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# Analysis of drug formulations by thermal decomposition

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**Abstract**

A survey is made of the application of thermoanalytical methods — differential thermal analysis (DTA), differential scanning calorimetry (DSC) and thermogravimetry (TG) — in the composition control of solid and soft dosage drug formulations. The suitability of the thermal decomposition curves of pharmaceutical preparations for the differentiation of particular drug formulations, for the identification of their components and for the quantitative determination of the content of the active components in the solid drug forms, and in ointments and creams, is demonstrated. In a separate section, the estimation of the moisture content in the final products and in their components is discussed.

## INTRODUCTION

The estimation of the value of a drug is of the highest importance. The pharmaceutical legislation foresees checking of the compliance of the final form of drug with the quality standards established for them. This obliges the producers to control the quality of the raw materials used in the manufacture of drug formulations and to check both the production process and the final product.

The program of analytical studies involves checking the appearance and designation of the final product package, organoleptic examination, verification of the content of drug in a container, determination of the loss on drying, the content of ash and active components, and the microbiological assay [1]. This is very difficult owing to the specific character of drugs and the diversity of their forms. Moreover, it requires a good knowledge of the technology of drug formulations and the utilization of physical, chemical and physico-chemical methods of analysis.

Certain possibilities in the realization of this program for the analysis of drugs have been offered by thermal methods of analysis, in particular differential scanning calorimetry (DSC), differential thermal analysis

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(DTA), thermogravimetry (TG) and derivative TG (DTG). This paper presents a literature review of the application of thermoanalytical methods in the examination of commercial drug formulations. This problem has not previously been the subject of a review article.

## DIFFERENTIATION OF DRUG FORMULATIONS

Wendlandt and co-workers have studied the thermal decomposition of internal analgesics [2], antacids [3] and vitamin preparations [4], representing powders, capsules and tablets. It was shown that the DTA (DSC) and TG curves of individual preparations differ [2]. Only the curves of the thermal decomposition of preparations containing aspirin and a small amount of binder are essentially identical with curves of the decomposition of pure acetylsalicylic acid. Small differences in the shape of the DTA (DSC) curves above 473 K may be due either to the packing density of the sample in the container or to the presence of a binder. Moreover, above 773 K a slight charred residue is observed due to their decomposition. However, when the drug formulations also contain caffeine and salicylamide, the DTA (DSC) curves are characterized by a broad endothermic peak in the range 423–523 K. A similar situation is observed when acenol or phenacetin is present. Moreover, in some preparations the extreme of the DTA peak due to melting of acetylsalicylic acid is shifted to lower temperatures by as much as 45 K. The different chemical compositions of the individual preparations are also reflected in the TG curves, as shown in Fig. 1. The same generalizations that apply to DTA (DSC) curves can be used in their discussion.

The DTA (DSC) and TG curves of individual antacid preparations are also different from each other [3]. Endothermic DTA (DSC) peaks due to the decomposition of calcium and magnesium carbonates are not observed

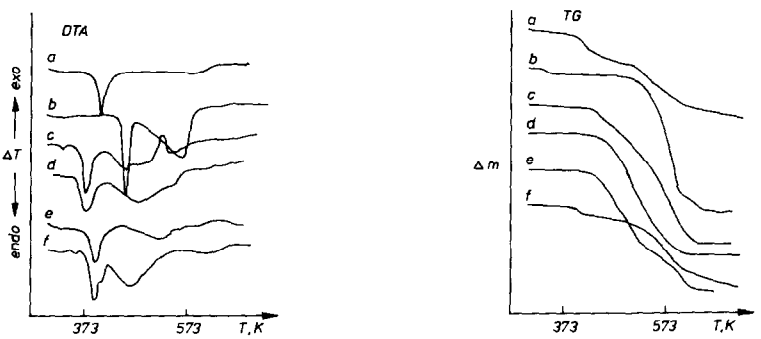


Fig. 1. DTA and TG curves of the thermal decomposition of analgesic preparations [2]: curve a, Bufferin; curve b, Tylenol; curve c, Empirin; curve d, Excedrin; curve e, Vanquish; and curve f, Stanback. Measurements were performed using Du Pont instruments, Model 900 DTA and Model 950 TG. Samples (5–20 mg) were heated at a rate of 10 K $min^{-1}$ in a dynamic nitrogen atmosphere.

because of the maximum temperature limitation of DTA devices. Some of the drug formulations contain similar peaks in the range 448–498 K although there are no common components in these preparations. It has also been shown that in some cases the initial temperatures of the thermal decomposition are sufficient for differentiation between preparations.

Owing to the chemical complexity of vitamin molecules, combined with the small quantities present in standard dosage forms, interpretation of the curves of vitamin preparations is exceedingly difficult [4]. It is only possible to recognize large thermal effects due to the decomposition of binders and fillers, because they are the fundamental constituents of these formulations. Moreover, the variety of compounding techniques and the wide choice of varying auxiliary components in the manufacture of various commercial vitamin products containing the same vitamin, means that DTA (DSC) and TG curves differ for similar tablets manufactured by different producers. Thus the qualitative identification of a particular vitamin should involve a comparison of the standard decomposition curve of the vitamin with those obtained for an unknown drug formulation, or should consider the occurrence of a DTA (DSC) peak within a specified temperature range as an indication of the presence of the vitamin in the decomposed preparation. The absence of this peak cannot be indicative of the absence of the vitamin in the sample, subtle thermal effects caused by minute concentrations of the vitamins are not often observed.

The problem with the thermal analysis of vitamin preparations is that an excessive volume expansion of the sample occurs, with evolution of gaseous products due to decomposition of the auxiliary components. This leads to very non-reproducible curves. To prevent, or at least reduce, this problem, a sample pelletizing technique was developed, in which a sample of powdered vitamin preparation is pressed between two layers of potassium bromide. A pure potassium bromide pellet is used as the reference material.

These studies confirmed that it is possible to use DTA (DSC) and TG methods in the identification of individual preparations [2–4] and the potential of these applications in criminal investigations has been demonstrated. DTA and DSC methods are generally the most helpful [2, 3].

It has also been shown that it is not possible to comment on the origin of each endothermic peak on the DTA (DSC) curve, due either to the complexity of the studied preparations or to the lack of exact information on their composition [3]. The presence of absorbed moisture can be detected by the appearance of new peaks, shifts in existing peaks or significant changes in the size of the peaks below 373 K [3, 4]. However, the ageing of a preparation can cause changes in the DTA (DSC) curves at higher temperatures [3].

Thermal analysis curves are easy to obtain and the instrumentation is relatively inexpensive and widely available [2, 3]. However, it should be

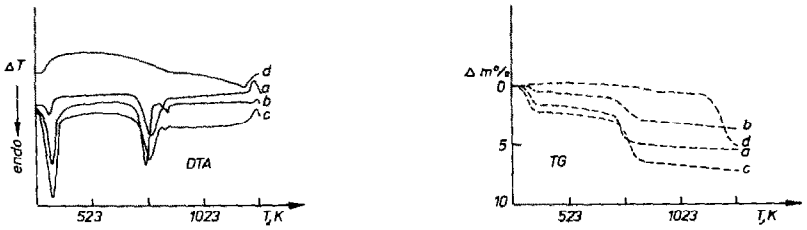


Fig. 2. DTA and TG curves of the thermal decomposition of the Chinese crude drug Kasseki [5]: curve a, Hong Kong market (1967); curve b, Osaka market (1974); curve c, Osaka market (1975); and curve d, talc. Measurements were performed using a Thermoflex DTA–TG instrument. Samples (10 mg) were heated at a rate of 5 K $min^{-1}$ and $\alpha$-$Al_2O_3$ was used as reference material.

noted that the shape of the curves is also dependent on instrumental variables such as heating rate, geometry of the sample container, furnace atmosphere, etc.

DTA, TG, X-ray diffractometry and X-ray fluorescence analysis were used by Ota et al. [5] to investigate the constituents of a Chinese crude drug "Kasseki". The results showed that the Kasseki specimens consisted mainly of $\alpha$-quartz, hydrated halloysite and sanidine, with traces of some elements. Various specimens of Kasseki resemble each other in composition. Using thermal methods of analysis, Kasseki may be distinguished from similar materials such as talc, see Fig. 2.

