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The thermoanalytical study of formulated terfenadine

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Abstract

The thermal behaviour of three terfenadine formulations was studied using thermogravimetric analysis and differential scanning calorimetry. The results are compared with those obtained in a previous study in which the thermal behaviour of pure terfenadine was characterized. A decrease in the decomposition temperature of formulated terfenadine was observed with respect to the pure product. Likewise, there is a variation in the decomposition enthalpies which is consistent with the variations observed in E_a calculated from the TG curves. However, there are practically no modifications in the temperature corresponding to the maximum of the endothermal effect of melting.

INTRODUCTION

The main requirements of a drug are efficacy and clinical safety. To ensure both within the context of a quality control, it is necessary to perform assays designed to predict the state of the drug after long storage times and, hence, its shelf-life.

In modern formulations, instability can often only be detected after considerable periods of storage time under normal conditions. To reduce study time, the drug is usually exposed to stressful conditions that will accelerate its deterioration, using Arrhenius plots to predict the drug stability against temperature under normal storage conditions [1].

Over the last few years, several studies have been published that combine thermal methods with other analytical techniques (X-ray diffraction, IR spectroscopy, HPLC, GLC, etc.) to characterize the compatibility of the excipients with each other and also with the active principle [2–5], in order to determine the degree of purity of both [6, 7] but, mainly, to detect the presence of polymorphous substances [8–12]. However, there are considerably fewer publications referring to the thermal stability of drugs in the solid state, perhaps because in this case

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instability is rarely spontaneous and requires other agents (moisture, the presence of oxygen, etc.) to trigger the reaction [13] and because the mechanisms of decomposition are not as well known as those involved in solutions [14].

In the present work we studied the behaviour and thermal decomposition kinetics of terfenadine formulations (microgranular and tablet form) and of a laboratory-prepared mixture of terfenadine and lactose, one of the most widely used excipients in drug formulation. The results are compared with those obtained in a previous work [15] in which we characterized the thermal decomposition kinetics of pure terfenadine.

EXPERIMENTAL

The terfenadine and microgranules (formulation A) were supplied by Aristegui Laboratories (Spain). Microgranules are a type of formulation that consists of a sugared nucleus covered by the active principle and protected by a covering of polymeric nature. In our case the microgranules were encapsulated and although the exact components of the formulation were unknown, the amount of active principle per capsule was 120 mg, so that it was possible to calculate that the proportion of terfenadine was 53.3%. The tablets (formulation B) used are marketed by Merrell Dow Laboratories under the name Triludan Forte®; this is known to contain lactose because this excipient is required to be declared. The amount of terfenadine declared per tablet is 120 mg, that is 18% of the active principle. Another formulation (formulation C), with a proportion of terfenadine similar to that of formulation B, was prepared by us at the laboratory simply by mixing the active principle and lactose-1-hydrate in a mortar, but without subjecting the mixture to humidification, granulation or compression.

TG, DTG and DSC curves were obtained on a Perkin-Elmer TGS-2 thermogravimetric analyser and a DTA–DSC-1700 high-temperature differential thermal analyser. TG and DTG curves were obtained with oven heating rates of 5, 10, 15 and 20°C min^{-1} and DSC curves were obtained at an oven heating rate of 12°C min^{-1}. In all cases a stream of N_2 was employed at a flow rate of 60 ml min^{-1}.

RESULTS

Figure 1 shows the TG and DTG curves of terfenadine, lactose and the three formulations studied, obtained at an oven heating rate of 20°C min^{-1}.

The TG and DTG curves of terfenadine (Fig. 1, curve a) show a 100% loss in weight between 269 and 419°C. The TG and DTG curves of formulation A (Fig. 1, curve b) disclose three weight losses of the order of 6%, 57% and 10% in the 241–298, 298–419 and 419–495°C ranges,

