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THERMAL DECOMPOSITION OF SOME DIURETIC AGENTS

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Abstract

Thermogravimetry-derivative thermogravimetry and differential scanning calorimetry were used to study the thermal behaviour of furosemide, hydrochlorothiazide, spironolactone, and amiloride hydrochloride. The results revealed the extents of their thermal stability and also permitted interpretations concerning their thermal decompositions.

Keywords: diuretic agents, thermal decomposition

Introduction

A number of investigations have been carried out on the application of differential thermal analysis (DTA), thermogravimetry (TG) and differential scanning calorimetry (DSC) for the study of drug substances, excipients, drug substances in dosage forms and drug substances in commerical dosage forms. Montagut and coworkers [1] investigated dipyrone by employing DTA and TG, and also examined the possibility of application of TG for quantitative study. Wendlandt and Collins [2] used the thermal analysis techniques of DTA and TG as aids in the characterization and identification of commercial non-prescription analgesics. Other investigations of the use of thermal analysis techniques for the study of drug substances and for applications in routine pharmaceutical analysis and in the pharmaceutical industry have also been described [3–11]. No reference has been found to the application of TG and DSC in the study of these diuretic agents.

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Experimental

Diuretic agents

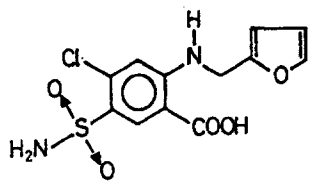
Furosemide, 5-aminosulfonyl-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid, was furnished by Hoechst of Brazil. Hydrochlorothiazide, 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, and amiloride hydrochloride, 3,5-diamino-N-aminoiminomethyl-6-chloropyrazinecarboxamide hydrochloride dihydrate, were furnished by Prodome Química e Farmaceutica Ltda, Campinas, Brazil. Spironolactone, 7α-acetylthio-17α-hydroxy-3-oxopregn-4-ene-21-carboxylic acid, was furnished by Biolab Industrias Farmaceuticas, Brazil.

TG-DTG and DSC curves were obtained by using a Mettler TA-4000 thermoanalyser system with an air flux of 150 ml min^{-1}, a heating rate of 5°C min^{-1} and a sample mass of about 7 mg. An alumina crucible was used for the TG-DTG curves, and an aluminium crucible with a perforated cover was used for the DSC curves.

Results and discussion

The TG-DTG and DSC curves of furosemide, hydrochlorothiazide, amiloride hydrochloride and spironolactone are shown in Figs 1–8.

Furosemide



The TG-DTG curves in Fig. 1 show that furosemide is thermally stable up to 200°C. The thermal decomposition observed in the TG curve occurs in three consecutive steps, with losses of 4.68% (200–250°C), 32.77% (250–360°C) and 61.22% (360–700°C) respectively, whereas the DTG curve shows four consecutive steps. Calculations based on the mass losses in the TG curve for the first and second steps suggest the elimination of the substituent groups on the benzene ring, NH_2SO_2 and COOH (TG=37.45%, Calc.=36.71%). The last step is ascribed to the final pyrolysis of the compound, with formation of a carbonaceous residue.

The DSC curve in Fig. 2 reveals endothermic and exothermic peaks. The endothermic peak at 218°C seems to be due to fusion. it is followed by a sharp

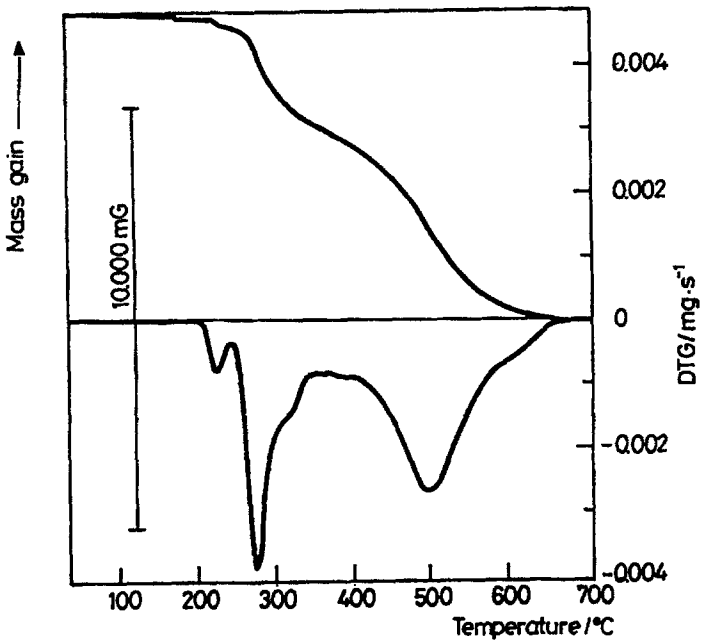


Fig. 1 TG-DTG curves of furosemide (7.156 mg)