The discrimination of pearl powder from pearl-layer powder is impossible by microscopy, scanning electron microscopy, chemical analysis, X-ray diffractometry or even IR spectroscopy. Both are aragonite with a small amount of calcite, but differ in their efficiency when applied in medicine and cosmetics. Tianrui et al. [6] have recommended that DTA be used to distinguish pearl powder from pearl-layer powder. The difference between them lies in the different amounts of amino acids present in the powders. The authors suggest that the medical efficiency of the various types of pearl powder and pearl-layer powder is determined by the amount of amino acids present. As shown in Fig. 3, differences between the specimens of pearl powder are most marked below 773 K.

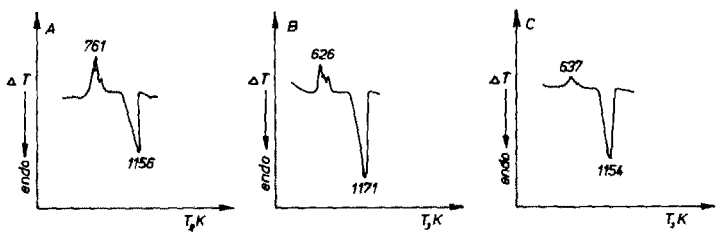


Fig. 3. DTA curves of the thermal decomposition of marine pearl powders origin from A, Guangdong; B, Guangxi; and C, fresh water (from ref. 6). Samples were heated at a rate of 20 K $min^{-1}$.

## IDENTIFICATION OF THE COMPONENTS OF PHARMACEUTICAL PREPARATIONS

The checking of the qualitative composition of drug formulations by thermal methods of analysis is based on the verification of the identity of the components from their thermal properties.

The suitability of DTA, TG and DTG methods for monitoring the composition of solid dosage forms was studied by Radecki and Wesołowski [7–14]. The investigation was preceded by an evaluation of the influence of the thermal decomposition of mixtures of the tablet components on the decomposition of the active components [7]. This is very important because it makes it possible to establish the characteristic features of the decomposition of the active components, which can be used for its identification, and enables the quantitative determination of the active component in drug formulations.

A similar problem was studied by Gucluyildiz et al. [15] who used isothermal TG to investigate the influence of selected tablet components on the evaporation of nitroglycerine from sublingual tablets. The results, confirmed by chemical analysis, showed that the volatility of nitroglycerine was dependent in various ways on the nature of the vehicles and the concentration ratios in which they were used. It was shown that TG is a simple, rapid and reliable means of assessing the influence of the vehicles on the liberation of the active components from the drug formulations containing them.

In order to observe on the DTA, TG and DTG curves the characteristic thermal effects due to the varying contents of a particular component in a mixture, the thermal decomposition of 14 model tablet masses was studied by Wesołowski [7]. It was shown that when changing the content of particular components in successive samples, the thermal decomposition of a mixture (granulate, tablet and coated pills), largely reflects the decomposition of the main component. As the content of this gradually decreases, the overall thermal effects of the decomposition of the mixture are less dependent on the decomposition of this component. Because of the poor sensitivity and detection limits of thermal methods of analysis, subtle effects due to the decomposition of a component present in minor amounts are very frequently not apparent on the DTA, TG and DTG curves. Only the parameters of the overall effects are influenced, namely the temperature of the beginning, end and extremum of the peak, and the height, width at half-height and area of the peak. This is presented graphically in Fig. 4.

The effects due to the decomposition of a particular component are more weakly reflected on the curves of a mixture, when the decomposition covers a broad temperature range and when it is accompanied by a small loss in weight; this is shown in the data compiled in Table 1. Components which are stable over the temperature range studied affect

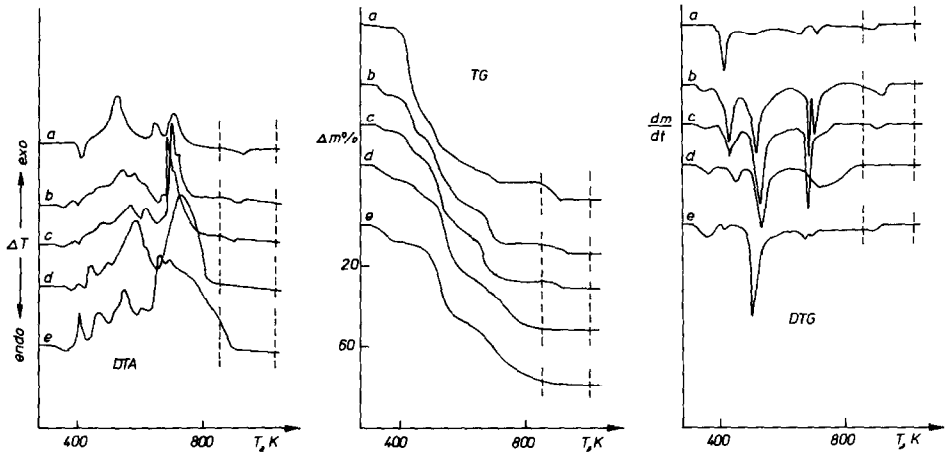


Fig. 4. DTA, TG and DTG curves of the thermal decomposition of (curve a) calcium gluconate, (curve e) tablet mass comprising starch, talc, magnesium stearate and gelatin, and its mixtures containing (curve b) 45%, (curve c) 30%, and (curve d) 15% of calcium gluconate [7]. The decarboxylation of calcium carbonate, arising from combustion of the organic groups of calcium gluconate, is indicated by the dashed line. Measurements were performed using a Derivatograph (model OD-130). Samples (200 mg) were heated at a rate of 5 K $min^{-1}$ in a static air atmosphere, and $\alpha$-$Al_2O_3$ was used as reference material.

only the thermal conductance and heat capacity of the sample, the diffusion of the volatile products of decomposition, and other parameters which are insignificant in the thermal decomposition of the mixture analysed.

To continue the investigations, more than 100 commercially available solid dosage forms were examined, including simple and effervescent powders, dusting powders, capsules, simple and effervescent granulates, internal tablets, tablets for sucking, and preparation of effervescent beverages, and coated pills [8, 9]. These were chemotherapeutic preparations [10, 12], expectorants [12], neuroleptic preparations [11, 13], vitamins [13], anti-inflammatory preparations and preparations used for the treatment of ulcers and mineral deficiency of the organism [14].

Analysis of the composition of the studied drug formulations shows that a particular drug form is a physical mixture of between two and eleven chemical compounds, differing in elemental composition, chemical structure, molecular weight and physico-chemical properties [10–14]. Particular components of these mixtures occurred in the ratio ranging from 1:50 to 1:250. Occasionally, the ratio ranged from 1:2000 to 1:5000. In these preparations the major component was usually an active one. Both organic and inorganic compounds are present which also differ in percentage content in the drug formulations.

It was shown that identification of an active component is most conveniently accomplished by comparing the temperature ranges, and the

TABLE 1

Results of the qualitative analysis of thermal decomposition of the model tablets containing selective active components [7]

| Tablet mixture | Active component | Temp. range[a] (K) | Loss in weight[a] (%) | Number of decompn. stages[a] | Content of active component[b] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 45.0% | | | 30.0% | | | 15.0% | | |
| TM-1 | Phenyl salicylate | 353–493 | 100.0 | 1 | + | + | + | + | + | + | + | + | + |
| | Salicylamide | 373–753 | 100.0 | 1 | + | + | + | + | + | + | + | (+) | (+) |
| | Acetylsalicyclic acid | 353–813 | 100.0 | 3 | + | + | + | + | + | + | + | + | + |
| TM-2 | Nitrofurantoin | 463–813 | 100.0 | 2 | + | + | + | + | + | + | + | (+) | (+) |
| | Ca pantothenate | 313-1013 | 89.0 | 5 | + | + | + | + | + | + | + | + | + |
| TM-7 | Antipyrine | 403–893 | 100.0 | 2 | + | + | + | + | + | + | + | + | + |
| | Carbromal | 383–893 | 100.0 | 2 | + | + | + | + | + | + | + | (+) | (+) |
| | Pyrazinamide | 413–713 | 100.0 | 3 | + | – | – | + | – | – | + | – | – |
| | Ca gluconate | 383–983 | 88.0 | 5 | + | + | + | + | + | + | + | (+) | (+) |
| | Al phosphate | 313–483 | 28.0 | 1 | + | (+) | (+) | + | (+) | (+) | + | (+) | (+) |
| | Mg trisilicate | 313–883 | 33.0 | 2 | + | (+) | (+) | + | (+) | (+) | + | – | – |
| TM-12 | Isoniazid | 433–813 | 100.0 | 1 | + | – | – | + | – | – | + | – | – |
| | Novalgine | 313–973 | 78.0 | 4 | + | + | + | + | + | + | + | (+) | (+) |

[a] Data characterizing decomposition of pure component.

