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Investigation of the thermal behavior of Labetalol

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ABSTRACT

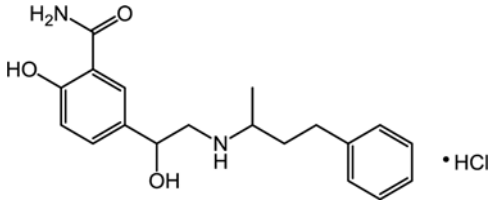
Thermal behavior of labetalol hydrochloride (2-hydroxy-5-[1-hydroxy-2-(4-phenylbutan-2-ylamino)ethyl]benzamide), a β-blocker antihypertensive drug, has been investigated using thermogravimetry (TG), differential thermal analysis (DTA), differential scanning calorimetry (DSC), thermogravimetry coupled to infrared spectroscopy (TG-FTIR), hot stage microscopy and gas chromatography coupled to mass spectrometry (GC–MS). TG/DTA and TG-FTIR analysis showed that labetalol decomposed after melting releasing water in the first step of mass loss. In sequence water and isocyanic acid (which decomposed in ammonia and carbon dioxide) were detected in the second step, and methylbenzene in the third decomposition step. The decomposition took place in the same way in nitrogen and air atmospheres until 550 °C, however in air there is one more step due the oxidative burning of the carbonaceous material, resulting in practically no residue at the end of the run. DSC curves demonstrated that the sample melted at T = 180.8 °C, without recrystallization on cooling. Hot stage microscopy confirmed that labetalol melted and decomposed releasing water from its structure. GC–MS analysis allowed characterizing some intermediates of the drug degradation and the identification of other degradation products. Based on these results a mechanism for labetalol hydrochloride thermal behavior was proposed.

1. Introduction

Hypertension (HTN) is a clinical condition characterized by persistently high levels of blood pressure, which is the cause of several health problems - and even death - in people worldwide. According to The American Heart Association in the last decade, the mortality rate due to HTN increased by 7.6%, becoming the largest cause of death due to heart problems. HTN is a chronic disease that requires drug treatment throughout life [1,2].

Nowadays a relatively large number of drugs to control the blood pressure are available. Such drugs are grouped in classes according to their biological action, including the β-adrenergic antagonists (or just β-blocker agents), which had been widely used since many years ago. This class of antihypertensives is effective in controlling blood pressure and recommended for many high-risk patients with associated heart problems, including diabetes. Labetalol (2-hydroxy-5-[1-hydroxy-2-(4-phenylbutan-2-ylamino)ethyl]benzamide), acts as an α and β-blocker to control HTN since 1970, being safe even during pregnancy [3].

Labetalol contains two chiral carbon atoms in its structure, resulting in four stereoisomers. Commonly used commercial formulation consists of an equimolar mixture of these four stereoisomers. The (*S,R*) isomer is responsible for most of the α_1-blocking whereas the β-blocking is attributed to the (*R,R*) isomer, also known as dilevalol. (*S,S*) and (*R,S*) forms are considered inactive [4,5]. The planar structural formula of labetalol hydrochloride is:



Applications of thermoanalytical techniques in pharmaceutical industry have been proposed for years [6–8]. These studies include polymorphism [9,10], drug formulation and interactions in the solid state [11,12], thermal stability and thermal degradation [13,14], purity [15], and a wide range of properties which can be measured by these techniques [16].

In addition, some innovative dosage forms can be obtained using thermoanalytical data, which are also essential in the determination of thermal stability of drugs [17–19]. Thermal and oxidative degradation studies of some widely used drugs are also presently used in the detection of drugs in urban waste before and after depuration [20].

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Besides providing all these information, if combined with appropriated spectroscopic techniques, thermoanalytical techniques can also provide information about the evolved gases and intermediates formed during drug decomposition. Several pharmacopoeias around the world had already recommend thermogravimetry (TG) and differential scanning calorimetry (DSC) procedures to measure these properties [21–23], demonstrating the significance of thermal analysis in the characterization of pharmaceuticals.

Although the number of publications concerning thermal analysis of pharmaceuticals is still increasing, there are many important drugs whose thermal behavior has not been fully investigated yet, including labetalol.

