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Thermal behavior of the β-blocker propranolol

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Abstract The thermal behavior of the β-blocker anti-hypertensive drug propranolol was investigated using thermoanalytical techniques TG–DTA, DSC and the evolved gas analysis by TG–FTIR, providing information regarding thermal stability, decomposition steps, melting point and heat of fusion of the compound. The results pointed for the decomposition in a single mass loss step, after melting. DSC data revealed that cold crystallization occurred in heat–cool–heat cycles, around 165 °C. TG–FTIR presented 1-naphthol, isopropylamine and HCl as principal decomposition products. A tentative mechanism for the thermal behavior of propranolol is presented.

Keywords Propranolol · TG–DTA · Thermal behavior · Evolved gas analysis

Introduction

The main objective of hypertension treatment is controlling the blood pressure in order to reduce cardiovascular morbidity and mortality. Thus, the anti-hypertensive drugs should not only control blood pressure within safe levels, but also avoid the risk of cardiovascular events [1, 2].

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The anti-hypertensive drugs are classified into different classes according to their therapeutic effect and action mechanism.

Thus, the drugs of β-blocker class block the β-adrenergic receptors in the central nervous system, causing vasodilatation. They are indicated for the treatment and prevention of the myocardial infarction, angina pectoris and cardiac arrhythmias. Sometimes, their use is limited by the occurrence of side effects, such as muscle fatigue in the lower extremities, general tiredness and impaired physical performance. Probably, many factors contribute to these symptoms.

Propranolol (Fig. 1) was the first successfully developed β-blocker [3] and can be used alone or in association with others drugs for the treatment of the hypertension, and it is available in the generic form of propranolol hydrochloride. The commercially available preparations of this active ingredient are tablets and injectable solutions.

Because of the numerous issues involved in drug formulation, usage, storage and final disposal, it is important to understand thermal properties of pharmaceutical materials [4, 5].

A recent literature survey showed that there are few studies regarding the thermal analysis of propranolol. Using microcalorimetry, Fagher and Monti [6] demonstrated that propranolol oral administration caused a decrease in thermogenesis in human skeletal muscle samples. Macedo et al. [7] studied the thermal behavior of some anti-hypertensive drugs, including propranolol. Their purities were determined by DSC, and the thermogravimetric data allowed determination of the kinetic parameters. In other paper, Macedo et al. [8] demonstrated that DSC of propranolol binary mixtures presented similar phase transition to propranolol drug. DSC-photovisual assay revealed an interaction similar to the Maillard

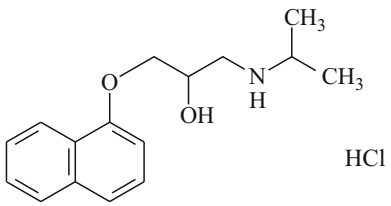

Fig. 1 Chemical formulae of propranolol

reaction, and TG isothermal study showed a difference in the profile between the drug and tablets due excipients quality and problems in manufacture process. Mônica et al. [9] revealed that propranolol plasma presented reduction in phase transition enthalpy comparable to the plasma denatured by perchloric acid in the last DSC cycles of freezing. Gerber and Lötter [10] studied the compatibility between propranolol hydrochloride and tablet excipients using differential scanning calorimetry (DSC). They verified that propranolol interacts with a number of commonly used tablet excipients.

Bartolomei et al. [11] investigated the polymorphism of (R,S) propranolol hydrochloride by DSC, TG and others techniques. The authors showed that propranolol hydrochloride existed in three different crystalline habits called forms I, II and III, according to their decreasing melting temperatures.

In the literature, reports regarding the analysis of the volatile products evolved during the propranolol decomposition were not found. Thus, this paper aims to investigate the gases evolved during heating of propranolol by TG–FTIR and together with DSC curves, proposing a mechanism for propranolol decomposition.

Materials and methods

Propranolol hydrochloride (Natural Pharma, Brazil) was stored in a refrigerator before analysis and used without further purification.

Simultaneous TG/DTG and DTA analysis were carried out in open α-alumina sample holders (90 μL) in a simultaneous SDT-Q600 modulus controlled by the Thermal Advantage Q-Series (version 5.4.0 software, both from TA Instruments). Experimental parameters for TG curves were: sample mass of 10 ± 1 mg (mass precision 0.1 μg) and heating rate of 10 °C min^{-1} under dynamic N_2 atmosphere flowing at 50 mL min^{-1} from room temperature to 600 °C. The apparatus was calibrated for temperature with a zinc standard as recommended by the manufacturer instructions.