[b] The three columns of symbols under each content value refer to the DTA, TG and DTG curves, respectively. Identification of drug: + = possible; – = impossible; and (+) = observed variations do not characterize the particular species unambiguously.

areas and shapes of the DTA peak of a pharmaceutical preparation, with those of authentic standard compounds [8, 9]. The measurements must be run under similar conditions using the same instrument.

Most important for the identification are the endothermic DTA peaks due to first-order phase transformations, particularly melting, evaporation, sublimation and polymorphic transformations [7, 8, 9]. The peaks are sharp, high, relatively broad and appear over a narrow temperature range. The parameters of these peaks change proportionally to the content of the active component.

The opposite situation is observed in the case of the exothermic effect due to combustion of the organic constituent of the drugs. The peaks differ in shape, area and temperature range from those of the individual combustion effects of particular components. The parameters of the overall exothermic combustion effects also change with the change in active component but it is difficult to use them for identification purposes.

In comparison with DTA, the TG and DTG curves are less suitable for the identification of an active component. This is confirmed in the results compiled in Table 1. The possibility of simultaneous recording of the DTA, TG and DTG curves makes it possible to observe more precisely any change in the velocity of weight loss of the mixture, thus facilitating the separation of successive stages of the thermal decomposition of the drug formulation. As with the DTA curves, identification is based on the comparison of temperature ranges and shapes of curves, and the weight losses accompanying particular decomposition steps.

## QUANTITATIVE ANALYSIS OF PHARMACEUTICAL PREPARATIONS

### *Analysis of solid dosage forms*

The quantitative determination of the content of the active component in a drug formulation is very important. Margomenou-Leonidopoulou et al. [16, 17] were the first to suggest the possibility of using thermal methods of analysis in this field. On the basis of differences in the shape of the DTA, TG and DTG curves of novalgine and *N*-butylscopolamine hydrobromide below 493 K, they were able to determine the contents of both components in their model mixture.

An endothermic DTA peak ($T_{max}$, 431 K) indicates the stage due to the dehydration of novalgine, and the loss in weight at this stage can be determined from the TG curve. By comparing its value with the weight loss due to dehydration of the novalgine standard, its content in the mixture can be estimated. The dehydration stage is also confirmed by the DTG peak whose area decreases proportionally to that of the novalgine standard. This is shown clearly in Fig. 5.

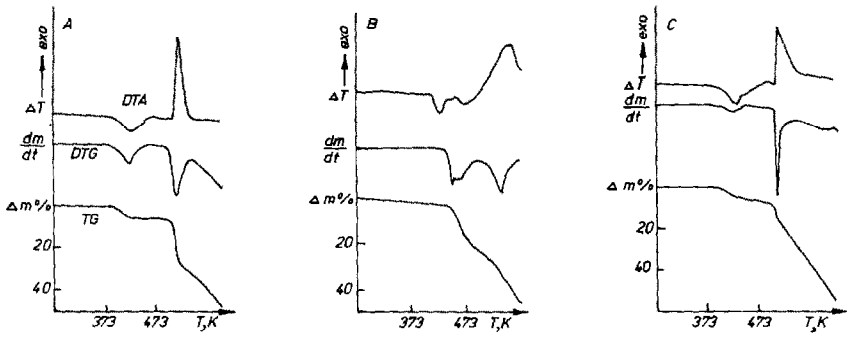


Fig. 5. DTA, TG and DTG curves of the thermal decomposition of (A), novalgine, (B), *N*-butylscopolamine hydrobromide, and (C), a mixture of both active components (26.4 mg and 1.0 mg) [16]. Measurements were performed using a Derivatograph (no. 879644). Samples (200–250 mg) were heated at a rate of 6 K $min^{-1}$ in a static air atmosphere.

Over the range 440–493 K, the loss in weight occurs at a constant rate of 1.68%. However, in the same temperature region the weight losses for novalgine and *N*-butylscopolamine hydrobromide are 0.92% and 21.6%, respectively. Thus, it is possible to assess the approximate proportion in which the components are mixed.

In addition, it should be noted that the loss in weight of the mixture recorded over the range 493–535 K is significantly smaller than those of the individual components. This is probably the result of the thermal reactions occurring in the mixture. Moreover, the less sharp endothermic DTA peak ($T_{max}$, 503 K) indicates the presence of an impurity in the novalgine arising from the oxidative degradation of *N*-butylscopolamine hydrobromide.

The possibility of the application of TG and DTA methods in the direct determination of the content of γ-hexachlorocyclohexane in Delitex powder was pointed out by Otto [18]. On the DTA curve of the preparation, the thermal decomposition shows an endothermic effect due to melting of γ-hexachlorocyclohexane. However, on the curve of the pure component, two endothermic DTA peaks are observed due to its melting and evaporation. Moreover, γ-hexachlorocyclohexane evaporates completely below 573 K, whereas when present in the powder it evaporates at a significantly lower temperature, see Fig. 6.

Taking into account that no loss in weight was observed on the TG curve of talc up to 673 K and no effect due to its phase transformation on the DTA curve was apparent, the changes in the shape of the TG and DTG curves described above should correlate with the content of γ-hexachlorocyclohexane in Delitex powder. This can be applied to the direct determination of its content.

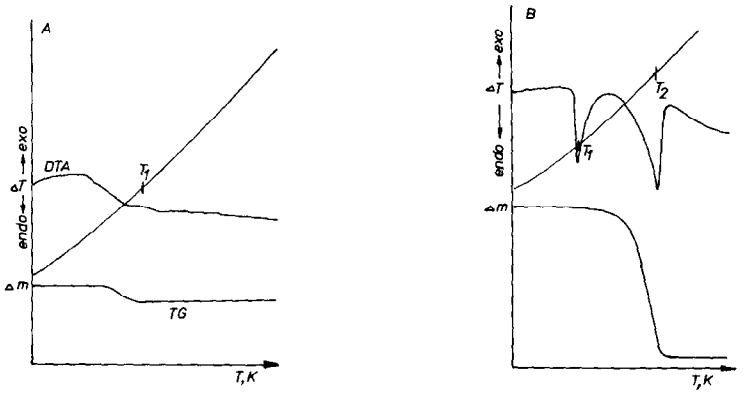


Fig. 6. DTA and TG curves of the thermal decomposition of (A) Delitex powder ($T_1 = 473$ K) and (B) γ-hexachlorocyclohexane ($T_1 = 392$ K and $T_2 = 546$ K) [18]. Measurements were performed using a Derivatograph (MOM, Hungary). Samples (200 mg) were heated at a rate of 6 K min$^{-1}$ in a static air atmosphere, and talc was used as reference material.

The data obtained as a result of the quantitative analysis of the Delitex powder by isothermal TG at 453 ± 2 K are shown in Table 2. The standard deviation values suggest that the method is generally accurate. Moreover, the total time of estimation is relatively short, being 1 h at most.

The γ-hexachlorocyclohexane content determined by DTA is calculated from the equation

$$m_x = \frac{m_2}{A_2} A_x$$

where $m_x$ is the content of the active component, $m_2$ is the content of the pure component, $A_x$ is the DTA peak area of the active component and $A_2$ is the DTA peak area of the pure component.