Up to our knowledge, the unique paper concerning thermal analysis of labetalol is that from Mathkar et al. [24], which described an evaluation of purity of pharmaceutical reference standards by DSC, including labetalol. However in that study the authors restricted the investigation to the melting of those substances and reported that the labetalol standard decomposes after melting. Unless for this report we could not found any complete thermal analytical study, involving a description of decomposition intermediates or description of volatiles evolved during the thermal degradation of this drug.

Thus, the main goal of the present work is to investigate the thermal properties of labetalol in order of proposing a complete mechanism for thermal behavior of the drug based on TG/DTG/DTA, DSC, TG-FTIR, Hot Stage microscopy and GC–MS.

2. Experimental procedures

2.1. Materials

Labetalol hydrochloride was purchased from Sigma Aldrich (≥ 98%) and used as received, unless by heating up to 80 °C just before each experiment, in order to eliminate humidity.

2.2. Thermogravimetry and differential thermal analysis (TG/DTA)

TG/DTG/DTA curves were obtained in a simultaneous TG/DTA SDT-Q600 modulus (TA Instruments), controlled by the Thermal Advantage software (v5.5.24, TA Instruments). TG curves were taken using sample masses of *ca.* 7.0 ± 0.1 mg in open *α*-alumina sample holders, at 10 °C min^{-1} heating rate from room temperature to 1000 °C, under both dynamic dry air and nitrogen atmospheres flowing at 50 mL min^{-1} at atmosphere pressure.

2.3. Differential scanning calorimetry (DSC)

The DSC curves were obtained in a Q10 Differential Calorimetric Module (TA Instruments), controlled by the Thermal Advantage Series software (v5.5.24, TA Instruments), using sample masses of *ca.* 4.0 ± 0.1 mg, in covered aluminum sample holder with a 0.7 mm pinhole in the center of the lid, using heating rate of 10 °C min^{-1}. The measurement was taken between room and 230 °C (1st cycle), 230 to −50 °C (2nd cycle) and -50 to 230 °C (3rd cycle) under dynamic nitrogen atmosphere flowing at 50 mL min^{-1} in the heat-cool-heat mode under atmospheric pressure. The apparatus was calibrated for temperature and enthalpy using Indium metal (> 99.9%) according to the manufacturer's instructions.

2.4. Hot stage microscopy

Hot stage microscopy was performed using a HS82 Hot Stage (Mettler Toledo) coupled with a BX51 microscopy (Olympus) and a SC30 digital camera (Olympus). The sample was heated from room temperature to 225 °C at 10 °C min^{-1}. For temperature ranges in which dehydration, melting and crystal changes could be present a 4 °C min^{-1} heating rate was used (80–120 °C and 170–225 °C). Representative micrographs were taken in the respective temperature.

2.5. Evolved gas analyses (EGA) by thermogravimetry coupled to vibrational spectroscopy in the infrared region (TG-FTIR)

The gaseous products evolved during the decomposition of labetalol were analysed in a SDT-Q600 (TA Instruments) coupled to an iS10 FTIR Spectrometer (Nicolet). The transfer line consisted of a thermally insulated stainless steel tube 120 cm long with 2 mm inner diameter, heated at a constant temperature of 230 °C. FTIR measurements were carried out with a DTGS detector in a gas cell heated at a constant temperature of 250 °C. The interferometer and the gas cell compartments were purged with nitrogen. In this case, TG curve was taken in N2 flowing at 60 mL min^{-1}, at 10 °C min^{-1} heating rate and sample mass about 13 mg.

2.6. Gas chromatography coupled to mass spectrometry (GC–MS)

Solid intermediates of thermal degradation were analyzed by GC–MS. Thus, labetalol hydrochloride drug was heated up to 230 °C in the thermobalance under the same experimental conditions described for TG experiments. The resulting solid was solubilized in methanol (HPLC grade) and subjected to GC–MS analysis in a gas chromatograph (Shimadzu) coupled to a quadrupole mass spectrometer GCMS-QP2010 (Ultra) in the EI mode (70 eV), with temperature of injector and interface kept at 230 °C in a split/splitless system with 1:50 division, using a SPB™-5 column of 30 m x 0.25 mm (Supelco), with nitrogen gas flow of 1.8 mL min^{-1} and ramp rate of 2 °C min^{-1} up to 60 °C and then 15 °C min^{-1} up to 230 °C.