DSC curves were obtained using sample mass of *c.a.* 6.0 ± 0.5 mg (mass precision 0.1 mg), heating rate of 10 °C min^{-1} under N_2 dynamic atmosphere flowing at 50 mL min^{-1}, in a temperature interval of −50 to 200 °C using covered aluminum pans with a central pinhole (ϕ = 0.7 mm) in the lid. Curves were obtained in the heat–cool–heat successive cycles. A TA DSC-Q10 unit controlled by the Thermal Advantage for Q-Series (version 5.4.0 software, both from TA instruments) coupled to the RCS cooling accessory was used. Calibrations of the equipment for temperature and enthalpy were performed using the indium metal standard (99.99 % purity), according to the manufacturer's recommendations.

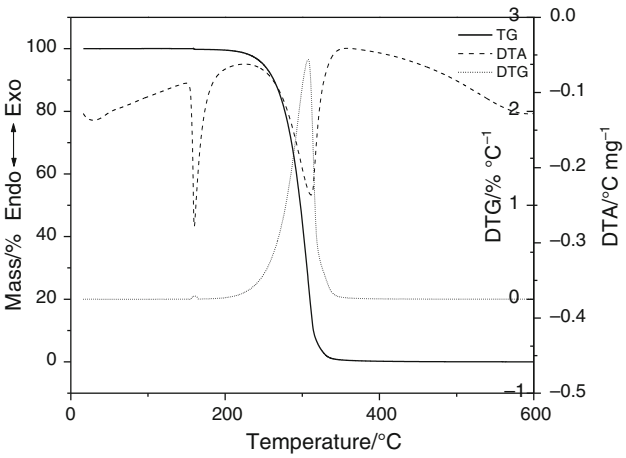

Fig. 2 TG/DTG-DTA curves of the propranolol (m = 10.40 mg) in N_2 atmosphere

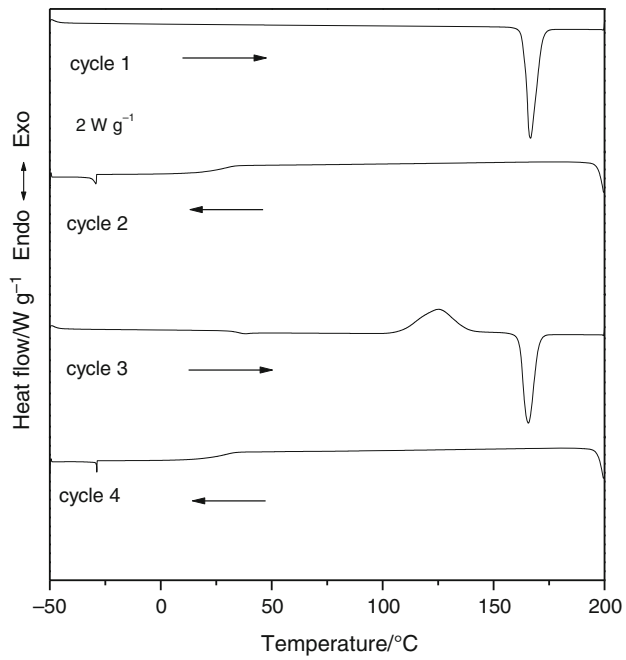

Fig. 3 Heat–cool–heat DSC curves of the propranolol (m = 5.90 mg)

The analyses of the evolved gaseous products was carried out by connecting the exhaust of the TG–DTA equipment to a Nicolet iS10 spectrophotometer (Thermo Scientific), with a gas cell operating at 250 °C and a DTGS KBr detector. The coupling was performed using a stainless steel line transfer (length 1200 mm; diameter 3 mm) heated at 225 °C and purged with nitrogen. FTIR spectra were recorded with 32 scans per spectrum at a resolution of 4 cm^{-1}. The interferometer and the gas cell compartments were purged with highly purified N_2 for 20 min previously to the TG run. The TG curve was taken using a heating rate of 10 °C min^{-1} and samples weighing about 12 mg in α-alumina crucibles, and the same purified N_2 for the furnace atmosphere control flowing at 50 mL min^{-1}.

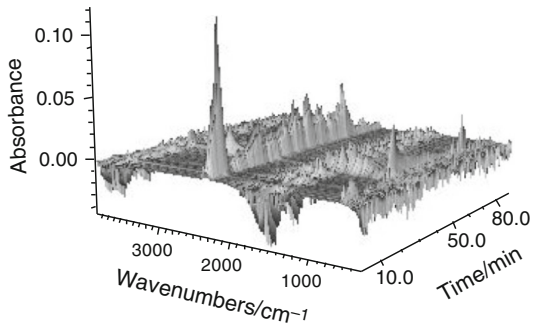

Fig. 4 3D-FTIR spectra of gaseous products evolved during the decomposition of propranolol, along the analysis time

Results and discussion

Propranolol TG/DTG-DTA curves are presented in Fig. 2. In TG curve, it can be observed that there is any mass loss until approximately 200 °C. However, at 160.6 °C an endothermic peak appeared in the DTA curve, corresponding to the melting of the drug with initial temperature at 151.8 °C.