TABLE 2

Statistical evaluation of the γ-hexachlorocyclohexane content in Delitex powder measured by isothermal TG and DTA [18]

| | Mixture of 20 mg γ-hexachlorocyclohexane and 1980 mg talc | Trade products | |
|---|---|---|---|
| | | A | B |
| *Isothermal TG measurements* | | | |
| Arithmetic average $\bar{x}$ | 0.98 | 0.80 | 1.02 |
| Standard deviation $s$ | 0.112 | 0.346 | 0.236 |
| Confidence interval $t_{0.95}$ | 0.086 | 0.266 | 0.181 |
| *DTA measurements* | | | |
| Peak area mm$^2$ | 102.8 | 72.4 | 107.2 |
| Arithmetic average $\bar{x}$ | 0.98 | 0.77 | 1.02 |
| Confidence interval $t_{0.90}$ | 0.117 | 0.131 | 0.148 |

The area of the effect is only proportional to the content of the active component in a mixture when its values (the heat of melting $\Delta H_f$ and the apparatus constant $K$ of the DTA device) do not change due to variations in the concentration. These measurements are generally only possible in analytical procedures in which the matrix remains inert, both during the enthalpy changes and the chemical reactions, within the range of thermal reaction of the active constituent.

The results are compiled in Table 2. The analysis of the values of the arithmetic average of the content of γ-hexachlorocyclohexane and the confidence interval indicates a close analogy with those of the isothermal TG measurements. There is good agreement in the values of the arithmetic average of the active component content in the commercial powders analysed. It must also be mentioned that the operation of the DTA device is very straightforward and a single measurement can be made in a short time.

It must be emphasized that when small samples are used, e.g. 200 mg, the probability of inhomogeneity in the sample should be taken into account, this contributing to the systematic error. A good homogeneity can be obtained when 1–2 g specimens are used. The value of the systematic error is also affected by the presence of impurities, especially volatile ones. Using these methods, the content of some of the impurities can be determined, e.g. mechanically bound water, which is marked clearly on the TG curve as a plateau.

The area under the endothermic DTA peak was also used by Mohamed and Tawakkol in the quantitative analysis of Cycloserine tablets [19]. The peak area can be described by the equation

$$A = \frac{Gm}{k} \Delta H$$

where $A$ is the peak area ($\Delta Tt$), ($\Delta T$ is the difference in temperature between sample and reference material and $t$ is the interval of time during which the phase change occurs), $G$ is a calibration factor that depends on the particle size and packing of the sample, $k$ is a constant related to the thermal conductivity, $\Delta H$ is the enthalpy change accompanying the melting process and $m$ is the weight of the sample.

The area under the $\Delta T$–$t$ curve was obtained by cutting and weighing xerox copies of the thermograms. Under the established experimental conditions, the relationship between peak area and the weight of cycloserine standard powder was linear when the weight of cycloserine varied between 1 and 5 mg. The amount of the active ingredient in Cycloserine tablets was determined graphically.

To verify the reproducibility of the method, samples of Cycloserine tablets were spiked with cycloserine standard powder and the results obtained are summarized in Table 3. The data reveal that the proposed

TABLE 3

Results of the quantitative determination of active ingredient in the Cycloserine tablets [19]

| Content of cycloserine (mg) | Cycloserine powder added (mg) | Found (mg) | Recovery (%) |
|---|---|---|---|
| 1.3 | 1.6 | 3.0 | 103.4 |
| 1.5 | | 1.45 | 96.6 |
| 2.6 | | 2.7 | 103.9 |
| 2.8 | 2.0 | 4.65 | 94.8 |
| 2.9 | | 2.8 | 96.5 |
| 3.4 | | 3.3 | 97.0 |
| 4.8 | | 4.9 | 102.0 |

method gives an accuracy of $99.1 \pm 3.2\%$ and a recovery of 99.1%. This shows that the method is accurate, as well as simple and rapid.

The quantitative analysis of the composition of pharmaceutical preparations has also been reported by Wesołowski and co-workers [7–14]. The content of the active component was determined solely on the basis of the loss in weight recorded by the TG curve [8, 9]. The determinations were facilitated by the DTG curves which allow distinct discrimination of the weight losses due to decomposition of the active component and subsequent thermal stages due to destruction of other matrix components. In the calculations the following equation was used [7]

$$x = \frac{m_x}{m_2} 100$$

where $x$ is the content of the active component, $m_x$ is the weight loss from the TG curve of the pharmaceutical preparation and $m_2$ is the weight loss from the TG curve of the pure component.

Considerable variations in the area under the DTA peak are presumably due to inhomogeneity of the sample, its size distribution and packing in the crucible, as well as the influence of variable instrumental parameters such as the heating rate, the asymmetric location of the crucibles for sample and reference material, etc. Because of the difficulties resulting from the multi-component composition of the dosage forms encountered in deriving the relation between the peak area and percentage content of the active component, the area under DTA peak was not utilized in these studies [8, 20].

It has been shown that the determination of the active component in pharmaceutical preparations depends on its concentration and the type of thermal decomposition process used [7]. A high content of the active constituent facilitates its quantitative determination because its thermal decomposition steps are better differentiated by the TG and DTG curves,

and, therefore, any effect from other components is correspondingly diminished. However, thermal decomposition processes which occur over a broad temperature range are least suitable. The decomposition frequently occurs over the temperature range of the thermal decomposition of the tablet mass, accompanied by a high weight loss.

Studies have shown that the thermal processes suitable for the determination of the active component in drug formulations can be categorized as follows [8].

1. Dehydration. The loss of crystallization or constitution water is accompanied by the formation of an intermediate compound of precisely defined composition and chemical structure. This occurs mostly over the range 333–573 K and manifests itself in a distinct plateau on the TG curve.

2. Decarboxylation. The loss of carbon dioxide from sodium hydrogen carbonate occurs in the range 333–473 K. Decarboxylation of calcium carbonate formed by combustion of organic anions of calcium salts 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 extending over several tens of degrees. This feature makes it much easier to read the loss in weight and thus to obtain relatively accurate results.

3. Weight loss due to reactions between components of an effervescent mixture. Reactions of sodium or potassium hydrogen carbonates with citric or tartaric acids are characterized by the loss of carbon dioxide and water. Because the reaction occurs in a temperature range close to that of the thermal decomposition of the excess metal hydrogen carbonate, it is difficult to discriminate between the loss in weight due to this reaction and that due to the decomposition of the metal hydrogen carbonate. Therefore, only the total content of the organic acid and metal hydrogen carbonate can be determined. The termination of the two processes is not accompanied by a distinct plateau.

4. Weight loss corresponding to inflections on the TG curve due to the formation of an intermediate can be interpreted as follows. (a) A product is formed whose composition and chemical structure can be determined. This facilitates determination of the stage of the thermal decomposition of a given active component. (b) An intermediate product of decomposition is formed whose composition or the structure cannot be established. In this case, calculations of the content of the active constituent are based on the comparison of the weight loss occurring between two adjacent inflections on the TG curves of a given preparation and of the standard compound. In this case, DTG curves which indicate the beginning and end of a given stage were very helpful.

5. Weight loss due to total evaporation or sublimation of the active component. Quantification of the results is only possible for those components whose thermal decomposition occurs over a narrow tempera-

ture range, and when no interference arises from decomposition of the remaining components of the preparation.

When the vehicles do not decompose within the temperature range studied, the content of the active principle can be evaluated on the basis of the loss in weight due to its complete combustion [20]. However, if the thermal decomposition of the remaining components of the dosage forms does not leave a residue, the residue left after decomposition of the active component can be used for its determination.

In the estimation of the content of active principles, several features must be taken into consideration [20]. Considering the dehydration process of the active component, decarboxylation of alkali metals hydrocarbonates, loss in weight due to chemical reaction between components of the effervescent mixture and complete evaporation or sublimation of the active principle, it is necessary to remember that in the narrow temperature interval considered, the release of mechanically bound and crystallization water of the common vehicles frequently occurs. This leads to high results.

The determination based on the weight loss between inflections on the TG curves should be treated with caution. These processes frequently occur over the range 373–773 K, corresponding to the highest weight loss of the majority of vehicles. For these reasons, the loss in weight at a defined stage of decomposition of the active principle is increased due to decomposition of components of the dosage form occurring over the same temperature range. In this case the determinations can be carried out only when the thermal decomposition stage of the active principle occurs over a very narrow temperature interval, in which there is no or only slight loss in weight due to decomposition of vehicles.