3. Results and discussion

3.1. Thermal analysis

TG/DTG/DTA curves of labetalol under N_2 and air atmospheres are shown in Fig. 1. According to these curves, labetalol was thermally stable up to 176 °C in both atmospheres, and decomposed after melting. In air atmosphere an additional event was observed at 550 °C associated to oxidative burning of the carbonaceous residue in both DTG and DTA curves.

Table 1 summarizes the quantitative data obtained by TG (experimental and calculated mass losses), temperature ranges and DTA peak temperatures. The attribution of these events will be better discussed in the TG-FTIR section.

In DTA curves it was possible to observe endothermic peaks at T = 193.2 °C (Fig. 1 (b), N_2) and T = 191.4 °C (Fig. 1(d), air) related to the melting of labetalol, followed by decomposition endothermic/exothermic peaks, in agreement with the events observed in TG/DTG curves. According to the literature [2] labetalol melts between 180 and 190 °C, which is quite similar to observed in this work.

DSC curves of labetalol hydrochloride were taken under dynamic nitrogen atmosphere in the heat–cool–heat mode, as presented in Fig. 2.

The first heating of labetalol showed one endothermic event related to the melting of the sample at T_{onset} = 180.8 °C, followed by an exothermic signal which was probably due the beginning of degradation process, once TG curves reveled mass loss in this temperature. This is in agreement with Mathkar, et al.[24], who reported the same DSC curve profile for labetalol and suggested that the drug decomposed just after melting. In the cooling and second heating, baseline deviations between 40–120 °C were observed, indicating the presence of amorphous material, without evidences of neither recrystallization on cooling or melting on the 2nd heating.

3.2. Hot stage microscopy

Hot stage micrographs, Fig. 3, corroborated with what was observed

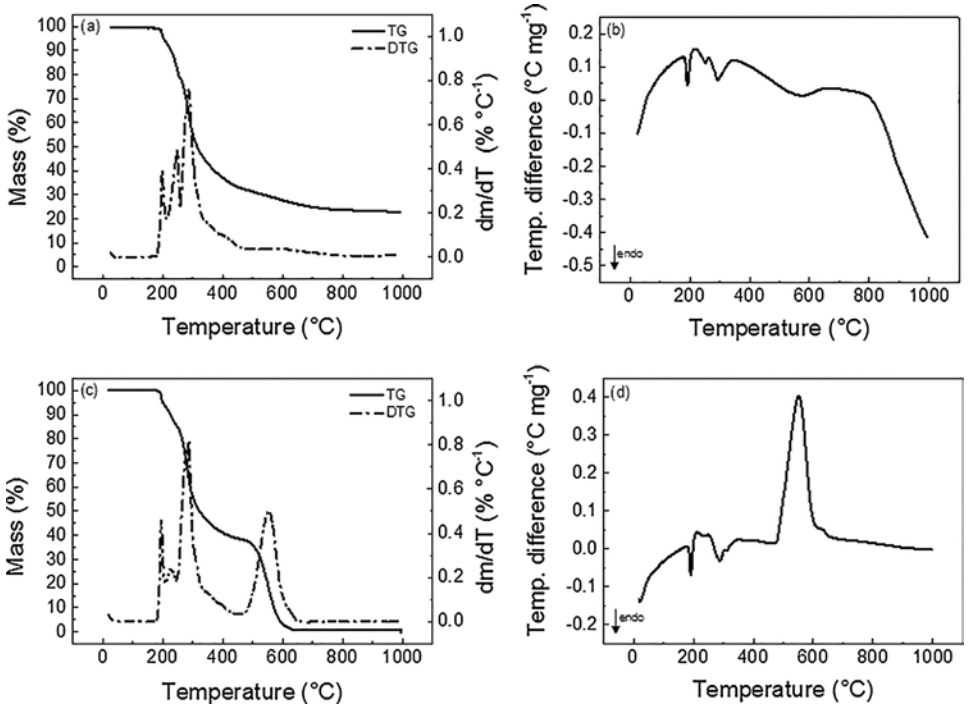


Fig. 1. TG/DTG (a,c) and DTA (b, d) curves of labetalol hydrochloride. Sample mass of 7.0 ± 0.1 mg, in open α-alumina crucible in (a,b) N_2 and (c,d) dried air, flowing at 50 mL min^{-1}.

in TG, DTA and DSC curves, confirming that labetalol started melting at 175 °C. The differences in melting temperatures could be attributed to the different conditions used in these techniques, such as heating rate and sample mass. Images also revealed a substantial change in the shapes of the particles (better observed in the larger ones) from 194 to 198 °C suggesting a swelling of the sample (Figs. 3e and f). Fig. 3h (209 °C) presents a magnification of the image of the particle at the up center in Fig. 3f, now at 209 °C, in which is clearly seen the presence of gas bubbles, attributed to water evaporation, associated to the mass loss observed in TG curves close to this temperature.

