Journal of Thermal Analysis and Calorimetry, Vol. 65 (2001) 599–605

THERMAL DECOMPOSITION OF PURINE DERIVATIVES USED IN MEDICINE

M. Wesołowski and P. Szynkaruk

Department of Analytical Chemistry, Medical University of Gdańsk, Al. Gen. J. Hallera 107, 80-416 Gdańsk, Poland

Abstract

Thermal decomposition of several purine derivatives used in medicine – theophylline, theobromine, caffeine, diprophylline and aminophylline was investigated. The analyses were performed using a derivatograph. It has been established, that the thermal decomposition of purine derivatives occurs via three stages. The stages of dehydratation of hydrate and evaporation of aminophylline are distinctly marked on the thermoanalytical curves, which may be used for the control of composition of the studied compounds. The ranges of temperature, in which the analyzed compounds can be technologically transformed without change of their physicochemical properties, were also established. Moreover, the influence of heating rate and sample size on the thermal decomposition of the examined compounds was evaluated.

Keywords: aminophylline, caffeine, diprophylline, DTA-TG-DTG, purine derivatives, theophylline, theobromine, thermal decomposition

Introduction

Thermal methods of analysis are widely used in the study of stability and thermal decomposition of substances used in medicine [1–5]. The evaluation of drug stability in the solid state is mostly made by analyzing their decomposition under isothermal or non-isothermal conditions. Usually, it proceeds along with mass loss in an irreversible way.

The decomposition reactions of drugs possess both practical and scientific significance [2, 6]. These reactions make possible to know the behavior of a drug substance at various temperatures, and that knowledge is important for the prediction of storage conditions for drug formulations. They also enable to get information on temperatures, at which the drug substance can be subjected to technological processes without loss of its specific physico-chemical and pharmacological properties. The decomposition reactions are also carried out in order to obtain the solid products, which are characterized by proper phase composition and activity for further technological applications.

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

1418–2874/2001/ $ 5.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

stability and decomposition of organic and inorganic compounds used in medicine. In recent years, the studies on probenecid [7], ciprofloxacin [8], ibuprofen [9,10], ascorbic acid [11], omeprazole [12], diclofenac salt [13], ampicillin trihydrate [14] and other ones were done. Furthermore, certain information about phase transformation [15, 16] and kinetics of hydration [17] of purine derivatives has also been given in literature. Regarding above, the aim of the study was the thermal decomposition of selected purine derivatives and evaluation of their thermal stability in the solid state.

Experimental

Materials

The following purine derivatives were used (manufacturers are given in parenthesis): theophylline, 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dion (A.C.E.F., Fiorenzuola D'arda, Piacenza, Italy); theobromine, 3,7-dihydro-3,7-dimethyl-tetrahydro-1H-purine-2,6-dion (Pharma-Zentrale Gmbh, Germany); caffeine, 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dion (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 (Polfa, Cracow, Poland) and aminophylline, dihydrate aethylenediamine 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dion (Pharma-Zentrale Gmbh, Germany). Purity of these compounds met requirements of European Pharmacopoeia.

Methods

DTA, TG and DTG curves of the thermal decomposition of purine derivatives were recorded using OD-103 derivatograph (MOM, Hungary). 50, 100 and 200 mg samples were heated in a platinum crucible under air atmosphere at a heating rate of 3, 5, 10 and 15 K min^{-1}, up to a final temperature of 1173 K. α-Al_2O_3 was used as a reference material.

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

Results and discussion

All of the studied drug substances – theophylline, theobromine, caffeine, diprophylline and aminophylline are purine derivatives, which differ from each other by location of methyl constituents and their quantity. The most important data about compounds analyzed are compiled in Table 1. However, DTA, TG and DTG curves of the thermal decomposition of these drugs are shown in Figs 1 and 2. On the basis of these data, the thermal decomposition of studied purine derivatives can be described as a three-stage process.

