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Thermal behavior of naproxen and ketoprofen nonsteroidal anti-inflammatory drugs

R. S. Medeiros[1] · A. P. G. Ferreira[1] · E. T. G. Cavalheiro[1]

Abstract

Nonsteroidal anti-inflammatory drugs naproxen (NAP) ((+)-(*S*)-2-(6-methoxynaphthalen-2-yl) propionic acid) and ketoprofen (KET) (*RS*)-(2-(3-benzoylphenyl)-propionic acid) were investigated by thermoanalytical techniques (TG/DTG/DTA, DSC and hot-stage microscopy) and evolved gas analysis (TG-FTIR) for evaluating their thermal behavior. In air, TG curve of NAP presented one mass loss step followed by the burning of carbonaceous material, with final residue of 1.5%, while in nitrogen, a single mass loss step was observed. After melting, if the sample is submitted to an isotherm it evaporates. According to DSC curve, NAP melts at 153.5 °C (ΔH_{fus} = 31.6 kJ mol^{-1}; ΔS_{fus} = 73.5 J K^{-1} mol^{-1}) and recrystallizes in the cooling step. These events were confirmed by hot-stage microscopy. TG-FTIR studies revealed that NAP decomposes by releasing 2-methoxynaphthalene and propionic acid. Ketoprofen TG curves in both atmospheres presented a single mass loss. When the sample was kept under isotherm, after melting, it evaporated. From DSC data, the melting at 93.3 °C (ΔH_{fus} = 28.4 kJ mol^{-1}, ΔS_{fus} = 76.9 J K^{-1} mol^{-1}) was observed, without crystallization or cooling.

Keywords Naproxen · Ketoprofen · Anti-inflammatory · Evolved gas analysis · Thermal behavior

Introduction

Naproxen (NAP) ((+)-(*S*)-2-(6-methoxynaphthalen-2-yl) propionic acid) and ketoprofen (KET) (*RS*)-(2-(3-benzoylphenyl)-propionic acid) are nonsteroidal anti-inflammatory (NSAIDs) drugs. Both present anti-inflammatory, anti-thermic and analgesic action, related to the inhibition of the cyclo-oxygenase enzymes, COX1 and COX2, which catalyze the production of prostaglandins, physiologically active lipids, that induce inflammation. Moreover, they are used in the treatment of rheumatic diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, menstrual cramps, pains and inflammations in skeletal muscle tissues [1, 2]. Structural formulas of naproxen and ketoprofen are:
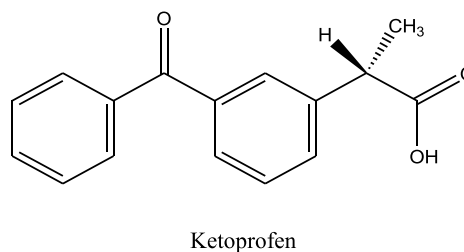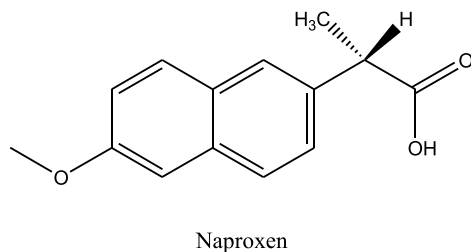
Naproxen

Ketoprofen

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In a general sense, the combination of thermal analysis with complementary spectroscopic techniques allows evaluation of the thermal behavior of a variety of materials, including drugs [3], making it possible to study thermal decomposition, thermal stability, solid-state reactions, purity evaluation, physical transformations, polymorphic transitions, melting point, crystallization, evolution of gases and many other transformations [3–6].

Studies on the thermal behavior of drugs have been presented in order to establish a complete description of thermal behavior based on thermoanalytical techniques (TG/DTG, DTA, DSC), coupled to TG-FTIR, evolved gas analysis and complementary spectroscopic date of intermediates and residues of thermal degradation (^{1}H-NMR, FTIR, XRD) [7–10]. Such studies are important regarding the presence of phase transitions, thermal stability determinations as well as characterization of the evolved gases in case of burning or discarding of lots of non-useful drug or environmental remediation.

Few thermoanalytical studies regarding NAP and KET thermal behavior have been presented in the literature. The investigation of the thermal behavior of some non-steroidal anti-inflammatory, ketoprofen, naproxen and ibuprofen, has also been presented. TG/DTA curves allowed determining the thermal stability of these compounds as well as temperature ranges in which mass losses occurred. DSC curves confirmed the melt temperature of these drugs [11].

Kinetics of NAP decomposition was studied, and parameters such as activation energy and pre-exponential factor were determined [12]. Moreover, studies of binary mixtures, solid dispersions, as well as structural studies by theoretical calculation were performed [13–16].

Tiţa et al. [17, 18] presented thermoanalytical studies of the active ingredients and commercial pharmaceutical formulations of ketoprofen, describing thermal degradation kinetic data and models for the degradation of these samples, using isothermic and non-isothermic methods.

Physicochemical properties of KET were investigated by thermoanalytical techniques, to elucidate the interaction between KET and excipients, improving its effectiveness and power of action [19, 20].

However, in all of these previous reports no detailed information regarding thermal decomposition mechanism for NAP and KET has been presented. Thus, in this work a detailed mechanism of thermal behavior of naproxen and ketoprofen is proposed based on thermal analysis (TG/DTG, DTA, DSC), evolved gas analysis TG-FTIR, hot-stage microscopy and FTIR.

Experimental

Naproxen (*S*-isomer, 99.5%) and ketoprofen (*R,S*-racemic mixture, 99.6%) were purchased from Pharma Nostra (Brazil) and Infinity Pharma (Brazil), respectively. The elemental analysis of these compounds is presented in Table 1.

Thermal analysis

TG/DTG/DTA curves were obtained using a simultaneous TG/DTA SDT-Q600 module (TA Instruments) managed by the Thermal Advantage software® for Q Series (version 5.5.24). The measurements were taken in dynamic dry air and nitrogen atmospheres, flowing at 50 mL min^{-1}, using sample mass of 7.0 ± 0.2 mg, temperature range of 25–1000 °C and heating rate of 10 °C min^{-1} in open α-alumina sample holder. NAP samples were pre-treated by heating up to 100 °C for 3 min before TG/DTG experiments.

