

Preparation of the Ca–diclofenac complex in solid state

Study of the thermal behavior of the dehydration, transition phase and decomposition

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Abstract The Ca–diclofenac compound was prepared. Thermogravimetry (TG), derivative thermogravimetry (DTG), differential scanning calorimetry (DSC), X-ray diffraction powder patterns, and microscopy analysis were used to characterize this compound. Details concerning the stages of dehydration, transition phase, and thermal decomposition as well as data of the kinetic parameters of these stages have been described here. The kinetic study of these stages was evaluated from several heating rates with a sample mass of 2 and 5 mg in open crucibles under nitrogen atmosphere. The obtained data were evaluated with the isoconversional kinetic method, where the value of activation energy ($E_a/\text{kJ mol}^{-1}$) was evaluated in function of the conversion degree (α). The results show that this compound is hygroscopic. The obtained data lead to a dependence on the sample mass, which results in two kinetic behavior patterns.

Keywords Diclofenac · Dehydration · Thermal decomposition · Kinetic parameters

Introduction

Solid state compounds of diclofenac, (2-[2,6-dichlorophenylamino]phenylacetate) is a drug frequently used as effective nonsteroidal anti-inflammatory agent for the treatment of rheumatoid arthritis [1]. The literature reports studies of diclofenac and also with several metal ions, which have been characterized and investigated by using thermoanalytical techniques (TG, DTA, and DSC), X-ray powder diffractometry, scanning electronic microscopy, and spectroscopy analysis, etc. Agatonovic-Kustrin et al. investigate the formation of the diclofenac by colorogenic reaction with iron (III) chloride and detection of this compound in the visible region of the spectrum [2]. Kovala-Demertzi reports the synthesis and study of several metal complexes with diclofenac and that were used as anti-inflammatory drugs and, therefore, as research area [3]. Maria Konstandinidou et. al, has prepared metal complexes in order to investigate the role of these compounds as anti-inflammatory drug. The results of this investigation show that the complexes Co(II), Ni(II), Pd(II), and Mn(II) have anti-inflammatory profile superior to diclofenac, which involves the activation of lipoxigenase or complementary systems [4].

Bucci et al. relate the spectroscopic characteristic and 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 study was detailed the first compound of the series of this divalent metals, but without thermoanalytical discussion of the others complexes [5]. Kenawi et al. investigate the interactions between cetrizine dihydrochloride diclofenac complexes of Ca(II), Mg(II), Zn(II), and Fe(III). As part of this study, the characterization by IR, H NMR, and mass spectrometric studies showed that cetirizine dihydrochloride interacted

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with diclofenac sodium even when the latter is coordinated to the metal ions [6].

In previous study, we reported the investigation of the thermal decomposition of iron(III)-diclofenac compound. In this study, we used sample mass of 2 and 5 mg, which allows a better evaluation of kinetic parameters [7].

In this study, we report on the preparation of a solid state of calcium with diclofenac. This compound was investigated by simultaneous TG–DTA, X-ray powder diffraction, and scanning electronic microscopy. The results of the present study add to the knowledge on this compound including the stages of dehydration, transition phase, and the first and second stages of thermal decomposition. Besides this, an investigation with two mass samples was carried out, in order to determine the effect of changing the experimental variables as well as the kinetic behavior. Furthermore, the isoconversional method was used not only as a way a of obtaining reliable and consistent kinetic information but also because it avoids the use of explicit kinetic models [7, 8]. Thus, the measurements are estimated at temperatures corresponding to fixed values of conversion degree (α) and the activation energy ($E_a/\text{kJ mol}^{-1}$) data were obtained applying the isoconversional method proposed by Capela and Ribeiro [9].

Experimental

The synthesis of calcium-(Diclof)₂ compound was prepared by the stoichiometric addition of Ca(II) chloride on potassium diclofenac salt, both in water solutions. The obtained precipitate was filtered, washed with distilled water, dried at room temperature, and stored in a desiccator over anhydrous calcium chloride until a constant mass was achieved.

