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THERMAL BEHAVIOR OF LORATADINE

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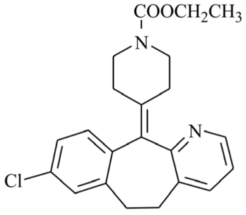
Simultaneous thermogravimetry (TG) and differential thermal analysis (DTA) techniques were used for the characterization the thermal degradation of loratadine, ethyl-4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidine)-1-piperidine-carboxylate. TG analysis revealed that the thermal decomposition occurs in one step in the 200–400°C range in nitrogen atmosphere. DTA and DSC curves showed that loratadine melts before the decomposition and the decomposition products are volatile in nitrogen. In air the decomposition follows very similar profile up to 300°C, but two exothermic events are observed in the 170–680°C temperature range.

Flynn–Wall–Ozawa method was used for the solid-state kinetic analysis of loratadine thermal decomposition. The calculated activation energy (E_a) was 91±1 kJ mol^{-1} for α between 0.02 and 0.2, where the mass loss is mainly due to the decomposition than to the evaporation of the decomposition products.

Keywords: *decomposition kinetic, DTA, loratadine, thermogravimetry*

Introduction

Loratadine, ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate is a long acting non-sedative antihistaminic agent that was developed for the treatment of seasonal allergic rhinitis [1] whose action is more effective than the other commercially available antihistaminic drugs. It is a white to off-white powder, *m.p.* 136°C, not soluble in water, but very soluble in acetone, alcohol, ether and chloroform [2]. The structural formula of loratadine is:



Thermal analytical techniques can provide important information regarding storage and stability of pharmaceuticals. Examples of the importance of such studies are given in [3, 4].

Solid-state kinetic studies have increasing importance in thermal analysis, in which the main purposes are to calculate the parameters of the Arrhenius equation and to determine the mechanism(s) of pyrolysis reaction. These data can provide valuable information about time and condition of storage. The knowledge of such parameters for pure drugs and for drug–excipient mixtures is also meaningful in order to elucidate miscibility/incompatibility and its effects on thermal stability.

In this work TG/DTG and DTA were used to characterize the decomposition pathways of loratadine both in air and nitrogen atmospheres. Flynn–Wall–Ozawa method [5, 6] was used for kinetic analysis on the thermal decomposition of loratadine, since few information on E_a of the thermal decomposition of loratadine obtained from TG/DTA analysis is reported in the literature.

Experimental

Loratadine, pharmaceutical grade min. 99.48% (Natural Pharma, Brazil) was used without further purification. Simultaneous TG/DTG - DTA runs were carried out with initial sample mass of 7.0 mg, in alumina pans (90 μL), using simultaneous SDT-Q600 equipment (TA Instruments). Dynamic nitrogen and air atmospheres (flow rate of 50 mL min^{-1}) and heating rates of 2, 4, 8, 12, 16 and 32°C min^{-1} were used. The apparatus was calibrated for temperature with zinc standard. For the kinetic study, the experiments were performed at least in duplicates, using the above described conditions. Standard calibration weights were used for mass calibration recommended by TA Instruments in Thermal Advantage for Q-Series software.

DSC curves were recorded using 3.0 mg of initial sample mass, a covered aluminum pan with a cen-

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tral pinhole in the lid, 10°C min^{-1} heating rate under a 50 mL min^{-1} nitrogen flow. TA DSC-910 unit coupled to a TA-2000 Thermal Analyzer (both from TA Instruments). Temperature and enthalpy calibration of the equipment have been done using metal indium with 99.99% purity.

Results and discussion

Thermal behavior

Thermal decomposition of loratadine in nitrogen atmosphere lead to 100% mass loss between 200 and 400°C (Fig. 1a).

The thermal decomposition in air starts at 170°C and about 80% mass loss occurs in the first step (up to 410°C) resulting a carbonaceous residue, (Fig. 1b). Between 410 and 680°C, the remaining 20% of initial mass is lost in a second decomposition step, accompanied by the burning of the carbonaceous residue.

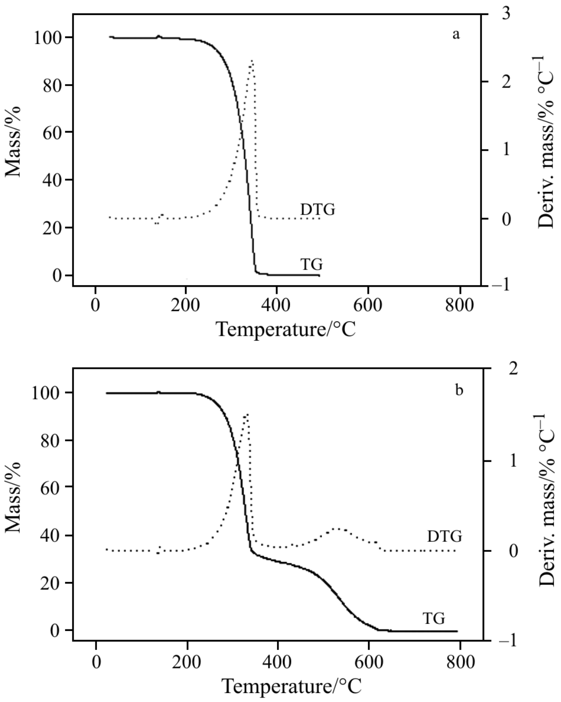

Fig. 1 —– TG and ··· – DTG curves of loratadine in a – nitrogen and b – air

The DTG curve in nitrogen atmosphere exhibits one peak (peak temp.: 345°C). The DTG curve in air atmosphere shows two peaks at 332 and 533°C.

