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Preparation and thermal study of Mg-diclofenac compound in solid state

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Abstract The thermal behaviour of Mg-diclofenac compound was evaluated by simultaneous TG-DTA and DSC. The profile of the DSC curves showed that this compound possesses two transition phases: endothermic and exothermic between 170–180 °C and 185–195 °C, respectively. The endothermic reaction is reversible (enantiotropic). Thus, different experimental conditions, i.e. masses sample, open and crimped lids crucible, static and dynamic atmospheres were utilized for DSC analysis for evaluation of this transition phase. In a static atmosphere the enantiotropic reaction was not observed. The obtained data were utilized to obtain the kinetic parameters, which were calculated by the Capela and Ribeiro method. The results show that the activation energy for the transition phase depends on the different experimental conditions.

Keywords Mg-diclofenac · DSC · Transition phase

Introduction

Diclofenac deserves special attention because it is a widely marketed anti-inflammatory drug. Some studies have been accomplished regarding the compounds formed with diclofenac [1]. Bucci et al. relate the thermal properties of the solid compounds obtained by the reaction of diclofenac with manganese(II), iron(II), cobalt(II), nickel(II), copper(II) and zinc(II). In this work the first compound of the series of these divalent metals were detailed, but without thermoanalytical discussion of the other complexes [2]. Kenawi et al. investigated the interactions between cetrizine dihydrochloride and diclofenac complexes of Ca(II), Mg(II), Zn(II) and Fe(III) which form stable adducts. As part of this work, it was shown that cetirizine dihydrochloride also interacted with diclofenac sodium and also when the metal ion is linked to diclofenac [3]. Recently, Fini et al. investigated some diclofenac salts, where it was verified that the magnesium compound presents a crystalline transition [4]. However, other characteristics of the thermal behaviour of this compound were not detailed. In a previous work, the preparation and thermal characterization of iron(III)-diclofenac was reported on. In this work we used a sample mass of 2 and 5 mg, which allow a better evaluation of kinetic parameters [5]. Recently, the preparation of calcium-diclofenac was also reported on as well as the thermal behaviour and kinetic evaluation of the dehydration, thermal decomposition and transition phase of this compound [6]. In addition, we also have reported on the synthesis of cobalt-diclofenac complex, which exhibits a transition phase. The objective of this study was the evaluation of the transition phase by DSC method with different sample masses and using a cover on the crucible as well as crimped lids. In these different conditions, the effects of the different masses employed demonstrated that the activation energy becomes lower with an increase in the sample mass [7].

Therefore, as part of our research into understanding the behaviour of the transition phase of complex metals, specially using the diclofenac drug as a ligand, this work reports on the preparation of magnesium(II)-diclofenac

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compound (Mg(Diclof)$_2$). Thus, the aim of this work was to evaluate the thermal behaviour and obtain the variation of activation energy (E_a/kJ mol^{-1}) vs. degree conversion (α) of the transition phase observed in this compound. DSC curves were carried out in an open and crimped aluminium pan and with three different sample sizes under non-isothermal conditions in nitrogen and static atmospheres, in order to determine the effect of changed experimental conditions on the kinetic behaviour and thus to obtain reference values of activation energy. Furthermore, the isoconversional method was used as a way of obtaining reliable and consistent kinetic information and, because the measurements are estimated, the temperatures correspond to fixed values of conversion degree (α) and also avoid the use of explicit kinetics models. Thus, the activation energy (E_a/kJ mol^{-1}) data were obtained applying the isoconversional method proposed by Capela and Ribeiro [8–12].

Experimental

The Mg(Diclof)$_2$ compound was prepared by the stoichiometric addition of magnesium(II) sulphate on potassium diclofenac salt, both in methanol solutions, as described by Fini et al. [4]. The obtained precipitate was filtered, washed with methanol, dried at room temperature and stored in a desiccator over anhydrous calcium chloride until a constant weight was achieved.