DSC curves were obtained in a Q10 differential scanning calorimetric module, controlled by Thermal Advantage Series® software (version 5.5.24), both from TA Instruments, using sample mass of 5.0 mg ± 0.1 mg, at a heating rate of 10 °C min^{-1}, under dynamic N$_2$ atmosphere, flowing at 50 mL min^{-1}, in the heat–cool–heat mode, in a closed alumina sample holder with a pinhole ($\phi = 0.7$ mm) in the center of the lid and. For NAP, the measurements were taken between 25 and 210 °C (heating cycle 1), -50 and 210 °C (cooling), followed by a second heating in the same temperature range. For KET, the measurements were taken between 20 and 160 °C (heating cycle 1), -50 and 160 °C (cooling), followed by a second heating in the same temperature range.

Evolved gas analysis

SDT-Q600 (TA Instruments) coupled to an iS10 FTIR Nicolet spectrophotometer was used to characterize the gaseous products evolved during the heating of the naproxen and ketoprofen. The transfer line was composed of a 120-cm-long stainless steel tube with 2 mm internal diameter, heated

Table 1 Elemental analysis of naproxen and ketoprofen

Compound	Formula	Mol mass/g mol^{-1}	Element, exp (calc)/%		
			C	H	O
Naproxen	C$_{14}$H$_{14}$O$_3$	230.26	73.6 (73.0)	6.24 (6.13)	20.1 (20.8)
Ketoprofen	C$_{16}$H$_{14}$O$_3$	254.28	76.6 (75.6)	5.78 (5.55)	17.6 (18.9)

at constant temperature of 230 °C. The measurement of FTIR was taken with a DTGS detector in a gas cell heated at constant temperature of 250 °C. The interferometer and the compartment of the gas cell were purged with nitrogen. The thermogravimetric curve was obtained in dynamic N_2 atmosphere flowing at 60 mL min^{-1}, heating rate of 10 °C min^{-1} and sample mass of *c.a.* 15 mg.

Hot-stage microscopy

Hot-stage microscopy experiments were performed using a hot-stage Mettler Toledo HS82 coupled to an Olympus BX51 optical microscope equipped with a SC30 Olympus digital camera. NAP thermal behavior was investigated in the range of 130–180 °C using a heating rate of 4 °C min^{-1}. KET behavior was observed in the 70–150 °C range at a heating rate of 4 °C min^{-1}.

Elemental analysis

Elemental analysis was performed in a FlashSmart, Thermo Scientific equipment, using 10.0 mg of NAP and KET.

Infrared spectroscopy

The vibrational spectra in the infrared region were obtained in an IRAffinity-1 FTIR spectrometer (Shimadzu) between 4000 and 400 cm^{-1}, resolution of 4 cm^{-1} and 64 scans. The samples were prepared in the proportion of 5.0 mg of sample to 95 mg of KBr, in disks.
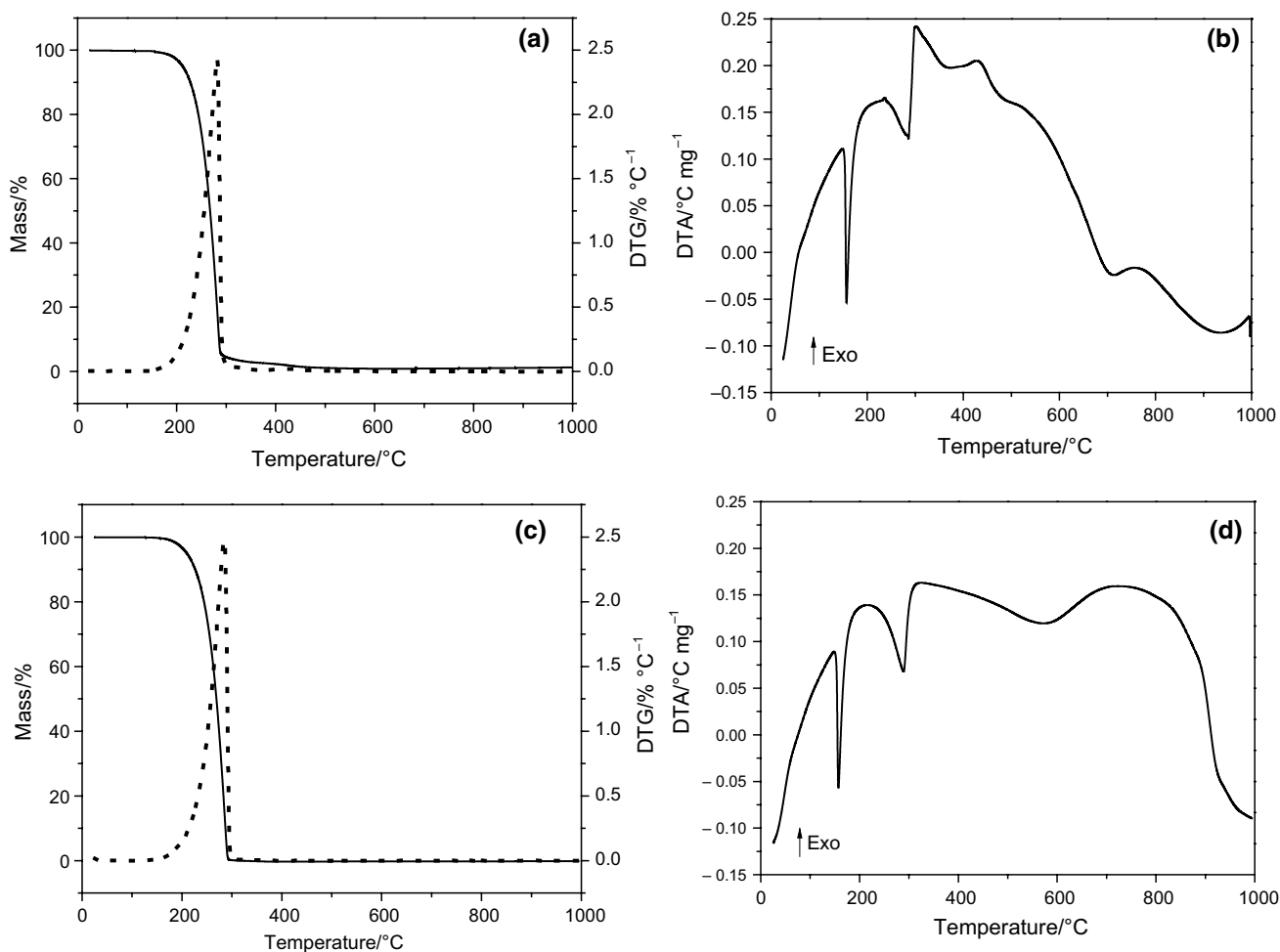
Fig. 1 **a** TG/DTG and **b** DTA curves of naproxen in dynamic air atmosphere, **c** TG/DTG and (d) DTA curves of naproxen in dynamic N_2 atmosphere, with flow rate of 50 mL min^{-1}, sample mass of 7.0 ± 0.2 mg, in open holder sample of α-alumina, heating rate of 10 °C min^{-1}