Simultaneous TG–DTA and DSC curves were obtained from a SDT 2960 and a DSC 2910, both from TA Instruments, respectively. The stoichiometry was obtained by TG–DTA analysis using sample sizes around 7.5 mg (± 0.05 mg) in an α -alumina crucible and heating rates of 20 °C min⁻¹ under synthetic air atmosphere (100 mL min⁻¹). Kinetic evaluation of the steps of dehydration and thermal decomposition were obtained using a sample mass of 2.0 and 5.0 mg (± 0.05 mg) with heating rates of 5, 10, and 20 °C min⁻¹ under a nitrogen atmosphere (100 mL min⁻¹) from 30 to 400 °C in an alumina crucible. The DSC curves were also obtained with a sample mass around 2.0 and 5.0 mg, but placed in an aluminum crucible (open), under a nitrogen flow of 50 mL min⁻¹ and heating rate of 2.5, 5 and 10 °C min⁻¹.

This compound was also examined using Scanning Electron Microscopy (SEM). The particles were sputter coated with a thin and uniform layer of gold using a

vacuum evaporator and then examined using a JEOL Scanning Microscope, model JSM-T-330A at an accelerating voltage of 20 kV.

The X-ray diffraction patterns were obtained from a Siemens D-500 X-ray diffractometer using Cu K α radiation ($\lambda = 1.54 \text{ \AA}$) and settings of 40 kV and 30 mA.

Kinetic methodology

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

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

where $\beta = dT/dt$ 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 a function of the extent of reaction α , A is the pre-exponential factor, E is the activation energy and R is the gas constant.

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

In this study, the kinetic parameters are obtained using an isoconversional method on approximation to the temperature integral based on the convergent of a Jacobi fraction, proposed by Capela et al. [2–4]. This approximation is a rational function, given by the following equation:

$$\int_x^{\infty} \frac{\exp(-z)}{z^2} dz = \frac{\exp(-x)}{x} \frac{x^3 + 14x^2 + 46x + 24}{x^4 + 16x^3 + 72x^2 + 96x + 24}. \quad (2)$$

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_x for temperature, values E_x for activation energy and values A_x 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 a function of $x_x = 10^3/RT_x$

$$\beta = \frac{\exp(B_x - E_x z_x)}{x_x} \frac{E_x^3 z_x^3 + 14E_x^2 z_x^2 + 46E_x z_x + 24}{E_x^4 z_x^4 + 16E_x^3 z_x^3 + 72E_x^2 z_x^2 + 96E_x z_x + 24}, \quad (3)$$

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

$$B_x = \ln \left(\frac{10^3 A_x}{Rg(\alpha)} \right). \quad (4)$$

The estimates of the E_x and B_x can be obtained by the non-linear fitting of the Eq. 3 to the β values as a function of x_x .

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 the following equation:

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

Results and discussion

Characteristics properties

Simultaneous TG/DTG and DTA curves of Ca–diclofenac complex are shown in Fig. 1. The first and the second mass losses only at the stage between 75 to 110 °C and 135 to 165 °C (TG), corresponding to the endothermic peaks (106 and 160 °C) in the DTA curve, are due to the dehydration stages with losses of 2.71 and 2.68%, respectively, which corresponds to two water molecules. After dehydration, between 240 and 1120 °C the mass loss occurs in four stages with a loss of 84.67%. The first decomposition stage, from 240 to 285 °C (2.25%), is attributed to the initial decomposition of this compound which corresponds to the exothermic peak (263 °C) in the DTA curve. This mass loss is probably due to a reaction that occurs on the surface of the sample which extinguishes quickly. The second decomposition stage corresponds to a mass loss of 23.62% but the absence of a large exothermic peak is notorious, which is probably due to the existence of equilibrium between the exothermic and endothermic process, which

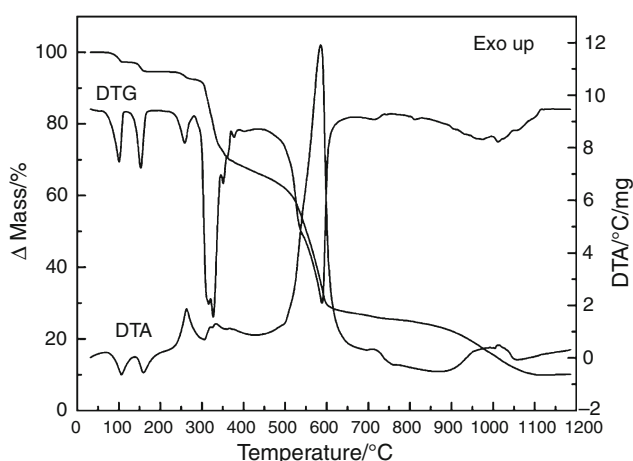


Fig. 1 Simultaneous TG/DTG and DTA curves of the Ca(Diclof)₂·2H₂O compound in synthetic air and heating rate of 20 °C min⁻¹