Simultaneous TG-DTA and DSC curves were obtained from a SDT 2960 and a DSC 2910, both from TA Instruments, respectively. The TG-DTA analysis experiment was performed using sample sizes of about 7 mg in an a-alumina crucible with heating rates of 20 °C min^{-1} in synthetic air atmosphere (100 mL min^{-1}). The DSC curves were obtained using several heating rates (5, 10 and 20 °C min^{-1}) from 30 to 220 °C. Powdered samples having a particle size around 250 mm and sample mass of 1, 5 and 10 mg (±0.05 mg) were placed in an aluminium crucible, either open or with crimped lids. The analyses were evaluated at a nitrogen flow of 50 mL min^{-1}, as well as without the flow of gas (static atmosphere). The diffraction patterns were obtained from a Siemens D-500 X-ray diffractometer using Cu Kα radiation ($\lambda = 1.54$ Å) and settings of 40 kV and 30 mA.

Kinetic methodology

To perform the kinetic analysis under non-isothermal conditions is usually to consider the integral kinetic equation, defined by

$$\beta = \frac{AE}{Rg(\alpha)} \int_{E/RT}^{\infty} \frac{\exp(-z)}{z^2} \mathrm{d}z\,, \tag{1}$$

where $\beta = \mathrm{d}T/\mathrm{d}t$ is a constant heating rate (T is the temperature and t is the time), $g(\alpha)$ is the integral form of the reaction model as function of the extent of reaction α, A is the pre-exponential factor, E is the activation energy and R is the gas constant.

The estimates of the kinetic parameters are obtained by fitting equation (1) to experimental data. As consequence, is required the evaluation of the integral on the right side of the equation (1), known as temperature integral. A difficulty results from the fact that this integral does not have an exact analytical solution. Thus, is convenient to approximate the integral of temperature for some function that yields suitable estimations to these kinetic parameters.

In this work, the kinetic parameters are obtained through isoconversional method using an approximation to the temperature integral based on the convergent of a Jacobi fraction, proposed by Capela et al. [8]. This approximation is a rational function, given by the following equation:

$$\int_{x}^{\infty} \frac{\exp(-z)}{z^2} \mathrm{d}z = \frac{\exp(-x)}{x} \frac{x^3 + 14x^2 + 46x + 24}{x^4 + 16x^3 + 72x^2 + 96x + 24} \tag{2}$$

A characteristic experimental curve presents the conversional fraction, α, as a function of the temperature for a given heating rate, β. For each fixed value of α there are corresponding values T_α for temperature, values E_α for activation energy and values A_α for pre-exponential factor.

Replacing the integral in Eq. 1 by the approximation given in Eq. 2 is obtained the following expression for heating rate β as function of the $x_\alpha = 10^3/RT_\alpha$:

$$\beta = \frac{\exp(B_\alpha - E_\alpha x_\alpha)}{x_\alpha} \frac{E_\alpha^3 x_\alpha^3 + 14E_\alpha^2 x_\alpha^2 + 46E_\alpha x_\alpha + 24}{E_\alpha^4 x_\alpha^4 + 16E_\alpha^3 x_\alpha^3 + 72E_\alpha^2 x_\alpha^2 + 96E_\alpha x_\alpha + 24}, \tag{3}$$

where the activation energy is in kJ/mol and the parameter B_α is defined as:

$$B_\alpha = \ln\left(\frac{10^3 A_\alpha}{Rg(\alpha)}\right) \tag{4}$$

The estimates of the E_α and B_α can be obtained by the non-linear fitting of the Eq. 3 to the β values as function of x_α.

Once the $g(\alpha)$ function has been determined for each conversional fraction α, the estimation of the Arrhenius pre-exponential factor can be obtained from Eq. 4 and is given by following equation:

$$\hat{A}_{\alpha} = \frac{R}{10^3}\exp(\hat{B}_{\alpha})g(\alpha) \quad (5)$$

Results and discussion

Thermal behaviour

Simultaneous TG-DTA curves of Mg $(\mathrm{Diclof})_2$ are shown in Fig. 1a. The first mass loss (17.76%) between 30 and 120 °C, corresponding to the endothermic peak in DTA curve, is due to methanol loss. The second, third and fourth mass losses occurred from 288 to 375 °C (35.46%), from 375 to 650 °C (22.23%) and from 650 to 820 °C (18.54%), respectively. For both mass losses, the corresponding DTA events were attributed to the thermal decomposition of the ligand. Calculations based on the mass loss up to the final temperature, is in agreement with the formation of MgO as the final residue. An exothermic peak seen between 176 and 215 °C, having its maximum at 195 °C, which did not show a corresponding mass loss at the TG curve, is attributed to the transition phase. This fact was verified by X-ray powder data pattern which revealed to be amorphous, but after this transition phase, became crystalline. The X-ray patterns of this compound are shown in Fig. 2a–c. In Fig. 2a, b, the characteristic of this compound with and without methanol, respectively, is shown where it is demonstrated that there are alterations for the non-crystalline state. In Fig. 2c, after the crystallization step (Fig. 1 and Fig. 3), the presence of some characteristic lines can be seen which are attributed to the weak crystallinity.