Table 2 Description of the process for each step in TG/DTA curves of naproxen: temperature ranges, mass losses and temperature peaks

Process	TG data		DTA peaks/°C
	T_{range}/°C	Mass loss/%	
Nitrogen			
$C_{14}H_{14}O_3$ (s) $\rightarrow$ $C_{14}H_{14}O_3$ (l)	–	–	156.6 (endo)
$C_{14}H_{14}O_3$ (l) $\rightarrow$ $C_{11}H_{10}O$ (g) $+ C_3H_6O_2$ (g)	153.5–305.2	100	289.0 (endo)
			570.6 (endo)
Air			
$C_{14}H_{14}O_3$ (s) $\rightarrow$ $C_{14}H_{14}O_3$ (l)	–	–	156.6 (endo)
$C_{14}H_{14}O_3$ (l) $\rightarrow$ $C_{11}H_{10}O$ (g) $+ C_3H_6O_2$ (g)	152.5–365.8	97.0	285.3 (endo)
			301.4 (exo)
Burning of carbonaceous material	365.8–479.6	1.5	430.3 (exo)
Residue	1000	1.5	
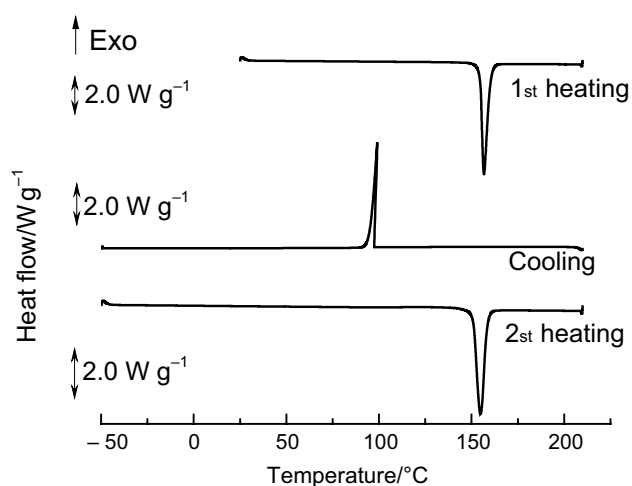
Fig. 2 DSC curves of naproxen in atmosphere of N_2, flowing at 50 mL min^{-1}, sample mass of approximately 4 mg, in aluminum sample holder central with a pinhole in the lid, heating rate of 10 °C min^{-1}

Results and discussion

Naproxen

Figure 1 presents TG/DTG (Fig. 1a) and DTA (Fig. 1b) curves of naproxen in dynamic dry air atmosphere. These curves revealed that naproxen was thermally stable up to 152.5 °C, after which a mass loss occurred in the range of 152.5–365.8 °C, corresponding to 97.0% of starting mass. A mass loss of 1.5% between 365.8 and 479.6 °C was attributed to the burning of carbonaceous material, with a 1.5% residue at the end of the experiment.

In DTA curve in air atmosphere (Fig. 1b), a sharp endothermic peak related to melting of naproxen was observed, at 156.6 °C in agreement with the literature [11]. Other endothermic and exothermic peaks assigned to the degradation process of the drug were also observed in agreement with the described for the TG curve.

In N_2 atmosphere, TG/DTG curve in Fig. 1c shows a single mass loss between 153.5 and 305.2 °C, without residue at the end of the run. DTA curve in N_2 (Fig. 1d) presented a sharp endothermic peak corresponding to the melting of the drug at 156.6 °C, and endothermic and exothermic peaks, due to degradation of the drug. Quantitative date, temperature intervals and DTA peak temperature are presented in Table 2.

DSC curves obtained in the heat–cool–heat mode are presented in Fig. 2. During the first heating, a sharp endothermic peak at 153.5 °C (onset) referent to the melting of the drug was observed. In the cooling step, an exothermic peak at 93.8 °C (onset) was observed, representing the crystallization of the drug. The presence of the endothermic peak at 150.0 °C (onset) in the second heating suggests the

Table 3 Main thermodynamical parameters obtained for DSC curves in the first and second heating of naproxen

Cycle	ΔH_{fus}/kJ mol^{-1}	ΔS_{fus}/J K^{-1} mol^{-1}	T_{fus}/K
First heating	31.57	73.44	429.9
Second heating	29.49	68.72	427.9
	ΔH_{cryst}/kJ mol^{-1}	ΔS_{criyt}/J K^{-1} mol^{-1}	T_{cryst}/K
Cooling	22.57	60.64	372.2

