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Kinetic study of the thermal decomposition of terfenadine

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Abstract

The thermal decomposition kinetics of terfenadine were studied using differential thermal analysis and thermogravimetric analysis. From the thermogravimetric curves, recorded at different oven heating rates, the frequency factor (3.31×10^{12} min^{-1}) and the activation energy (155.6 kJ mol^{-1}) for the decomposition process were calculated. The latter value was slightly higher than that obtained by applying the Kissinger method (146.5 kJ mol^{-1}). The values determined for the rate constants and decomposition half-lives of terfenadine point to its good stability, the effect of temperature below 140°C being negligible.

INTRODUCTION

Among preformulation assays, the investigation of the intrinsic stability of a drug is of particular importance because recommendations can then be made on formulation approaches, and types of excipients, specific protective additives and packaging which are likely to improve the integrity of the drug and product may be indicated [1].

Bearing in mind that the physical and chemical processes responsible for instability both involve changes in enthalpy, thermal analysis offers an alternative to traditional methods for the detection of instability. The potential advantage of thermal methods still lies in the possibility of calculating stability data from a single run [2], thus considerably reducing the time and number of assays necessary.

Terfenadine, α-[4-(1,1-dimethylethyl)-phenyl]-4-(hydroxyphenylmethyl)-1-piperidinebutanol, is a new specific agonist of peripheral H_1 receptors that mediate the histamine reaction. The advantage of this compound is that it has none of the undesirable effects on the central nervous system shown by other anti-histamines [3].

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As part of a broader study on the properties and characteristics of terfenadine, the present work studies its thermal decomposition kinetics, regarding which little information is available [4,5]. Differential thermal analysis (DTA), thermogravimetric analysis (TG) and differential scanning calorimetry (DSC) were used.

EXPERIMENTAL

The drug terfenadine was supplied by Laboratorios Aristegui (Spain).

The TG, DTA and DSC curves were obtained on a Perkin-Elmer TGS-2 thermogravimetric analyser and DTA–DSC 1700 high-temperature differential thermal analyser. TG and DTA curves of terfenadine were obtained with heating rates of 5, 10, 15 and 20°C min^{-1}. DSC curves were obtained with a heating rate of 12°C min^{-1}. In all cases, a stream of N_2 was employed at a flow of 60 ml min^{-1}. The X-ray diagrams were obtained with a Philips 1730 diffractometer and the IR spectra with a Bomem Michelson 100 Series spectrophotometer, using the KBr pellet technique.

RESULTS AND DISCUSSION

The TG and DTG curves of terfenadine (Fig. 1(A)) obtained at an oven heating rate of 20°C min^{-1}, reveal a thermal decomposition of the compound between 269 and 419°C, with 100% weight loss. A shift in the range of decomposition temperatures towards lower values is seen as the heating rate decreases, as shown in Table 1. The table also shows the temperatures corresponding to mass losses of 5%, 10%, 15% and 20%, at the four heating rates used.

The activation energy E_a and the pre-exponential or frequency factor Z of the Arrhenius equation were determined from the TG curves using a method based on the observations of Ozawa [6] and Flynn and Wall [7]. These authors showed that the plot of the logarithm of the heating rate against the reciprocal of the absolute temperature, for the same loss in weight, is a straight line that allows one to calculate E_a and Z from the slope and the ordinate at origin, respectively, regardless of the reaction order. Using the Arrhenius plots at heating rates of 5, 10, 15 and 20°C min^{-1}, considering weight losses of 5%, 10%, 15% and 20% and assuming a first-order kinetic process, values of 155.6 kJ mol^{-1} and 3.31×10^{12} min^{-1} were obtained for E_a and Z for the thermal decomposition of terfenadine. Table 2 shows the values of the rate constants K and half-lives of decomposition of terfenadine at different temperatures. The results indicate that the drug is very stable because the effect of temperature is negligible below 140°C. However, this effect should not be ignored because changes in temperature of 20°C lead to important changes in kinetic parameters.

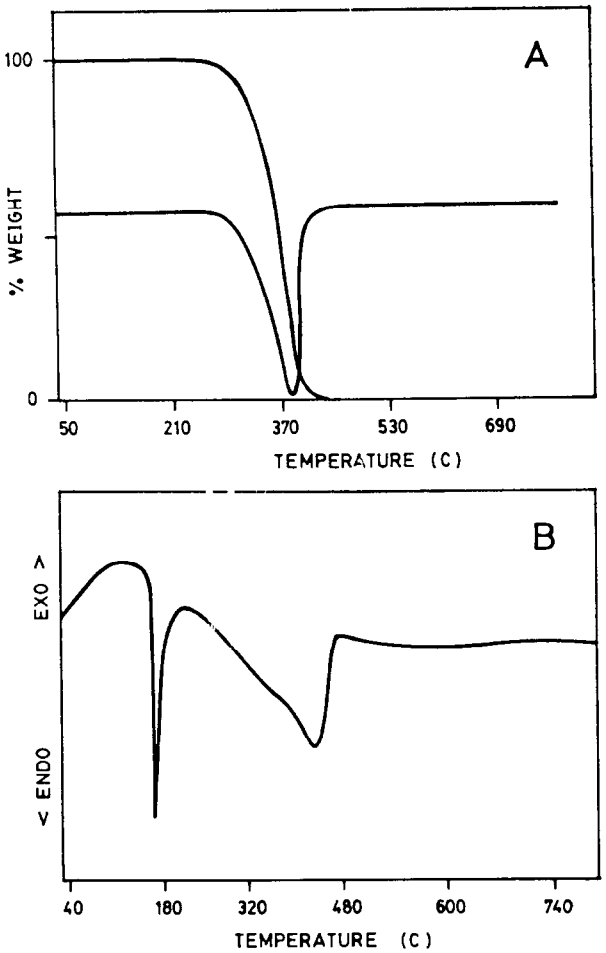

Fig. 1. (A) TG and DTG curves, and (B) DTA curve of terfenadine.

