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THERMAL DECOMPOSITION OF ENALAPRIL MALEATE STUDIED BY DYNAMIC ISOCONVERSIONAL METHOD

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Enalapril maleate (EM) is an angiotensin-converting enzyme inhibitor indicated in the hypertension and congestive heart failure treatment. The thermogravimetry (TG) and differential scanning calorimetry (DSC) techniques were used for the thermal characterization of EM. TG analysis revealed that the thermal degradation occurs in two steps, in the 150–340°C range. Each thermal degradation stage results an endothermic peak in the DSC curve, where the melting transition is also observed just before the decomposition starts. The Ozawa–Flynn–Wall isoconvertional method was used for a kinetic analysis on the thermal decomposition of EM. In the lower temperature thermal degradation step a complex pyrolysis mechanism was observed. The calculated apparent activation energy (E_a) decreases from 200 to 80 kJ mol^{-1} in this event. In the second stage, for α>0.3 conversions, an E_a of 100 kJ mol^{-1} was obtained.

Keywords: *enalapril maleate, model-free kinetics, Ozawa–Flynn–Wall method, thermogravimetry*

Introduction

Kinetic studies have become a crucial point in thermal analysis, in which the main purpose is to determine the mechanism(s) of pyrolysis reaction and to calculate the parameters of the Arrhenius equation. These data can provide valuable information about time and condition of storing. The knowledge of such parameters for pure drugs and for associations of the drug with other components is also meaningful in order to elucidate miscibility/compatibility and its effects on thermal stability.

The methods proposed for the kinetic study of thermal decomposition are commonly classified in model-fitting and model-free methods. In each case, data from isothermal and/or non-isothermal experiments can be used. Model-free isoconversional methods are considered as the most reliable ones, especially the Friedman–Ozawa method [1, 2], because of its theoretical and experimental advantages. Through isoconversional methods it is possible to obtain the apparent activation energy (E_a) as a function of the extent of conversion (α) which has specific interest when the thermal decomposition occurs in more than one step.

In this work, an isoconversional method, called to Ozawa–Flynn–Wall [3, 4] was used for a kinetic analysis on the thermal decomposition of enalapril maleate (EM). This compound is a strong angiotensin-converting enzyme inhibitor and used in the treatment of hypertension and congestive heart failure. Studies on chemical and physical stability of EM have been reported which include results on pure EM and effects of solution and the matrix nature [5–9], presence of metal ions [10] among others. Nevertheless, little information about the E_a on the thermal decomposition of EM obtained from TG/DSC analysis is reported in the literature. Cotton *et al*. [11] studied the influence of microcrystalline cellulose and compression force on the thermal stability of EM. Recently, Staniz [5] studied the humidity influence on the EM stability and kinetic data were obtained from HPLC using the 'curve fitting method'.

Experimental

Enalapril maleate was a pharmaceutical grade from Gerbras Química Farmacéutica Ltda, Lot N° NF196568.

DSC runs were carried out with initial sample masses of 2–10 mg, in aluminum pans with a pinhole, using a Shimadzu DSC-50 calorimeter. Nitrogen gas atmosphere (flow rate of 20 mL min^{-1}) and heating rates of 2.5–20°C min^{-1} were used. The apparatus was calibrated with zinc and indium standards.

Initial sample masses were 2–10 mg in open platinum pans were subjected to TG measurements using a Shimadzu TGA-50 thermogravimetric analyzer. Nitrogen flux and heating rates were the same used in the DSC analysis. For the kinetic study, the experiments

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were performed at least in duplicates, with initial mass of 6.2±0.2 mg and base line correction was made using an empty pan.

Results and discussion

Thermal behavior

Several mass loss steps and peaks were recorded during the TG and DSC analysis of the EM (Fig. 1). The thermal decomposition starts at 150°C and about 27% of mass loss occurs in the first step, upto 230°C. This corresponds to the loss of one molecule of maleic acid together with one molecule of water, which is eliminated in an intramolecular cyclization reaction of the enalapril molecule [6]. Between 230 and 335°C, the remaining 73% of mass is lost in the second step. The DTG curve is characterized by two peaks, the minimum of each peak corresponds to the maximum degradation rate attained in each stage and are centered at temperatures (T_{max}) of 174 and 323°C. Both peaks are non-symmetrical. In the peak at lower temperature, the maximum is shifted to the left and while the maximum of the second peak moved to the right. DSC curve shows two superimposed peaks in the 150–200°C range. A more intense and sharp one centered at 150°C due to the melting process, and a larger and weaker one centered at 170°C due to the first step of thermal degradation reaction of the sample. A third endothermic event occurs at higher temperature and its peak position coincides with that of the second stage of the thermal degradation observed in the DTG curve.