presents only one small exothermic peak as a result of these simultaneous reactions. However, this fact can also probably be due to the amount of heat absorbed in the thermal decomposition which is not enough to produce an exothermic peak. The last two mass losses between 370–850 °C (40.29%) and 850–1290 °C (18.51%) are due to the oxidation and the thermal decomposition of the intermediate, leading to the calcium oxide. Calculations based on the mass loss up to 1120 °C are in agreement with the formation of CaO as final residue (9.90%).

Figure 2 shows the TG/DTG curves of dehydration of Ca(Diclof)₂. These curves show that this compound is hygroscopic. Initially, the compound was dehydrated up to 100 °C and maintained at an ambient temperature for 20 min. Then, it was reheated again up to 180 °C and it was observed that the first dehydration is similar. In this new heating (up to 180°), the second dehydration stage was observed. After heating, the compound was cooled at ambient temperature and maintained during 20 min. It was again heated (heating up to 170 °C) and the last TG curve obtained, which demonstrated that this compound it is still hygroscopic, but it can be seen that this new dehydration did not occur in the same manner as the first re-hydration. This fact, probably occurs because the second stage of dehydration alters the molecular conformation. Moreover, this fact also suggested that the first water molecule is weakly linked (constituent water) and that the second is strongly linked (structural water).

The DSC curves, Fig. 3, were evaluated after the dehydration process (180 °C). These curves were obtained from heating rates of 2.5, 5, and 10 °C, because the amplitude of the transition phase peak decreases with the increase of the heating rate and consequently becomes much more difficult to establish the range of the values for kinetic study. The exothermic event between 185 and

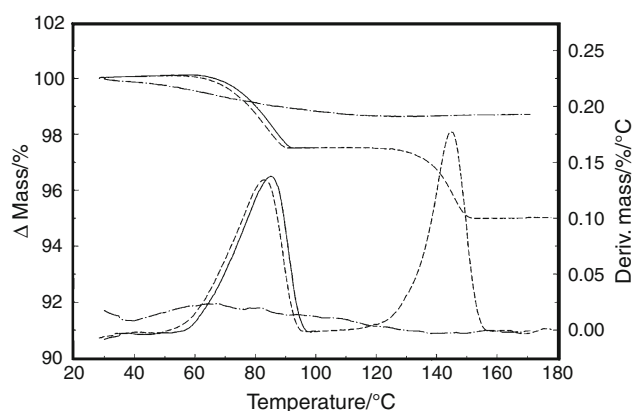


Fig. 2 Simultaneous TG/DTG curves of the dehydration and hydration behavior of Ca(Diclof)₂ compound with heating up to 100 °C (solid line curve), with reheating up to 180 °C (short dash) and again reheating up to 170 °C (dash dot)

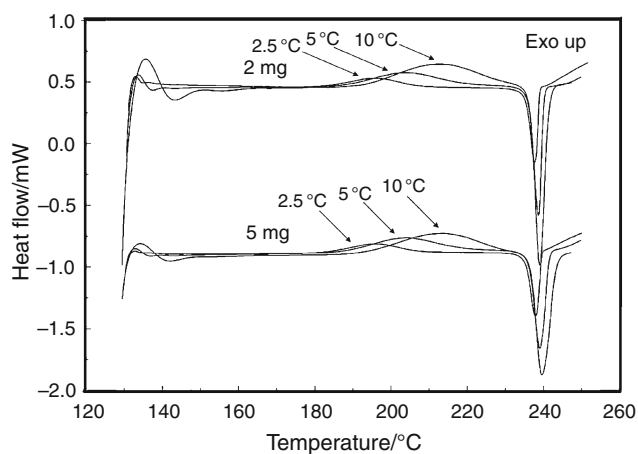


Fig. 3 DSC curves of $\text{Ca}(\text{Diclof})_2$ compound in nitrogen atmosphere at heating rate of 2.5, 5 and 10 $^{\circ}\text{C min}^{-1}$, in aluminum crucible (open)

230 $^{\circ}\text{C}$ was attributed to the transition phase and the endothermic peak is due to the fusion of the compound, followed by thermal decomposition.