Fig. 3 Hot-stage images of naproxen at **a** 133.0 °C, **b** 149.0 °C, **c** 150.0 °C, **d** 155.0 °C and **e** 161.0 °C, magnification of 200X
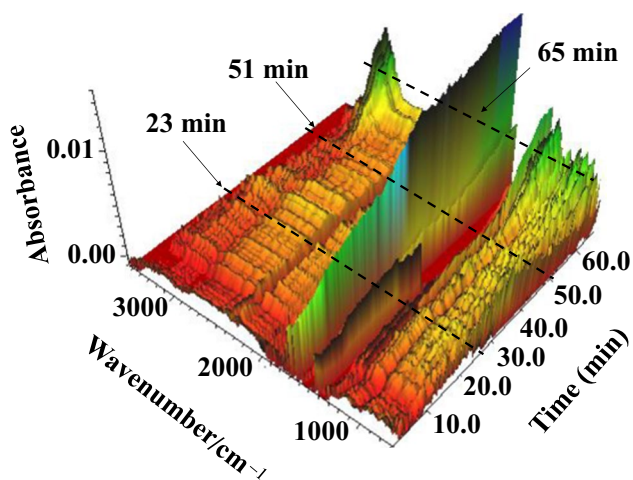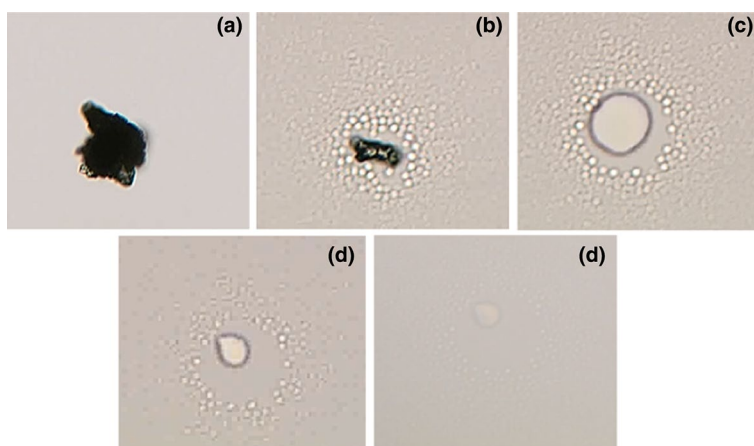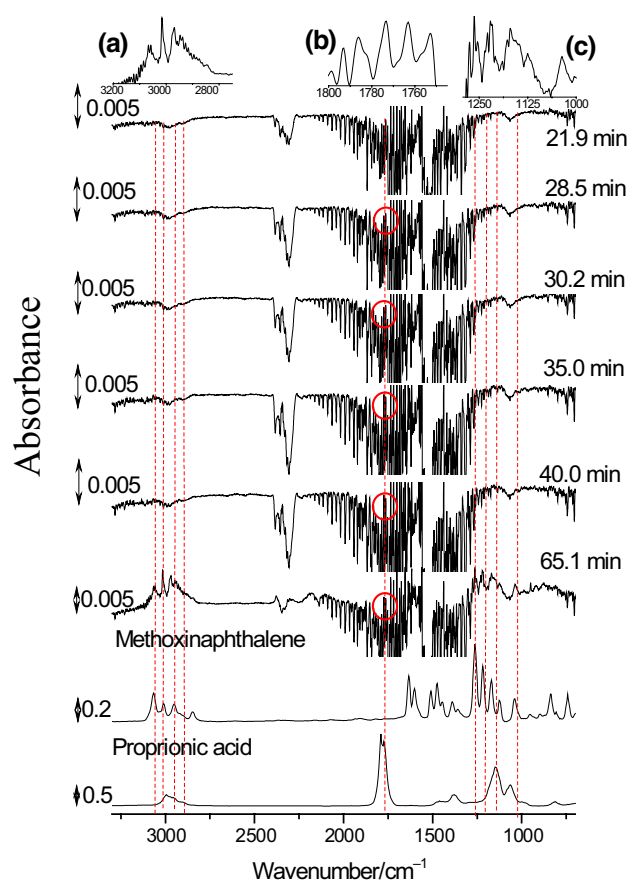

Fig. 4 3D graph recorded during NAP heating under N_2 in which absorbance evolution is represented as a function of time and wavenumber. Conditions as in text

Fig. 5 FTIR spectra of the gaseous products of naproxen in different times and database spectra. Details of the application of spectral regions referent to 2-methoxynaphthalene at 65.1 min (**a**, **c**) and propionic acid at 30.2 min (**b**)

reversibility of this process. No polymorphic transformations were observed in these curves.

From peaks in DSC curve, thermodynamical data related to melting process were calculated and are reported in Table 3.

Hot-stage microscopy experiments were performed in order to better understand the events observed in the heating step of DSC curves of naproxen. Images are presented in Fig. 3. It was possible to observe that melting occurred from 142.0 until 150.0 °C in agreement with DSC data. Small differences observed in temperatures of the events were attributed to different experimental conditions and sample mass in both techniques.

After melting, a turbidity in the upper glass slide that protects the microscope lens was attributed to volatilization of the sample. A video demonstrating such events is presented in Supplementary material (SV1).

Gases evolved during the heating of naproxen were also characterized by evolved gas analysis, using thermogravimetry coupled to Fourier transform infrared vibrational spectroscopy (TG-FTIR).

Figure 4 presents a 3-D mapping of the experiment. In this case, high intensities of gas evolution obtained at 23, 51 and 65 min (corresponding to 255.5, 535.5 and 676.5 °C, respectively).

The interpretation of the spectra was performed with the help of NIST and EPA Vapor Phase databases for comparison [21, 22]. Figure 5 presents the spectra obtained in different times (temperatures) of: 21.9 (244.5 °C), 28.5 (310.5 °C), 30.2 (327.5 °C), 35.0 (375.5 °C), 40.0 (425.5 °C) and 65.1 min (676.5 °C), revealing the gaseous products evolved during heating of naproxen compared to those of 2-methoxynaphthalene and propionic acid of library [21, 22].

Thus, between 21.9 and 30.2 min it can be observed a slight increase in bands at 1780–1750 cm^{-1} that according to the databases is referent to propionic acid. From 65.1 min bands between 3100–2900 cm^{-1} and 1250–1000 cm^{-1} ranges became evident. Such signals are referent to 2-methoxynaphthalene [21, 22]. A more detailed bands description for these events compared with those from database are presented in supplementary material (Table ST1).