The gases evolved during labetalol decomposition were characterized using thermogravimetry coupled to infrared spectroscopy (TG-FTIR). The Gram-Schmidt plot (supplementary material) revealed intense gas evolution at 24 min and the maximum of gas detection at 33.5 min, corresponding to *c.a.* 355 °C.

Interpretation of the data was made by comparison among the

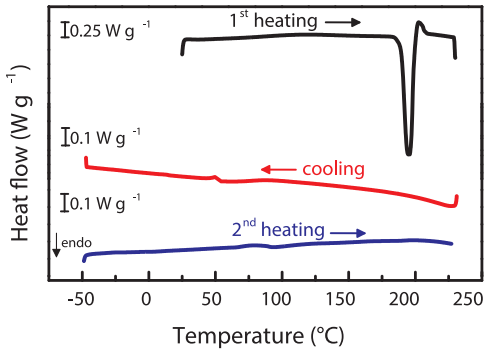


Fig. 2. DSC curves of labetalol hydrochloride in nitrogen flowing at 50 mL min^{-1}, sample mass of 4.0 ± 0.1 mg, in aluminum crucible.

Table 1
Proposed events, temperature ranges, mass loss and DTA peaks obtained during heating under N_2 and air.

	TG data			DTA data
	T_{range} (°C)	Mass Loss (%)		
		TG	Calculated	T (°C)
Nitrogen				
$C_{19}H_{24}N_2O_3 \cdot HCl_{(s)} \rightarrow C_{19}H_{22}N_2O_2 \cdot HCl_{(l)} + H_2O_{(g)}$	176.7-204.6	4.97	4.9	193.2 (endo)
$C_{19}H_{22}N_2O_2 \cdot HCl_{(l)}\ C_{18}H_{21}N \cdot HCl_{(l)} + CHNO_{(g)} + H_2O_{(g)}$	204.6-260.3	16.6	16.7	215.0 (exo), 252.1 (endo)
$C_{18}H_{21}N \cdot HCl_{(l)} \rightarrow C_{11}H_{15}N \cdot HCl_{(l)} + C_7H_{(g)}$	260.3-310.4	26.8	25.6	293.8 (endo)
$C_{11}H_{17}N \cdot HCl_{(l)} \rightarrow$ carbonaceous residue	310.4-491.0	20.0	–	574.2 (endo)
$C_{11}H_{17}N \cdot HCl_{(l)} \rightarrow$ pyrolysis carbonaceous residue	491.0-1000	8.93	–	
Air				
$C_{19}H_{24}N_2O_3 \cdot HCl_{(s)} \rightarrow C_{19}H_{22}N_2O_2 \cdot HCl_{(l)} + H_2O_{(g)}$	176.2-199.8	4.89	4.9	191.4 (endo)
$C_{19}H_{22}N_2O_2 \cdot HCl_{(l)} \rightarrow C_{18}H_{21}N \cdot HCl_{(l)} + CHNO_{(g)} + H_2O_{(g)}$	199.8-266.0	16.7	16.7	213.9 (exo), 233.1 (endo)
$C_{18}H_{21}N \cdot HCl_{(l)} \rightarrow C_{11}H_{15}N \cdot HCl_{(l)} + C_7H_{8(g)}$	266.0-310.5	25.6	25.6	287.2 (endo)
$C_{11}H_{17}N \cdot HCl_{(l)} \rightarrow$ burned residue	310.5-473.1	14.8	–	550.7 (exo)
$C_{11}H_{17}N \cdot HCl_{(l)} \rightarrow$ burned residue	473.1-1000	37.2	–	

*Residue at 1000 °C: 22.7% in N_2 and 0.744% in air; exo – exothermic; endo – endothermic.