The X-ray powder patterns of these compounds are shown in Fig. 4a–d. Figure 4a and b shows the characteristic X-ray diffraction of the hydrated and re-hydrated compound as described in TG curves of Fig. 2. This reveals the presence of some characteristic lines which are attributed to the crystalline compound, but are different from them, which indicate that the dehydration–re-hydration processes alter the crystalline structure of this compound. However, after the second dehydration (180 $^{\circ}\text{C}$) or phase transition (250 $^{\circ}\text{C}$) diffraction lines were not observed

Fig. 4 Characteristic parts of X-ray diffraction pattern: before (a) and after the first (b) dehydration, as in Fig. 2; c after 180 $^{\circ}\text{C}$ and d up to 230 $^{\circ}\text{C}$

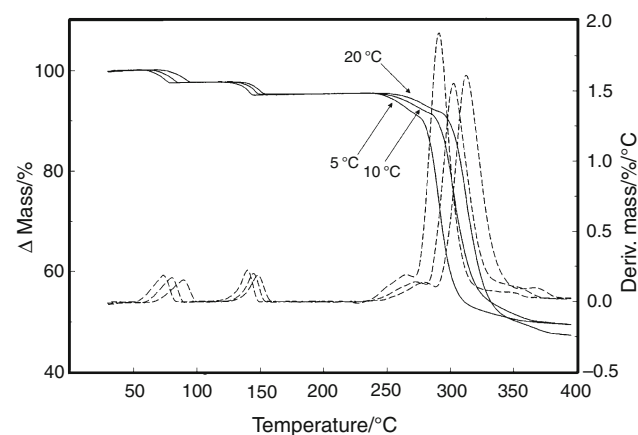
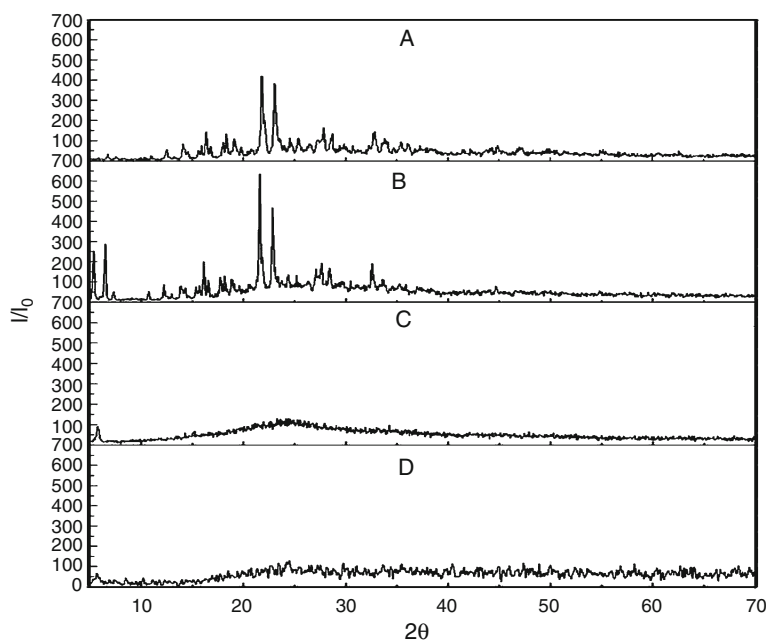


Fig. 5 TG/DTG curves of the $\text{Ca}(\text{Diclof})_2$ compound, 2 mg under nitrogen atmosphere, heating rates of 5, 10 and 20 $^{\circ}\text{C min}^{-1}$

(Fig. 4c, d), which demonstrates that this compound becomes non-crystalline.

