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ORIGINAL ARTICLE

Thermal behavior study and decomposition kinetics of amiodarone hydrochloride under isothermal conditions

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Abstract

Thermogravimetry (TG) and differential scanning calorimetry (DSC) are useful techniques that have been successfully applied in the pharmaceutical industry to reveal important information regarding the physicochemical properties of drugs and excipient molecules, such as polymorphism, stability, purity, formulation compatibility, among others. AMI presents a thermal stability of up to 431 K and a fusion onset temperature of 432 K. The drug has proven to be incompatible with magnesium stearate, eskis red pigment, and yellow iron oxide. In the present study, this drug presented degradation upon undergoing basic hydrolysis and oxidation; the degradation product produced under basic hydrolysis is 2-butyl-3-benzofuranyl-3,4-dihydroxy-5-iodophenylketone. Assessing the degradation kinetics, the drug presented a shelf life (t_{90}) of 43 years, while a pharmaceutical formulation showed a t_{90} of 1.7 years, which is consistent with commonly understood incompatibilities in pharmaceutical formulations.

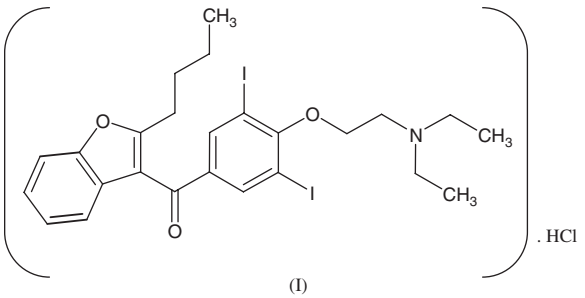
Keywords: Amiodarone hydrochloride, thermal analysis, degradation kinetics, characterization

Introduction

Several reports in the literature demonstrate the importance of thermal analysis by thermogravimetry (TG) and differential scanning calorimetry (DSC) in the characterization, the polymorphism identification, the purity evaluation of drugs, the compatibility studies for the pharmaceutical formulation, the stability, as well as the drug's thermal decomposition (Wendlandt, 1986; Hassan et al., 1997; Leitão et al., 2002; Macedo et al., 2002; Caira et al., 2004; Oliveira et al., 2005; Craig and Reading, 2007; Freitas et al., 2007; Laszcz et al., 2007; Gabbott, 2008; Porter et al., 2008; Stulzer et al., 2008).

AMI is used to treat ventricular tachycardia or ventricular fibrillation. AMI is an antihypertensive drug that is widely consumed in Brazil and is included in the national list of essential drugs for the cardiac treatment of arrhythmias (BRAZIL, 2006).

AMI (I), $C_{25}H_{29}I_2NO_3$ HCl, is a crystalline powder that fuses at 429 K. There are reports of crystals that recrystallize in acetone at a melting point of 432 ± 2 K. This drug is freely soluble in chloroform (445.1 mg/mL) and dichloromethane (192.0 mg/mL), soluble in methanol (99.8 mg/mL), sparingly soluble in ethanol (12.8 mg/mL), slightly soluble in propanol (1.3 mg/mL), and very slightly soluble in water (0.7 mg/mL) and hexane (0.3 mg/mL) (Budavari, 2000). Since its molecule is a derivative of haloaryl halide, AMI can undergo a photolytic degradation (Singh and Bakshi, 2000). Nakata (1997) reported that AMI, in an oral suspension formulation, shows no stability problems and presents a high permeability and log *P* (octanol/water) of 6.66 (Chatelain and Laruel, 1985).



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AMI is a class II drug with a low solubility and a high permeability, according to the biopharmaceutics classification system (BCS) (Amidon et al., 2004), in which the dissolution process is a rate-limiting step toward absorption and an *in vivo–in vitro* correlation (IVIVC) can be expected (FDA, 1997). Hence, it is important to evaluate drug features, such as the presence of polymorphism, stability, and compatibility of the pharmaceutical formulation, given that some changes may directly influence its bioavailability.

Therefore, the aim of the present study was to evaluate the thermal characterization of AMI using a variety of techniques, including TG, DSC, Fourier transform infrared spectroscopy (FTIR), liquid chromatography, and X-ray diffraction (XRD). The search for polymorphism and degradation products, together with formulation compatibility studies and thermal degradation kinetics, were carried out to aid in understanding the solid-state characterization, in turn evaluating the quality control and stability of this important active pharmaceutical ingredient.