In order to characterize the residues formed during heating of naproxen, an amount of drug was heated until 260.0 °C in a glass tube and aliquots of solid phases formed were submitted to FTIR analysis, in KBr disks. An image of the glass tube at the end of the experiment and FTIR spectra of different solids is presented in Fig. 6.

During the experiment, the upper portion of the glass tube is colder than the portion that is immersed in glycerin bath allowing the recrystallization of volatiles evolved from the heated sample after melting (Fig. 6a).

In the upper portion of the tube, there is a white crystallite solid whose FTIR spectrum is quite similar of that of naproxen expect for the broadband centered at 3250 cm^{-1} related to hydration of the original sample. If the sample is not pre-treated, this humidity could be detected in preliminary TG experiment (curves not presented). The presence of naproxen condensed in the cold wall of test tube revealed that the sample can volatilize from the melted compound.

At the bottom of the tube, there is a brownish solid probably degraded once the height of the sample column prevents the volatilization of this part of the pharmaceutical allowing it to decompose by receiving heating from the walls of the tube. FTIR spectra of the brownish material are different from those of naproxen (Fig. 6c); the main differences are in the 3250, 1750 and 600 cm^{-1} regions, respectively, related to carboxyl and carbonyl groups, suggesting a possible loss of propionic acid in agreement with the TG-FTIR data results, as discussed above. Similar differences were observed for orange and yellowish condensates in the glass tube (Fig. 6b, c) which presents FTIR spectra similar to that of brownish solid, suggesting that the last can also volatilize from the melt.

In order to better investigate the volatilization, a NAP sample was heated up to 210 °C in the thermobalance, which takes the first 20 min in Fig. 7, and kept in isotherm for 170 min. According to TG and DSC results at such temperature, the drug is already melted, but did not decompose. Figure 7 presents the results obtained.

It can be observed that the sample mass remained constant until reaching 210 °C after which it started losing mass up to 100 min, resulting in 5.3% of residue, probably
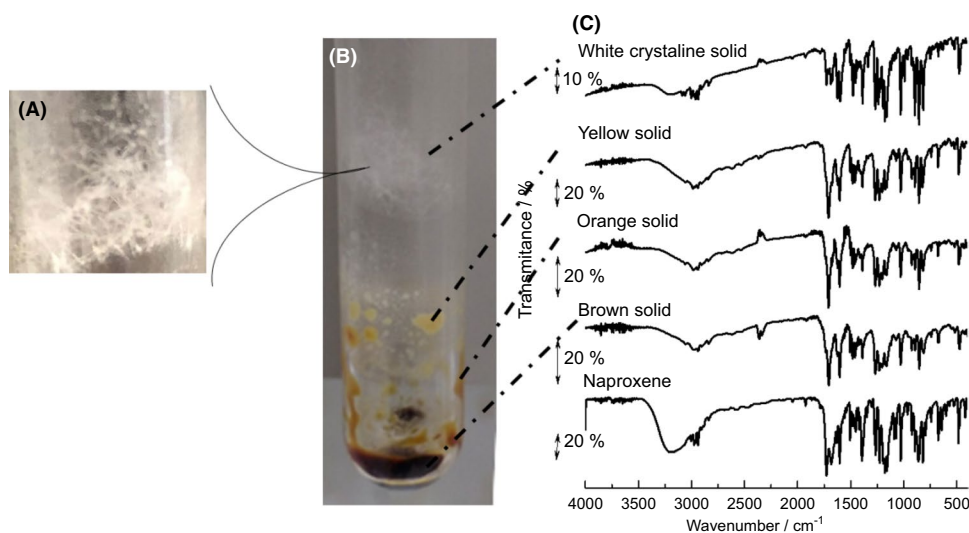
Fig. 6 Results from the heating of naproxen in open glass tube up to 260 °C. **a** Details of the white crystals formed in the upper cold part of glass tube, **b** general view of the glass tube and the different solids observed after cooling and **c** spectra of FTIR corresponding to the each region in the tube: brown solid, orange in the wall, yellow in upper wall and white crystal in the cold wall
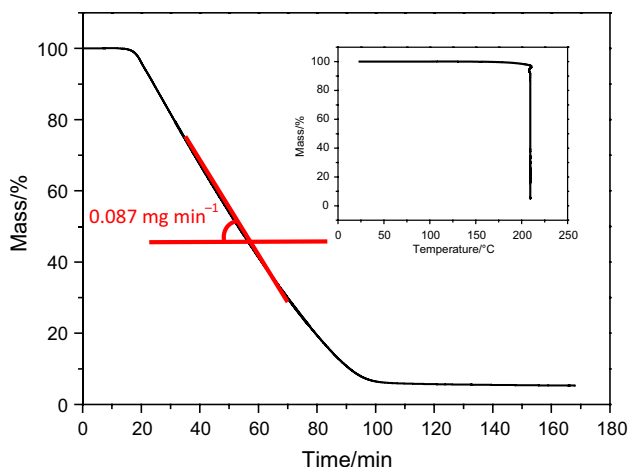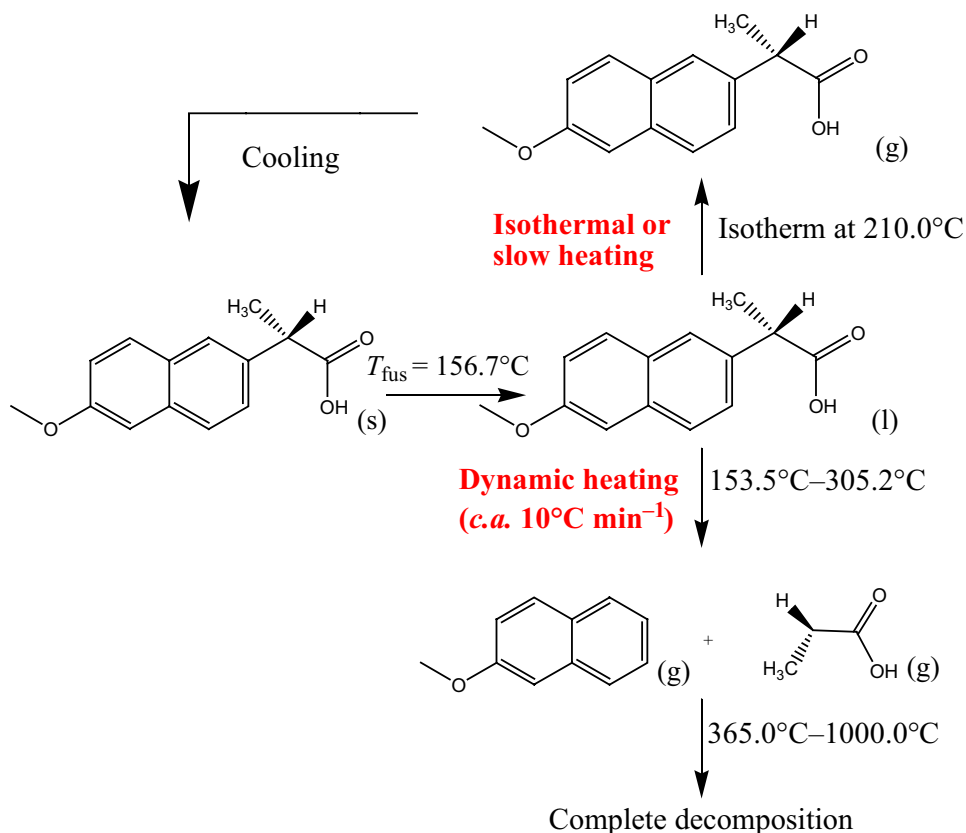
Fig. 7 TG curve for NAP in isothermal at 210 °C. Details of the curve of mass loss as a function of temperature. Sample mass of 7 mg, dynamic atmosphere of air, in open holder sample α-alumina, heating of rate of 10 °C min^{-1}