Figures 5 and 6 show the TG/DTG curves for $\text{Ca}(\text{Diclof})_2$ compound in a nitrogen atmosphere with a sample mass of 2 and 5 mg, respectively. As observed, the stages of dehydration and the first thermal decomposition occur similarly to that of synthetic air (Fig. 1). However, for the second stage of thermal decomposition, the mass losses correspond to around 47.40%, which is very different from synthetic air. Thus, in an inert atmosphere the less thermal stability of the compound is probably due to the non-oxidation of the compound and, therefore, the same is less stable during thermal decomposition.

Scanning electron microscopy (SEM) was used to characterize the textural changes that occur in $\text{Ca}(\text{Diclof})_2$

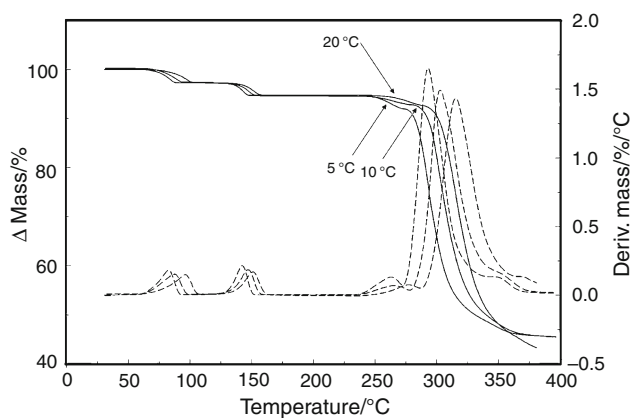


Fig. 6 TG/DTG curves of the Ca(Diclof)₂ compound, 5 mg under nitrogen atmosphere, heating rates of 5, 10 and 20 °C min⁻¹

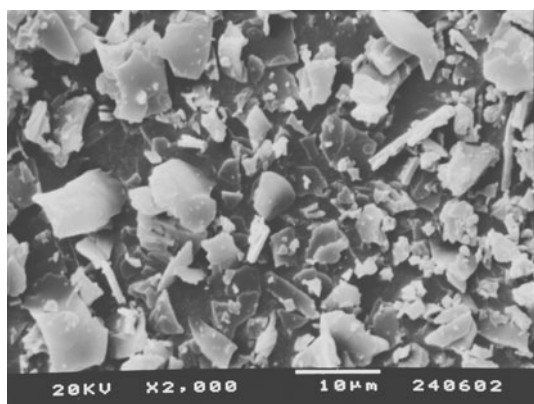


Fig. 7 Scanning electron microscopy showing the hydrated Ca(Diclof) 2H₂O compound

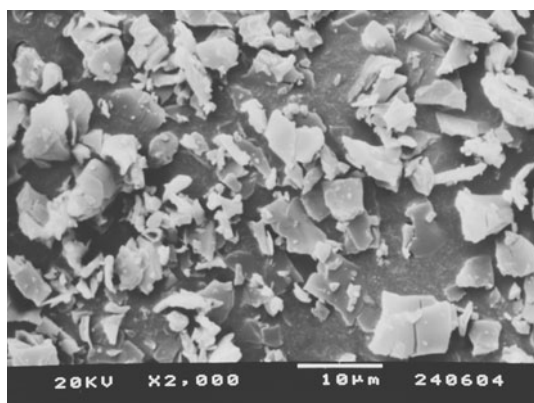


Fig. 8 Scanning electron microscopy showing the Ca(Diclof)₂ compound after first-stage dehydration (100 °C)

compound. The images in hydrated and dehydrated conditions are shown in the Figs. 7, 8, and 9. From the hydrate and re-hydrate compounds as shown in Figs. 7 and 8, we can see that the crystals have the same crystalline profile. Figure 9 corresponds to the compound heated up to 180 °C, which