Experimental

AMI characterization was performed in the present study using TG, DSC, and infrared (IR). The TG curve (TGA50H Shimadzu thermobalance) conditions used included a 10 K/min heating rate, from room temperature up to 1023 K, and a nitrogen flow rate of 50 mL/min, together with a mass of 5.0 mg in an alumina crucible. DSC curves (DSC50 Shimadzu calorimeter) were obtained under a nitrogen flow rate of 50 mL/min, a heating rate of 10 K/min, from room temperature up to 673 K. The aluminum crucible was partially closed, containing ~0.5 mg of the sample. The DSC purity assessment was performed by applying the van't Hoff equation using the Shimadzu Purity Determination Program Software, version 2.20.

IR experiments were carried out using a Perkin Elmer Spectrum One spectrometer by means of dispersion KBr disks.

Compatibility studies were performed by DSC technique, considering three local market formulations of AMI-coated tablets: a generic formulation containing 100 mg of drug per tablet (A), a generic formulation containing 200 mg of drug per tablet (B), a reference formulation containing 200 mg of drug per tablet (C), and a simulated pharmaceutical formulation (D) presented in the *Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products* (Niazi, 2004). The excipients of each formulation were (i) A: lactose M-100, microcrystalline cellulose, corn starch, povidone 30, sodium croscarmellose, silicon colloidal dioxide, magnesium stearate, eskis red pigment, red ponceau 4r lacquer pigment, yellow iron oxide, and ethyl alcohol; (ii) B: lactose M-100, microcrystalline cellulose, corn starch, povidone 30, sodium croscarmellose, silicon colloidal dioxide, magnesium stearate, eskis red pigment, red ponceau 4r lacquer pigment, yellow iron oxide, and ethyl alcohol; (iii) C: corn starch, lactose, silicon dioxide, povidone, and magnesium stearate; and (iv) D: monohydrate lactose, corn starch, povidone 30, magnesium stearate, silicon colloidal dioxide, and water (Niazi, 2004).

All ingredients listed for the development of the tablets were individually evaluated by DSC. In addition, a 1:1 binary mixture ratio of drug to excipient of the commercial pharmaceutical formulations and placebo formulation (D) were tested to evaluate the AMI thermal behavior as well as the compatibility of pharmaceutical formulations. To search for drug–excipient interactions in the binary mixtures, 5 mg of drug were added to the same amount of excipient in an attempt to maximize the probability of interaction. Next, multicomponent mixtures, as found in dosage forms, were evaluated (Balestrieri et al., 1996; Bazzo and Segatto Silva, 2005; Cides et al., 2006).

Chromatographic studies using HPLC/UV-DAD (HP1200, Agilent) and HPLC/MS-MS (Quattro LC, Micromass) in the positive mode of electrospray ionization (ESI) were performed. The search to identify degradation products after drug stress conditions could possibly be correlated with the degradation products from the incompatibilities found within DSC thermoanalytical studies. The stress conditions (intrinsic stability) of AMI were systematically investigated after 4 h of exposure under distinct conditions: (i) dry heat at 378 K, (ii) reflux over a steam bath in water, (iii) in 1 M NaOH, (iv) in 1 M HCl, (v) in 3% H_2O_2, and (vi) UV light (254 nm). The chromatographic conditions used included: RP18 column (ODS, 250 × 4.6 mm, 5 µm, Merck, Germany), mobile phase: acetonitrile/acetic acid 0.3% v/v pH 4.9 (70:30), 2 mL/min and an injection volume: 10 µL, UV-DAD detection 240 nm, 303 K, samples concentration 40 µg/mL in acetonitrile (British Pharmacopeia, 2007).

Drug recrystallization under different conditions was assessed using dichloromethane, methanol, ethanol, water, acetone, or hexane, at room (303 K) or cooled (263 K) temperatures, in saturated or diluted solutions. Analyses were performed by DSC, thermo-optical analysis (TOA) (FP90 and FP82OA Mettler Toledo), optical microscopy attached to a camera (Siedentopf), and XRD. For the XRD experiments, a Geigerflex Rigaku diffractometer with cobalt tube (CoKα), operating at a voltage of 32.5 kV and a 25.0 mA current, was used.