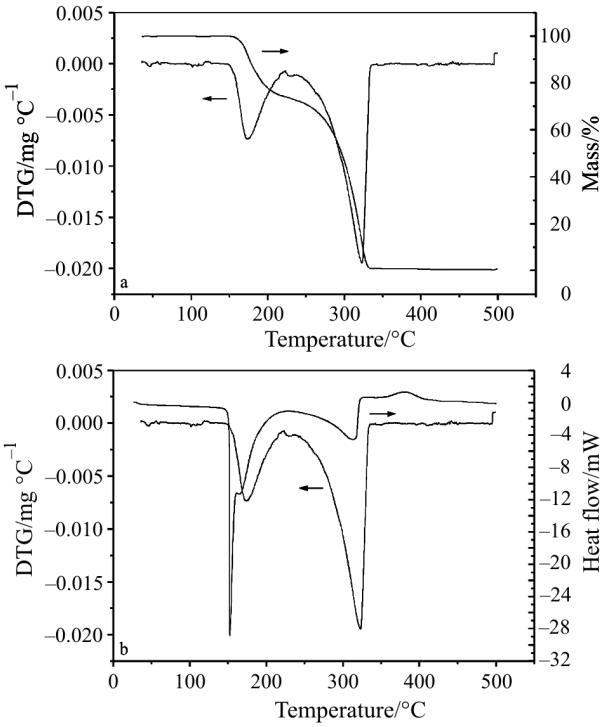

Fig. 1 a – TG and DTG curves of EM and b – DSC and DTG curves of EM. (6.1 mg, 10°C min^{-1}, 20 mL min^{-1}, N_2 atmosphere, TG: Pt open pan, DSC: Al closed pan with a pinhole)

Effect of the experimental conditions on the TG curves

The TG experiments have been performed at four different heating rates (2–20°C min^{-1}) and also with five different sample masses (2.1–9.8 mg). The obtained TG curves revealed that the whole curve is moved towards higher temperatures when the heating rate or the sample mass is increased (Figs 2 and 3), without alteration of the onset mass loss temperature. In this way, no reaction/reaction mechanism change was detected in the investigated experiments conditions and ranges [12]. The observed effects just stands for the temperature gradient

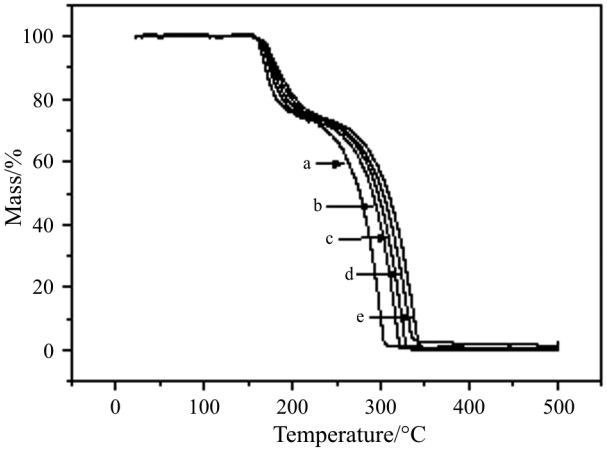

Fig. 2 Overlaid TG curve for EM using different sample sizes at a heating rate of 10°C min^{-1} dry nitrogen atmosphere. a – 2.07 mg, b – 4.29 mg, c – 6.07 mg, d – 8.02 mg, e – 9.81 mg

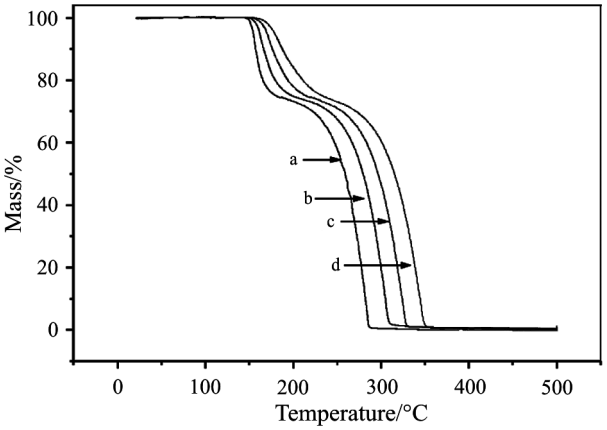

Fig. 3 Overlaid TG curves of EM using different heating rates under dry nitrogen atmosphere. a – 2°C min^{-1}, b – 5°C min^{-1}, c – 10°C min^{-1}, d – 20°C min^{-1}

created (inside and outside the sample particles) during the analysis [13].

Kinetic analysis

In spite of the good definition of the DTG peaks, there is a certain degree of superposition between them because the curve do not achieve the zero level in that interval (190 to 270°C, Fig. 4). This fact complicates the analysis of isolated events. Therefore, the Ozawa–Flynn–Wall equation (given below) was applied to the overall degradation reaction and the activation energy was calculated as a function of the reaction degree.

$$\log\beta = -0.4567\left(\frac{E_a}{RT}\right) - 2.3115 + \\ + \log\left(\frac{AE_a}{R}\right) - \log[g(\alpha)]$$

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.