as decomposed fraction as observed in the glass tube experiment. The slope of the curve during the isothermal step was 0.087 mg min^{-1} that represents the volatilization rate under these conditions.

The combination of TG/DTG, TG/DTA, DSC, TG-FTIR and hot-stage microscopy leads to the tentative mechanism

proposed in Fig. 8. Thus, after the naproxen melting, if it still under isotherm at 210 °C, the compound is volatilized; however, under dynamic heating condition the drug undergoes decomposition in 2-methoxynaphthalene and propionic acid.

Although the thermoanalytical data concerning mass loses and melting of naproxen are in agreement with previously reported data [11, 12], those articles did not describe the volatilization or degradation processes based on TG-FTIR evolved gas analysis, FTIR of the condensates and hot-stage microscopy data.

Ketoprofen

TG/DTG and DTA curves of ketoprofen in dynamic atmosphere of air and N$_2$ are presented in Fig. 9.

In both atmospheres, ketoprofen presented a single mass loss step, with no residue at the end of the experiment. In air, the mass loss took place between 156.3 and 338.4 °C, while in nitrogen it occurred between 163.9 and 328.9 °C. No evidences of burning or pyrolysis of residual material were noticed in these curves, suggesting that the sample does not decompose, but evaporates after melting.

According to Fig. 9, DTA curves presented a similar profile in both atmospheres with an endothermic peak assigned to melting at *c.a.* 95.9 °C, followed by another endothermic peak related to evaporation of melted material. Quantitative

Fig. 8 Tentative mechanism for naproxen thermal behavior in nitrogen
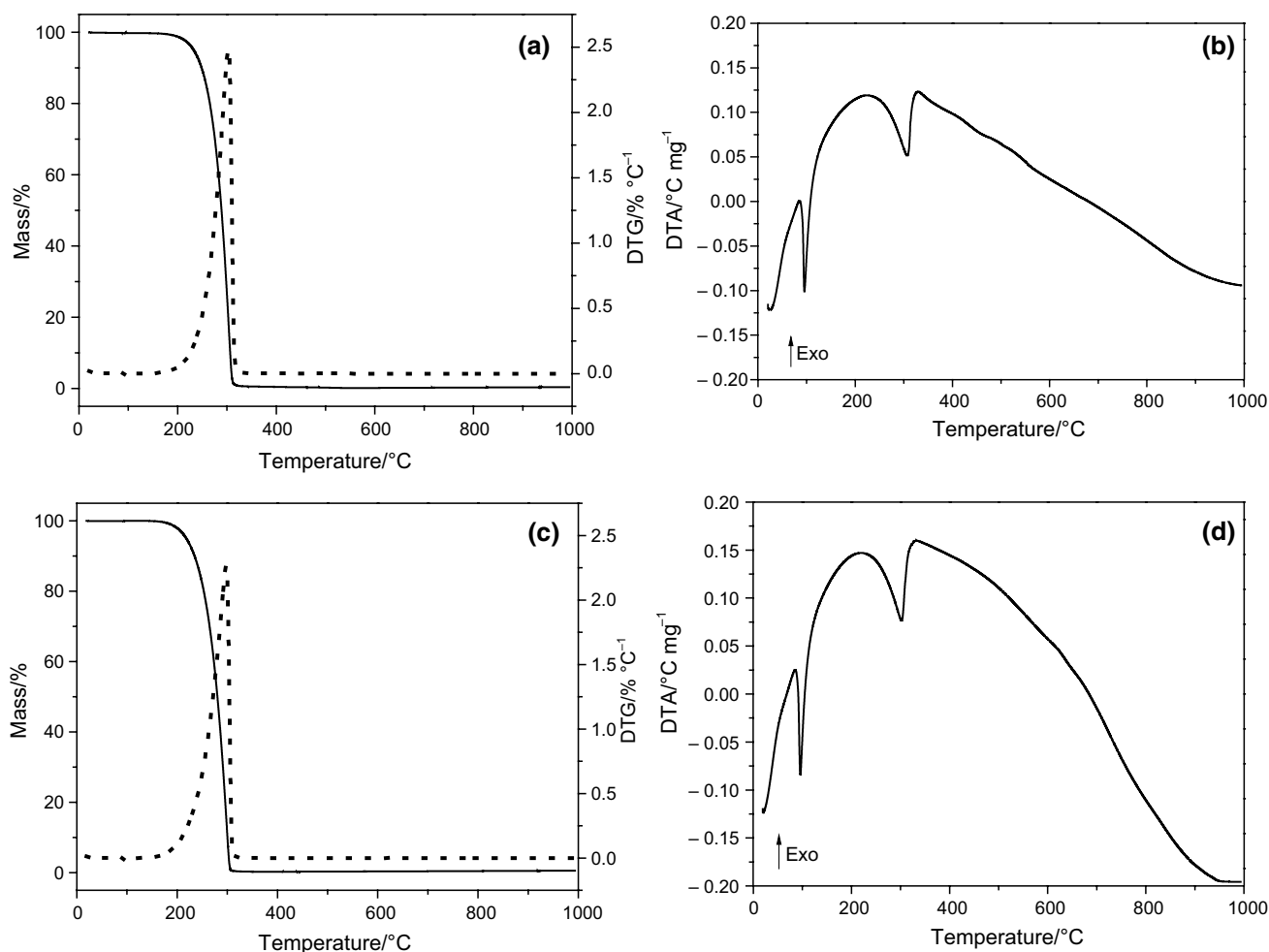
Fig. 9 **a** TG/DTG and **b** DTA curves of ketoprofen in dynamic air atmosphere, **c** TG/DTG and (d) DTA curves of ketoprofen in dynamic N_2 atmosphere, with flow rate of 50 mL min^{-1}, sample mass of 7 mg, in open α-alumina sample holder and heating rate of 10 °C min^{-1}