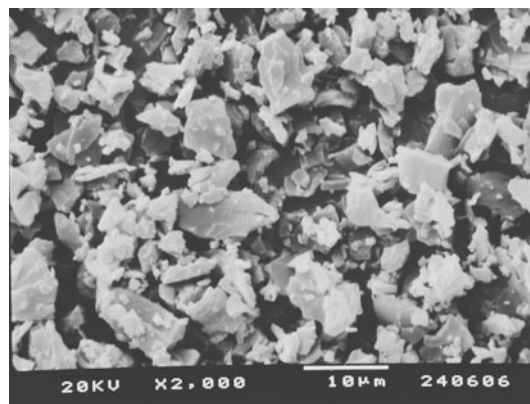


Fig. 9 Scanning electron microscopy showing the Ca(Diclof)₂ compound after second-stage dehydration (180 °C)

shows crystals with the same crystalline profile. This stage demonstrates that the dehydration and consequent re-hydration process does not alter the structural features of the crystal, although this compound does not return to its previous crystalline characteristics (Fig. 4C). Thus, it is suggested that the re-hydration reaction mechanism of the amorphous product decreases with the availability of water vapor at normal or room atmospheric pressure and therefore, the progressive growth of particles (because is the slowest stage) occurs without re-crystallization [10].

Kinetic parameters

The kinetic parameters of the dehydration, thermal decomposition, and transition phase of this compound were evaluated from DSC and TG curves (Figs. 3, 5, 6, respectively).

Figure 10 shows the accomplished calculations for the activation energy and correlation coefficient (r) for the first dehydration step for the 5 mg sample. It can be observed that the adjustment of the variation for E_1 values (activation energy) was done by distribution of the heating rate (β) in function of the $1000/RT_x$. The average values of the activation energy (E_a) of the kinetic data of the different experimental adjustments (5 to 95%) for all steps are shown in Table 1. The resulting correlation coefficient has a good close linear fit (r) except for 5 mg where both the first dehydration and decomposition stages present discrepant values. The activation energy (E_a) versus conversion degree (α) values for the first and second dehydration and decomposition stages of sample masses of 2 and 5 mg are shown in Figs. 11 and 12, respectively.

Dehydration and decomposition stages

For the dehydration stage, Fig. 11, we can see that there are tendencies of the plots to maintain the same features as

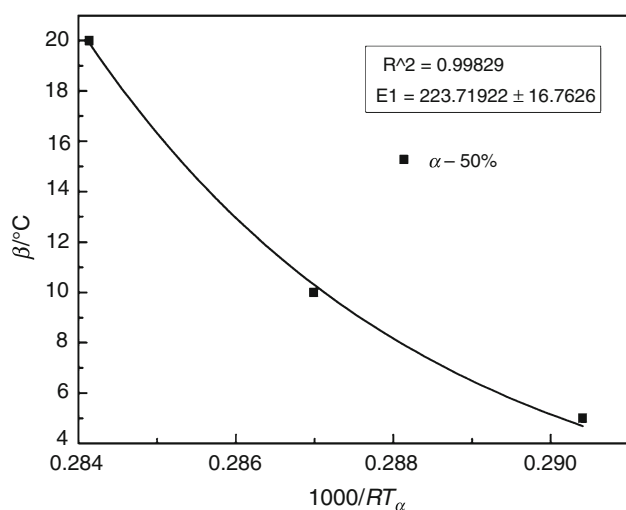


Fig. 10 Diagram of dispersion of β versus degree conversion (α —50%) of the $\text{Ca}(\text{Diclof})_2$ compound in the first dehydration stage for 5 mg, with an adjustment for functions

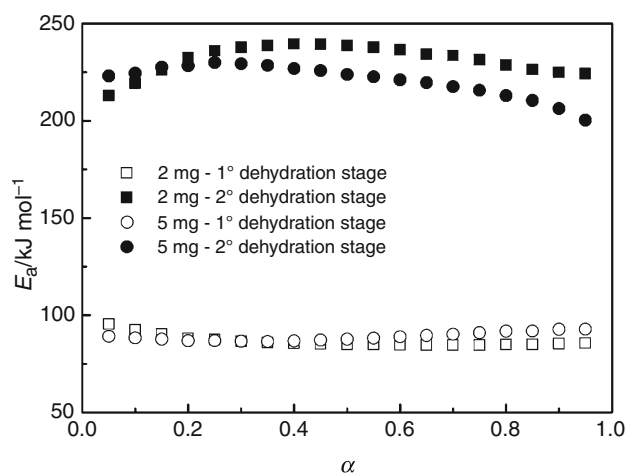


Fig. 11 The calculated $E_a/\text{kJ mol}^{-1}$ as a function of α for the first and second stages of dehydration

each other. Therefore, this indicates that kinetic dehydration occurs the same way for every extension of conversion degree (α) of both mass samples. Furthermore, it is clear that the values of activation energy for the first stage of dehydration are invariable, which indicate that it can be regarded as a single step reaction. Now, for the second stage of dehydration the activation energy values are high and vary with the conversion degree (α) in more than a single stage. This was attributed to the water structure as described above. Such differences among the stages of dehydration could be due to the increase in temperature and consequently in molecular water vibrations for the second stage.