By applying the above processes, the content of the active component was determined in more than 50 of the analysed solid dosage forms without the necessity of separation from the tablet mass [10–14]. Moreover, in some preparations the content of two active components was simultaneously determined. The results obtained in this study are in good agreement with those calculated from the manufacturer's information.

A statistical evaluation of the results is shown in Table 4, indicating that the results are generally accurate. The values of the relative error are lower than 5% for the majority of determinations. Taken together with a low accuracy of reading of the weight loss from the TG (DTG) curves and, frequently, a several percent content of the component to be determined, this can be considered as satisfactory [20]. The results also show that the TG and DTG methods are precise and that individual determinations are mostly reproducible.

The calculations also indicate that a larger loss in weight at a particular stage of the decomposition of the active principle and an increase in the

TABLE 4

Statistical evaluation of the determinations of active components in the selected tablets [20]

| Trade name | Content of the active component (%) | | | Standard deviation | | Confidence interval $t_{0.95}$ | Coefficient of variation (%) |
|---|---|---|---|---|---|---|---|
| | Calc. [a] | $\Delta m$ [b] | Found | $s$ | $s_{\bar{x}}$ | | |
| PAS-Natrium | 92.6 | 15.68 | 92.26 [c] | 0.44 | 0.18 | 0.46 | 0.48 |
| Pyralginum | 86.2 | 4.35 | 87.00 [d] | 1.27 | 0.52 | 1.33 | 1.45 |
| Calcipiryna | 19.2 | 8.32 | 18.90 [e] | 0.30 | 0.12 | 0.32 | 1.60 |
| Calcium pantothenicum 100 mg | 62.5 | 5.67 | 61.60 [f] | 0.56 | 0.23 | 0.59 | 0.91 |
| Calcium lacticum | 92.7 | 13.42 | 93.83 [g] | 0.53 | 0.22 | 0.55 | 0.56 |
| Calcium gluconicum | 89.3 | 9.08 | 92.69 [h] | 1.00 | 0.41 | 1.05 | 1.08 |
| Polopiryna S | 50.0 | 17.63 | 55.11 [i] | 0.68 | 0.28 | 0.71 | 1.22 |
| Natrium salicylicum | 83.3 | 40.17 | 89.26 [j] | 0.45 | 0.19 | 0.48 | 0.51 |
| Sulphamethazinum | 76.9 | 28.57 | 78.27 [k] | 1.12 | 0.46 | 1.17 | 1.43 |
| Nitrofurantoin | 28.6 | 20.67 | 32.29 [l] | 0.64 | 0.26 | 0.67 | 1.97 |
| Acenol | 80.7 | 66.75 | 80.91 [m] | 0.84 | 0.34 | 0.88 | 1.03 |
| Salolum | 76.9 | 69.40 | 77.11 [n] | 0.85 | 0.35 | 0.89 | 1.10 |

[a] Calculated from the producers information. [b] Value of the loss in weight from which the content of active principle was determined. (Calculations are based on 6 determinations.) [c] Sodium *p*-aminosalicylate. [d] Novalgine. [e] Calcium carbonate. [f] Calcium pantothenate. [g] Calcium lactate. [h] Calcium gluconate. [i] Acetylsalicylic acid. [j] Sodium salicylate. [k] Sulphamethazine. [l] Nitrofurantoin. [m] *N*-acetyl-*p*-aminophenol. [n] Phenyl salicylate.

content of the active component, decrease the coefficient of variation, whose values demonstrate that this method can be used for less accurate scientific measurements.

Compared with DTA, DSC has a much larger significance in the study of drug formulations. In spite of the fact that thermodynamic equilibrium is not usually achieved, DSC provides much valuable information characterizing the phase transitions of samples and allowing a relatively accurate determination of a series of thermodynamic constants. Some of them are related to the content of the active component in dosage forms.

Jinfang et al. [21] applied DSC in the quantitative assay of Ibuprofen tablets. The measurements were based on a linear relationship between the heat of melting and the weight of the active component. The area under the peak on the DSC curve of Ibuprofen tablets indicates the heat of melting. Tablet excipients do not interfere with the determination. The average recovery of Ibuprofen in the tablets was 99.59%. This suggests that the method is accurate, rapid and reproducible.

DSC studies on isosorbiddinitrat and its mixtures with lactose and sodium chloride were performed by Wächter et al. [22]. The ratio of the heat of melting of a mixture of isosorbiddinitrat with either excipient to that of the pure drug was linearily related to the content of active ingredient. The results of the analysis are in good accordance as compared with those obtained by polarimetry (Table 5).

Curini et al. [23] applied DSC and TG methods for the direct analysis of cocaine and the more common cuts found in cocaine sold on the illegal market. To determine the calorimetric behaviour, DSC analyses were carried out on very pure samples of cocaine, anaesthetic and inert cuts, and caffeine. Figures 7(A) and 7(B) show the DSC curves of the analysed standards, and Table 6 lists the enthalpy values corresponding to the

TABLE 5

Results of quantitative determination of isosorbiddinitrat in the drug formulations by DSC and polarimetric analysis [22]

| Series | Isosorbiddinitrat content (%) | | Purity by DSC (mol.%) | Melting point by DSC (K) |
|---|---|---|---|---|
| | DSC | Polarimetry | | |
| *Active component in mixture with lactose* (4/6 by weight) | | | | |
| 25047 | 40.7 | 40.5 | 99.95 | 342.68 |
| 25046 | 39.8 | 40.3 | 99.95 | 342.67 |
| 25005 | 39.9 | 40.7 | 99.92 | 342.67 |
| *Active component in mixture with sodium chloride* (1/9 by weight) | | | | |
| 13025 | 10.00 | 10.35 | 99.93 | 342.37 |
| 23041/2 | 9.85 | 10.03 | 99.93 | 342.37 |
| 31572/0 | 10.40 | 10.70 | 99.94 | 342.34 |

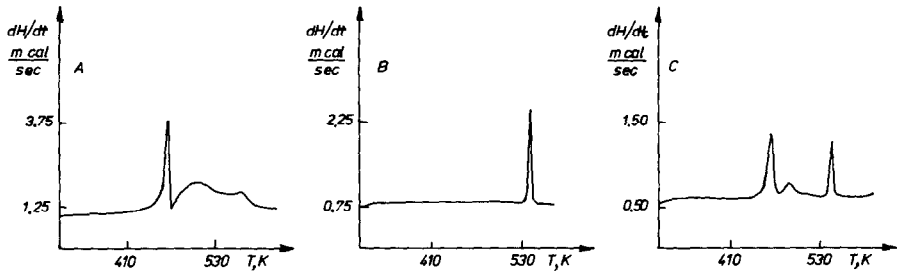


Fig. 7. DSC curves of (A) cocaine, (B) carbocaine, and (C) a mixture of both components (1:1 by weight) [23]. Measurements were performed using a Perkin-Elmer DSC-2B instrument. Samples were heated at a rate of 10 K $min^{-1}$ in a dynamic nitrogen atmosphere.

characteristic peaks of each compound. A series of synthetic cocaine–cut mixtures with variable concentrations of cocaine were prepared to obtain calibration curves of cocaine–enthalpy and of cut–enthalpy. These may be used in the determination of the content of cocaine and cuts found in forensic samples.

The DSC peaks corresponding to the cocaine and to the cuts are well separated and can also be used to obtain a correct qualitative analysis by comparing the curves of the illegal samples with those of the pure substances and of the synthetic mixtures. For example, Fig. 7(C) shows the DSC curves of a synthetic mixture.