The stability evaluation and pharmaceutical formulation of the drug were performed by thermal analysis to determine its shelf life at 298 K by means of isothermal degradation kinetics. Dynamic TG curves and the definition of the initial stage of degradation for both the drug and the pharmaceutical formulation were obtained. After, isotherms' TG curves were carried in onset degradation temperatures, for both the drug and pharmaceutical formulation, in order to assess the best fit of mathematical models for isotherms at zero order (time versus %mass), first order (time versus log %mass), or second order (time versus 1/%mass). The mathematical model that provides the best linear correlation coefficient (r closer to 1.0000) represents the standard isothermal degradation. After

establishing the reaction order, the reaction rate (K) at 298 K was calculated through extrapolation using the Arrhenius equation. Using the K_{298} value, the shelf life and t_{90} were calculated for both the drug and pharmaceutical formulation. t_{90} represents the time interval required for the drug concentration to reach 90% of the initial concentration value and is in turn accepted as the determined shelf life (Macedo and Nascimento, 2002; Kim, 2004; Oliveira et al., 2005; Rodrigues et al., 2005).

Results and discussion

In the TG and DSC drug characterization, AMI (Figures 8 and 1 bottom, respectively) presented a thermal stability of up to 431 K, an onset melting temperature of 432 K, a melting point peak at 437.7 K, with an endothermic characteristic and fusion heat of ΔH 88.2 J/g. After fusion, the dynamic TG curve presented a compound degradation of 87%. The IR spectrum showed no change when compared with the reference spectrum, presenting main peaks at 1630, 748, 1245, 1558, 1170, and 998 cm^{-1} (Moffat et al., 2004; British Pharmacopeia, 2007).

In compatibility studies, thermal analysis techniques allow for the prior choice of more stable pharmaceutical formulations within a very short period of time by evaluating the interactions that may exist, first in their binary mixtures and later in multicomponent mixtures. The quality of the provided information, along with the speed of analysis, is desirable for the pharmaceutical industry but does not replace the conventional stability studies implied by law (ICH Q1A, 2003). The DSC curves applied to compatibility studies may show changes in the fusion range, shape or area of the peaks, as well as the appearance and disappearance of thermal events after mixing two components, thus indicating interactions or chemical reactions, which must be confirmed by other analytical techniques.

By assessing the formulation compatibility using binary mixtures (Figure 1), AMI presented a change in the fusion range and enlargement of the peak when associated with magnesium stearate, eskis red pigment, and yellow iron oxide, suggesting an incompatibility. These excipients contain metals, such as Mg, Al, or Fe, that are most likely responsible for the catalysis of degradation reactions. For other excipients, the drug melting occurred in an almost unchanged manner, and minor changes proved to be related to the presence of excipients, which does not characterize any incompatibility (Mura et al., 1998; Macedo and Nascimento, 2002). For liquid excipients, water and ethanol, AMI was compatible, as can be seen in the DSC curves in Figure 1.

In multicomponent mixtures, pharmaceutical formulations A, B, and C, a significant decrease in the melting range from 434 to 426 K (T peak) could be observed, as