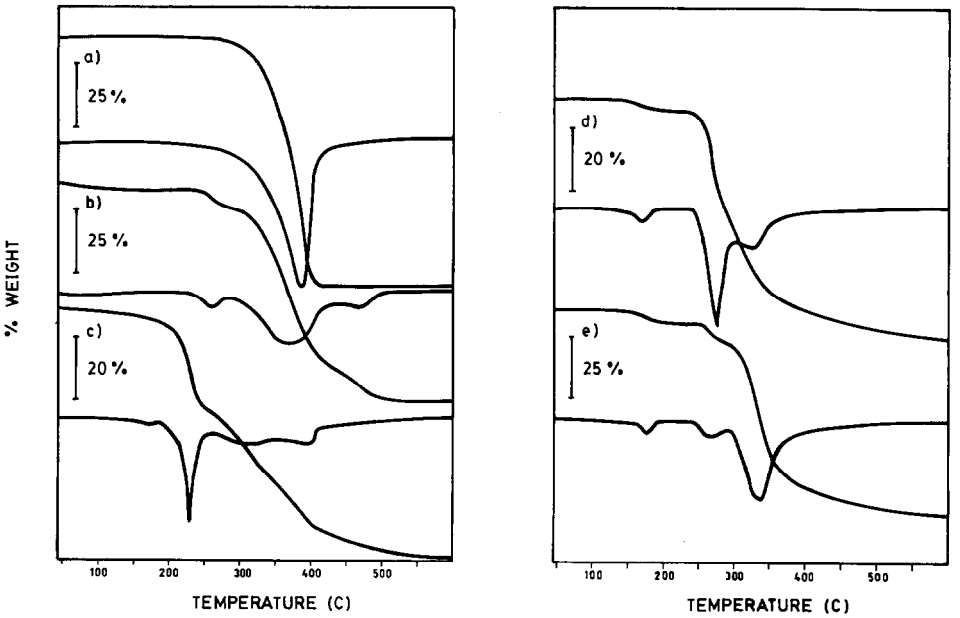

Fig. 1. TG and DTG curves. Curve a, terfenadine; curve b, formulation A; curve c, formulation B; curve d, formulation C; and curve e, lactose-1-hydrate.

respectively, which must correspond to the decomposition of the three components of this formulation: nucleus, active principle and covering. The curves obtained for the B formulation (Fig. 1, curve c) show three weight losses of 27%, 18% and 21% in the 181–251, 251–326 and 326–410°C temperature ranges, so that this formulation can be assumed to contain some additive other than lactose. Formulation C (Fig. 1, curve d) also shows three weight losses of 4%, 32% and 18% in the 127–227, 227–287 and 287–351°C temperature ranges, respectively. The first of these can be attributed to a loss of water contained in the lactose-1-hydrate and the second to the decomposition of lactose itself which occurs in the 251–390°C range (Fig. 1, curve e). From the temperatures at which the weight losses occur with respect to that of the pure product (269–419°C) and from the weight losses involved, the observed effects in the 298–419°C (formulation A), 251–326°C (formulation B) and 287–351°C (formulation C) temperature ranges can be attributed to the decomposition of terfenadine. In the case of formulation A, a slight increase in the temperature at which the decomposition of terfenadine begins is observed with respect to the pure product. In the case of the formulations containing lactose (B and C), the temperature range of the decomposition of terfenadine is displaced towards lower values with respect to the decomposition range of non-formulated terfenadine. In addition, a displacement in the decomposition temperature towards lower values of the lactose incorporated in the formulations (181–251°C for formulation B

TABLE 1

Decomposition ranges of terfenadine in the three formulations studied at different oven heating rates

Heating rate (°C min^{-1})	Decomposition interval of terfenadine (°C)		
	Formulation A	Formulation B	Formulation C
5	279–371	230–305	248–306
10	288–400	237–312	274–332
15	288–409	244–319	281–339
20	298–419	251–326	287–351

and 227–287°C for formulation C) is seen with respect to pure lactose-1-hydrate (230–390°C), as is the case with terfenadine, this being more pronounced in formulation B than in C.

The TG curves recorded at lower oven heating rates (15, 10 and 5°C min^{-1}) reveal a decrease in the decomposition temperatures of terfenadine parallel to the decrease in the heating rate (Table 1).

Table 2 shows the activation energies E_a and pre-exponential factors Z of the Arrhenius equation, previously determined for pure terfenadine [15], and those determined in the present work for terfenadine in the three formulations using the methods based on the observations of Ozawa [16] and Flynn and Wall [17] from the decomposition temperatures for

TABLE 2

Activation energies E_a and pre-exponential factors Z of the Arrhenius equation, rate constants K and decomposition half-lives of terfenadine in the three formulations studied

Formulation	E_a (kJ mol^{-1})	Z (min^{-1})	Temperature (°C)	K (min^{-1})	Half-life			
					Years	days	h	min
Terfenadine	155.6	3.31×10^{12}	140	7.03×10^{-8}	18	278	2	44
			160	5.69×10^{-7}	2	115	17	16
			180	3.83×10^{-6}		125	14	53
			200	2.20×10^{-5}		21	22	9
A	129.5	4.82×10^{10}	140	2.04×10^{-6}		235	18	2
			160	1.16×10^{-5}		41	8	24
			180	5.69×10^{-5}		8	10	58
			200	2.12×10^{-4}		2	6	30
B	247.6	1.06×10^{24}	140	3.88×10^{-8}	33	350	13	17
			160	1.10×10^{-6}	1	73	7	30
			180	2.31×10^{-5}		20	19	37
			200	3.76×10^{-4}		1	6	42
C	214.7	5.85×10^{22}	140	3.22×10^{-5}		14	22	32
			160	5.84×10^{-4}			19	50
			180	8.21×10^{-3}			1	24
			200	9.22×10^{-2}				8

different degrees of conversion (5%, 10%, 15% and 20%). An important reduction in the thermal stabilities of formulations A and C can be seen. This loss of stability becomes apparent in the half-life value of the decomposition of terfenadine at 140°C; above this value the effect of temperature is relevant for this drug [15]. This half-life value decreases from 18 years, 278 days, 2 h and 44 min for the pure product to 235 days, 18 h and 2 min for terfenadine in formulation A and falls as low as 14 days, 22 h and 32 min for terfenadine in formulation C. In contrast, an increase in the thermal stability of terfenadine occurs in formulation B, supporting the presence, observed in the TG curves, of another additive with stabilizing properties apart from lactose.