The analysis of the inorganic components is easily carried out by TG with a maximum error of less than 1%. The TG curve of cocaine shows a main decomposition step in the range 483–563 K and a second small stage in the range 563–843 K. Therefore, the decomposition of calcium carbonate is not influenced by the cocaine decomposition. TG can also help in

TABLE 6

Enthalpy values corresponding to the characteristic peaks of cocaine and each compound [23]

| Standard | $\Delta H$ (cal $g^{-1}$) |
|---|---|
| Cocaine | 44.3 |
| Carbocaine | 26.2 |
| Lidocaine | 35.3 |
| Novocaine | 30.4 |
| Tetracaine | 14.7, 19.9 |
| Tropocaine | 29.1 |
| Glucose | 38.1 |
| Lactose | 34.6, 33.0 |
| Mannitol | 28.4 |
| Caffeine | 19.5 |

the resolution of a cocaine–lactose mixture. The first stage of the lactose decomposition is clearly isolated on the TG curve of the mixture and this helps to confirm the DSC results.

The proposed method is time-saving and reliable, with a maximum analytical error of the order of about 4%, while the mean error is of the order of about 2%. Finally, the DSC method requires only very low quantities of sample and the time required for the analysis is very short, about 30 min at a heating rate of 10 K $min^{-1}$.

In order to apply DSC to the determination of the content of native protein in dosage forms, Izutsu et al. [24] studied the relationship between denaturation enthalpy and the amount of $\beta$-galactosidase. The denaturation enthalpy was estimated for various amounts of $\beta$-galactosidase lyophilized powder which was the most highly purified enzyme, as well as $\beta$-galactosidase powder formulation. The enzyme is monomeric and the apparent molecular weight is about 10 500. Figure 8 illustrates denaturation enthalpy as a function of enzyme content. The enthalpy is proportional to the content of $\beta$-galactosidase in both cases which illustrates the applicability of the denaturation enthalpy measured by DSC to determine the native protein, although large standard errors were observed in the case of the powder formulation. DSC seems to be more convenient than conventional activity assay methods, and should be useful for following protein denaturation during the manufacturing and storage of dosage forms.

A DSC method was also used to determine quantitatively the concentration of solid drugs dispersed in a polymeric matrix [25]. Polydimethylsiloxane was selected as the matrix material because it has been widely used as a rate-controlling membrane in sustained-release drug delivery devices.

The DSC curve of a film sample containing cholesterol or progesterone

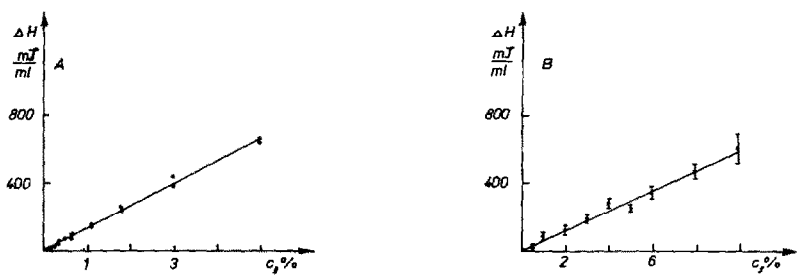


Fig. 8. $\beta$-Galactosidase concentration in the lyophilized powder (A) and powder formulation (B) as a function of the denaturation enthalpy [24]. Each point represents the mean of triplicate measurements and the bar indicates standard deviation. Measurements were performed using a Shimadzu DSC-41 M instrument. Samples (25 $\mu$l of 1% solution of lyophilized powder or 10% solution of powder formulation) were heated at a rate of 5 K $min^{-1}$ in a pre-autoclaved aluminium cell.

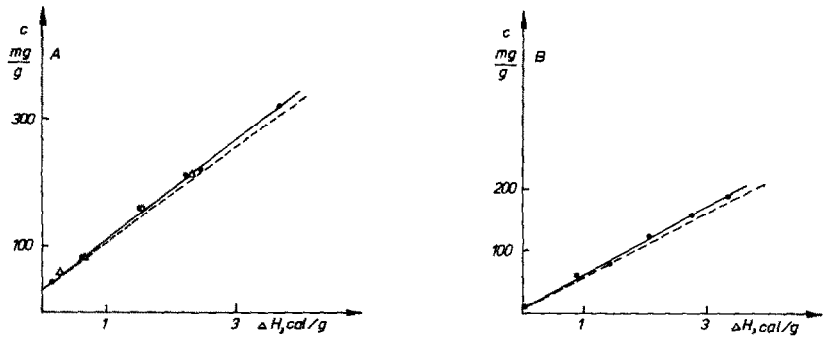


Fig. 9. Cholesterol (A) and progesterone (B) concentration in the film samples as a function of the enthalpy [25]. The solid line is the average line through the experimental data and the broken line is the calculated line from the drug solubility intercept and heat of melting of the pure drug: (●) is the heat at first melting and (△) is the heat at second melting. Measurements were performed using a Perkin-Elmer DSC-1B instrument. Samples (20 mg) were heated at a rate of 10 K $min^{-1}$ in aluminium pans.

shows an endothermic peak at the melting point of the steroid. The peak observed at a heating rate of 10 K $min^{-1}$ was found to be the same for an identical sample when the heating was started from room temperature or when the sample was held for several minutes a few degrees below the melting point of the steroid. Because of this and because of the presence of the drug in the homogeneous fine dispersions, it was assumed that the polymer was continuously in equilibrium with the excess of steroid. Thus, at each temperature, the equilibrium amount of drug is dissolved in the matrix. At the melting point, the observed endotherm then corresponds to the melting of the residual undissolved drug.

The melting of cholesterol in the film samples was observed at the same temperature as for pure substance, and the endothermic heats for films containing different concentrations of steroid are shown in Fig. 9(A). Using these calibration data, the total concentration of cholesterol in any other sample of polydimethylsiloxane can be determined to within ±10 mg per g of polymer. The intercept of the line in Fig. 9(A) at 35 mg cholesterol per g of film is the solubility of the drug at the melting point, and concentrations below 35 mg per g of film cannot be detected by the DSC method. The intercept in Fig. 9(B) gives the solubility of progesterone in the matrix which is found to be 6 mg per g of film. The difference between the lines gives the heat of mixing calculated from the relevant equations.

*Analysis of suppositories, ointments and creams*

Suppositories are also classified in the group of solid dosage forms. The shape of the curves of their thermal decomposition differs fundamentally

from those of the decomposition of powders, granulates and tablets. However, their shape is very similar to the curves of the decomposition of ointments. This is due to similar properties of the components of the bases of suppositories and ointments. For these reasons, the usefulness of DTA and TG methods in monitoring the composition of suppositories [26], as well as ointments and creams [27], was studied separately.

Suppositories, ointments and creams, as with tablets and coated pills, are complex dosage forms in which particular components occur in variable amounts, ranging from 1:5 to 1:4000 [26, 27]. Moreover, the high base contents of suppositories and ointments complicates the checking of their composition. An analysis of the DTA, TG and DTG curves of frequently used base components also shows very small differences in their shapes. For this reason, they did not show any characteristic features with which to differentiate between the particular bases or to identify their components.

Taking into account the close similarity of the physico-chemical properties of the components of ointment bases, the influence of the vehicles on the thermal decomposition of the active components can be extended. Figure 10 shows an example of the analysis of the decomposition of selected ointments, in which a mixture of equal parts of white petrolatum and hydrated lanolin constitutes the ointment base. Up to 413–453 K, the base is quite stable, with little influence on the thermal