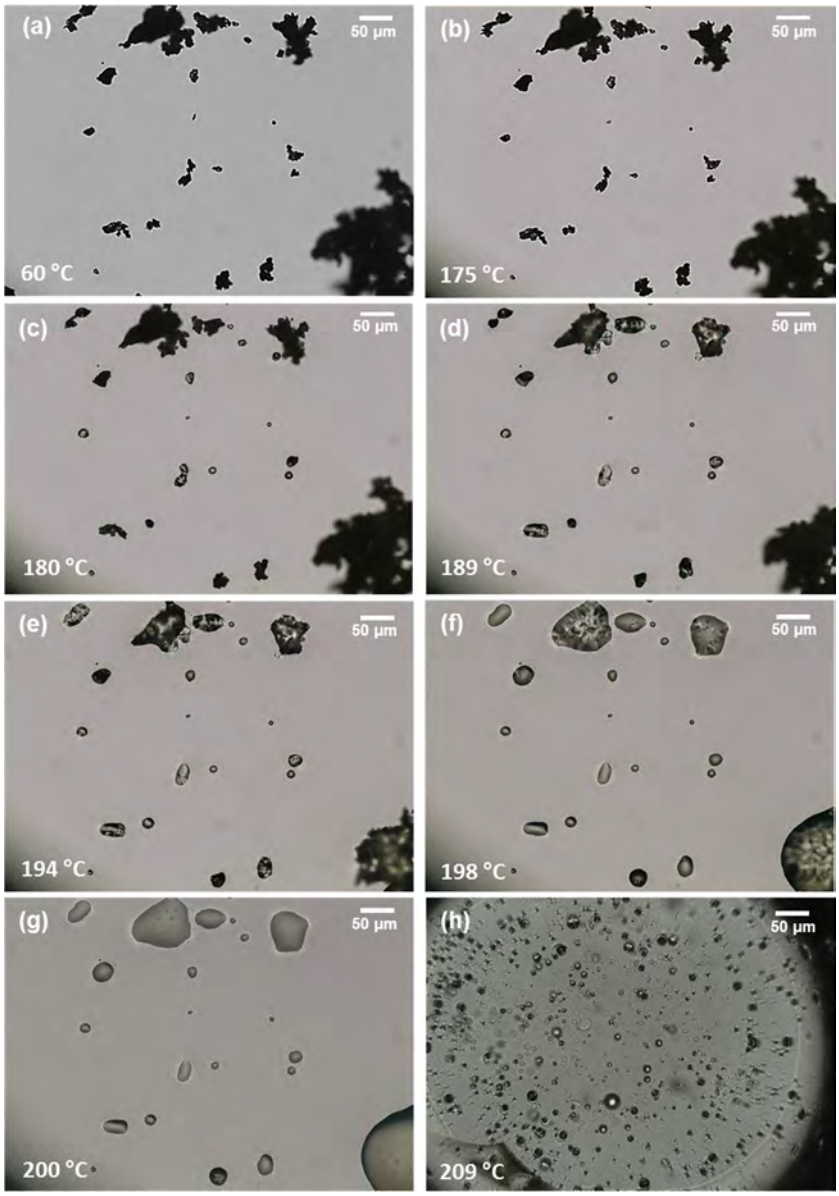


Fig. 3. Hot stage microscopy photographs of labetalol in the 60–209 °C range in air (magnification 200x).

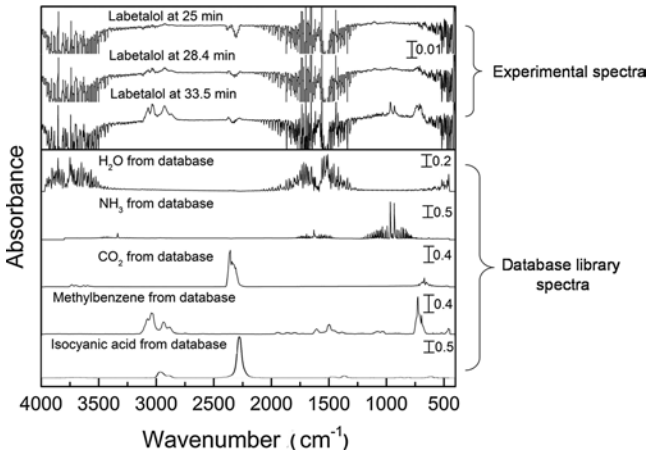


Fig. 4. FTIR spectrum of gaseous decomposition products of labetalol at 25.0, 28.4 and 33.5 min of analysis and spectra from NIST and Nicolet TGA Vapor Phase databases for water, ammonia, carbon dioxide, methylbenzene and isocyanic acid [25,26].

