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Note

THERMAL ANALYSIS OF PHARMACEUTICAL COMPOUNDS. VI. THERMAL ANALYSIS OF FLUORIDE-CONTAINING STEROIDS

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Introduction of a 9-α-fluorine atom in some steroidal molecules was found to enhance their activity [1,2]. The presence of a 16-α-hydroxyl group eliminates the undesirable salt-retention activity [1]. Glucocorticoid and anti-inflammatory activities, in the case of flucinolone acetonide, are both enhanced by the formation of the ketal through condensation with acetone. This is thought to be due to the prevention of intermolecular hydrogen bonding with fluorine atoms [1]. In other cases, the introduction of a 16-β-methyl group appears to neutralize the unfavourable electrolyte properties without diminishing the anti-inflammatory effect [1].

Analysis of some fluoride-containing steroids (fludrocortisone acetate, fluorometholone and fluocinolone acetonide) was achieved by spectrophotometry, gas–liquid chromatography and high pressure liquid chromatography [3,4].

The present work is a continuation of a series of studies by the author on the thermal analysis of pharmaceutical compounds [5–9], and records the thermal analysis of some fluoride-containing steroids. This was carried out using TG, DTG, and DTA. A thorough study of the thermal behaviour and different transformations was carried out in order to identify the compounds and emphasize their correlation, if any. The determination of some constants and characteristics by thermal analysis is also considered.

EXPERIMENTAL

Materials and apparatus

Samples

All samples were obtained from Lark S.P.A., Milano, Italy:

(1) fludrocortisone 21-acetate, BP 80 ($C_{23}H_{31}FO_6$), M.W.422.5;

(2) fluorometholone NF XV ($C_{22}H_{29}FO_4$), M.W. 376.47;

(3) fluocinolone 16,17 acetonide USP XX ($C_{24}H_{30}F_2O_6$), M.W. 452.5.

0040-6031/84/$03.00

Apparatus

(1) DuPont 951 thermogravimetric analyzer (TGA) which measures changes in weight as a function of temperature and provides derivative TGA data (DTG);

(2) DuPont 910 DTA intermediate cell;

(3) DuPont 990 thermal analyzer programmer/recorder;

(4) DuPont 1090 thermal analysis/data system; microcomputer, automated;

(5) Gallen Kamp melting point apparatus, cat. No. 30, MF-370, Gt. Britain.

Procedure

The determinations were carried out on samples ranging from about 5 to 30 mg, under the following conditions.

TG and DTG scans

Heating rate: 20°C min^{-1}, starting from room temperature.
Range of *T*-axis: 25°C cm^{-1}.
Shift: +10 cm.
Time constant: 2 s.
d*y*: 20 mV cm^{-1}.
Atmosphere: nitrogen 50 ml min^{-1}.
TGA: 0.05 mg mV^{-1}.
DTG: 0.05 mg min mV^{-1}.
Suppression: 0 mg.

DTA scans

T-axis: prog. rate: 20°C min^{-1}
range: 0.2 mV cm^{-1}
DTA: range: 20/5 mV cm^{-1}
reference: aluminium oxide.

For studying interesting reactions, variations may be made in the previous conditions (for example, the first reaction of fluocinolone acetonide).

RESULTS AND DISCUSSION

Figures 1, 2 and 3 show the TG, DTG and DTA curves of fludrocortisone acetate, fluorometholone and fluocinolone acetonide, respectively. Table 1 presents the data concerning the main thermal reactions of the examined compounds. Table 2 gives the corresponding DTA reactions.

On thermal treatment, fluoride-containing steroids undergo one main reaction which is attributed to decomposition of the compounds. This