The transition phase is a phenomenon that can occur in several organic or inorganic compounds, which consists of a physical or chemical alteration of the molecules. If solid state compounds are considered, such as pharmaceutical compounds, two main types of transition phases will occur: enantiotropic and monotropic. In the first, a reversible transition of the structure occurs, in other words, the compound goes back to its original conformation. In the second, the transition occurs as an irreversible rearrangement of the structure [13–16].

The DSC curves of this compound are shown in Fig. 3. Two events were observed, from 160 to 175 °C and from 175 to 200 °C, which are attributed to transition phases enantiotropic (endothermic peak) and monotropic (exothermic peak) stages, respectively. To certify these facts, a

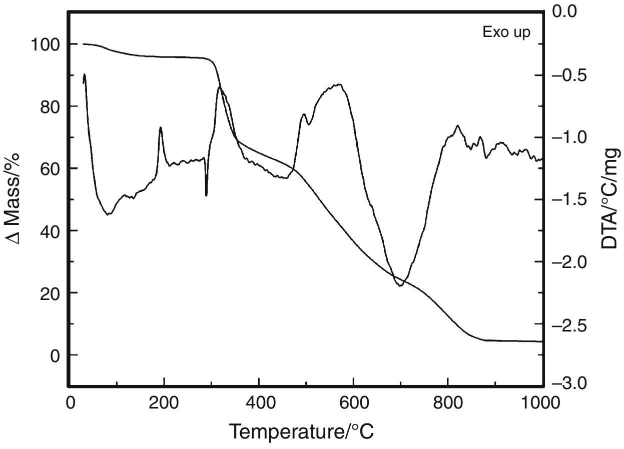

Fig. 1 Simultaneous TG/DTG and DTA curves of the $\mathrm{Mg(Diclof)_2}$ compound in synthetic air and heating rate of 20 °C $\mathrm{min^{-1}}$

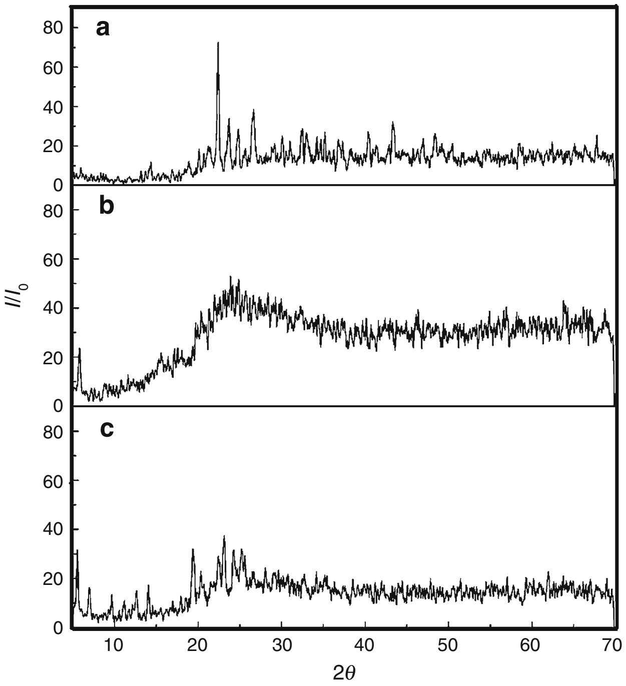

Fig. 2 Characteristic parts of X-ray diffraction pattern before (**a**) and after (**b**) the loss of methanol and (**c**) after the crystallization step