Table 4 Description of the temperature ranges, mass losses and temperature peaks in TG/DTA curves of ketoprofen

Process	TG data		DTA peaks/°C
	T_{range}/°C	Mass loss/%	
Nitrogen			
$C_{16}H_{14}O_3$ (s) → $C_{16}H_{14}O_3$ (l)	–	–	95.9 (endo)
$C_{16}H_{14}O_3$ (l) → $C_{16}H_{14}O_3$ (g)	163.9–328.9	100	302.3 (endo)
Air			
$C_{16}H_{14}O_3$ (s) → $C_{16}H_{14}O_3$ (l)	–	–	95.9 (endo)
$C_{16}H_{14}O_3$ (l) → $C_{16}H_{14}O_3$ (g)	156.3–338.4	100.0	306.1 (endo)

date, temperature intervals and DTA peaks observed in these curves are presented in Table 4.

The heat–cool–heat DSC curves of ketoprofen are presented in Fig. 10, in the − 50 to 160 °C temperature.

DSC curve of the ketoprofen (Fig. 10) in the heat–cool–heat mode revealed that in the first heating, a sharp endothermic peak at 93.3 °C (onset) referent to

melting appears. No other peaks were observed on cooling or second heating, suggesting the irreversibility of the process. A baseline deviation at *c.a.* 0 °C, typical of a glass transition, in both cases suggests that an amorphous phase is formed on cooling.

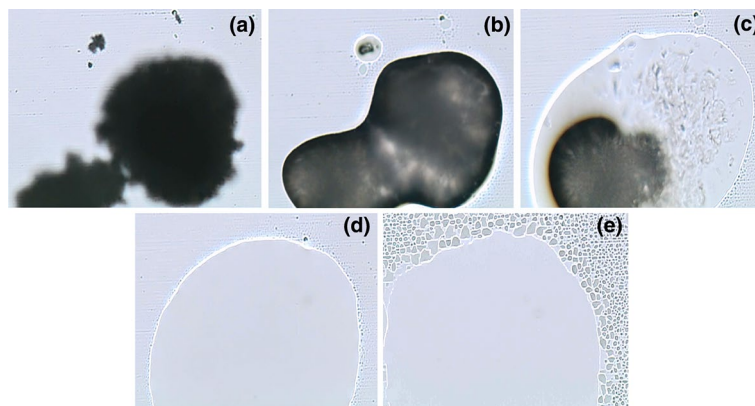From endothermic peaks of DSC curve, it was possible to calculate the thermodynamical data relative to
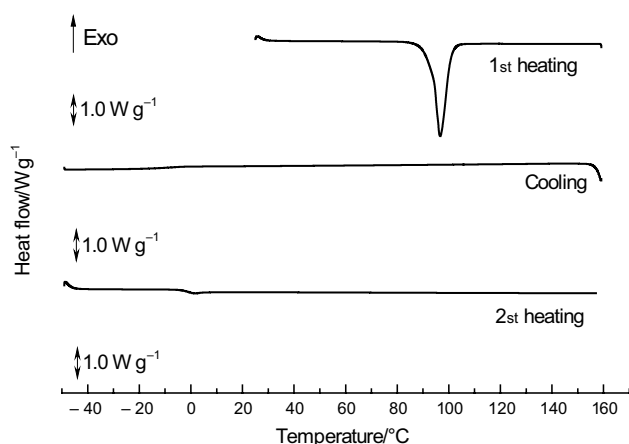
Fig. 10 DSC curve of ketoprofen in dynamic atmosphere of N_2, with flow rate of 50 mL min^{-1}, sample mass of approximately 4 mg, in aluminum sample holder with central pinhole in the center of lid, heating rate of 10 °C min^{-1}

melting process. Taking the $T_{peak} = 369.8$ K, these values are: $\Delta H_{fus} = 28.43$ kJ mol^{-1} and $\Delta S_{fus} = 76.88$ J K^{-1} mol^{-1}.

Hot-stage microscopy experiments were performed to visualize the events observed in the heating step of DSC curves of ketoprofen. Figure 11 depicts the images obtained during heating in different temperatures. It was possible to observe that melting occurred from 80.0 until 90.0 °C. Temperature difference from DSC data was assigned to differences in experimental conditions and sample mass in both techniques.

After melting, it was possible to observe that the sample vanishes, while at higher temperature (110.0 °C) the volatiles condense on the upper glass slide of the system. These results corroborate the hypothesis that ketoprofen does not decompose, but evaporates after melting in an open crucible.

