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CHARACTERISTICS OF THE THERMAL DECOMPOSITION OF ANTITUBERCULOUS DRUGS

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Abstract

The thermal decomposition of antituberculous drugs–ethambutol (base and dihydrochloride), isoniazid, ethionamid and pyrazinamid has been studied by DTA, TG and DTG techniques. General remarks have been made on their thermal destruction. The effect of sample size over the range 20–200 mg and heating rate over the range 3–15 deg·min^{-1} on the thermal degradation has also been investigated. Moreover, based on the Kissinger's equation, the values of the kinetic parameters were determined.

Keywords: antituberculous drugs, drugs, kinetics

Introduction

Thermoanalytical techniques, especially differential thermal analysis (DTA), differential scanning calorimetry (DSC) and thermogravimetry (TG) play an important role in solving a variety of scientific and industrial problems in pharmacy. They are increasingly finding applications for the determination of temperatures of phase transitions of drugs and values of their thermodynamic constants, the determination of phase diagrams and purity, the evaluation of compatibility among the components of dosage forms, the qualitative and quantitative analysis of drug formulations and for the stability tests and determination of kinetic parameters [1–13].

Thermoanalytical techniques are also used for the determination of the thermal stability of organic compound [14–16]. It is important problem, especially for the technology of drug formulations. Taking into account the foregoing aspect, the thermal stability of antituberculous drugs has been studied by using DTA, TG and derivative TG (DTG) techniques.

Experimental

Materials

In these studies have been used the following antituberculous drugs – N,N'-(ethylenediamine)-di-2-butanol-1 (Ethambutol) – base and dihydrochloride;

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4-pyridine carboxylic acid hydrazide (isoniazid); 2-ethyl-4-pyridinethiocarboxylic acid amide (Ethionamid) and 2-pyrazine acid amide (Pyrazinamid).

These materials were obtained from the Pharmaceutical Works 'Polfa' and the Chemical and Pharmaceutical Co-operatives. With regard to purity, conformed to criteria for pharmaceutical substances.

Thermal analysis

The DTA, TG and DTG curves of the thermal decomposition were carried out using a OD-103 derivatograph (MOM, Hungary). The 200, 100, 50 and 20 mg samples were heated in a platinum crucible at a heating rate of 3, 5, 10 and 15 deg·min^{-1} in the furnace atmosphere. α-Al_2O_3 was used as the reference material.

Elemental analysis, UV-VIS and IR spectroscopy

The temperatures to isolate intermediate products of decomposition were selected on the basis of the results obtained from the DTA, TG and DTG curves. 200 mg samples were heated in a platinum crucible at the heating rate of 3 deg·min^{-1} up to the lowest selected temperature. The furnace was quickly turned up, a small amount was withdrawn from the heated sample to analysis and the residue was heated up to the next selected temperature.

Elemental analyses were made using a flash-combustion method. UV–VIS absorption spectra were recorded with a UV–VIS Specord Carl Zeiss Jena, whereas IR spectra were recorded with a Pay Unicam 200 spectrophotometer, using KBr disc.

Results and discussion

General characteristics of the thermal decomposition

Analysis of the results allows to distinguish three stages of the thermal decomposition for all of the compounds studied.

In the temperature range of the first stage, the analysed compounds are stable. There are no changes in the chemical composition and structure of the compound and no mass loss is observed on the TG and DTG curves. On the DTA curve only endothermic peaks appeared due to melting. This process is not accompanied by mass loss but in some cases small loss in mass occurred due to evaporation of the molten compounds. This is confirmed by the second endothermic DTA effect. This peak is lower and relatively broad.

The second stage of decomposition to be conditioned by chemical structure of the analysed compounds. In this stage one or more intermediate products of the decomposition are formed. Taking into account multidirectional course of

the decomposition of organic structure it is very difficult to establish the composition and structure of an intermediate product.

In the second stage of isoniazid destruction, propanol and ethylenediamine are formed as intermediate products. These compounds evaporate successively from crucible.

In the case of pyrazinamid, cyanic acid and pyrazine are formed due to rearrangement of its structure. Evaporation of cyanic acid occurs simultaneously with melting of pyrazinamid:

$$(C_4H_3N_2)CONH_2 \rightarrow C_4H_4N_2 + H{-}O{-}CH$$

Pyrazine is an unstable compound and for this reason it decomposed without formation of intermediate products.

The coked residue after the decomposition of intermediate products burned in the third stage. This process is accompanied by a wide and shallow effect on the DTG curve and by an exothermic DTA effect. The surface area of this peak is proportional to the heat released during the burning.

