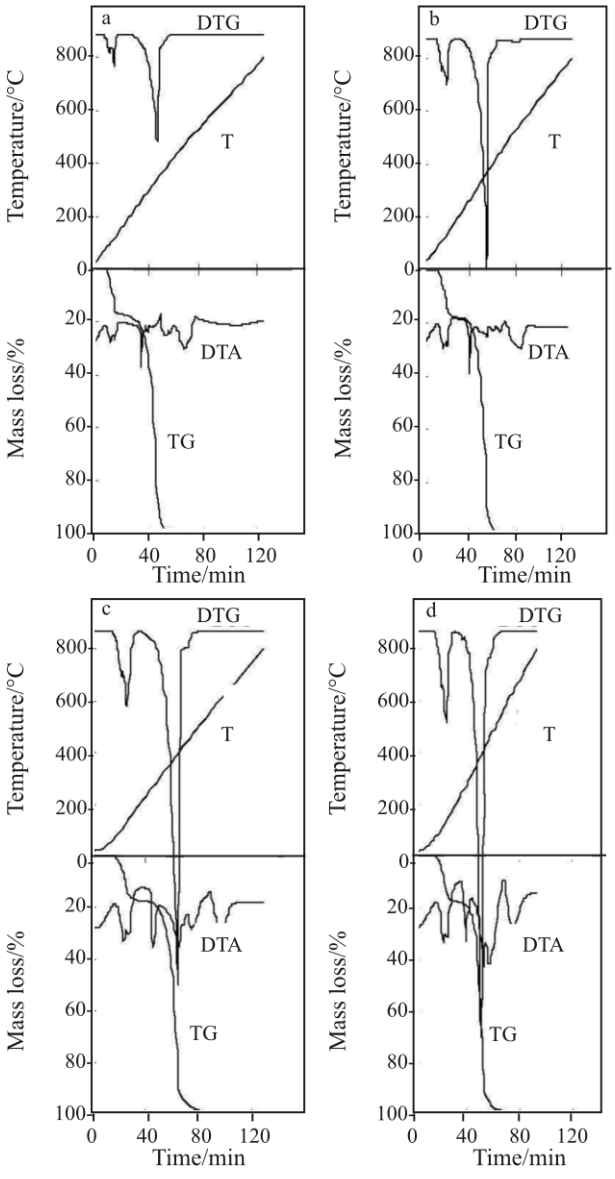

Fig. 4 DTA, TG and DTG curves of the thermal decomposition of 100 mg sample of aminophylline at the heating rates: a – 3, b – 5, c – 10 and d – 15°C min^{-1}

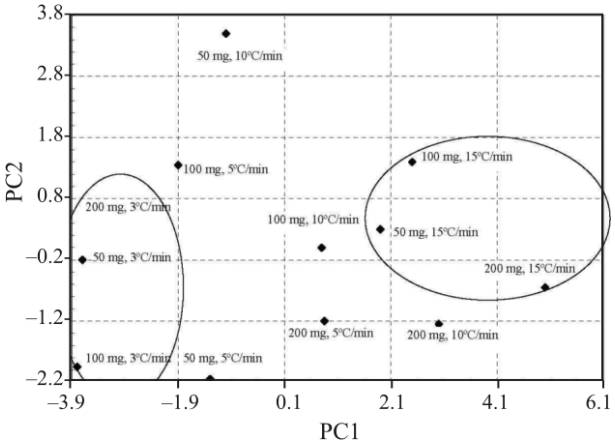

Fig. 5 Scatter plots of the first two principal component vectors for the results of the thermal decomposition of theophylline at different sample sizes and heating rates

and its end towards higher values is observed. On the other hand, the DTA, TG and DTG curves exemplified the influence of a heating rate on the decomposition of aminophylline are presented in Fig. 4. As it has been shown, along with the increase of heating rate, the temperature range in which the endo- and exothermic peaks occurs and the temperature of peak maximum become shifted into the higher values.