The first stage includes the range of temperatures in which any processes connected with changing the chemical structure of the analyzed compound do not take place. DTA peaks occurring in this stage are related to the first-order phase transi-

tions. The effect of temperature results in the transition of the studied compounds, from one crystalline form to another of different structure (polymorphic transformation) or in change of physical state (melting, evaporation, sublimation). This could be exemplified by melting of diprophylline and polymorphic transformations of caffeine.

Table 1 Chemical formulas and molar masses of the purine derivatives (melting points determined in this work are given in parenthesis)

Compound	Formula or molar mass	Melting point/K
Theophylline $C_5H_2O_2N_4(CH_3)_2$	$C_7H_8O_2N_4$ 180.17	543–547[a] (548–549)
Theobromine $C_5H_2O_2N_4(CH_3)_2$	$C_7H_8O_2N_4$ 180.17	630[b], 563–568[b s]
Caffeine $C_5HO_2N_4(CH_3)_3$	$C_8H_{10}O_2N_4$ 194.19	507–512[a], 509–511[b], 451[b s] (512)
Diprophylline $C_5HO_2N_4(CH_3)_2 \cdot C_3H_5(OH)_2$	$C_{10}H_{14}O_4N_4$ 254.25	433–438[a] (433–434)
Aminophylline $2C_5H_2O_2N_4(CH_3)_2 \cdot C_2H_8N_2 \cdot H_2O$	$C_{16}H_{28}O_6N_{10}$ 456.44	543–547[a] (547–548)

[a]European Pharmacopoeia, 3rd ed., Council of Europe, Strasbourg Cedex 1997
[b]The dictionary of substances and their effects, The Royal Society of Chemistry, London 1994
[s]Sublimation

The second stage of the thermal decomposition is determined by the chemical structure of analyzed compounds. In this stage one or more intermediate products of

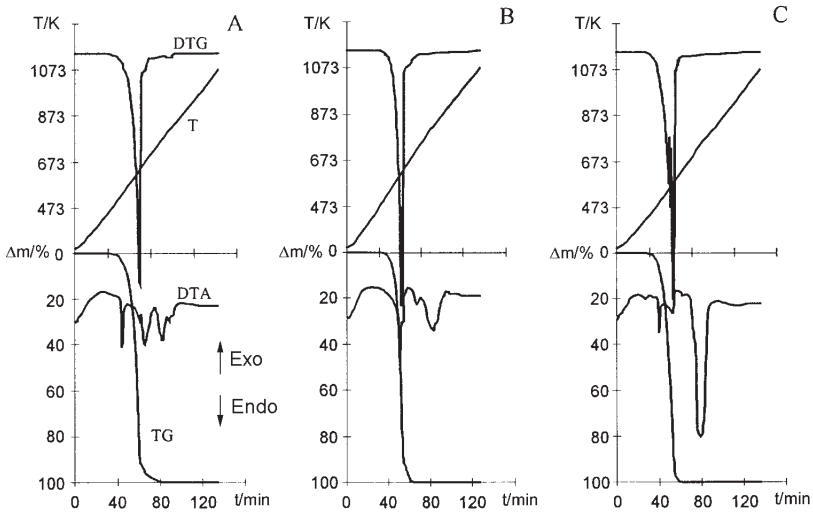

Fig. 1 DTA, TG and DTG curves of the thermal decomposition of: A – theophylline, B – theobromine and C – caffeine. 100 mg samples were heated at a heating rate of 5 K min^{-1}

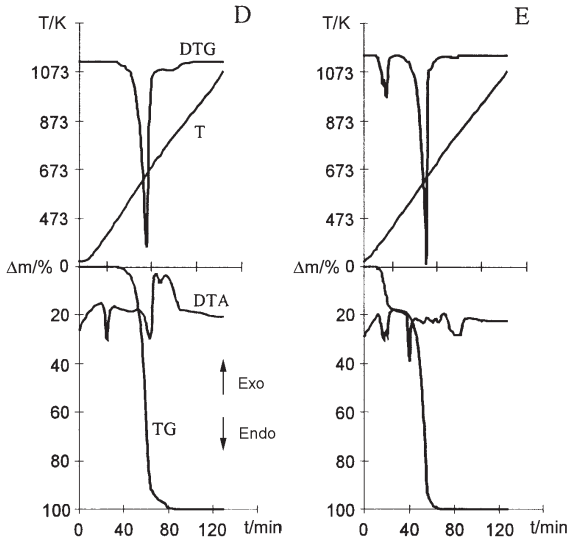

Fig. 2 DTA, TG and DTG curves of the thermal decomposition of: D – diprophylline and E – aminophylline. 100 mg samples were heated at a heating rate of 5 K min^{-1}