Table 2
Comparison among bands present in the gaseous decomposition products of labetalol at 33.5 min and ammonia, carbon dioxide, methylbenzene and isocyanic acid, from NIST and Nicolet TGA Vapor Phase databases [25,26].

Labetalol – 33.5 min (355 °C) Wavenumber (cm^{-1})	Database Wavenumber (cm^{-1})
	Ammonia
967.0	966.0
932.3	931.8
	Carbon dioxide
2378.4	2364.1
703.9	698.1
	Methylbenzene
3071.9	3078.2
3033.2	3039.7
2930.5	2938.4
2876.1	2885.7
739.9	730.2
700.1	695.7
	Isocyanic acid
2280.5	2278.5
718.1	716.7

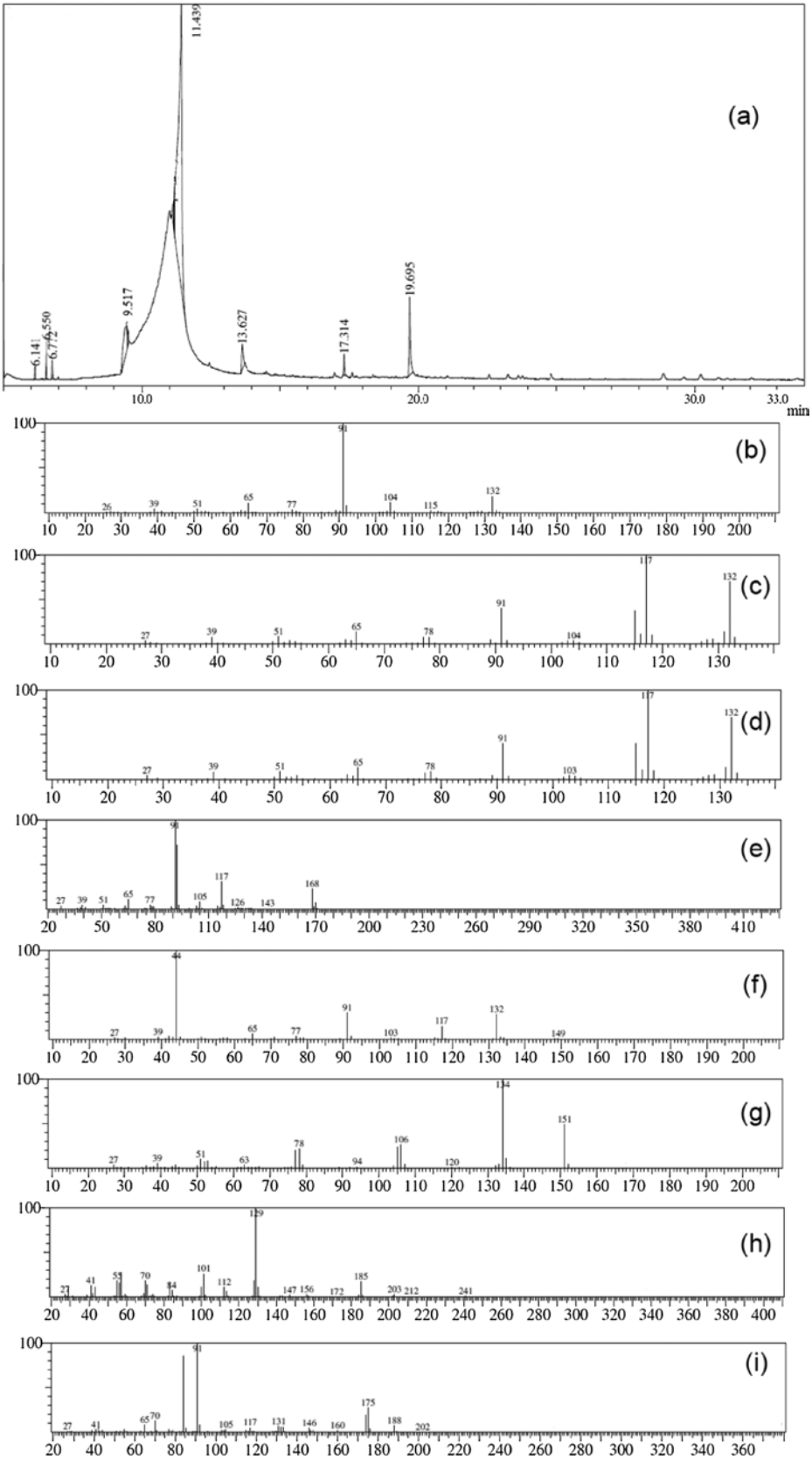
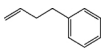
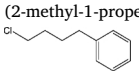
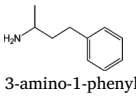
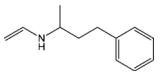