According to TG/DTG curves, the propranolol presented a single mass loss step between 199.6 and 369.9 °C in

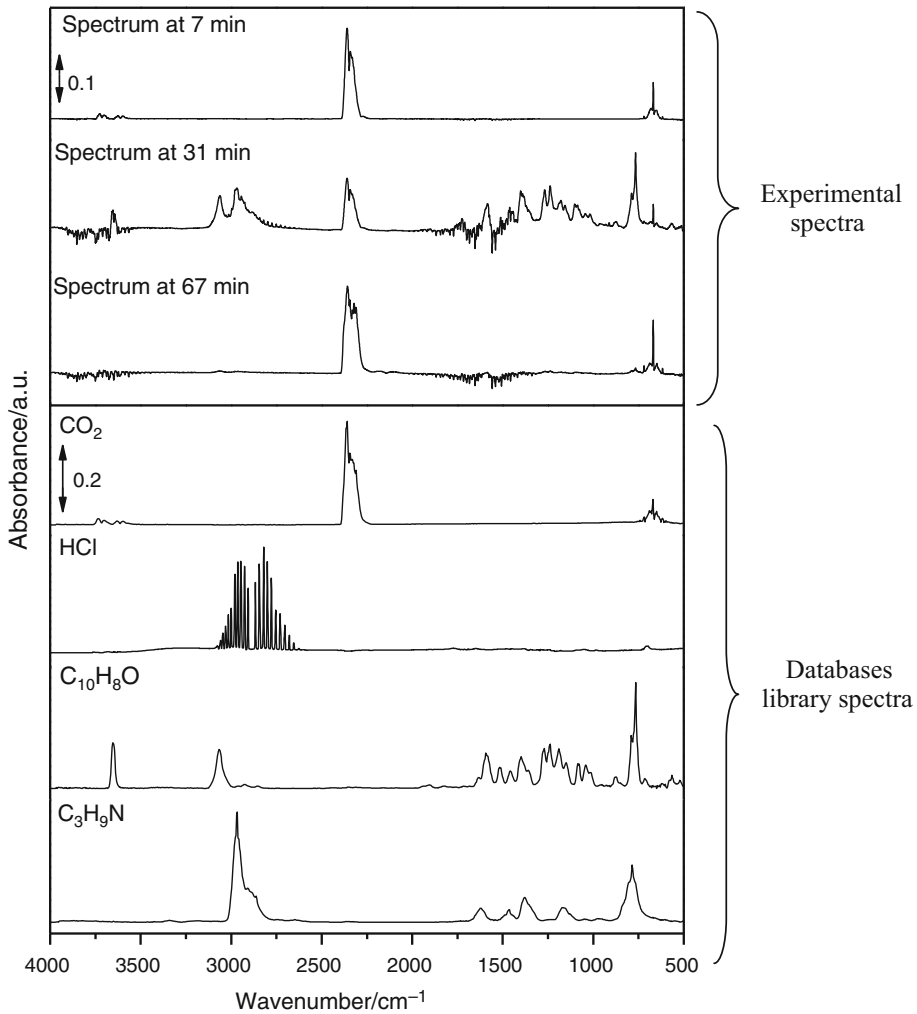

Fig. 5 Experimental and database [13] FTIR gas-phase spectra for the three compounds suggested as evolved gases during propranolol decomposition

which 99.80 % of the initial sample mass is lost corresponding to decomposition of the drug. In the same temperature range, there is an endothermic peak at 312.0 °C in the DTA curve.

Figure 3 presents propranolol heat–cool–heat DSC curves. In the first heating, an endothermic peak at 166.7 °C (T_{onset} = 163.9 °C, ΔH_{fus} = 16.31 kJ mol^{-1}) relative to the melting process was observed in agreement with previously reported results [12]. In the first cooling, crystallization was not observed, instead of that a glass transition, typical of amorphous compounds, was detected *c.a.* 30 °C.

In the second heating, one can observe the reversion on the glass transition, represented by baseline deviation *c.a.* 30 °C, an exothermic event centered at 125.3 °C (ΔH_{cryst} = 13.10 kJ mol^{-1}), probably associated with a cold crystallization event, followed by a melting endothermic process with peak at 165.7 °C (T_{onset} = 161.7 °C, ΔH_{fus} = 15.42 kJ mol^{-1}) [12]. During the second cooling, the same characteristics of the first cooling were observed.