In Fig. 12, we can see the dependence of the activation energy on the extent of conversion for the first and second stages of decomposition, respectively. Comparing the results

Table 1 E_a (kJ mol^{-1}) and correlation coefficient (r) for the stages of dehydration, thermal decomposition and transition phase

| Compound | Sample mass | E_a (kJ mol^{-1}) | r^a |
|------------------------------|------------------------------|--------------------------------|----------|
| $\text{Ca}(\text{Diclof})_2$ | 2 mg 1st dehydration stage | 86.66 ± 0.03 | 0.99733 |
| | 5 mg 1st dehydration stage | 88.99 ± 0.02 | 0.976358 |
| | 2 mg 2nd dehydration stage | 231.44 ± 0.03 | 0.99766 |
| | 5 mg 2nd dehydration stage | 220.71 ± 0.03 | 0.99889 |
| | 2 mg 1st decomposition stage | 185.43 ± 0.05 | 0.99794 |
| | 5 mg 1st decomposition stage | 185.56 ± 0.09 | 0.98631 |
| | 2 mg 2nd decomposition stage | 167.96 ± 0.05 | 0.99744 |
| | 5 mg 2nd decomposition stage | 165.49 ± 0.05 | 0.99995 |
| | 2 mg transition phase | 145.25 ± 0.07 | 0.99904 |
| | 5 mg transition phase | 150.22 ± 0.14 | 0.99986 |

^a Average

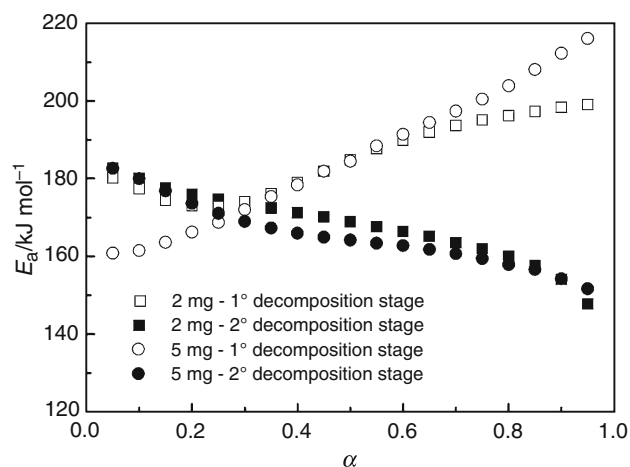


Fig. 12 The calculated $E_a/\text{kJ mol}^{-1}$ as a function of α for the first and second stages of decomposition

of the first stage of decomposition (with mass loss around 2.25%), it is suggested that the shape of the conversion degree (α) results from two reaction processes particularly up to $\alpha = 0.30$. Furthermore, it is evident that the apparent activation energy is low and becomes higher by increasing the conversion degree, which could be associated with a complex superficial reaction on the sample as above mentioned. In the second stage of thermal decomposition of both sample masses, it is evident that the apparent activation energy is high and decreases on the conversion degree (α). Thus, it is suggested that these thermal stages of decomposition are characterized by overlapping reactions from both masses.

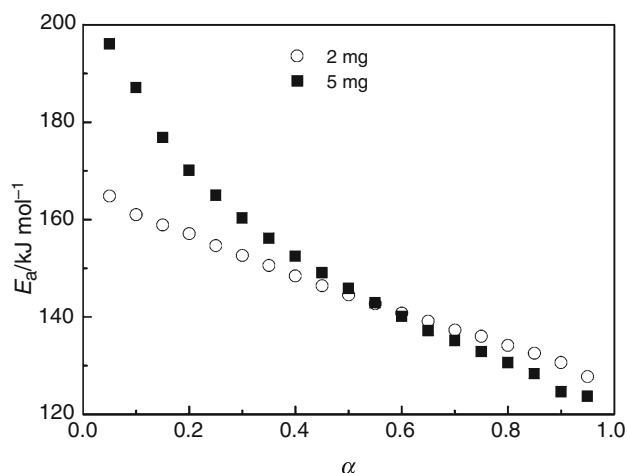


Fig. 13 The calculated $E_a/\text{kJ mol}^{-1}$ as a function of α for the transition phase stage