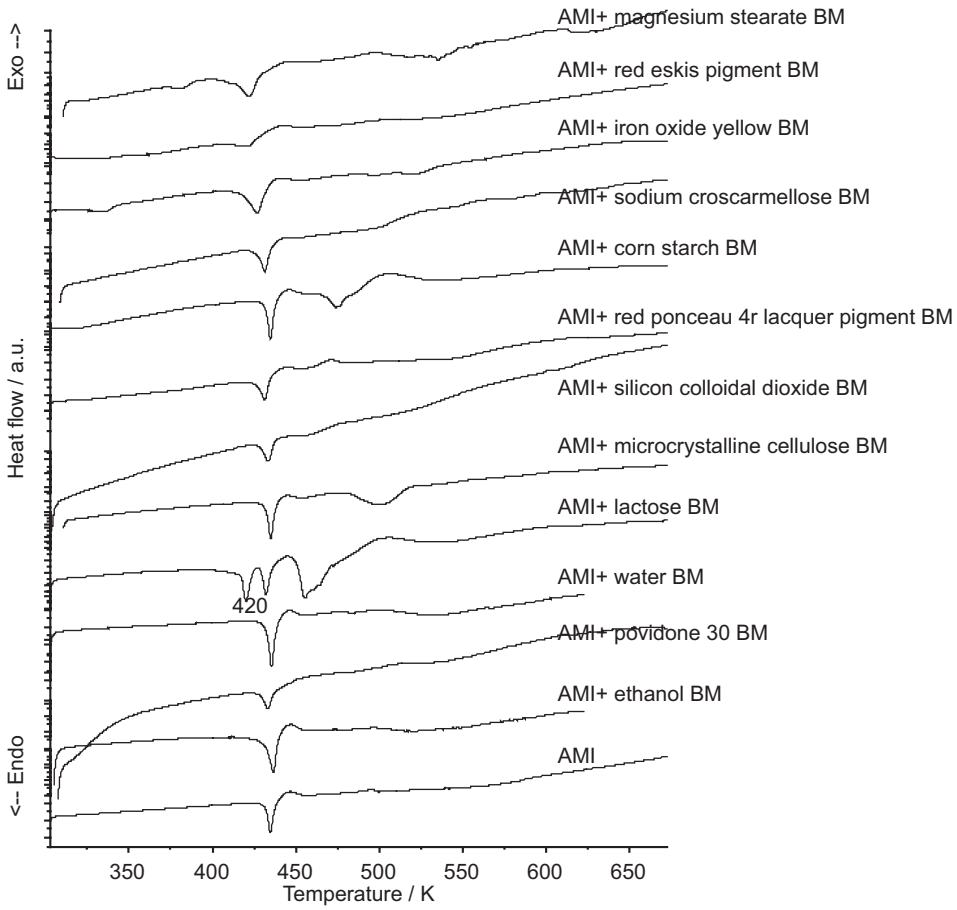

Figure 1. DSC curves for amiodarone hydrochloride and its binary mixtures (BM, 1:1).

illustrated in Figure 2A. It could be observed that placebo formulations (Figure 2B) presented the same fusion range at 426 K. As shown in Figure 1, the lactose melts at 420 K and is present in 18.5% of the pharmaceutical formulation, whereas AMI represents 40.2% of the formulation. The fact that the drug melting point disappears in the multicomponent mixture can be associated with either the solubilization/fusion of AMI at 426 K, due to the lactose effect, or incompatibilities founded with excipients: magnesium stearate, eskis red pigment, and yellow iron oxide. The pharmaceutical formulation may, therefore, have stability problems. Studies of isothermal degradation kinetics with extrapolation to room temperature can evaluate the stability of the pharmaceutical formulation against the drug.

A HPLC/UV-DAD method was validated for AMI in the presence of degradation products. A retention time (t_R) of 18.4 min, a retention factor (k') of 22.9, a peak symmetry (As) of 1.1, a theoretical plates/column (N) of 2816, repeatability and intermediate precision (RSD < 1%), intra-day and inter-days accuracy with a percentage recovery of 99.61% and 100.25%, respectively, were satisfactorily obtained. The linear correlation coefficient (r) was greater than 0.99 in the range of 1–60 μg/mL, whereas the detection limit was of 1.62 mg/mL, and the quantification limit was of 4.91 mg/mL. Selectivity studies, performed after drug stress conditions, and robustness were appropriate.

The chromatograms of AMI obtained before and after exposure to each stress condition can be seen in Figure 3. Data illustrate that degradation was predominantly due to basic hydrolysis and oxidation.

The present study evaluated the correlation of the peaks of degradation products found under conditions of

