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GENERAL REMARKS ON THE THERMAL DECOMPOSITION OF SOME DRUGS

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Abstract

The thermal decomposition of antituberculous, local anaesthetic and calcium salts of organic acids used as the drugs has been studied by differential thermal and thermogravimetric techniques. General characteristics of their thermal decomposition has been made. 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 been investigated. The values of the kinetic parameters has been also determined.

Keywords: drugs, DTA-TG, kinetics, thermal decomposition

Introduction

The determination of the thermal stability of organic compound is the most important problem, especially for the technology of drug formulations. The thermal stability of the physiologically active substance depends on the particle size, degree of crystallinity, purity, temperature of storage and the surrounding gas atmosphere.

As an example, differential thermal analysis (DTA), thermogravimetry (TG) and derivative TG (DTG) techniques have been used for characterization of the thermal behaviour of furocoumarins [1], erythromycin [2], β-lactan antibiotics [3] and calcium lactate [4]. Taking into account the foregoing aspects, a complex estimation of the thermal stability of antituberculous, local anaesthetic and calcium salts of organic acids used as the drugs has been carried out by using DTA, TG and DTG techniques.

Experimental

Materials

In these studies have been used:

a) antituberculous drugs: N,N'-(ethylenediamine)-di-2-butanol-1 (Ethambutol) – base and dihydrochloride; 4-pyridine carboxylic acid hydrazide (Isoni-

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azid); 2-ethyl-4-pyridinethiocarboxylic acid amide (Ethionamid) and 2-pyrazine acid amide (Pyrazinamid),

b) local anaesthetic drugs: 4-aminobenzoic acid ethyl ester (Anestezine); 4-aminobenzoic acid diethylaminoethyl ester (Procaine) – base and hydrochloride; 2-diethylamino-N-(2,6-dimethylphenyl)-acetamide (Lignocaine) – base and hydrochloride and diethylaminoethyl amide of 2-butoxyquinoline-4-carboxylic acid (Percaine) – base and hydrochloride,

c) calcium salt of organic acids: calcium salt of 2-hydroxypropionic acid (Calcium lactate pentahydrate); calcium salt of pentahydroxycaproic acid (Calcium gluconate hydrate); double calcium salt of lactic and gluconic acids (Calcium lactogluconate); calcium salt of N-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-β-alanine (Calcium pantothenate); calcium salt of 5-(1-cyclohexen-1-yl)-5-ethyl pyrimidine trione (Calcium cyclobarbital) and double salt of 3-pyridinecarboxylic acid diethylamide and calcium thiocyanate (Calcio cardiamid).

These materials were obtained from the Pharmaceutical Works 'Polfa', the Pharmaceutical Supply Enterprise 'Cefarm' as well as 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 an OD-103 derivatograph (MOM, Hungary). The 200, 100, 50 and 20 mg samples were heated in a platinum crucibles 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 platinum crucibles 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 four 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 is no changes in the chemical composition and structure of the compound and no mass loss is observed on the TG and DTG curves. As it is seen in the DTA curves (as example Figs 1–3) only endothermic DTA peaks appeared. The peaks are sharp, high, narrow and appear over a narrow temperature range. These peaks are due to the first-order phase transformations. There are accompanied by absorption or evolution of the latent heat of transformation and change of the molar volume of the compound. As the result of these changes the compound passes on from one crystalline form to another (polymorphic transformation) or changes the physical state (melting, evaporation or sublimation).

Melting 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, and reflects the heat of evaporation.

Mass loss takes place also in the process of sublimation and is accompanied by a single endothermic DTA peak.

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.

The end of the second decomposition stage is not distinctly pronounced on the TG and DTG curves since it overlaps the beginning of the third stage. 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. The peak overlaps that due to endothermic effect of desorption of gaseous combustion products.

In this stage calcium carbonate is the final decomposition product of all the calcium salts. Calcium sulfate is formed only during the decomposition of calcio cardiamid.