Fig. 5. GC–MS data for residue collected at 230 °C. Gas chromatogram (a) and mass spectra referent to each chromatographic peak according to the respective retention times (min): 6.14 (b); 6.55(c); 6.77(d); 9.51 (e); 11.4 (f); 13.6 (g); 17.3 (h) and 19.7 (i).

Table 3
Attribution of the main peaks in the GC chromatogram of the product of labetalol heated at 230 °C.

Retention time / min	*m/z*	Attribution	Reference / Database NIST MS n°
6.14	132	 3-butenylbenzene	232267 CAS: 768-56-9
6.55, 6.77	132	 (2-methyl-1-propenyl)benzene (*cis*, *trans*)	160,886 CAS: 768-49-0
9.51	168	 (4-chlorobutyl)benzene	114686 CAS: 4830-93-7
11.4	149	 3-amino-1-phenylbutane	236590 CAS: 22374-89-6
13.6	151	 2-hydroxy-5-methylbenzamide	*
17.3	–	Not identified	–
19.7	175	 N-ethenyl-4-phenylbutan-2-amine	*

*attributed according fragmentation profile in EI MS spectra (Fig. 5).

experimental spectra and those from NIST and Nicolet TGA Vapor Phase databases [25,26]. Fig. 4 presents the spectra of the gases evolved during labetalol heating at 25.0, 28.4 and 33.5 min of analysis compared with the spectra of water, ammonia, carbon dioxide and methylbenzene from database.

In the spectra of the gases evolved at 25.0 min (270 °C) it was possible to see the evolution of water and some low intensity bands at 2920 and 2875 cm^{-1}. At 28.4 min (304 °C), those low intensity bands became more intense while new ones can be noticed at 3077, 3033, 2930, 2876, 2378, 2280 cm^{-1} and 730 cm^{-1}. Finally after 33.5 min (355 °C) new bands raised at 962 and 930 cm^{-1} in addition to those previously described, while the intensity of the previous ones still increases. The attributions of such signals are summarized in Table 2, and they are related to water, isocyanic acid, carbon dioxide, methylbenzene and ammonia, that appeared in this order.

These results are in agreement with TG mass losses as presented in Table 1. Decomposition of isocyanic acid generates ammonia and carbon dioxide inside the transfer line as previously reported [27,28].

3.3. Gas chromatography coupled to mass spectrometry (GC–MS)

In order to characterize the solid intermediates formed during the thermal decomposition, labetalol was heated in the thermobalance up to 230 °C and the residue was characterized by GC–MS. The chromatogram and mass spectra results are presented in Fig. 5.

The gas chromatogram presented eight peaks in their respective retention times. The presence of such relatively high number of substances is attributed to fact that decomposition takes place by successive events according to the DTG curve (Fig. 1). Thus at 230 °C it is expected to find not only the main products of the first step in DTG curves, but also the products of the second and third steps. Table 3 summarizes the results of the GC–MS analysis. The attributions in Table 3 were based on comparison with spectra listed in NIST database [29] or by analysis of the EI MS spectra as indicated in that table. The structural confirmation of the analytes should be given by the injection of standard substances or by injection of the synthesized product.

The most intense peak is the one with retention time t_R = 11.4 min, identified as 3-amino-1-phenylbutane (m/z = 149, Fig. 5f) according to the NIST database [29]. The peaks at t_R = 6.14; 6.55; 6.77; and 9.51 min, were also characterized according to the same database as being 3-butenylbenzene (m/z = 132, Fig. 5b); (2-methyl-1-propenyl) benzene (*cis, trans* isomers, m/z = 132, Fig. 5c and d) and (4-chlorobutyl)benzene (m/z = 168, Fig. 5e), respectively.

