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STUDIES ON USE OF DIFFERENTIAL THERMAL AND THERMOGRAVIMETRIC TECHNIQUES FOR CHECKING COMPOSITIONS OF SOME DRUG FORMULATIONS

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The suitability of the differential thermal and thermogravimetric techniques for the determination of compositions of solid and soft drug formulations has been studied. A total of 117 pharmaceutical preparations have been examined, including powders, dusting powders, capsules, granulates, tablets, tablets for sucking, effervescent tablets, dragees, suppositories and ointments. Both techniques have been shown to be applicable for identification of pharmaceutical preparations. A specification has been made of thermal processes which can be employed for assaying the main components of the preparations. A rough estimate of the relative errors has been given.

Differential thermal analysis and thermogravimetry play an important role in solving a variety of scientific and industrial problems. However, the techniques have not received due attention in the pharmaceutical sciences. One of the possibilities of using these techniques is to employ DTA curves, as well as those of DSC and TG, for identification of pharmaceutical preparations containing active principles belonging to the groups of analgesics [1], antacids [2] and vitamins [3]. The shapes of the thermal decomposition curves of these preparations have been found to be determined by the presence of fillers and binding agents. The assignment of the thermal effects to the decompositions of the appropriate compounds has been found to be greatly complicated by complex compositions of preparations and, in many cases, by a lack of information about the composition. Large changes in the composition due, for instance, to adsorption of water, can manifest themselves in the appearance of new peaks, the shift of existing ones or, changes in their shapes. The TG curves have also been demonstrated to be useful for quantitative determination of the mechanically bound and crystallization water in powders and granulates comprising lactose, gelatin and (or) caffeine, amidopyrine and phenacetine [4].

Taking into account the foregoing aspects, a complex estimation of the suitability of the DTA, TG and DTG techniques for monitoring of the compositions of solid and soft formulations has now been made.

As pharmaceutical preparations are complex materials containing drugs and vehicles, the decompositions have been studied of all drugs and vehicles employed for granulation and tabletting or used as bases for ointments and suppositories.

The knowledge of even an approximate mechanism of their thermal decompositions and of the compositions of pharmaceutical preparations will undoubtedly facilitate interpretation of the results.

Experimental

Reagents and materials

The thermal decompositions have been studied of 117 drugs available in chemist's shops belonging to the group of solid drug forms such as simple powders, effervescent powders, dusting powders, capsules, simple and effervescent granulates, internal tablets, tablets for sucking, tablets for preparation of effervescent beverages, dragees and suppositories. Ointments have been studied as drugs belonging to soft forms. The preparations were manufactured by the "Polfa" Pharmaceutical Works (Poland) as well as by Chemical and Pharmaceutical Co-operatives. From these producers, pure drugs, vehicles and information about their compositions have also been obtained.

Apparatus and method

DTA, TG and DTG curves were taken on an OD-130 (MOM Hungary) derivatograph (Paulik – Paulik – Erdey system). All experiments were performed under identical conditions: 100 mg samples were placed in Pt crucibles (∅ 9.5 mm) and heated in a furnace atmosphere at a rate of 5° min^{-1} up to 600 – 1000°, using α-Al_2O_3 as reference material.

All preparations, except for powders and ointments, were finely powdered prior to analysis. One sample comprised three tablets or dragees.

To isolate intermediates, the heating was interrupted at the appropriate temperature and the residue was analysed.

Results and discussion

I. *Thermal decomposition of vehicles*

Studies on the thermal decompositions of a few tens of organic and mineral vehicles belonging to various classes of chemical compounds such as carbohydrates, proteins, fats, polymers, carboxylic acids and their salts, as well as mineral compounds, allow the conclusion that elucidation of the mechanism of thermal decomposition, as well as isolation and identification of intermediates, poses a difficult problem. The difficulties are mainly due to the fact that the substances are mostly high-molecular weight compounds of a complex, difficultly determinable composition.

The poor selectivity of the DTA and TG techniques employed simultaneously

means that the differences in thermal decomposition patterns of high-molecular weight isomeric compounds cannot be traced. This is particularly evident during study of the thermal decompositions of certain carbohydrates, proteins and fats.