The fourth stage appeared exclusively in the case of the decomposition of calcium salts of organic acids. Decarboxylation of calcium carbonate occurs over the range 873–1073 K. The formation of calcium oxide, as for calcium carbonate, is accompanied by the appearance of a distinct plateau on the TG

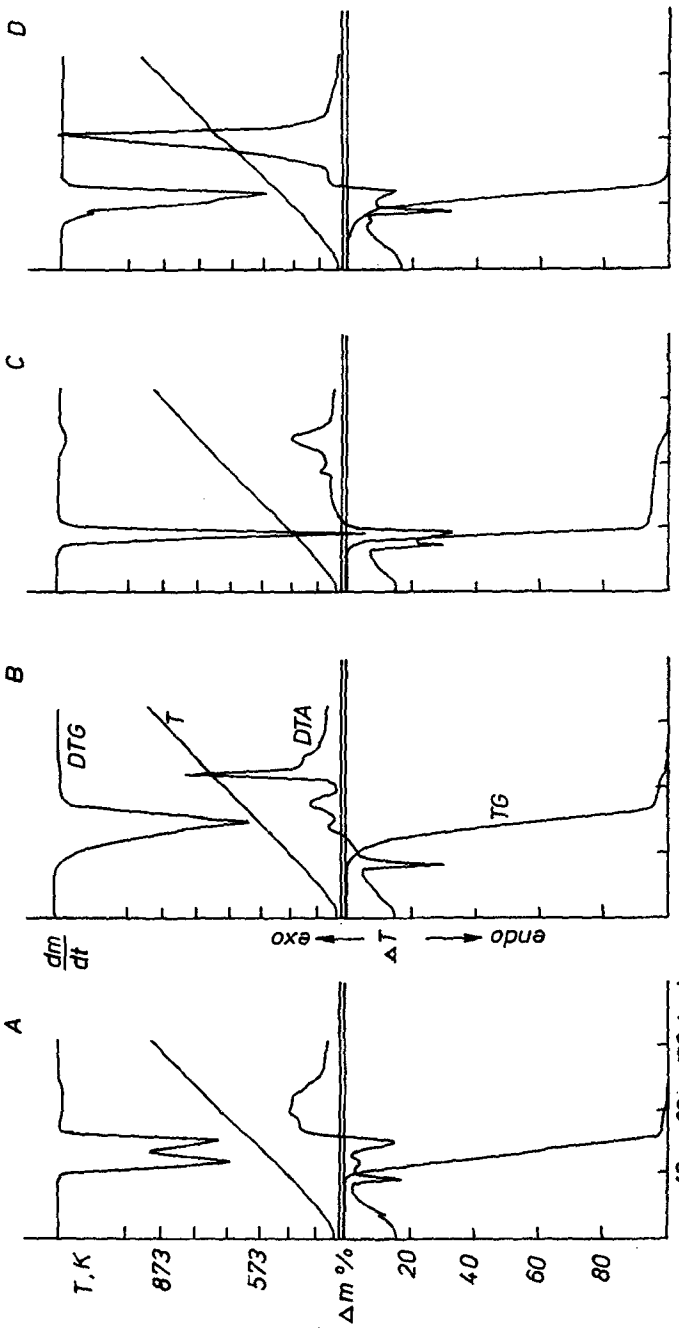

Fig. 1 DTA, TG and DTG curves of the thermal decomposition of: (A) ethambutol, (B) isoniazid, (C) ethionamid and (D) pyrazinamid. 100 mg samples were heated at a rate of 5 deg.min^{-1}