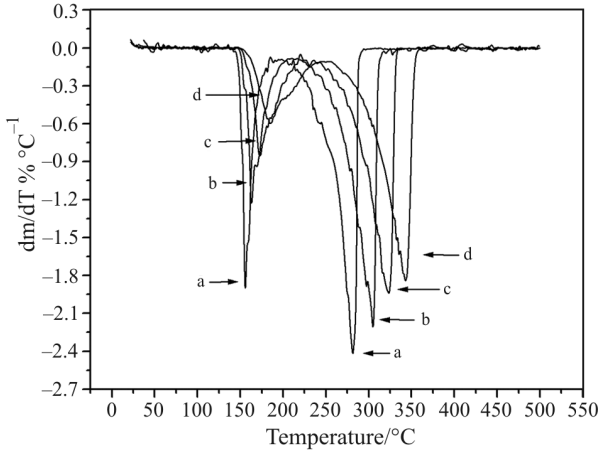

Fig. 4 Overlaid DTG curves of EM using different heating rates under dry nitrogen atmosphere. a – 2°C min^{-1}, b – 5°C min^{-1}, c – 10°C min^{-1}, d – 20°C min^{-1}

Straight lines were obtained for the logβ *vs.* $1/T$ plots, for α between 0.02 and 0.98, with correlation coefficients larger than 0.999. Some examples are shown in Fig. 5. The results of the E_a in Fig. 6 show two well-defined regions. The first one, in which the conversion varies from 0.00 to 0.27, starts with a E_a of 200 kJ mol^{-1} and decreases nearly linearly down to 80 kJ mol^{-1}. In this stage the formation of the diketopiperazin ring of EM takes place [6]. The dependence of E_a on α shows the complexity of the kinetics of this stage. Vyazovkin pointed to similar behavior

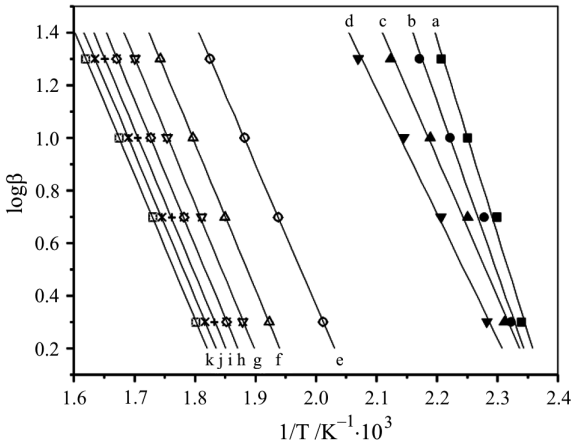

Fig. 5 Plot of logβ *vs.* the reciprocal temperature $1/T$ for EM at a – 5%, b – 10%, c – 15%, d – 20%, e – 30%, f – 40%, g – 50%, h – 60%, i – 70%, j – 80% and k – 90% conversion

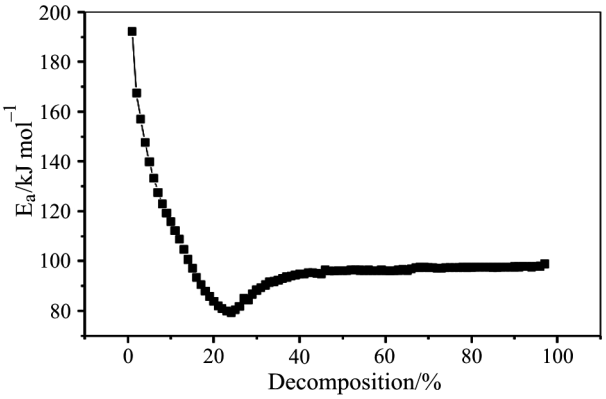

Fig. 6 Dependence of the apparent activation energy on the decomposition degree using dynamic isoconversional method (dim) for EM

in the dehydration of calcium oxalate monohydrate in N_2, where gas and solid phases are in equilibrium [14]. In the second stage, reaction occurs with apparent activation energy of 100 kJ mol^{-1}.

Conclusions

Enalapril maleate pyrolyzes in a complex way. TG analysis showed two stages of thermal degradation. The first stage, corresponding to the decomposition of the molted solid, with apparent activation energy decreasing from 200 to 100 kJ mol^{-1}. For the second stage, corresponding to $\alpha>0.3$, an apparent activation energy around 100 kJ mol^{-1} was calculated. The dependence of E_a with α does not allow the application of the curve fitting method on the determination of the thermal triplet (A, E_a and $f(\alpha)$).

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