II. *Thermal decomposition of pharmaceutical preparations*

Studies on the thermal decompositions of more than one hundred pharmaceutical preparations afforded useful experimental evidence allowing estimation of the usefulness of DTA and TG techniques for qualitative and quantitative control of their compositions.

A. *Identification of components of pharmaceutical preparations*

A particular compound can only be identified by comparing the temperature ranges as well as the areas and shapes of the DTA peaks of the analyzed and standard compounds. The measurements must be run under similar conditions and on the same instrument. The use of the DTA technique for identification of com-

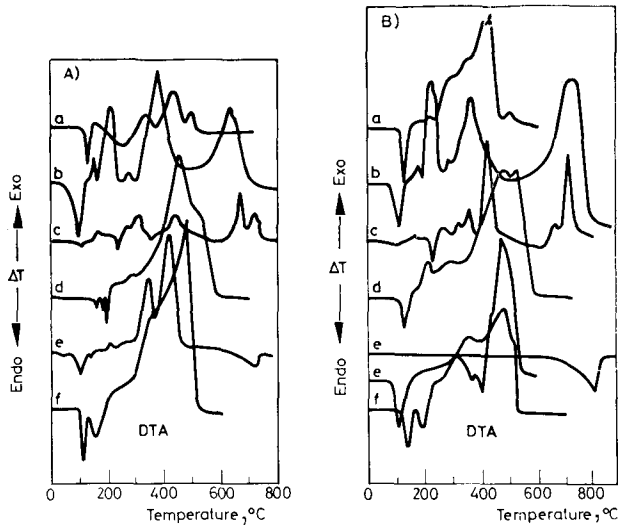

Fig. 1. DTA curves of the thermal decompositions of: (A) selected pharmaceutical preparations, (B) medicinal agents providing main components of peparations subjected to thermal decomposition. (a) Salicylamidum (tablets, "Polfa" Pharmaceutical Works, Starogard Gd.) and salicylic acid amide; (b) PAS-Natrium (tablets, "Polfa" Pharmaceutical Works, Kraków) and sodium p-aminosalicylate dihydrate; (c) Kalium guaiacolosulfonicum (tablets, "Galena", Pharmaceutical Co-operative, Wrocław) and potassium guaiacolosulphonate; (d) Detreomycyna (dragees, "Polfa" Pharmaceutical Works, Kraków) and chloramphenicol palmitate; (e) Polopiryna S (tablets, "Polfa" Pharmaceutical Works, Starogard Gd.) and calcium carbonate and acetylsalicylic acid; (f) Vibovit (powder, "Polfa" Pharmaceutical Works, Kutno) and glucose as vehicle

ponents of a multicomponent mixture is problematic, however, because mutual dilution of the components results in a decrease in peak areas, frequently accompanied by a change in their shapes, as is the case during superposition of effects occurring at close temperatures.

A thorough analysis of the compositions of pharmaceutical preparations revealed that they provide 2 – 11-component mixtures, whose components are present in various proportions. In this situation the shape of the DTA curve can be utilized for identification of one, and exceptionally, two or three components. Subtle thermal effects due to the remaining components are completely or almost completely obscured. The components only slightly affect the shapes of the DTA peaks, but alter the thermal conductance and heat capacity of the mixture, as well as the diffusion of volatile products and other parameters.

More encouraging results were obtained from analysis of TG curves. The possibility of simultaneous recording of TG and DTG curves allows a more precise observation to be made of each variation in the rate of weight loss of a mixture, thus providing better discrimination of particular steps of decomposition. Similarly as in the case of the DTA curves, the identification was based on comparison of temperature ranges, shapes of curves, and weight losses accompanying a particular decomposition step, thus allowing deduction of equations of chemical reactions. The TG and DTG curves of an analyzed and standard compound were accounted for.

B. *Quantitative checking of compositions of pharmaceutical preparations*

Due to the complex compositions of pharmaceutical preparations, there are serious difficulties in deriving correlations between percentage compositions and thermal effects expressed in terms of peak areas under DTA curves. Hence, the determination of the components on the basis of their DTA curves is difficult. To overcome these difficulties, use was made of weight losses in TG curves. Quantitative interpretation of TG curves is simple, owing to the possibility of clear discrimination between particular steps by means of the DTG curves. Only that component of a mixture can be determined whose percentage exceeds 30. Moreover, the TG curves should display clearly separated decomposition steps.