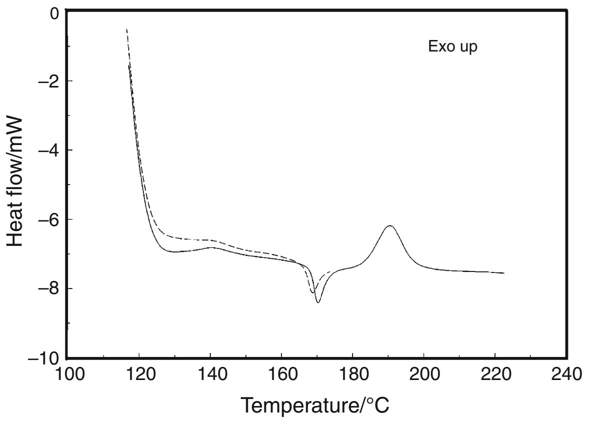

Fig. 3 DSC curves of $\mathrm{Mg(Diclof)_2}$ compound with mass sample of 1 mg, in nitrogen atmosphere at heating rate of 10 °C $\mathrm{min^{-1}}$, in aluminium crucible (open). *Dashed line* sample heated up to a temperature a little before to the exothermic transition and *solid line* is the same sample mass re-heated

sample mass of about 1 mg was heated up to a little before the exothermic reaction, and after that quickly cooled (dashed line). Then, this sample was again re-heated, as observed in Fig. 3 (solid curve). Therefore, these results (Fig. 3) suggest that the first endothermic peak is an enantiotropic reaction because this event will occur again. Thus, the exothermic reaction (solid curve) was attributed to the irreversible transition process (monotropic reaction), because this event alters the structure of this compound (Fig. 2c).

Figures 4 and 5 showed the DSC curves for Mg(Diclof)$_2$ in a nitrogen atmosphere at heating rates of 5, 10 and 20 °C min^{-1}, either with open or with crimped lids, respectively. For the compounds at dynamic atmosphere, the transition steps progressively occur around 160 and 205 °C. As observed in Fig. 4 (open crucibles), in the curves with heating rates of 10 and 20 °C min^{-1}, for the endothermic event, displacement occurs with the increase of the mass of the sample. It has also been observed that with the increase of the heating rate, the endothermic reaction tends to occur early, which makes the curve more accentuated at 20 °C min^{-1}, and therefore, shows a tendency to obtain less sharp peaks. For crimped lids (Fig. 5), the endothermic event tends to decrease with an increase of the mass and of

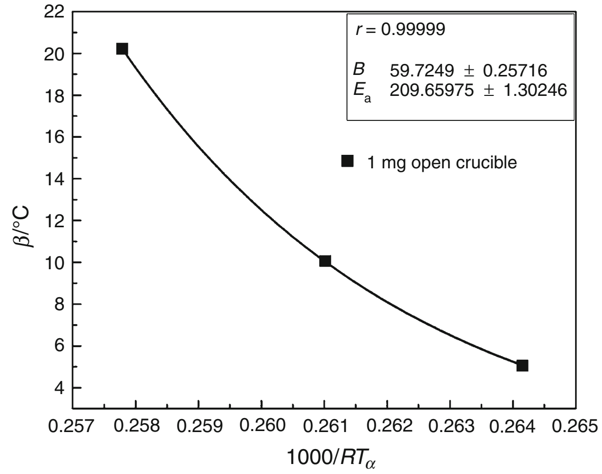

Fig. 6 Diagram of dispersion of β versus degree conversion (α—50%) for 1 mg in an open crucible with the adjustment function

Fig. 4 DSC curves of Mg(Diclof)$_2$ compound with mass sample of 1, 5 and 10 mg, in nitrogen atmosphere at heating rate of 5, 10 and 20 °C min^{-1}, in aluminium crucible (open)

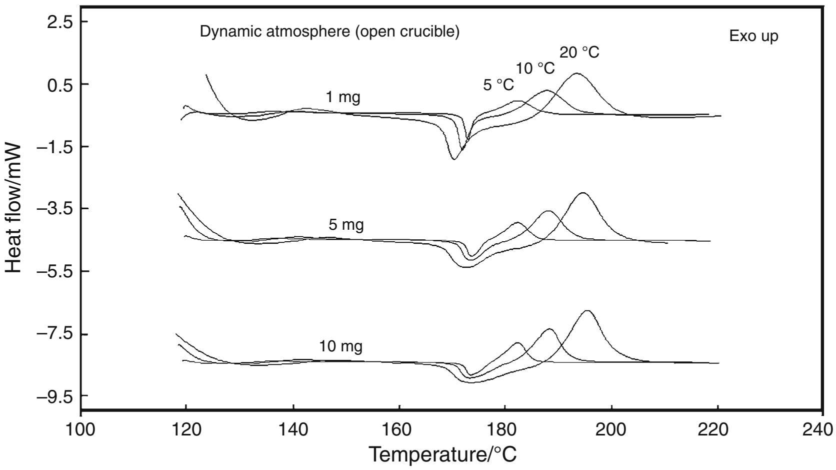

Fig. 5 DSC curves of Mg(Diclof)$_2$ compound with mass sample of 1, 5 and 10 mg, in nitrogen atmosphere at heating rate of 5, 10 and 20 °C min^{-1}, in aluminium crucible (crimped lids crucibles)