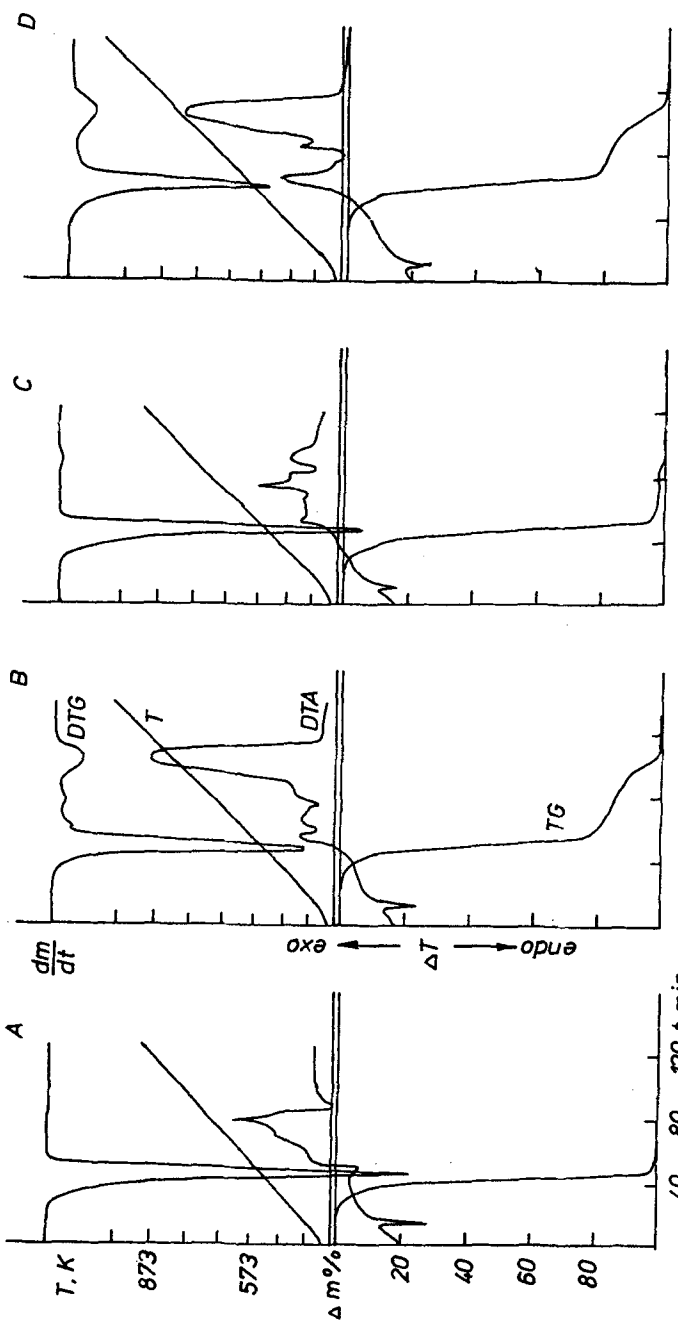

Fig. 2 DTA, TG and DTG curves of the thermal decomposition of: (A) anestezine, (B) procaine, (C) lignocaine and (D) percaine. 100 mg samples were heated at a rate of 5 deg.min^{-1}