However, the terfenadine in formulation B is highly sensitive to temperature variations: above 160°C the terfenadine in this formulation has a decomposition half-life that is shorter than that of the pure product. After a temperature of 200°C has been reached, only the terfenadine mixed with lactose-1-hydrate (formulation C) has a shorter half-life than that observed in formulation B.

Figure 2 shows the DSC curves of terfenadine and of the three formulations, recorded at an oven heating rate of 12°C min^{-1}. The curve corresponding to formulation A (Fig. 2, curve b) has six peaks, all of them

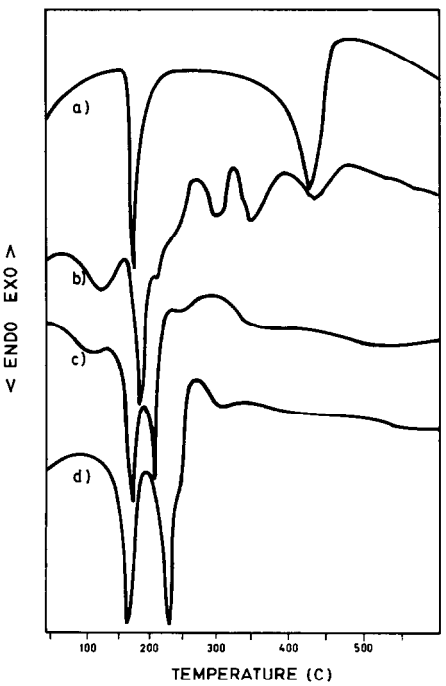

Fig. 2. DSC curves. Curve a, terfenadine; curve b, formulation A; curve c, formulation B; and curve d, formulation C.

endothermal. The first three (103, 165 and 194°C) must correspond to the melting of the three components of the formulation because no weight losses were observed in the TG curves at these temperatures. The other three (284, 343 and 434°C) must correspond to the pyrolysis of these components. In the case of formulation B, there are five peaks (Fig. 2, curve c), also endothermal, at temperatures of 98, 164, 203, 253 and 349°C. The first of these is due to a loss of water, and the rest to the melting and pyrolysis of lactose and terfenadine. In the case of formulation C (Fig. 2, curve d), there are three endothermal peaks at 161°C, which can be attributed to the melting of terfenadine, at 224°C with a small shoulder after the minimum, suggestive of the combined melting and decomposition of lactose, and at 292°C, corresponding to the decomposition of terfenadine.

The temperature corresponding to the maximum of the endothermal effect of decomposition of terfenadine is lower when the drug is formulated (343, 349 and 292°C in formulations A, B and C, respectively) than for the pure product (410°C). However, there are practically no modifications in the temperature corresponding to the maximum of the endothermal effect of melting, which rises from 162°C for pure terfenadine to 165°C for formulation A, to 164°C for formulation B and slightly decreases to 161°C for formulation C.

The enthalpy values of melting and decomposition, and the temperatures of these processes for the pure compound and when formulated, determined by DSC, are shown in Table 3. For terfenadine in formulation A, a slight increase in its temperature and enthalpy of fusion, and a decrease in its temperature and enthalpy of decomposition, are observed, with respect to the pure product. In the case of formulations B and C, a considerable increase is seen in the enthalpies of melting and decomposition of the formulated terfenadine with respect to the pure terfenadine. The variation occurring in the decomposition enthalpies of formulated terfenadine is consistent with the variations observed in E_a calculated from the TG curves.

TABLE 3

Melting enthalpy ΔH_m and decomposition enthalpy ΔH_d of terfenadine in the formulations studied and the temperatures of the processes

Formulation	T_m (°C)	ΔH_m (kJ mol^{-1})	T_d (°C)	ΔH_d (kJ mol^{-1})
Terfenadine	162	19.5	417	54.4
A	165	26.5	343	25.2
B	164	227	349	185.9
C	161	414.7	292	172.4

The thermal behaviour of formulations B and C, which are similar in composition, are very similar to each other but different from that characterizing formulation A, which has a more complex composition and elaboration. Regarding formulations B and C, very close values are seen for the parameters calculated, the exception being the rate constants and, therefore, the decomposition half-lives. This can be attributed to the above-mentioned presence in formulation B of some additive with stabilizing properties.

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