In nitrogen the endothermic peak at 137°C is related to the melting of the sample (DTA curve, Fig. 2a) while the broader one at 345°C (in agreement with TG/DTG data) is due to the evaporation of the sample.

Small amount of loratadine was heated in a 20 cm long open glass tube, under nitrogen. It was observed that heated up to 300°C a non-volatile liquid was obtained. The non-volatile nature of the liquid was confirmed since no any drops referring to condensation have been observed in the cold part of the tube. When the temperature reached 320°C the liquid becames yellowish and a liquid condensate was observed in the upper part of the tube. At 350°C the liquid becomes brownish and evaporates without condensation.

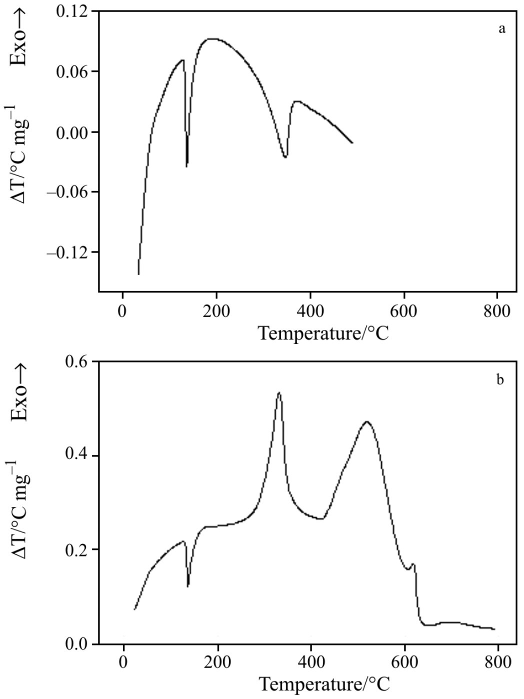

Fig. 2 DTA curves of loratadine in a – nitrogen and b – air

Under air (Fig. 2b) an endothermic melting peak was observed at 137°C. However, in this case the decomposition was represented by two exothermic events with peaks at 332 and 525°C. A peak at 618°C represents the burning of the carbonaceous residue.

A DSC curve obtained under nitrogen (Fig. 3) shows the melting endotherm at 138°C (ΔH_f= 33.2 kJ mol^{-1}). Then the decomposition can be observed starting with a small exotherm peak followed

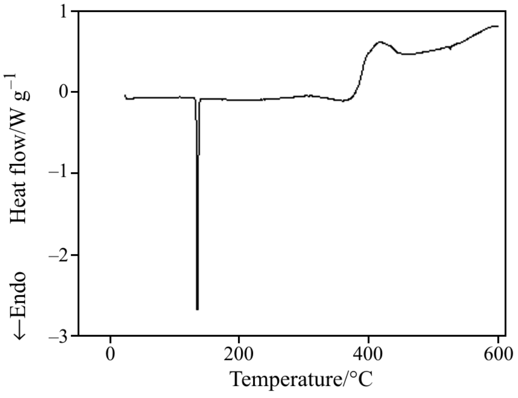

Fig. 3 DSC curve of loratadine in nitrogen

by a broad endotherm one at 376°C and again an exotherm appears at 415°C.

This is in agreement with the observation of the heating in an open tube (see above).

Thus one can conclude that upon heating the thermal behavior of loratadine involves a fusion, followed by decomposition and evaporation of the decomposition product.

Kinetic studies

Considering that loratadine in liquid state is not volatile, but only its decomposition products evaporate, the kinetic parameters were calculated as it is described below.

Non-isothermal kinetic analysis was based on TG experiments performed at six different heating rates 2, 4, 8, 12, 16, 32°C min^{-1} in nitrogen atmosphere (flow rate of 50 mL min^{-1}). The TG and DTG curves shifted to higher temperatures with increasing heating rates (Figs 4 and 5).