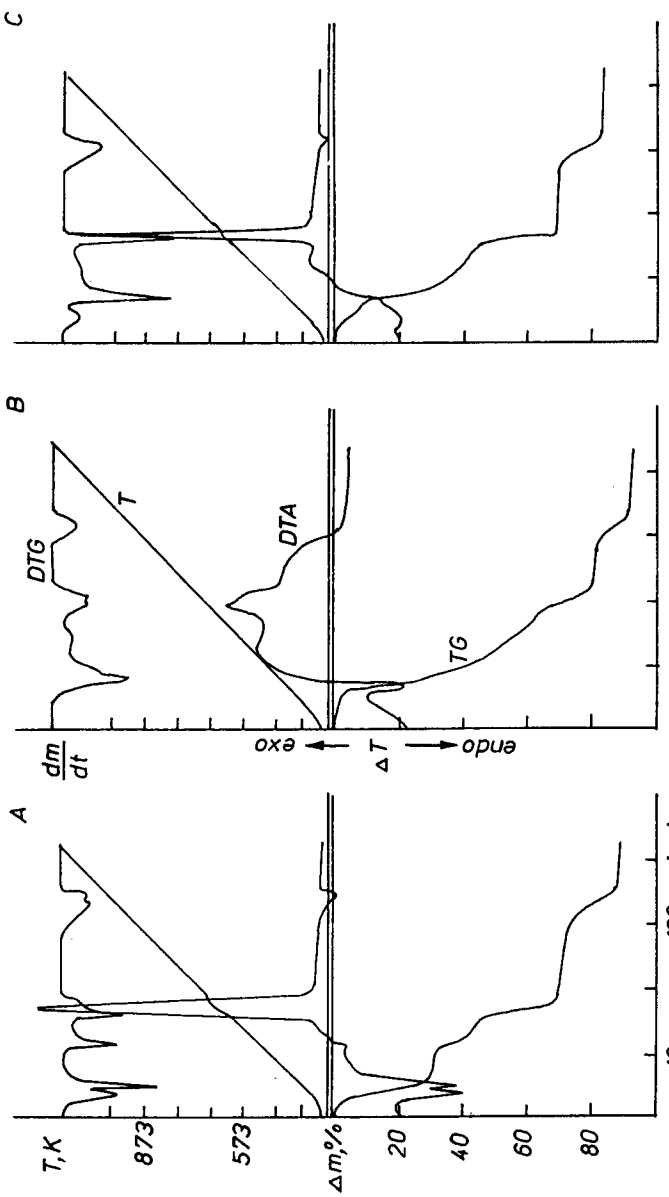

Fig. 3 DTA, TG and DTG curves of the thermal decomposition of: (A) calcium lactate pentahydrate, (B) calcium gluconate hydrate and (C) calcium lactogluconate. 100 mg samples were heated at a rate of 5 deg.min^{-1}