decomposition are formed. The ranges of temperatures connected with formation and then destruction of intermediate products of decomposition are not distinctly specified on DTA, TG and DTG curves. This is caused by parallel courses of many reactions in which decomposition products are formed and overlapping effects connected with these reactions. It was also shown that in the narrow range of temperatures of the second stage, above 90% mass loss is observed. The high temperature at which the second stage finishes causes carbonization of melted remains.

In the third stage, as a result of further increase of temperature, the decomposition products are subject to final destruction together with complete deflagration of carbonated remains. After the analysis any residue in the crucible was found.

In order to evaluate the influence of heating rates and sample sizes on the thermal decomposition of purine derivatives, 50, 100 and 200 mg samples were heated at the increasing heating rates – 3, 5, 10 and 15 K min^{-1}.

Based on the analysis of DTA, TG and DTG curves of the examined compounds, recorded as a result of a heating rate increase, it was concluded, that the heating rate has significant influence on the temperature range and the shape of thermoanalytical curves. Along with the increase of heating rate, the temperature ranges, at which the endo- and exothermic effects and the peak temperatures occurred, become shifted into the higher values. On the other hand, the curves recorded as a function of temperature, peaks become higher and wider, whereas TG curves become flatter. When the curves are recorded as a function of time, DTA and DTG peaks become more narrow and the TG curve becomes steeper. Above changes are due to the increase of the degree of reactivity of compound in a short period of time and the tem-

Table 2 Results of the thermal decomposition of purine derivatives registered for 50, 100 and 200 mg samples heated at a heating rate of 3, 5, 10 and 15 K min^{-1}

Compound	50 mg, 3 K min^{-1}				50 mg, 5 K min^{-1}				50 mg, 10 K min^{-1}				50 mg, 15 K min^{-1}			
	T_i	T_f	ΔT	T_p	T_i	T_f	ΔT	T_p	T_i	T_f	ΔT	T_p	T_i	T_f	ΔT	T_p
Theophylline	468	793	325	603	458	838	380	648	433	813	380	628	468	873	405	663
Theobromine	468	668	200	598	488	713	225	628	488	733	245	638	483	768	285	653
Caffeine	413	598	185	563	398	613	215	548	408	628	220	573	418	683	265	598
Diprophylline	453	783	330	613	478	818	340	653	483	858	375	668	493	878	385	683
Aminophylline	343	643	300	593	323	663	340	603	338	703	365	628	333	743	410	643
Compound	100 mg, 3 K min^{-1}				100 mg, 5 K min^{-1}				100 mg, 10 K min^{-1}				100 mg, 15 K min^{-1}			
	T_i	T_f	ΔT	T_p	T_i	T_f	ΔT	T_p	T_i	T_f	ΔT	T_p	T_i	T_f	ΔT	T_p
Theophylline	463	688	225	643	448	828	380	633	463	863	400	663	463	878	415	668
Theobromine	478	688	210	613	473	693	220	628	473	748	275	633	483	803	320	658
Caffeine	423	638	215	593	418	623	205	578	413	683	270	603	418	683	265	618
Diprophylline	458	818	360	663	463	833	370	658	478	893	415	688	498	943	445	703
Aminophylline	338	663	325	618	348	703	355	633	333	743	410	663	343	778	435	678
Compound	200 mg, 3 K min^{-1}				200 mg, 5 K min^{-1}				200 mg, 10 K min^{-1}				200 mg, 15 K min^{-1}			
	T_i	T_f	ΔT	T_p	T_i	T_f	ΔT	T_p	T_i	T_f	ΔT	T_p	T_i	T_f	ΔT	T_p
Theophylline	463	823	360	643	473	868	395	663	468	918	450	688	468	938	470	683
Theobromine	488	713	225	638	483	753	270	648	488	823	335	653	488	823	335	668
Caffeine	423	628	205	573	428	643	215	583	418	683	265	608	418	758	340	638
Diprophylline	438	803	365	633	473	908	445	693	518	923	405	708	483	1043	560	713
Aminophylline	338	703	365	633	348	743	395	653	343	783	440	683	333	798	465	688