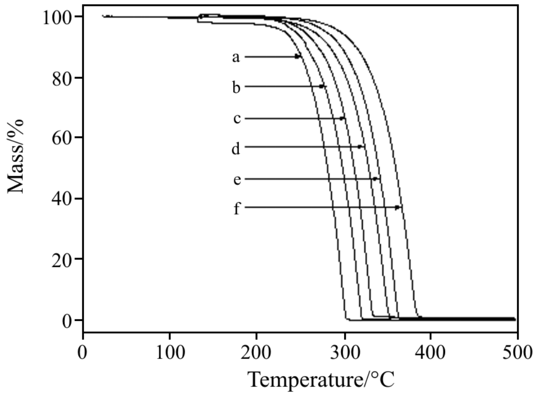

Fig. 4 TG curves of loratadine at different heating rates under dry nitrogen atmosphere. a – 2, b – 4, c – 8, d – 12, e – 16 and f – 32°C min^{-1}

Therefore, Ozawa–Flynn–Wall equation (Eq. (1)) was applied to describe the overall degradation reaction and the activation energy was calculated as a function of the degree of reaction.

$$\log\beta = -0.4567\left(\frac{E_\mathrm{a}}{RT}\right) - 2.3115 + \log\left(\frac{AE_\mathrm{a}}{R}\right) - \log[g(\alpha)] \quad (1)$$

where β – heating rate, E_a – apparent activation energy, R – gas constant, T – absolute temperature, A – pre-exponential factor and $g(\alpha)$ – mathematical expression related to the TG curve. Guinesi *et al*. presented a detailed description how Eq. (1) was obtained [7].

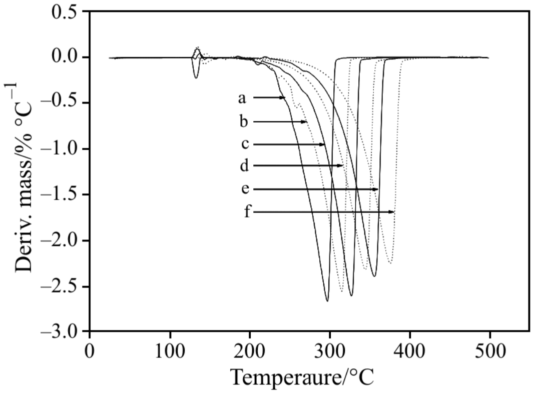

Fig. 5 Overlaid DTG curves of loratadine using different heating rates under dry nitrogen atmosphere. a – 2, b – 4, c – 8, d – 12, e – 16 and f – 32°C min^{-1}

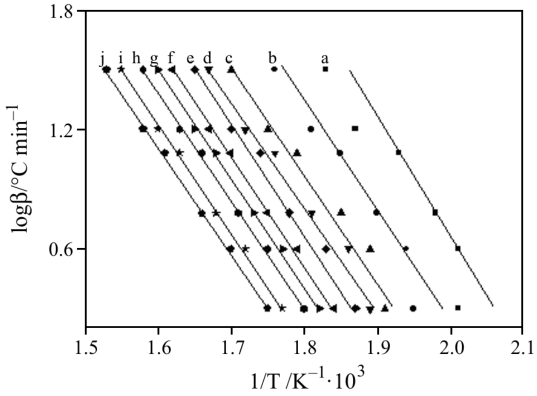

Fig. 6 logβ *vs*. 1/*T* plots for loratadine at a – 2, b – 5, c – 10, d – 15, e – 20, f – 30, g – 40, h – 50, i – 70 and j – 90% conversion

Straight lines were obtained for the logβ *vs*. 1/*T* plots (Fig. 6). Between α=0.02–0.9, when α>0.1, the correlation coefficients are larger than 0.999.

Figure 7 shows the dependence of the activation energy as a function of conversion (%). There are linear parts, suggesting changes in the decomposition mechanism. The first related to the decomposition of

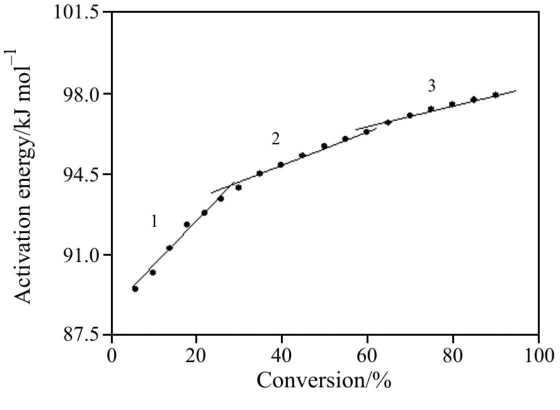

Fig. 7 Dependence of the activation energy *vs*. degree of conversion for loratadine in nitrogen for 0.06<α<0.9

the liquid loratadine, the second is representative to a process involving decomposition and evaporation of the decomposition products and the third one mostly related to the evaporation of the brownish decomposition product (see above).

These results suggested E_a=91±1 kJ mol^{-1} and A=7.2±0.2 min^{-1} in the first linear portion where the mass loss is the mainly due to the thermal decomposition, in the $0.06<\alpha<0.22$ range.

Conclusions

These studies suggest that the decomposition of loratadine occurred after melting in a single step in nitrogen atmosphere, when the sample is heated from 300 to 350°C, with E_a=91±1 kJ mol^{-1} and A=7.2±0.2 min^{-1}. Only the decomposition products are volatile. In air after melting decomposition took place with the formation of carbonized residue.

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