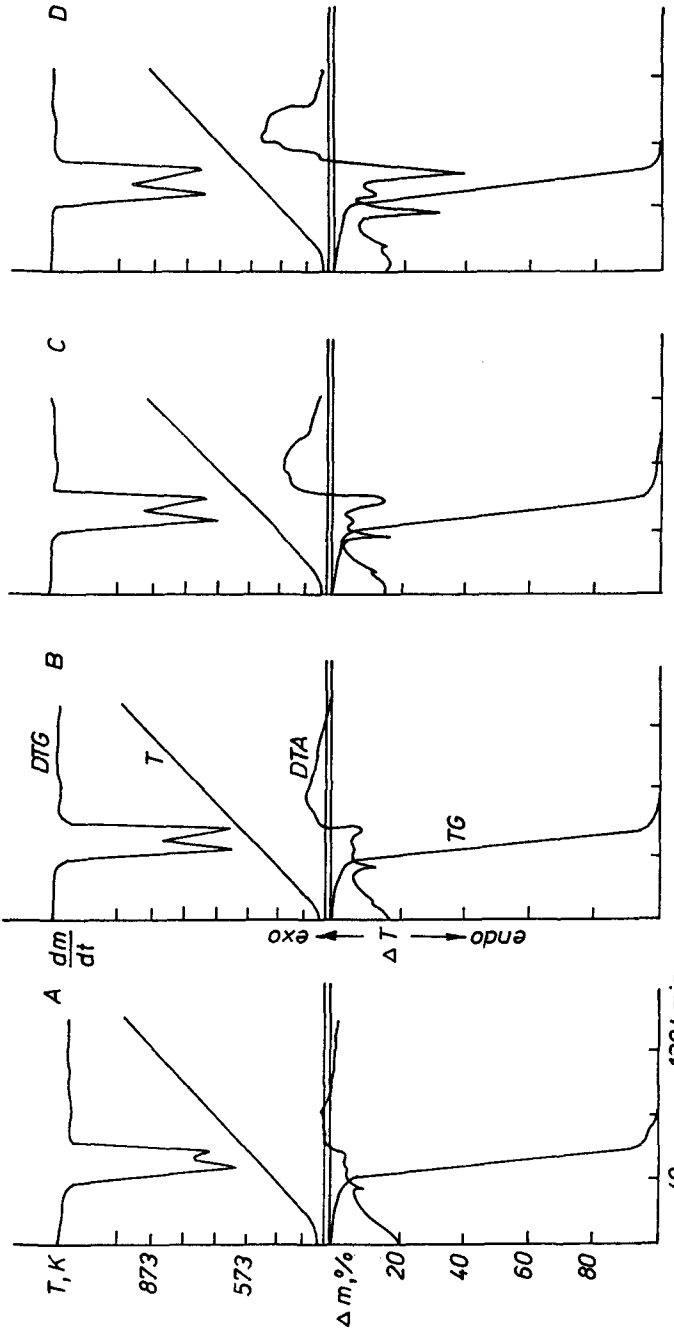

Fig. 4 DTA, TG and DTG curves of the thermal decomposition of ethambutol for the sample sizes: (A) 20, (B) 50, (C) 100 and (D) 200 mg. Samples were heated at a rate of 5 deg.min^{-1}

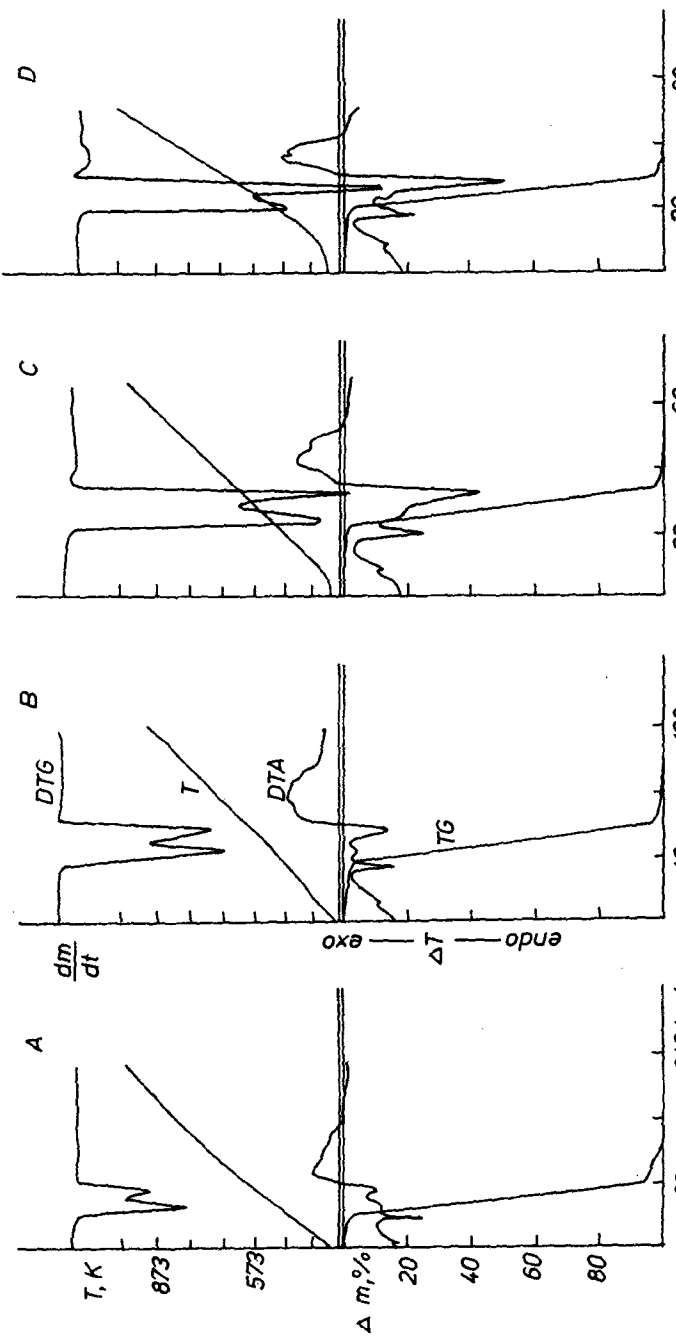

Fig. 5 DTA, TG and DTG curves of the thermal decomposition of 100 mg sample of ethambutol at the heating rates: (A) 3, (B) 5, (C) 10 and (D) 15 deg.min^{-1}

curve extending over several tens of degrees. This process is accompanied by a wide and shallow effects on the DTA and DTG curves.