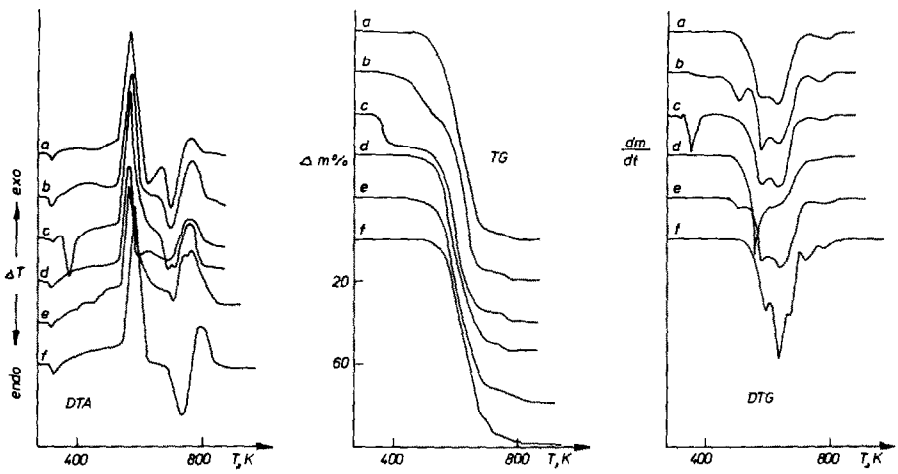


Fig. 10. DTA, TG and DTG curves of the thermal decomposition of (curve a), ointment base which is a mixture of white petrolatum and hydrated lanolin (1:1 by weight), and ointments: (curve b), Ung. Methylii salicylici, (curve c), Ung. Ammonii sulfobituminici; (curve d), Ung. Xeroformii; (curve e), Ung. Sulphathiazoli; and (curve f), Linomag [27]. Measurements were performed using a Derivatograph (model OD-130). Samples (200 mg) were heated at a rate of 5 K $min^{-1}$ in a static air atmosphere, and $\alpha$-$Al_2O_3$ was used as reference material.

decomposition of the active component. For the majority of the base components, the 523–673 K range is characterized by an almost rectilinear section of the weight loss on the TG curve, owing to the liberation of the volatile products of pyrolysis. This temperature range is particularly inconvenient because the massive loss in weight overlaps the decomposition range of the majority of organic and of some inorganic active components. This hinders the development of well-shaped stages on the DTA, TG and DTG curves of suppositories and ointments due to the decomposition of active components, thus making difficult their identification and quantitative analysis.

Charred products of the decomposition of active components are combusted above 673 K, changing both the shape and slope of the final section of the TG curve of the suppository and ointment bases. Due to the lack of any characteristic features, these changes are not useful for the identification.

It can be shown that the larger the loss in weight of the active component at a particular stage of its decomposition, occurring over a narrow temperature range and, possibly, in a different temperature range than that of the decomposition of the suppository and ointment bases, the less the influence of the base on the thermal decomposition of the active component. This offers greater possibility for its identification and quantitative determination, based exclusively on those stages of decomposition of the active component which occur below 523 K and above 673 K.

In the quantitative interpretation of the thermal decomposition of suppositories and ointments, thermal processes such as those described in the case of the solid dosage form are used [8]. Using this method, the content of the active components has been determined in scores of suppositories and ointments, without the necessity of separation from the base. Moreover, the determination of the amount of water present in dosage forms according to the recipe is also possible. The liberation of water occurs at a relatively low temperature and is discriminated from other stages of the decomposition by a distinct horizontal.

A statistical evaluation fully confirmed the conclusions reached for solid dosage forms. Only in the determination of organic active components were much larger differences exceptionally obtained. These are due to the broadened temperature range of their evaporation, partly overlapping the beginning of the decomposition of the ointment base. Results higher than the actual ones are also obtained in some cases in the determination of the water content in creams. This is presumably owing to simultaneous partial evaporation of other liquid components of the creams.

*Evaluation of the moisture content*

The moisture content markedly affects the stability of the active components, excipient materials and finished products, and also compli-

cates the technology of their manufacture. The moisture content of powdered drugs and granulated pharmaceutical products must be known and controlled before tabletting. The tablets crumble if the water content is lower than an optimum value, but if it is too high the powder or granulate cannot be tabletted. Moreover, in determinations of the active ingredients in pharmaceutical products, the moisture contents, also have to be known. For this reason, the determination of the moisture content in both the excipient materials and the final product is a very important problem.

Dávidné Kenéz [28] has shown that it is necessary to know how much moisture is present as physical, chemical and physico-chemical water in order to be able to determine and evaluate correctly the material properties. It has been shown that, in most cases, the moisture content can be interpreted as forming a "non-stoichiometric compound" with some ingredients of a pharmaceutical preparation. Experimental examples illustrating this emphasis that it is important to check the moisture content in pharmaceutical preparations and their ingredients.

The studies carried out by Paulik et al. [29] showed that DTA, TG and DTG can be used as fast, accurate methods for the determination of the moisture content (mechanically bound water) and crystallization water (due to the presence of, for example, lactose) in pharmaceutical powders and granulates. The TG and DTG curves on which each kind of water is liberated in a separate stage are suitable; the moisture is released up to 383 K (on the DTG curve, an almost flat section is observed in the range 363–393 K), and the crystallization water is released up to 458 K. The total water content determined from the TG and DTG curves differs slightly (up to ±0.13%) from that determined by the Karl Fischer method. The presence of small quantities of other components of powders and granulates does not influence the accuracy of these determinations, as is shown in Table 7.

However, measuring the crystallization water or the total water content using a drying apparatus is unsatisfactory. After several hours, lactose heated at 375 K had lost most of its crystallization water; following a sufficient heating time, its total liberation was observed.

At 458 K, the thermal decomposition of the active constituents is already clearly noticeable, although the crystallization water has not been entirely expelled from either powder or tablet. Both processes overlap in such a way that the boundary between them can be exactly drawn with the aid of the DTG curve. This makes possible the accurate determination of the content of crystallization water.

In the synthesis of a number of pharmaceutical products, the final process is recrystallization from an organic solvent. These products may therefore contain absorbed water and also solvent of crystallization. The removal of water and solvent proceeds simultaneously, or in overlapping

TABLE 7

Content of the mechanically bound and crystallization water (%) in the model powders and granulates [29]

| Approximate composition | | TG and DTG measurements | | | Karl Fischer titration | Drying apparatus | | |
|---|---|---|---|---|---|---|---|---|
| | | Mechanically bound water | Crystallization water | Total content of water | | Time of drying at 375 K 2 h | 5 h | 10 h |
| Lactose | | | 4.9 | 4.9 | 5.0 | 0.2 | 0.8 | 1.5 |
| Lactose+ | 100 g | | | | | | | |
| water | 3 ml | 2.7 | 4.9 | 7.6 | 7.9 | 3.9 | 4.4 | 5.2 |
| Lactose+ | 100 g | | | | | | | |
| 10% sol. of gelatin | 0.5 ml | 0.1 | 4.7 | 4.8 | 5.1 | 0.3 | 1.4 | 2.1 |
| Lactose+ | 30 g | | | | | | | |
| caffeine+ | 30 g | | | | | | | |
| amidopyrine+ | 30 g | | | | | | | |
| 10% sol. of gelatin | 10 ml | 8.1 | 1.7 | 9.8 | 9.8 | 9.7 | 9.8 | 9.8 |
| Lactose+ | 25 g | | | | | | | |
| caffeine+ | 25 g | | | | | | | |
| amidopyrine+ | 25 g | | | | | | | |
| phenacetin+ | 25 g | | | | | | | |
| 10% sol. of gelatin | 10 ml | 7.9 | 1.3 | 9.2 | 9.2 | 8.6 | 9.1 | 9.2 |

processes, in nearly the same temperature interval during thermal decomposition, and cannot be separated by means of the TG and DTG curves. The TG curves show the total weight loss due to the removal of the two substances. Bayer and Liptay [30] studied the decomposition of vitamin $B_{12}$ recrystallized from acetone. On the basis of an inflection point in the DTG curve at 333 K, the acetone content of the sample can be more or less established as 4%. From the TG curve it can be said that the sum of water and acetone is 20%.

Touré et al. [31] compared three methods used in the determination of the moisture content: a gravimetric method, a chemical method (Karl Fischer titration) and a physical method (measuring the dielectric constant). A powdered potato starch (sample 0) and its granulates obtained by wet granulation (samples 1–6) were studied.

The determinations were run on an IR-type thermobalance by infrared heating of 10 g samples for 30 min. The temperature during the measurements was varied between 333 and 443 K depending on several factors such as the intensity of radiation, the physical features of the heated product, its quantity and thickness, and the moisture content of the air.

By comparing the results of the TG determinations with those of the Karl Fischer titration and the dielectric method, it was shown that the TG method was characterized by the best reproducibility. The coefficient of variation (on average 1%) slightly exceeded the value of the relative physical error, evaluated as 0.3%. The statistical evaluation of the determinations is shown in Table 8.