perature interval between surface and interior of sample under examination, which grows up together with increase of heating rate.

By analysing the influence of a sample size on the results of the thermal decomposition of purine compounds, one can conclude, that along with the increase of the sample size at the same heating rate, proceeds change in the shape of DTA and DTG curves. The height of peaks and their area enlarge proportionally to the heat value being exchanged by a sample with the environment. Simultaneously, a slight displacement of the temperature of the peak and its end towards higher values were observed.

Conclusions

Results of the studies showed that thermoanalytical methods can be useful to determine the temperature ranges corresponding to the thermal stability of organic compounds. This is a very important problem because the determination of the temperature range, in which a given drug substance is stable both in its structure and pharmacotherapeutic action, is crucial from the point of view of drug storage, its technological transformation and technology of drug formulations.

A considerable effect of heating rate and sample size on the thermal decomposition of purine derivatives may be due to a complexity of the thermal rearrangement of examined compounds to the intermediate products. It can be concluded that the heating rate influences the thermal decomposition of the analyzed compounds at a higher extent than sample size. Examining the effect of sample size at constant heating rate, it was ascertained that the sample size at a rate of 3 K min^{-1} influences the thermal decomposition at a less degree as compared with higher heating rate – 15 K min^{-1}.

References

1 M. Wesołowski, Drug Dev. Ind. Pharm., 11 (1985) 493.
2 K. A. Connors, G. L. Amidon and V. J. Stella, Chemical stability of pharmaceuticals. A handbook for pharmacists, 2nd ed., Wiley & Sons, New York 1986.
3 M. Nebuloni, Analitica, 22 (1987) 36.
4 M. Wesołowski, Thermochim. Acta, 209 (1992) 223.
5 D. Giron and C. Goldbronn, J. Thermal Anal., 48 (1997) 473.
6 J. Dereń, J. Haber and R. Pampuch, Chemia ciała stałego (Solid state chemistry), PWN, Warszawa 1977.
7 J. P. Elder and L. A. Rosen, Thermochim. Acta, 282/283 (1996) 469.
8 I. Turel and P. Bukovec, Thermochim. Acta, 287 (1996) 311.
9 S. Lerdkanchanaporn and D. Dollimore, J. Thermal Anal., 49 (1997) 879.
10 S. Lerdkanchanaporn, Thermochim. Acta, 340 (1999) 131.
11 S. Lerdkanchanaporn, D. Dollimore and K. S. Aleksander, J. Thermal Anal., 49 (1997) 887.
12 M. A. Ruiz, I. Reyes, A. Parera and V. Gallardo, J. Therm. Anal. Cal., 51 (1998) 29.
13 A. Fini, P. J. Sanchez-Soto, M. J. Fernandez-Hervas and M. A. Holgado, Int. J. Pharm., 165 (1998) 79.

14 J. Han, S. Gupte and R. Suryanarayanan, Int. J. Pharm., 170 (1998) 63.
15 D. Giron, P. Piechon, C. Goldbronn and S. Pfeffer, J. Therm. Anal. Cal., 57 (1999) 61.
16 M. Epple, H. K. Cammenga, S. M. Sarge, R. Diedrich and V. Balek, Thermochim. Acta, 250 (1995) 29.
17 Y. Yoshihashi, M. Makita, S. Yamamura, E. Fukuoka and K. Terada, Chem. Pharm. Bull. (Tokyo), 46 (1998) 1148.