Influence of the sample size and the heating rate

Sample size influences on the mechanism of thermal decomposition of antituberculous drugs. The combustion process is predominant in the case of smaller sample sizes, whereas the evaporation process dominates for the larger ones. The causes for this phenomenon lie, among others, in the temperature gradient between the crucible wall and the inside of the sample, and also in the chemical composition and structure of the compound studied.

It was found that increasing the heating rate led to the shifting of the particular thermal processes to higher temperatures. This was reflected in the most characteristic way by the DTA and DTG curves. At higher heating rates an overlapping of endothermic DTA peaks has been observed since their parameters – the height and width at half-height of the effect were increased. This results form the increase in the extent of over-reacting the substances in the time until and since the formation of a greater spatial temperature gradient inside the sample.

Kinetics of the thermal decomposition

The Kissinger equation has been employed for the determination of kinetic parameters of the thermal decomposition of studied compounds. The equation relates the shift of temperature of the extreme endothermic DTA peak to the heating rate [17]. As is shown on Fig. 1 the straight line which slopes to be

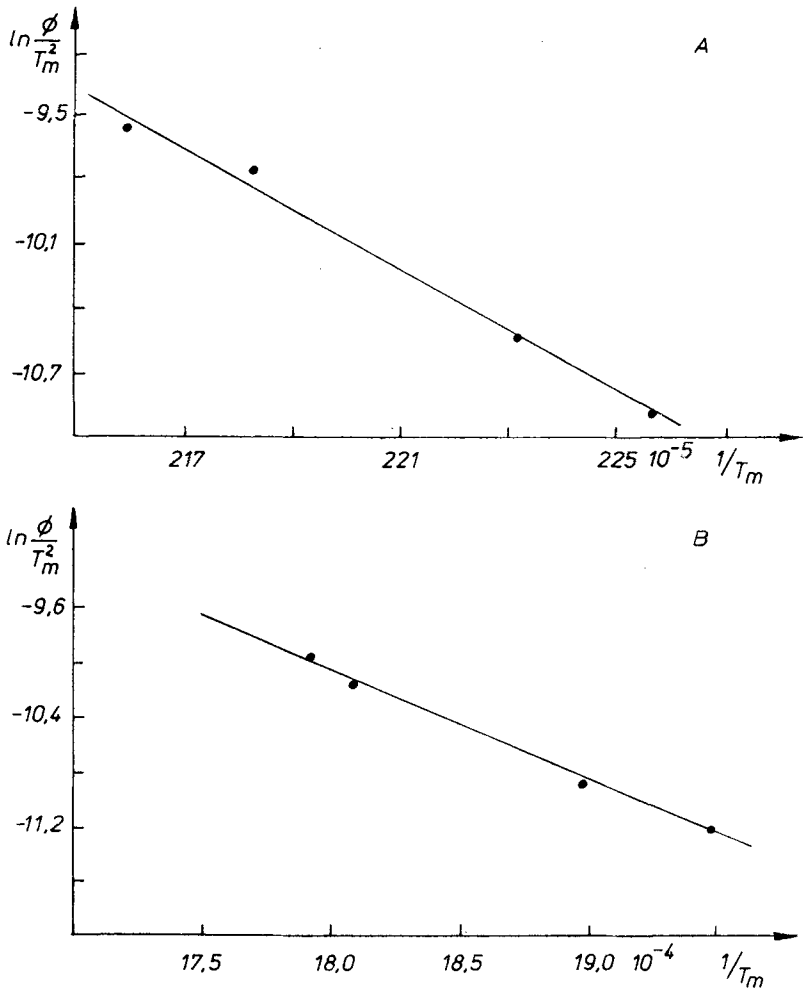

Fig. 1 The relationship between $\ln(\Theta/T_{m2})$ and $1/T_m$ for – (A) the second and (B) the third endothermic peak of pyrazinamide

equal to E_a/R. It allows to calculate the activation energy. Statistical parameters such as the values of the correlation coefficient, standard error of estimation and probability level were also calculated [18]. There are specified in Table 1. A negative and approximate to unit values of the correlation coefficient indicates the strong, indirect dependence between the both values. All remaining statistical parameters are characterized by values higher than critical value at a probability of 0.01.