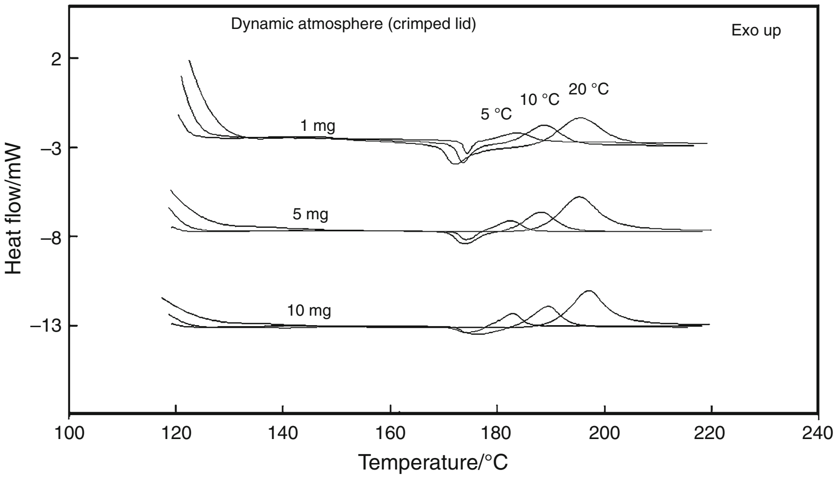

Table 1 Average of the activation energy (E_a/kJ mol^{-1}) and correlation coefficient (r) for the transition phase

Sample mass	Condition	E_a/kJ mol^{-1}	r
1 mg dynamic atmosphere	Open	209.53 ± 0.05	0.99995
	Crimped lids	182.44 ± 0.05	0.99442
1 mg static atmosphere	Open	213.21 ± 0.15	0.99618
	Crimped lids	166.66 ± 0.12	0.99675
5 mg dynamic atmosphere	Open	180.52 ± 0.07	0.99956
	Crimped lids	180.45 ± 0.07	0.99954
5 mg static atmosphere	Open	182.79 ± 0.09	0.99974
	Crimped lids	168.43 ± 0.09	0.99417
10 mg dynamic atmosphere	Open	161.37 ± 0.06	0.99748
	Crimped lids	154.98 ± 0.08	0.99884
10 mg static atmosphere	Open	142.77 ± 0.11	0.99794
	Crimped lids	139.82 ± 0.12	0.99945

the temperature. Thus, at 20 °C min^{-1} and with a mass of 5, and 10 mg there is a complete disappearance of this event. Fini et al. [4], working with this compound did not observer the endothermic event shown, probably due to some experimental variation. In the DSC curves in a static atmosphere (no shown the endothermic peaks completely disappear. This indicates that the sample depends on the experimental conditions.

Kinetic parameters

The kinetic parameters of the crystallization stage (exothermic reaction) of this compound were evaluated from the DSC curves, in both dynamic and static atmospheres. In the Fig. 6, the distribution of the heating rate b, in function of $1000/RT_\alpha$ is shown. It can be observed that the linear fit adjustment between the three points have low variation for E_a values, which correspond to the linear fit for the activation energy proposed by Capela and Ribeiro [8]. The average values of the activation energy of the kinetic data for all compounds are shown in Table 1, where the resulting correlation coefficient (r) has a good close linear fit.