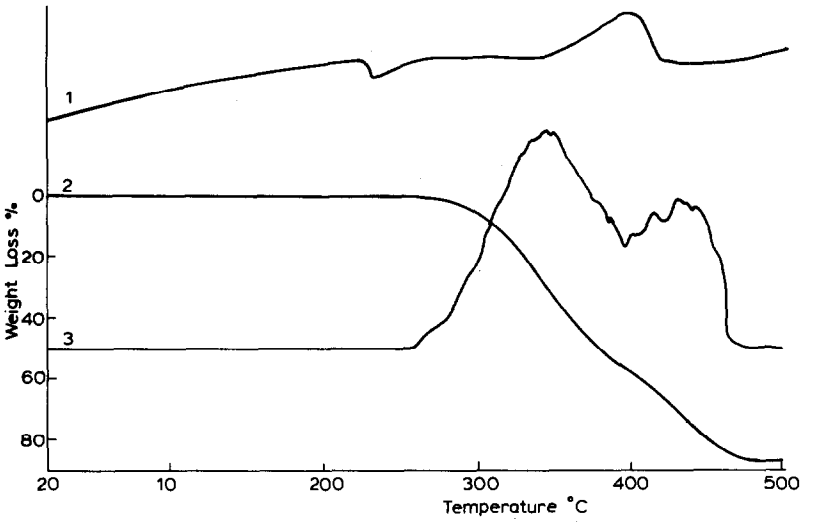

Fig. 1. Thermoanalytical curves of fludrocortisone acetate. 1, DTA; 2, TG; 3, DTG.

reaction starts at 260, 285 and 285°C, and ends at 486, 540 and 550°C with a percentage weight loss of 86, 85 and 69 for fludrocortisone acetate, fluorometholone and flucinolone acetonide, respectively. The main reaction in all cases seems to consist of two stages; the first ends at 397, 400 and 355°C with a weight loss of 57, 46 and 31% for fludrocortisone acetate, fluorometholone and flucinolone acetonide, respectively.

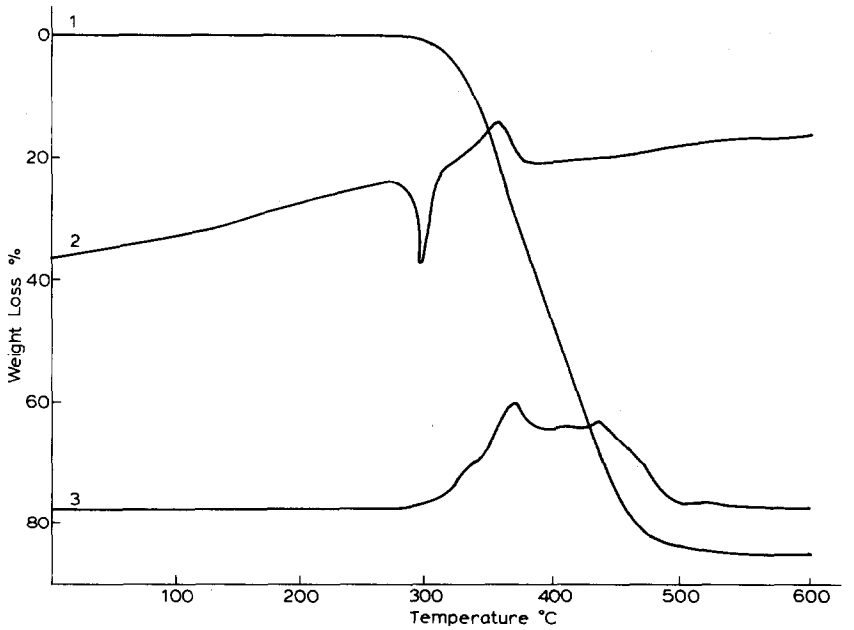

Fig. 2. Thermoanalytical curves of fluorometholone. 1, TG; 2, DTA; 3, DTG.