Table 1 Values of the correlation coefficient, standard error of estimation, probability level and activation energy for the thermal decomposition of antituberculous drugs

Endothermic effect	*Correlation coefficient*	*Standard error of estimation*	*Probability level*	Activation energy Kcal·mol^{-1}
Ethambutol				
(3)	–0.9969	$5.64 \cdot 10^{-2}$	$3.12 \cdot 10^{-3}$	22.09
Ethionamid				
(2)	–0.9999	$3.71 \cdot 10^{-3}$	$2.81 \cdot 10^{-3}$	16.88
Pyrazinamid				
(2)	–0.9961	$6.81 \cdot 10^{-2}$	$3.94 \cdot 10^{-3}$	27.89
(3)	–0.9960	$6.43 \cdot 10^{-2}$	$4.02 \cdot 10^{-3}$	15.56

(2) the second- and (3) the third endothermic peak

In some cases no correlations exist for the values obtained at the heating rate 15 deg·min^{-1}. For these reasons it has been decided to eliminate the results acquired at this heating rate.

Conclusions

Similar physicochemical properties of the antituberculous drugs cause that mechanism of the thermal decomposition is similar and occurred via three stages.

Thermal methods of analysis can be useful for determination of the temperature ranges to be correspondent with thermal stability of organic compounds. This is especially important for the technology of drug formulations.

A considerable effect of the sample size over the range 20–200 mg and heating rate over the range 3–15 deg·min^{-1} on the thermal decomposition of compounds examined may be due to a complexity of thermal rearrangement of organic substance to the intermediate products.

The possibility of determination of the activation energy on the basis of the DTA results has been confirmed now. The kinetic parameters of the formation of the intermediate products in the second stage of decomposition were determined.

References

1 S. A. Botha, A. P. Lotter and J. L. du Preez, Drug. Dev. Ind. Pharm., 13 (1987) 1197.
2 F. A. Chrzanowski, L. A. Ulissi, D. J. Fegely and A. C. Newman, Drug. Dev. Ind. Pharm., 12 (1986) 783.
3 A. A. van Dooren, Drug. Dev. Ind. Pharm., 9 (1983) 43.
4 P. J. Sanches-Soto, J. M. Gines, A. M. Rabasco, A. Justo and J. L. Perez Rodriguez, Thermochim. Acta, 158 (1990) 225.

5 J. L. Ford, Pharm. Acta Helv., 58 (1983) 101.
6 M. Sumnu, STP Pharma, 2 (1986) 299.
7 G. P. Bettinetti, F. Giordano, G. Fronza, A. Italia, R. Pellegata, M. Villa and P. Ventura, J. Pharm. Sci., 79 (1990) 470.
8 W. Wächter and U. Münch, Acta. Pharm. Technol., 26 (1980) 296.
9 M. Wesołowski, Mikrochim. Acta, I (1980) 199.
10 M. Wesołowski, Int. J. Pharm., 11 (1982) 35.
11 M. Wesołowski, Pharm. Ind., 43 (1981) 1138.
12 K. Izutsu, S. Yoshioka and Y. Takeda, Chem. Pharm. Bull., 38 (1990) 800.
13 S. Kitamura, S. Koda, A. Miyamae, T. Yasuda and Y. Morimoto, Int. J. Pharm., 59 (1990) 217.
14 P. V. Allen, P. D. Rahn, A. C. Sarapu and A. J. Vanderwielen, J. Pharm. Sci., 67 (1978) 1087.
15 J. Martin-Gil, F. Martinez Villa, M. C. Ramos-Sanchez and F. J. Martin-Gil, J. Thermal Anal., 29 (1984) 1351.
16 K. Yano, T. Oomura, H. Sugiura, T. Hikosaka and H. Kawata, Res. Lab., 3 (1977) 117.
17 H. E. Kissinger, Anal. Chem., 29 (1957) 1702.
18 J. B. Czerminski, A. Iwasiewicz, Z. Paszek and A. Sikorski, Metody statystyczne dla chemikow (Statistical methods for chemists), 2nd ed., PWN, Warszawa 1992.

Zusammenfassung — Mittels Differentialthermoanalyse (DTA), Thermogravimetrie (TG) und DTG wurde die thermische Zersetzung von Antituberkulotika - Ethambutol (Base und Dihydrochlorid), Isoniazid, Ethionamid und Pyrazinamid - untersucht. Dabei wurden allgemeine Bemerkungen zum thermischen Abbau gemacht. Außerdem wurde der Einfluß der Probengröße (im Bereich 20 bis 200 mg) und der Aufheizgeschwindigkeit (im Bereich 3 bis 15 deg/min) auf den thermischen Abbau untersucht. Darüber hinaus wurden anhand der Kissinger-Gleichung die Werte für die kinetischen Parameter bestimmt.