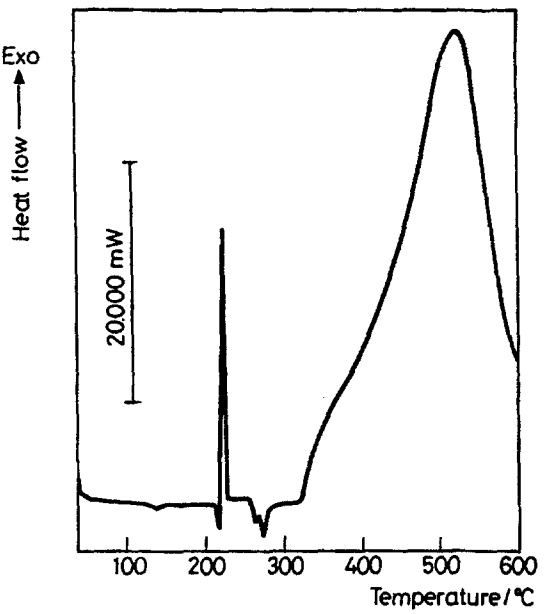
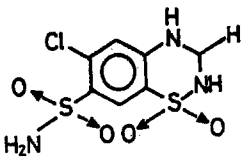


Fig. 2 DSC curve of furosemide

exothermic peak at 220°C, and by two small endothermic peaks at 260 and 275°C, attributed to the thermal decomposition, corresponding to the first and the second mass losses observed in the TG curve. The large exothermic peak at 520°C is ascribed to the final pyrolysis of the compound.

Hydrochlorothiazide



The TG-DTG curves in Fig. 3 show that hydrochlorothiazide is thermally stable up to 260°C; its thermal decomposition occurs between 260 and 680°C. These curves also show that the mass loss up to 375°C begins with a fast process, followed by a slow process. The first step, which involves a mass loss of 46.41%, is probably due to the partial elimination of the substituent groups from the benzene ring (SO_2NH_2 and NH–CH–NH). The final loss of 53.55% is ascribed to the pyrolysis of the compound.

The DSC curve in Fig. 4 exhibits endothermic and exothermic peaks. The first endothermic peak, at 270°C, is due to the fusion of the compound. The

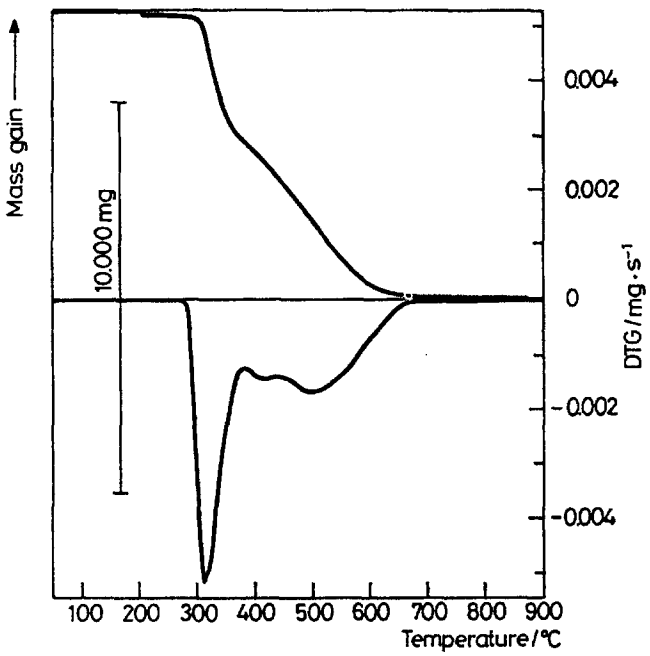


Fig. 3 TG-DTG curves of the hydrochlorothiazide (7.160 mg)