The investigation of gases evolved during the propranolol thermal decomposition revealed peaks of gas evolution at 7, 31 and 67 min (respectively at 90, 330 and 690 °C), as presented in Fig. 4. The identification of the species was made according to Nicolet TGA Vapor Phase and EPA Vapor Phase database library contained in the Omnic 8.0 software (Thermo Scientific) [13].

In the first peak, CO_2 and traces of H_2O were detected, and in the last one, only CO_2 appeared although this gas could be detected all along the experiment. The first detection could be related to carbon dioxide from the residues on the line/furnace and at higher temperature the gas was released from the decomposition of the residues of the sample.

Table 1 Tentative FTIR peak attribution for the evolved gases from propranolol decomposition

Compound	Wave number/cm^{-1}	Attribution[a]
1-Naphthol	3647	O–H stretch
	1525, 1412	C=C ring stretch
	1286	O–H bend
	1205	C–O stretch
	1008	C–H
Isopropylamine	3055	N–H stretch
	2914, 2872	C–H stretch
	1092	C–N stretch
Hydrochloric acid	2840–2660	H–Cl stretch

[a] According to Silverstein et al. [14]

In agreement with the TG curve, one can observe an intense gas release in the 27.5 to 40.0 min interval, corresponding to 290–420 °C. According to the database records, in this temperature range there are the characteristic peaks in the FTIR spectra of 1-naphthol at 3647, 1525, 1412, 1286, 1240, 1205, 1046, 1008 cm^{-1}; isopropylamine at 3055, 2967, 2914, 2872 cm^{-1} and HCl in the 2840–2660 cm^{-1} range. A comparison of the experimental and data base peaks for the three compounds suggested here is presented in Fig. 5. A tentative attribution of such peaks is presented in Table 1.

Thus, one can conclude that propranolol decomposed in the 199.6–369.9 °C range releasing 1-naphthol, isopropylamine and HCl. It should be expected the release of isopropanol once it is also part of the molecule. However, a secure detection of this alcohol could not be performed once the isopropanol IR spectra peaks are similar to those of the other constituents, but we can suggest the evolution of such alcohol during decomposition as well, but not confirmed. A tentative mechanism for such decomposition is presented in Fig. 6.

It is interesting to note that in other β-blockers atenolol, nadolol [15] and carvedilol [16] already investigated it was found that the molecules start decomposition from the aliphatic branch including the isopropylamine. However, in the present case the structure of the molecule seems to provide conditions for the entire decomposition followed by volatilization of the 1-naphthol, a volatile compound not present in the other β-blockers.

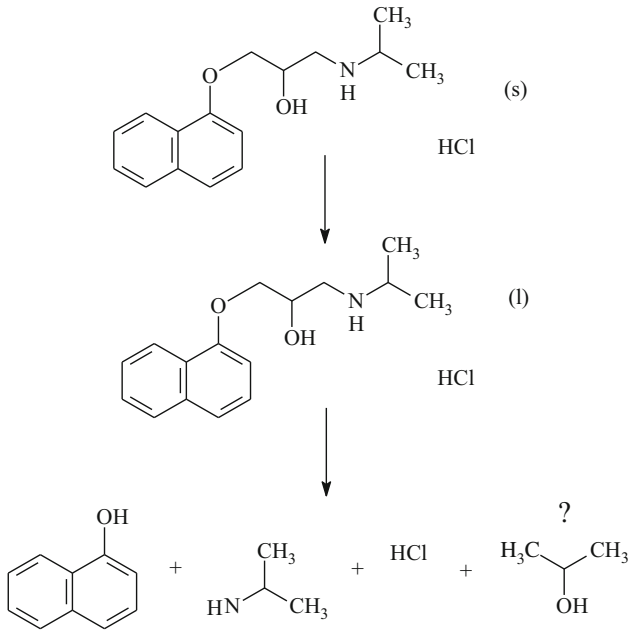

Fig. 6 Tentative mechanism for the thermal behavior of propranolol

Conclusions

TG, DTG, DTA and DSC curves and FTIR spectra provide information on the thermal behavior of the propranolol hydrochloride, such as melting and stability of the drug.

The evolved gas analysis during the thermal decomposition of the drug using TG–FTIR presented as principal decomposition products 1-naphthol, isopropylamine and HCl, being the rest of the molecule represented by isopropanol, not detected in the evolved gas analysis by TG–FTIR. A tentative mechanism for the thermal behavior of propranolol was proposed.

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