Because of full assessment of the above issue is a multivariate problem, in this work an attempt was made to evaluate the influence of a sample mass and of a heating rate on the thermal decomposition of methylxanthines, by using PCA.

The results of PCA calculations are compiled in the Table 3. Interpretation of these data revealed, that the first two main components PC1 and PC2 explain totally more than 80% of the total variances and eigenvalues of PC1 and PC2 are greater than 2. This creates sufficient condition for investigation of the relation between sample masses and heating rates for each compound in two-dimensional space, PC1 *vs*. PC2.

As an example, the graphic interpretation of PCA calculations for theophylline was shown in

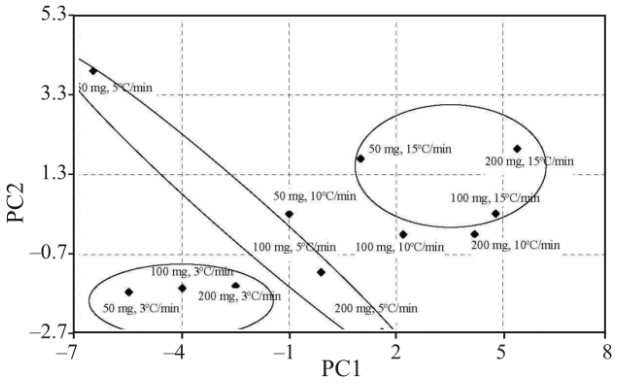

Fig. 6 Scatter plots of the first two principal component vectors for the results of the thermal decomposition of aminophylline at different sample sizes and heating rates

Fig. 5. The scatter plot clearly reflects differences in the experimental conditions in which thermal analyses were performed. On the left side of the plot are located results for thermal decomposition of 50, 100 and 200 mg samples of theophylline, which were obtained at low heating rate, 3°C min^{-1}. On the opposite, the right side of the graph, there can be found results for 50, 100 and 200 mg samples of theophylline, which were received at high heating rate, 15°C min^{-1}. As a result, it can be concluded that first of all the heating rate influences on the results of thermal decomposition. Examining influence of the sample mass at the constant heating rate it was ascertained that sample mass at heating rate 3°C min^{-1} in less degree influences on the results of thermal decomposition of theophylline as compared with higher heating rate, 15°C min^{-1}.

Another, good example which confirms above observations is presented in Fig. 6. The scatter plot for aminophylline also clearly reflects differences in experimental conditions in which thermal decomposition was performed. Similarly as in the case of theophylline, on the left side of the plot are located results for thermal destruction of 50, 100 and 200 mg samples of aminophylline, which were obtained at low heating rate, 3°C min^{-1} and on the right side of the graph – results for the same samples, which were received at high heating rate, 15°C min^{-1}. Based on these data, it can be concluded that the most advantageous results of the thermal analysis of methylxanthines can be obtained taking into account scatter points (sample masses and heating rates), located in the central part of the graph. According to these observations, the approximate results could be obtained for 100 mg samples heated at 10°C min^{-1} and for 200 mg samples heated at 5°C min^{-1}.

Analysis of the principal components loadings revealed that on the such localization of scatter points in two-dimensional space, PC1 *vs*. PC2, in the least degree influences the temperatures of melting and polymorphic transformation of the compounds under study.

Conclusions

PCA calculations of the thermal decomposition data for methylxanthines received at different sample masses and heating rates revealed that first of all the heating rate influences on the results of thermal decomposition. The most advantageous results can be obtained taking into account sample masses and heating rates located in the central part of the two-dimensional PCA graph. According to these observations, similar results could be obtained for 100 mg samples heated at 10°C min^{-1} and for 200 mg samples heated at 5°C min^{-1}.

Examining influence of the sample mass at the constant heating rate it was ascertained that sample mass at low heating rate in less degree influences on the results of thermal decomposition of theophylline than higher heating rate.

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