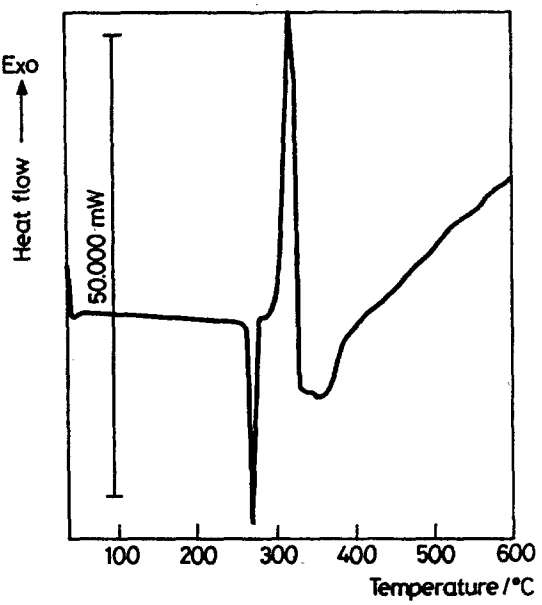
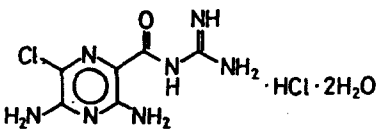


Fig. 4 DSC curve of the hydrochlorothiazide

sharp exothermic peak at 310°C and the endothermic peak at 360°C are attributed to the thermal decomposition, corresponding to the first mass loss observed in the TG-DTG curves. The exotherm between 380 and >600°C is due to the final pyrolysis of the compound.

Amiloride hydrochloride



The TG-DTG curves of amiloride hydrochloride in Fig. 5 show mass losses in four steps between 40 and 700°C. The first mass loss, up to 135°C, is ascribed to dehydration, with the elimination of $2H_2O$ (TG=12.09%, Calc.=11.93%), with subsequent thermal stability up to 240°C. The second step (240–310°C), involving a loss of 22.32%, and the third step (310–465°C) with a loss of 28.43%, suggest the loss of HCl and the partial loss of the substituent groups from the aromatic ring ($2NH_2$ and O=C–NH–C–NH–NH_2; TG=50.75%, Calc.=51.17%). The last step (465–700°C) occurs as a slow process with a loss of 37.16%, and is due to the final pyrolysis of the compound.

In the DSC curve in Fig. 6, the first endothermic peak, at 125°C, is ascribed to the dehydration, and corresponds to the first mass loss observed in the TG-DTG curves. The sharp endothermic peak at 295°C is due to fusion and is fol-

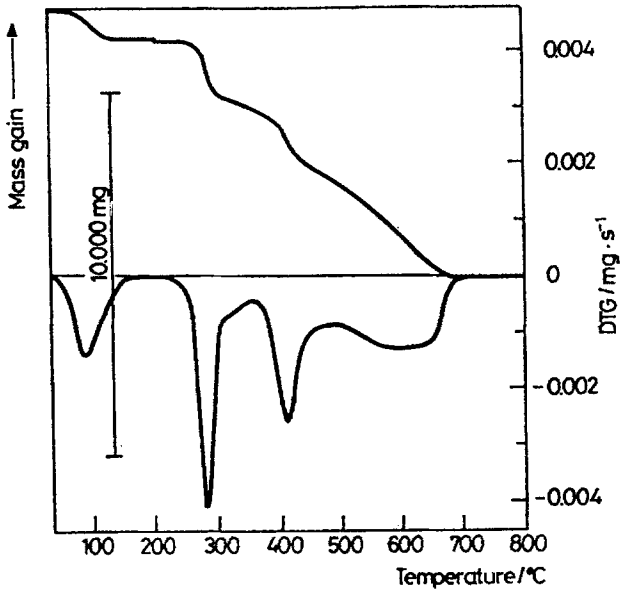


Fig. 5 TG-DTG curves of the amiloride hydrohcloride (7.228 mg)

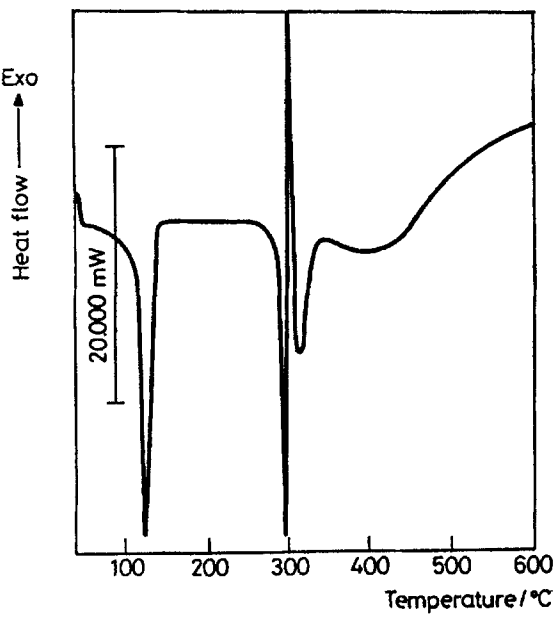
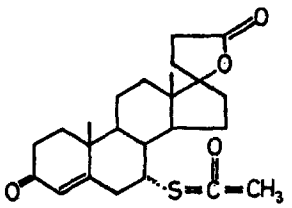


Fig. 6 DSC curve of the amiloride hydrochloride

lowed by a sharp exothermic peak at 300°C, an endothermic peak at 315°C and an endotherm between 350–430°C, all corresponding to the second and third mass losses in the TG-DTG curves. The exotherm between 430 and >600°C is ascribed to the final pyrolysis of the compound.