The activation energy versus degree conversion (α) values, are shown in Fig. 7, curves a, b and c, respectively. From these curves, a tendency can be seen where the plots

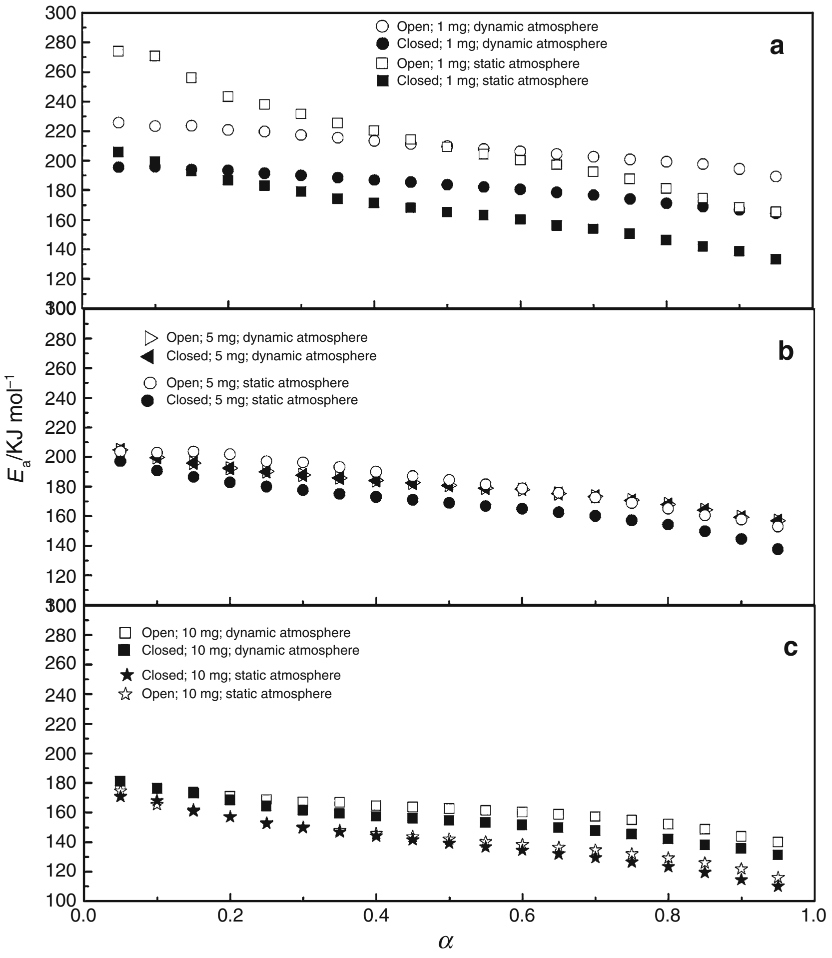

Fig. 7 The calculated E_a/kJ mol^{-1} as a function of α for the transition phase stage in different experimental conditions

maintain the same profile and almost run parallel to each other. But the values of E_a vary for each compound due to the difference between the mass of the sample and experimental conditions. This indicates that crystallization occurs in a same way for every extension of a, what is probably due to a simultaneous process of diffusion and/or nucleation-growth.

If the sample masses are evaluated comparatively (Fig. 7) and either used in an open or as crimped lid crucible, it can be observed that there is a difference between the plots of activation energy versus the conversion degree. For this compound, these differences observed were attributed to the thermal conductivity of the different masses utilized. For 1 mg, in an open crucible in static or dynamic atmospheres, we can see that the difference great. However, for the same mass of 1 mg, but in a crimped lid crucible condition, the activation energy tends to decrease. Another effect observed was in relation to the increase in mass sample (5 and 10 mg). In these cases, it can be seen that the differences between the values of activation energy in the different conditions utilized tend to approach each other. Thus, for a mass of 10 mg the activation energy in both conditions practically overlap. This indicates that the increase of sample, in both open and crimped lid crucibles, it is possible to obtain activation energy with values close to each other.

Conclusions

Simultaneous TG-DTA curves show the thermal behaviour of $Mg(Diclof)_2$ compound. The X-ray powder diffraction patterns show that the original compound is amorphous before the transition phase, and after this it has a crystalline structure.

The thermal studies carried out by DSC analysis on non-isothermal conditions show that there are two transition phases. The different experimental conditions in dynamic and static atmospheres provide an understanding of the behaviour of the transition phase. Furthermore, the presented results clearly indicate that the use or not of the crimped lid has an influence of an increase or decrease on the activation energy values. On the other hand, the sample mass also determines a decrease of the activation energy values. Therefore, we can see that the different kinetic results are conditioned by the contributions of different experimental factors, which allowed an evaluation of the values of activation energy in a more appropriate way.

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