Consequently, thermal processes suitable for the determination of the main components of pharmaceutical preparations were categorized as follows:

1. Dehydration: the loss of crystallization or constitutional water is accompanied by formation of an intermediate compound of precisely defined composition and structure. The processes occur mostly over the temperature range 60 – 300° and manifest themselves in a distinct plateau in the TG curve.

2. Decarboxylation: the loss of carbon dioxide from sodium hydrogen carbonate occurs over the range 60 – 200°. On the other hand, decarboxylation of calcium carbonate arising upon ignition of an organic residue of a calcium salt occurs over the range 600 – 800°. The formation of calcium oxide, similarly as for calcium

carbonate, is accompanied by the appearance of a distinct plateau extending over a range of a few tens of degrees. This feature is helpful in obtaining relatively accurate results.

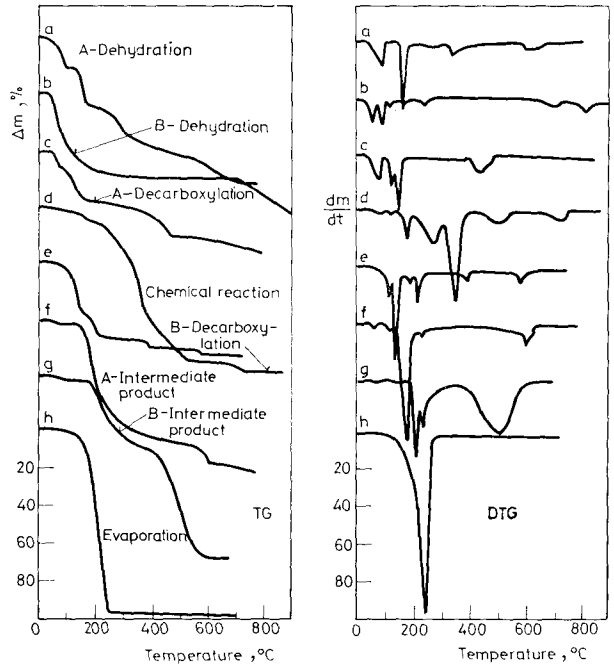

Fig. 2. TG and DTG curves of the thermal decompositions of selected pharmaceutical preparations, used for quantitative determinations. (a) Napashin, tablets containing sodium p-aminosalicylate dihydrate ("Polfa" Pharmaceutical Works, Kraków); (b) Pulvis pro irrigatione, powder containing boric acid ("Cefarm" Galenic Laboratory, Gdańsk); (c) Gargarin, powder containing sodium hydrogen carbonate ("Cefarm" Galenic Laboratory, Gdańsk); (d) Reladorm, tablets containing calcium cyclobarbital ("Polfa" Pharmaceutical Works, Tarchomin); (e) Sal Ems factitium, effervescent tablets containing sodium hydrogen carbonate and tartaric acid as vehicles ("Ziołolek" Pharmaceutical-Chemical Co-operative, Poznań); (f) Pyrosalofen, tablets containing sodium salicylate ("Polfa" Pharmaceutical Works, Starogard Gd.); (g) Sulfamethazinum, tablets containing sulphamethazine ("Polfa" Pharmaceutical Works, Starogard Gd.); (h) Urotropinum, tablets containing hexamethylenetetramine ("Organica" Chemical Works, Łódź)

3. Weight loss due to reactions between components of an effervescent mixture: reactions of sodium or potassium hydrogen carbonates with citric or tartaric acids, resulting in the loss of carbon dioxide and water. As the reactions occur over a temperature range close to that of the thermal decomposition of the metal hydrogen carbonate, it is difficult to discriminate between the weight losses due to these reactions and that due to thermal decomposition of the metal hydrogen carbonate in excess. For this reason, only the total content of acid and hydrogen carbonate

can be assessed. The termination of the two processes is not accompanied by a distinct plateau.

4. The weight losses corresponding to inflections in the TG curves, due to the formation of intermediates, can be interpreted as follows: (i) a product is formed whose composition and structure can be determined, thus facilitating determination of steps due to the decomposition of a given component; (ii) neither the composition nor the structure of the intermediate can be established. In this case calculations were based on the comparison of weight losses occurring between two adjacent inflections in the TG curves of a given preparation and of the standard. In this case, DTG curves which indicated the beginning and the end of a given step were very helpful.