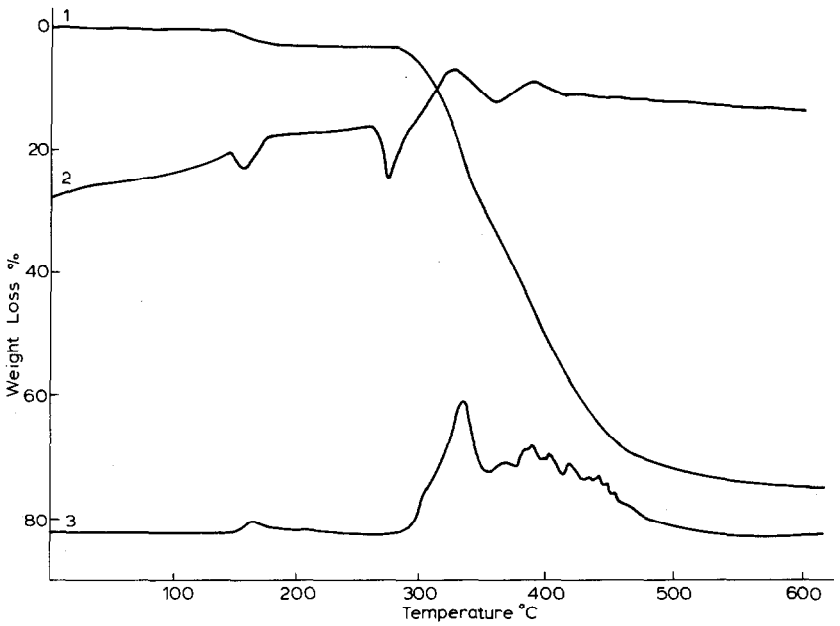

Fig. 3. Thermoanalytical curves of fluocinolone acetonide. 1, TG; 2, DTA; 3, DTG.

TABLE 1

Main thermal reactions of fluoride-containing steroids

Sample	Reaction temp. (°C)		Wt. loss (%)	
	Start	End	Total	Specific [a]
Fludrocortisone acetate	260	486	86	86
Fluorometholone	285	540	85	85
Fluocinolone acetonide	285	550	73	69

[a] The weight loss occurring only in the given reaction and not including the weight loss due to the preceding reaction(s), cf. total weight loss.

TABLE 2

DTA reactions of fluoride-containing steroids

Sample	Peak temp. (°C)	
	Endothermic reactions	Exothermic reactions
Fludrocortisone acetate	234	400
Fluorometholone	300	360
Fluocinolone acetonide	155, 275	326, 388

The main thermal decomposition reaction is found to be exothermic in nature. The DTA curve of fludrocortisone acetate shows a flattened exothermic peak with its maximum at 400°C. In the case of fluorometholone, the exothermic DTA reaction has its peak at 360°C. For fluocinolone, DTA illustrates two exothermic peaks corresponding to the thermal decomposition reaction with temperature maxima at 326 and 388°C.

The main reaction in the case of fluocinolone acetonide is preceded by another small reaction which starts at 142°C and ends at 235°C, with a weight loss of 3.3%. The reaction is endothermic in nature (having a peak temperature at 155°C). It is attributed largely to drying of the sample, since the studied compounds are stated to be hygroscopic and the powder should contain not less than 96% and not more than 104% with reference to the dried material [10].

Regarding the thermal stability of the compounds, it can be concluded from their decomposition reactions that fludrocortisone acetate is the least stable. It starts to decompose at a lower temperature than the other two which seem to be of equal stability. It is also found that introduction of a fluorine atom into the molecule increases the stability of the compound (hydrocortisone starts to decompose at 140°C, cf. fludrocortisone) [11].

In addition to the reactions mentioned above, the compounds undergo an endothermic reaction which is not accompanied by weight loss. The reaction has its maximum at 234, 300 and 275°C for fludrocortisone acetate, fluorometholone and fluocinolone acetonide, respectively. This reaction is endothermic and may be due to melting of the compounds.

The melting temperatures of the fluoride-containing steroids were determined using the melting point apparatus. Table 3 presents the melting points of the compounds obtained by DTA and the melting point apparatus. The results are compared with the data stated in the literature [12,13].

It is clear that the results of the DTA method are comparable with the literature figures and hence can be used for melting point determination.

In conclusion, the studied fluoride-containing steroids are characterized by undergoing one main thermal decomposition reaction which is ex-

TABLE 3

Melting point determination of fluoride-containing steroids

Sample	Melting temp. (°C)		
	DTA method	m.p. apparatus	Lit.
Fludrocortisone acetate	234	223–224	225–233
Fluorometholone	300	258–259	280–295
Fluocinolone acetonide	275	257	270

othermic and consists of two stages. In addition to stability studies, thermal analysis is of value for determining moisture content (loss on drying), since the compounds are hygroscopic, and melting temperatures.

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