Transition phase stage

The kinetic parameters to the transition phase stage of this compound were evaluated from the DSC curves (Fig. 3), in a dynamic atmosphere. The average values of the activation energy data for the compound are shown in Table 1, where the resulting correlation coefficient has a good close linear fit.

The activation energy versus degree conversion (α) values for 2 and 5 mg are shown in Fig. 13. From these curves, a tendency can be seen where the plots maintain the same contour as each other. However, the difference between the values of the activation energy is attributed to a difference in the thermal conductivity of the sample mass. Moreover, it is clear that both the analysis conditions are characterized from more than one reaction but this indicates that they obey a single kinetic mechanism.

Conclusions

The thermal studies carried out on non-isothermal TG in N_2 and in air, provide an understanding of the behavior during thermal analysis. The TG/DTG curves in synthetic air established the stoichiometry of the compound in its solid state. Furthermore, the TG curves of this compound also reveal that the same is hygroscopic after the first stage of dehydration without altering the TG curve, which was attributed to the constituent water. After the second stage of dehydration, it was observed in the TG curve that the compound has another re-hydration behavior pattern. DSC curves show that this compound has an exothermic event

which corresponds to the transition phase after the stages of dehydration.

The X-ray powder diffraction patterns reveal that this complex has a crystalline structure before the first stage of dehydration but with the re-hydration process this compound again showed a crystalline structure. After the second stage of dehydration, it was verified that a non-crystalline state was obtained.

Moreover, it can be seen from the resemblance between different conditions, conditioned by contributions of two different mass samples, allow a better evaluation of kinetic parameters. Thus, for the decomposition process a dependence on the sample mass was found. Finally, in the present case for the steps of dehydration, the observed low value of activation energy for first step was attributed to the constituent water and the second stage of dehydration is due to the strongly linked water structure.

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References

- Moser P, Sallmann A, Wiesenbergt I. Synthesis and quantitative structure-activity relationships of diclofenac analogues. *J Med Chem.* 1990;33:2358–68.
- Agatonovic-Kustrin S, Zivanovic Lj, Zecevic M, Radulovic D. Spectrophotometric study of diclofenac–Fe(III) complex. *J Pharm Biomed Anal.* 1997;16:147–53.
- Kovala-Demertzi D. Transition metal complexes of diclofenac with potentially interesting anti-inflammatory activity. *J Inorg Biochem.* 2000;79:153–7.
- Konstandinidou M, Kourounakis A, Yiangou M, Hadjipetrou L, Kovala-Demertzi D, Hadjidakou S, Demertzis M. Anti-inflammatory properties of diclofenac transition metalloelement complexes. *J Inorg Biochem.* 1998;70:63–9.
- Bucci R, Magri AD, Magri AL, Napoli A. Spectroscopic characteristics and thermal properties of divalent metal complexes of diclofenac. *Polyhedron.* 2000;19:2515–20.
- Kenawi Ihsan M, Barsoum Barsoum N, Youssef Maha A. Cetirizine dihydrochloride interaction with some diclofenac complexes. *Eur J Pharm Sci.* 2005;26:341–8.
- Kobelnik M, Bernabé GA, Ribeiro CA, Capela JMV, Fertoni FL. Kinetic of decomposition of iron (III)-diclofenac compound. *J Therm Anal Calorim.* 2009;97:493–6.
- Souza JL, Kobelnik M, Ribeiro CA, Capela JMV. Kinetics study of crystallization of PHB in presence of hydrociacids. *J Therm Anal Calorim.* 2009;97:525–8.
- Capela JMV, Capela MV, Ribeiro CA. Nonisothermal kinetic parameters estimated using nonlinear regression. *J Math Chem.* 2009;45:769–75.
- Galwey AK, Brown ME. Thermal decompositions of ionic solids. 1st ed. Amsterdam: Elsevier; 1999.