5. Weight losses due to total evaporation, sublimation or combustion of a component. Quantization of results is possible only for those components whose thermal decompositions occur over a narrow temperature range, and when no interference arises from decomposition of the remaining components.

Table 1

Relative errors of determinations of components of pharmaceutical preparations, based on appropriate processes of the thermal decompositions

Process	Number of preparations	Average relative error, %
1. Dehydration. Loss of:		
A. crystallization water	7	2.6
B. constitutional water	2	6.1
2. Decarboxylation:		
A. of sodium hydrogen carbonate	1	2.9
B. of calcium carbonate	15	2.9
3. Weight loss due to chemical reaction between components of effervescent mixture	3	6.9
4. Weight loss corresponding to inflections in the TG curve. The composition and structure of an intermediate:		
A. were established	13	5.5
B. could not be established	10	2.6
5. Weight loss due to complete evaporation, sublimation or combustion of the component	11	5.0

One of the reasons for a large relative error in the determinations may be the poor accuracy of readings of the weight losses from the TG curves.

Conclusions

1. There are considerable difficulties in unambiguous determinations of both physical and chemical changes due to thermal decomposition of active principles and vehicles of pharmaceutical preparations. This point deserves further studies.

2. The quantitative interpretation of results of the thermal decomposition should be based on simultaneously recorded DTA, TG and DTG curves, because it is difficult to identify chemical reactions from the shapes of the DTA curves alone, whilst the TG curves alone do not furnish information about the energetic parameters.

3. The quantization of results of the thermal decompositions of pharmaceutical preparations, based on the TG and DTG curves, is simple, because no calibration of the apparatus is required and no time-consuming calculations need be performed. Moreover, the results are less dependent on the experimental conditions. Hence, the error is smaller.

4. In this study the active principle could be determined in 60 out of 117 pharmaceutical preparations. In two cases two components could be assayed simultaneously.

5. The possibility of assaying the vehicle when an active principle is present in a small quantity, is an advantage of the thermal techniques.

6. Detailed results of employing DTA and TG techniques for determination of the compositions of 117 pharmaceutical preparations will be presented in due course.

References

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RÉSUMÉ — On a étudié l'utilité des techniques ATD et TG pour déterminer la composition des préparations pharmaceutiques solides et molles. On a soumis à l'examen un total de 117 préparations pharmaceutiques comprenant des poudres, des talcs, des capsules, des granulats, des tablettes, des tablettes à sucer, des tablettes effervescentes, des dragées, des suppositoires et des onguents. Les deux techniques se sont montrées applicables à l'identification des préparations pharmaceutiques. On a effectué une spécification des processus thermiques qui se prêtent au dosage des composants essentiels des préparations. On a donné une évaluation approximative des erreurs relatives.

ZUSAMMENFASSUNG — Die Eignung der differentialthermoanalytischen und thermogravimetrischen Methoden zur Bestimmung der Zusammensetzung fester und weicher Arzeneipräparate wurde studiert. Eine Gesamtzahl von 117 pharmazeutischen Präparaten, einschliesslich Pulver, Streupulver, Kapseln, Granulate, Tabletten, Saugtabletten, Brausetabletten, Dragees, Suppositorien und Salben wurde untersucht. Beide Methoden erwiesen sich als anwendbar zur Identifizierung pharmazeutischer Präparate. Eine Spezifizierung der zur Bestimmung der Hauptkomponenten der Präparate geeigneten thermischen Prozesse wurde durchgeführt. Eine grobe Schätzung der relativen Fehler wurde gegeben.

Резюме — Изучена применимость дифференциального термического и термогравиметрического методов анализа для определения состава твердых и мягких форм приготовления лекарств. Были изучены 117 фармацевтических препаратов, включая порошки, пылевые порошки, капсулы, гранулы, таблетки, таблетки для всасывания, шипучие таблетки, драже, медицинские свечи и мази. Показано, что оба метода применимы для идентификации фармацевтических препаратов. Проведена спецификация термических процессов, которые могут быть применимы для анализа главных компонент препаратов. Приблизительно определены относительные ошибки.