The other two signals at t_R = 13.6 and 19.7 min were attribute as 2-hydroxy-5-methylbenzamide (m/z = 151, Fig. 5g) and N-ethenyl-4-phenylbutan-2-amine (m/z = 175, Fig. 5i), respectively. They were proposed based on calculations from their fragmentation profiles in the EI MS spectra and considering the original labetalol hydrochloride molecule. The peak with t_R = 17.3 min (Fig. 5h) could not be securely attributed.

Thus it is possible to infer that the 3-amino-1-phenylbutane and N-ethenyl-4-phenylbutan-2-amine are those with higher amount in the residue, thus the labetalol hydrochloride is cleaved after dehydration in both sides of the double bond generated, but preferentially in the amine side.

The presence of (4-chlorobutyl)benzene corroborates the proposition that HCl is not released at least until 230 °C. Once the m/z in the mass spectrum in Fig. 5i suggests the presence of a compound containing a double bond, this can confirm the dehydration of the alcohol group present in the original molecule, as proposed in both TG curves and hot stage micrographs.

According to the observed in TG/DTG/DTA and DSC curves, with FTIR spectra of the evolved gases and GC–MS analysis, it was proposed a mechanism for labetalol hydrochloride thermal behavior and decomposition, as shown in Fig. 6.

4. Conclusion

TG/DTG/DTA curves and TG-FTIR revealed that labetalol decomposes at 176.7 °C after melting, releasing water in the first step, water

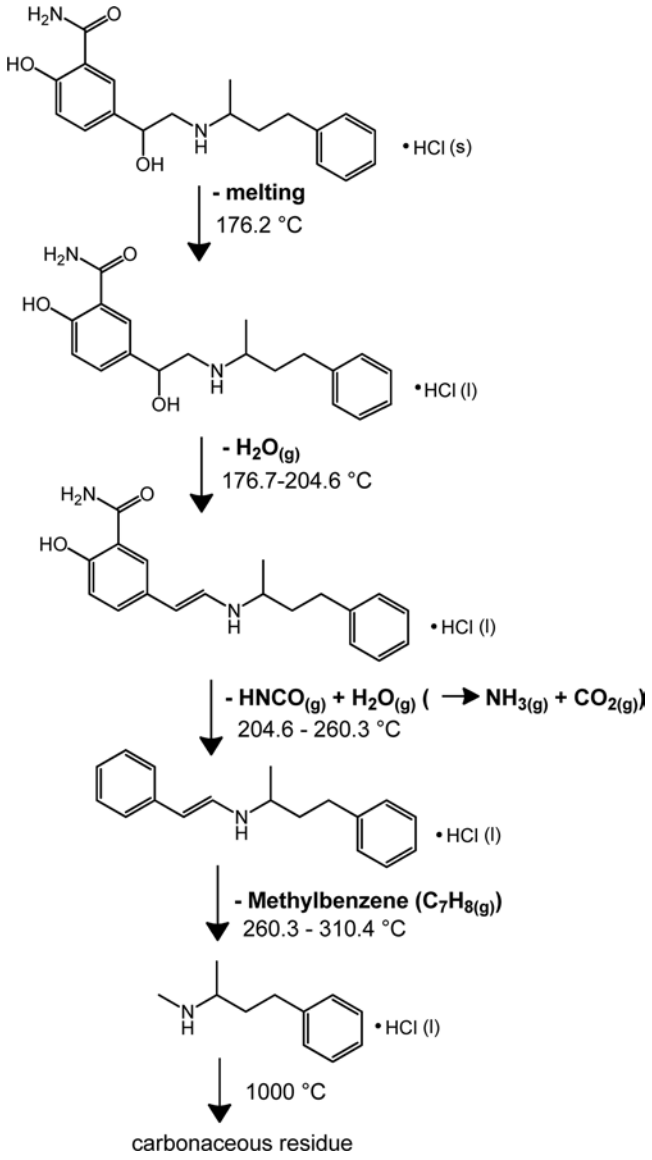


Fig. 6. Proposed mechanism for labetalol hydrochloride thermal decomposition, under N_2 atmosphere.

and isocyanic acid which decomposed in ammonia and carbon dioxide in the second step, and methylbenzene in the third step of mass loss, producing a carbonaceous material which is slowly degraded in nitrogen or burned in air. These results were confirmed by analysis of intermediates by GC–MS. DSC curves showed an event at 180.8 °C assigned to the melt of the drug and no crystallization or solid phase transformation was seen in the other cycles.

Acknowledgments

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