Spironolactone



The TG-DTG curves of spironolactone in Fig. 7 demonstrate that the compound is thermally stable up to 200°C, and that its thermal decomposition occurs between 200 and 620°C. Four consecutive steps are observed in the TG-DTG curves. The first step, up to 260°C, is ascribed to the elimination of the substituent group, $SCOCH_3$ (TG = 19.59%, Calc. = 19.33%). The second step (260–370°C), and the third and fourth steps (370–700°C) involve losses of 42.93% and 37.48%, respectively, but do not permit a suggestion as to which parts of the compound are eliminated in each step.

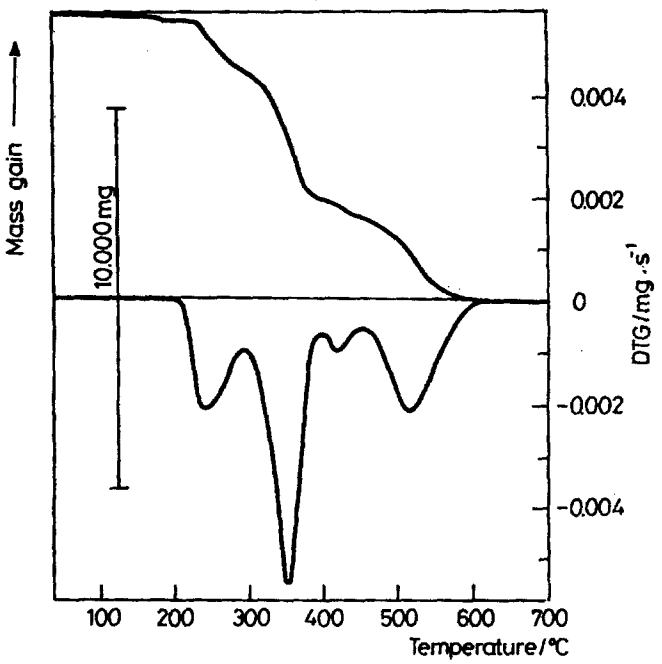


Fig. 7 TG-DTG curves of the spironolactone (7.284 mg)

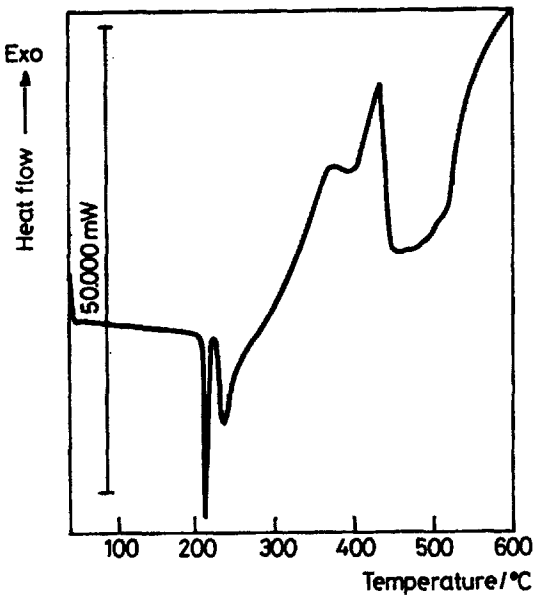


Fig. 8 DSC curve of the spironolactone

In the DSC curve in Fig. 8, the first endothermic peak, at 210°C, is due to fusion of the compound. The second endothermic peak, at 235°C, is attributed to the thermal decomposition, corresponding to the first mass loss in the TG-DTG curves. Two exotherms between 270 and 460°C and between 460 and >600°C are ascribed to the thermal decomposition, corresponding to the second, third and fourth mass losses in the TG-DTG curves.

Conclusions

The TG-DTG and DSC curves provide information on the thermal stabilities and thermal decompositions of the diuretic agents studied in this paper, and permit identification of some of the products of their thermal decompositions.

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