The DTA curves (Fig. 1(B)) recorded at a heating rate of 20°C min^{-1} show two endothermal peaks at 164 and 423°C, corresponding to the melting and decomposition of terfenadine, respectively. DTA curves were

TABLE 1

Range of decomposition temperatures and temperatures corresponding to the four conversion degrees determined for different oven heating rates

Rate (°C min^{-1})	Range (°C)	Temperature (°C)			
		5%	10%	15%	20%
5	221–381	292	306	315	322
10	241–400	308	321	330	337
15	269–409	311	327	337	344
20	269–419	312	328	338	346

TABLE 2

Values of the rate constant K and decomposition half-lives of terfenadine at different temperatures

Temperature (°C)	K (min^{-1})	Decomposition half-life			
		Years	Days	Hours	Minutes
120	7.016×10^{-9}	187	345	8	48
140	7.028×10^{-8}	18	278	2	44
160	5.601×10^{-7}	2	115	17	16
180	3.831×10^{-6}	–	125	14	53
200	2.195×10^{-5}	–	21	22	9

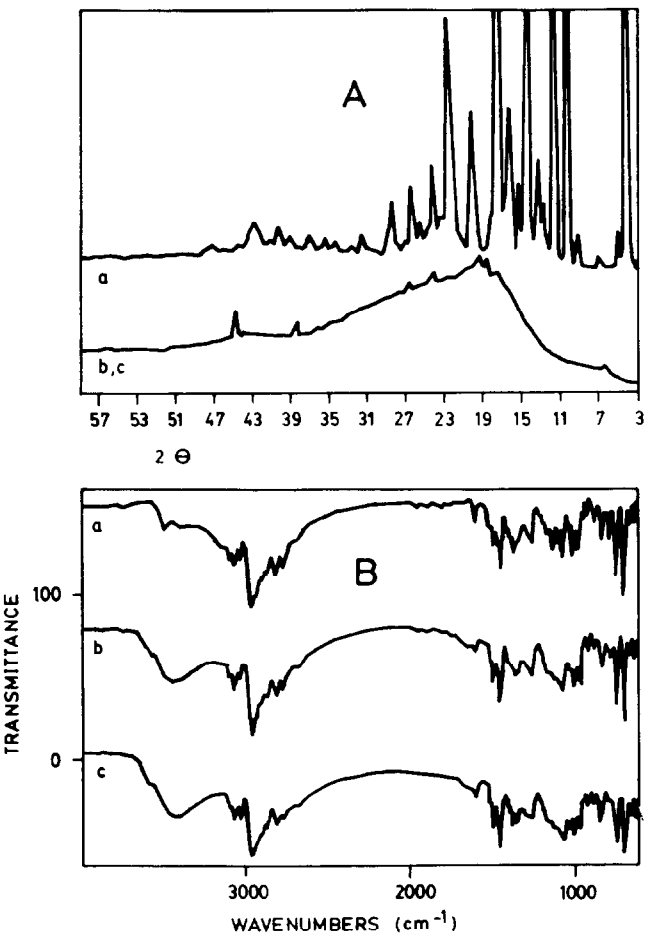

Fig. 2. (A) X-ray diffractograms, and (B) IR spectra of (curve a) terfenadine, (curve b) terfenadine melted in N_2 atmosphere, and (curve c) terfenadine melted in O_2 atmosphere.

also obtained at heating rates of 5, 10 and 15°C min^{-1}. It was observed that the temperature corresponding to the maximum of the endothermal melting effect decreases with the decrease in the heating rate: 165°C (20°C min^{-1}), 163°C (15°C min^{-1}), 162°C (10°C min^{-1}) and 159°C (5°C min^{-1}). The same is true of the endothermal effect corresponding to the decomposition occurring at 423, 420, 410 and 391°C at the same heating rates.

The value of E_a, calculated from the data obtained with the DTA curves and applying the Kissinger equation [8,9], is 146.5 kJ mol^{-1}, 5.8% lower than that determined by the above method. This therefore confirms the tendency of the latter method to undervalue this parameter by approximately 6% as a result of the deviation of the peak temperature at low heating temperatures with respect to the theoretical values [2].

The enthalpies of melting and decomposition of the drug were also determined by DSC; the values obtained were 19.5 kJ mol^{-1}, in the case of melting, and 54.4 kJ mol^{-1} for decomposition.

In order to determine if melting affects the structure of terfenadine, X-ray diffractograms and IR spectra were recorded of terfenadine and of the product removed from the oven above the melting temperature, and also of the product melted in an O_2 atmosphere. Melted terfenadine has a vitreous aspect and the X-ray diffractograms reveal the loss of its crystalline structure with respect to its initial structure (Fig. 2(A)). However, no alterations occurred, in either case, in the functional groups of the molecule, as seen by comparing the IR spectra (Fig. 2(B)). The oxidative degradation of terfenadine to terfenadona reported by other authors [4,5] was not observed. In the spectra there was only a broadening and slight displacement towards lower frequencies in the bands corresponding to the OH groups in the 3500–3300 cm^{-1} zone and at 1465 cm^{-1}, as the result of the variation in the degree of association of the drug molecules on passing from the crystalline to the vitreous state. The possible consequence of the loss of crystalline structure would be a modification of the solubility of terfenadine which could affect the absorption rate and disposition of the drug in the organism.

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