Influence of the sample size

The changes in the shape of the DTA, TG and DTG curves of the thermal decomposition of studied compounds have been shown to take an example of ethambutol (Fig. 4). The differences in the shape of these curves depict the influence of sample size on the mechanism of its decomposition. 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.

Influence of the heating rate

In Fig. 5 the DTA, TG and DTG curves of the thermal decomposition of ethambutol are presented as recorded at different heating rates. 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 from 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. In addition, the TG curve runs more steeply under the same conditions.

Kinetics of the thermal decomposition

The Kissinger equation has been employed for the determination of kinetic parameter of the thermal decomposition of studied compounds. The equation relates the shift of temperature of the extreme endothermic DTA peak to the heating rate [5]. The relationship between $\ln(\Theta/T_{m2})$ and $1/T_m$ is the straight line which slopes to be 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 [6]. 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. The pre-exponential coefficient has been calculated from the Wendlandt equation [7].

The values of the activation energy and pre-exponential coefficient decrease as the sample mass increases. This can be explained by assuming that diffusion of large quantity of gases evolved from the immediate vicinity of the sample is delayed in respect to increasing sample mass and heating rate. These results in an increase in partial pressure of the gas, thus prolong duration of the reaction. A definite value of heat conductivity leads to a temperature gradient between the surface and interior of the sample, extending thereby the reaction time.

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 and local anaesthetic drugs cause that mechanism of the thermal decomposition is similar and occurred via three stages. In the case of calcium salts, the decomposition occurred via four stages due to formation of calcium carbonate and its decarboxylation.

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 and pre-exponential coefficient on the basis of the DTA results has been confirmed now. The kinetic parameters of the dehydration, formation of the intermediate products in the second stage of decomposition and decarboxylation processes were determined.

References

1 S. H. Hilal, F. Khattab, M. Y. Haggag and I. Haroun, Egypt J. Pharm. Sci., 18 (1977) 77.
2 P. V. Allen, P. D. Rahn, A. C. Sarapu and A. J. Vanderwielen, J. Pharm. Sci., 67 (1978) 1087.
3 J. Martin-Gil, F. Martinez Villa, M. C. Ramos-Sanchez and F. J. Martin-Gil, J. Thermal Anal., 29 (1984) 1351.
4 K. Yano, T. Oomura, H. Sugiura, T. Hikosaka and H. Kawata, Res. Lab., 3 (1977) 117.
5 H. E. Kissinger, Anal. Chem., 29 (1957) 1702.
6 J. B. Czerminski, A. Iwasiewicz, Z. Paszek and A. Sikorski, Metody statystyczne dla chemikow (Statistical methods for chemists), 2nd ed., PWN, Warszawa 1992.
7 W. W. Wendlandt, J. Chem. Educ. 38 (1961) 571.

Zusammenfassung — Mittels DTA und TG wurde die thermische Zersetzung von Antituberkulotika, Lokalanästhetika und als Arzneimittel verwendeten Calciumsalzen von organischen Säuren untersucht. Es wurde eine allgemeine Beschreibung ihrer Zersetzung erstellt. Dabei wurde der Einfluß der Probengröße im Bereich von 20–200 mg und der Aufheizgeschwindigkeit im Bereich von 3–15 deg/min auf die thermische Zersetzung untersucht. Werte für die kinetischen Parameter wurden ebenfalls bestimmt.