Using regression equations, these methods were compared in pairs; the results are summarized in Table 9. Their evaluation has shown that the correlation is satisfactory if the results for sample 0 are eliminated. The correlation between the TG and the Karl Fischer methods was satisfactory even if the results for sample 0 were included. However, it is unsatisfactory in case of the dielectric method.

All the measurements performed have shown that the TG method, in spite of inconveniences such as the relatively long time of the determination and the destructive effect of the heat on the sample, offers a range of advantages, including a very high reproducibility and conformity of the correlation coefficients with the Karl Fischer method, independent of the physical structure of the sample. It must be mentioned that due to the heat used, decarboxylation, oxidation and the volatility of substances from which water is liberated can be observed. For this reason, a critical examination of the composition of the product to be studied must be performed, and in order to choose optimum conditions for the determinations, the kinetics of the weight loss at different temperatures should be studied.

It should be mentioned that the determination of the moisture content, either in the finished drug formulations or in the materials used in its

TABLE 8

Statistical evaluation of the determinations of the moisture content in powdered potato starch and its granulates by isothermal TG measurements [31]

| Sample | Number of measurements $n$ | Average moisture content (%) | Amplitude | Variance | Standard deviation | | Coefficient of variation (%) |
|---|---|---|---|---|---|---|---|
| | | | | | $s$ | $s_{\bar{x}}$ | |
| 0 | 6 | 18.28 | 0.1 | 0.00166 | 0.0408 | 0.01665 | 0.2 |
| 1 | 6 | 35.41 | 0.5 | 0.0376 | 0.1940 | 0.07920 | 0.5 |
| 2 | 6 | 10.83 | 0.1 | 0.00266 | 0.0516 | 0.021065 | 0.4 |
| 3 | 6 | 5.95 | 0.2 | 0.0070 | 0.0836 | 0.03413 | 1.4 |
| 4 | 6 | 5.36 | 0.2 | 0.0067 | 0.0816 | 0.03331 | 1.5 |
| 5 | 5 | 5.48 | 0.1 | 0.0020 | 0.0447 | 0.01999 | 0.8 |
| 6 | 5 | 5.38 | 0.3 | 0.0170 | 0.1303 | 0.05827 | 2.4 |

TABLE 9

Correlation between isothermal TG, Karl Fischer titration and dielectric measurements [31]

| | Regression 1. Isothermal TG Karl Fischer tit. | Regression 2. Dielectric method Karl Fischer tit. | Regression 3. Isothermal TG Dielectric method |
|---|---|---|---|
| *Sample 0 included* | | | |
| Coefficient of correlation | 0.99 | 0.94 | 0.95 |
| Coefficient of regression | 0.81 | 9.01 | 0.08 |
| Value of the ordinate shift | 0.52 | −23.1 | 2.76 |
| *Sample 0 not included* | | | |
| Coefficient of correlation | 0.99 | 0.99 | 0.99 |
| Coefficient of regression | 0.80 | 9.49 | 0.08 |
| Value of the ordinate shift | 0.35 | −26.6 | 2.84 |

formulation, can also be accomplished using the Du Pont 902 Moisture Evolution Analyser. The analysed sample is placed in an oven and heated so that the evolved water is carried to an electrolytic cell detector by a carrier gas. The water is absorbed by phosphorus pentoxide coated on a platinum electrode, and electrolysed to hydrogen and oxygen. The electrolytic current is integrated, scaled, and displayed as $\mu$g of water. In this way, the moisture content of effervescent [32] and vitamin C [33] tablets was determined. This is a quick, accurate method. Water levels as low as 10 $\mu g\,g^{-1}$ can be routinely determined. With special care, levels of accuracies down to 1 $\mu g\,g^{-1}$ are possible.

## GENERAL REMARKS

Thermal methods of analysis are extremely useful in the qualitative and quantitative control of the composition of solid and soft drug formulations, but only if the characteristics of the thermal decomposition of the components contained in the dosage form have been previously determined and catalogued [20]. A compound whose presence is not suspected in the dosage form, whose thermal decomposition characteristics are thus not available, may remain undetected or may affect the detection of other components. Several conditions can be specified as essential if the preparation is to be analysed. It is advantageous if the tablet components are stable over the temperature range of decomposition of the active component [7]. However, the least suitable situation is observed when the tablet mass undergoes decomposition in the range 373–773 K, with complete loss in weight, and in the case of suppositories and ointments when the decomposition of the active component occurs over the range 523–673 K [26, 27]. A knowledge of the temperature intervals of the

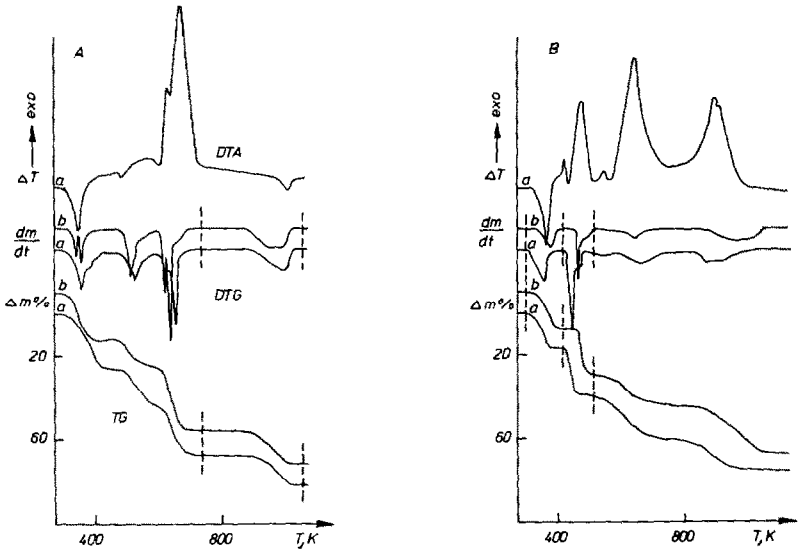


Fig. 11. DTA, TG and DTG curves of the thermal decomposition of (A) calcium lacticum tablet (curve a) and of its active component, calcium lactate (curve b); (B) PAS-Natrium tablet (curve a) and of its active component, sodium *p*-aminosalicylate (curve b) [20]. The stage of decomposition based on which the content of the active principle was estimated is indicated by the broken line. Measurements were performed using a derivatograph (model OD-130). Samples (200 mg) were heated at a rate of 5 K $min^{-1}$ in a static air atmosphere, and $\alpha$-$Al_2O_3$ was used as reference material.

individual stages of thermal decomposition of both the auxiliaries and the active component often allows discrimination of the temperature range within which the individual effects do not overlap. This allows the composition of the formulation to be monitored, as shown in Fig. 11.

The following conditions can be specified as essential if an active component is to be analysed qualitatively and quantitatively in a dosage form [7]. The active component must constitute at least 10% of the total mass of the preparation. Its thermal decomposition stages should occur over a narrow temperature range, and be accompanied by relatively large weight losses at each stage. The other components should not decompose over the temperature range examined. Intermediate decomposition products should be stable over a reasonably broad temperature range. In the case of simultaneous determination of two active components, their thermal decomposition should occur over different temperature ranges.

Thermal methods of analysis may be useful in many cases. Apart from the troublesome separation of active components from vehicles, they eliminate the necessity of application of chemical reagents and laboratory accessories, thus lowering the cost of analysis. Due to automatic recording of the thermal decomposition curves, they also reduce labour costs for the determinations. In spite of the long time required for recording one

thermogram, in comparison with classical methods of analysis it is possible to reduce the time necessary to carry out a particular determination. However, this is not worthwhile when a series of determinations of the same nature are being performed. The analyst carrying out parallel analyses of a dozen or so samples spends less time on a single determination. In consequence, thermal methods of analysis are particularily cost-effective when a single control analyses is needed from time to time. In addition, the data recorded from each analysis which may be interpreted at any time.

The disadvantages of these methods is the difficulty in quantifying those active components which have no distinct thermal decomposition stages or which contribute more than 10% to several decomposition stages. In the latter case, this is particularly disadvantageous in view of the fact that the active components are frequently very potent drugs and their determination is of particular importance. It is also difficult to analyse a sample for two active components.

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