A video demonstrating such events is presented in Supplementary material (SV2).
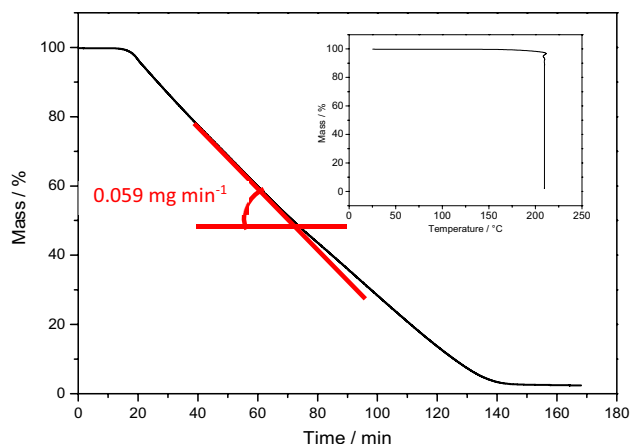
No volatiles were detected by evolved gas analysis using TG-FTIR during the heating of ketoprofen; probably due to the condensation of the sample in the transfer line heated at 230 °C, only residual water and CO_2 signals could be seen in the FTIR gas phase spectra (Figure S1).

Thus, ketoprofen was heated in a glass tube until 205 °C. Initially the drug melted at 96.0 °C, and after that, a white crystalline solid begun to deposit in upper colder glass tube walls, indicating that ketoprofen integrally evaporates. This proposition was confirmed when FTIR spectra of ketoprofen and the solid collected in the glass tube are compared as shown in Fig. 12. Wavenumbers related to main bands are given in Table ST2.

In order to better investigate the volatilization, a KET sample was heated up to 210 °C in the thermobalance, which takes the first 20 min in Fig. 13, and kept in isotherm at the same conditions employed to NAP. According to TG
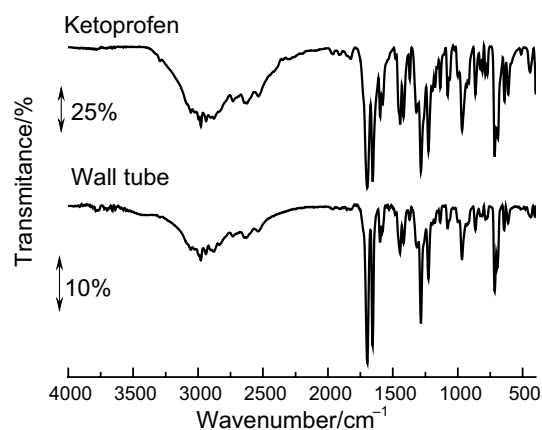
Fig. 12 FTIR spectra of ketoprofen and of the condensed white solid obtained in the walls of a glass tube when heated up to 205 °C

Fig. 11 Hot-stage images of ketoprofen at **a** 85.0 °C, **b** 86.0 °C, **c** 87.0 °C, **d** 90.0 °C and **e** 110.0 °C, magnification of ×200

Fig. 13 TG curve for KET in isothermal at 210 °C. Details of the curve against temperature. Sample mass of mg, dynamic atmosphere of air, in open holder sample α-alumina, heating of rate of 10 °C min^{-1}

and DSC results at such temperature, the drug is already melted, but did not decompose. Figure 13 presents the results obtained.

It can be observed that the sample mass remained constant until it reaches 210 °C after which it started losing mass up to 140 min, resulting in 2.7% at the end run possibly composed by carbonaceous material, as formed in the wall of the glass tube. The slope of the curve during the isothermal step was 0.059 mg min^{-1} that represents the volatilization rate under these conditions.

Data obtained from TG/DTG, TG/DTA, DSC, TG-FTIR and hot-stage microscopy confirmed that ketoprofen evaporates after melting, with no thermal degradation in open crucibles. A representation of the thermal behavior of ketoprofen based on the results described above and under the conditions used in the present work is presented in Fig. 14.

Here, the thermoanalytical data concerning mass loses and melting of ketoprofen are in agreement with previously reported data [17, 18]; however, those authors did not describe the volatilization processes based on TG-FTIR evolved gas analysis, FTIR of the condensates and hot-stage microscopy data.

Conclusions

According to TG/DTG/DTA curves, TG-FTIR, hot-stage microscopy and the experiments with test tubes, it was found that NAP presented two different behaviors after melting. If heated under a slow rate or even kept in isotherm, it evaporates and can condense as the original
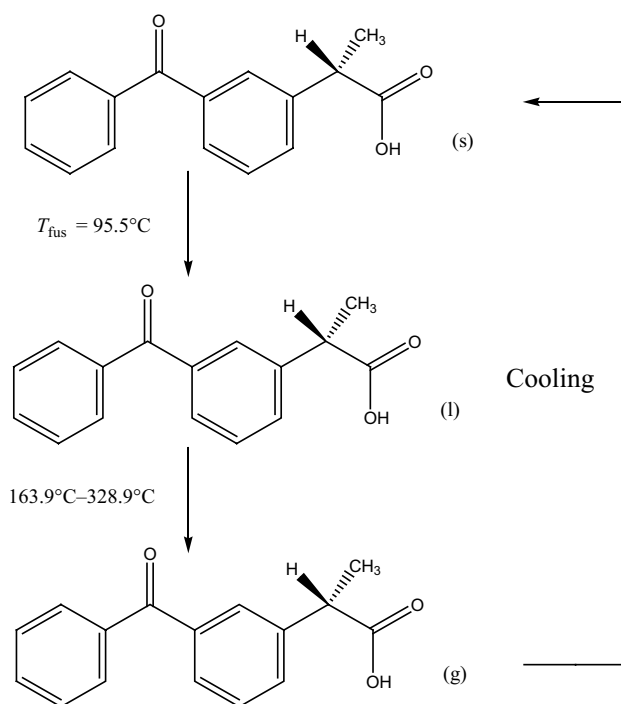
Fig. 14 Thermal behavior of ketoprofen under nitrogen atmosphere in an open crucible

drug on cooling. When heated in a dynamic temperature program, $c.a. \geq 10$ °C min^{-1} NAP decomposed in propionic acid and 2-methoxynaphthalene. DSC data revealed crystallization from the melted. The same techniques allowed to conclude that KET melted and evaporated without decomposition and residue at the end of the experiment. DSC curves do not presented crystallization on cooling from the melted form.

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