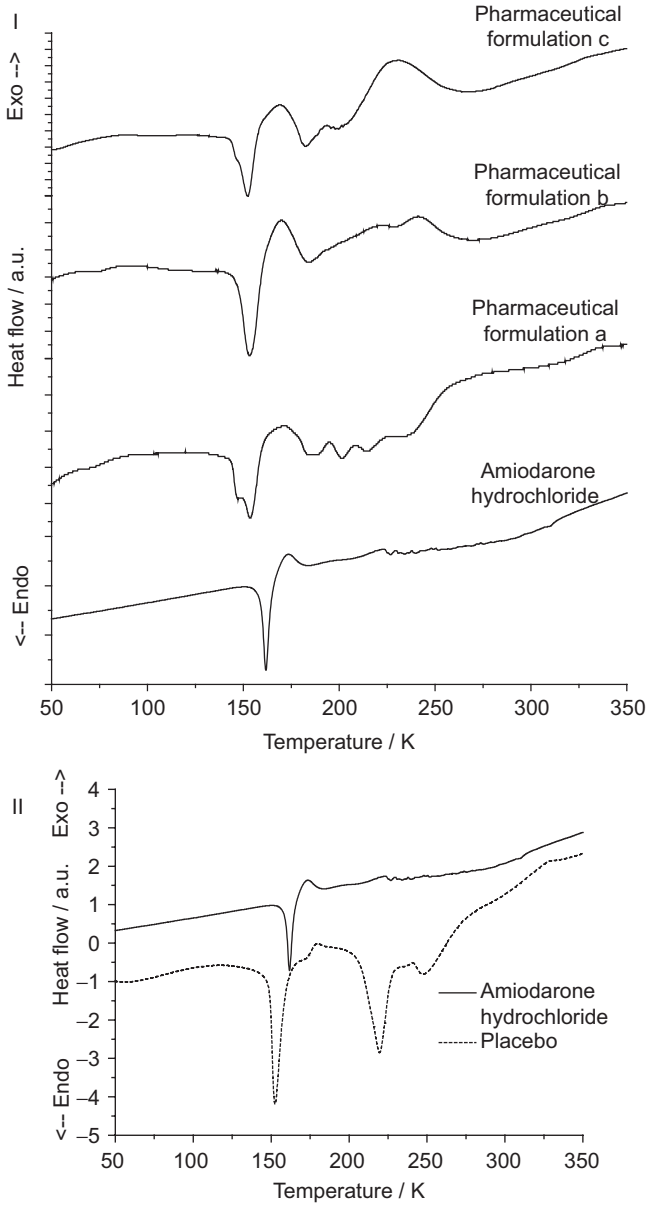

Figure 2. DSC curves: (A) amiodarone hydrochloride and commercial pharmaceutical formulations: A, B, and C, (B) amiodarone hydrochloride and placebo formulation.

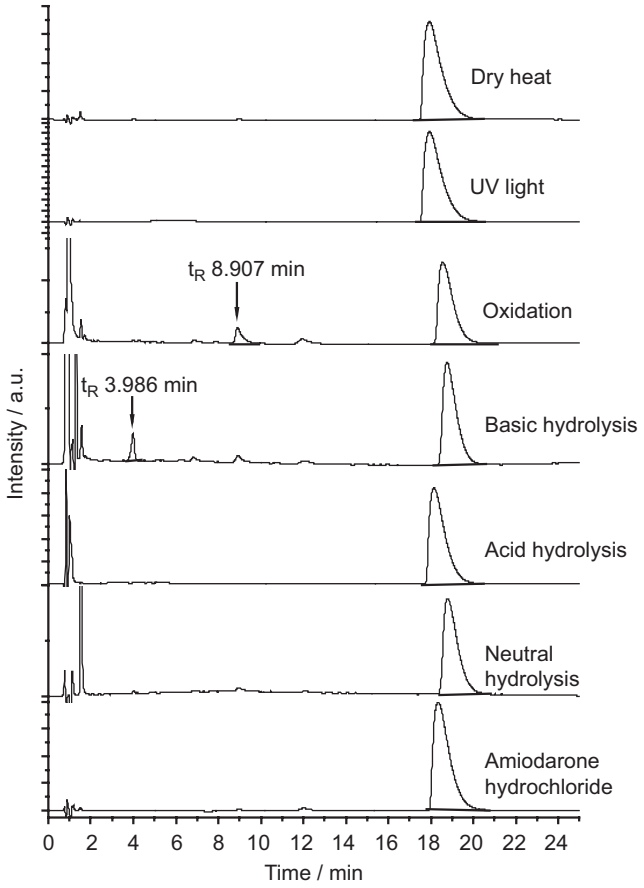

Figure 3. Amiodarone hydrochloride chromatogram before (bottom) and after stress conditions: neutral hydrolysis; acid hydrolysis; basic hydrolysis; oxidation; exposure to UV light; and exposure to temperature (dry heat).

basic hydrolysis and oxidation with AMI. In basic hydrolysis, it could be observed that the degradation product occurred at 3.986 min (k′ 4.2), with a UV spectrum of SI 0.9349 when compared with AMI (Figure 4A). However, the maximum and minimum absorption both proved to be present in the same wavelength, suggesting a similar structure between the chromophores. Under oxidation conditions, degradation could be observed. In addition, the peak of t_R at 8.907 min (k′ 10.6) illustrated a UV spectrum that was similar to (SI) 0.9870 when compared with AMI (Figure 4B).

When the retention time of the analyte peak is located as close as possible to the retention time of the reference peak, and both present SI spectra of greater than 0.99, the peaks refer to similar compounds (Moffat et al., 2004).

After intrinsic stability tests, the drug came into physical contact (4 h, 333 K) with magnesium stearate, eskis red pigment, and yellow iron oxide, which were determined to be incompatible by DSC, so as to assess and identify a possible degradation product produced by HPLC. However, no degradation product peak, nor reduction of AMI peak area, was formed. This demonstrates that under simulated conditions it was impossible to identify chemical reactions using the chromatographic method (HPLC).

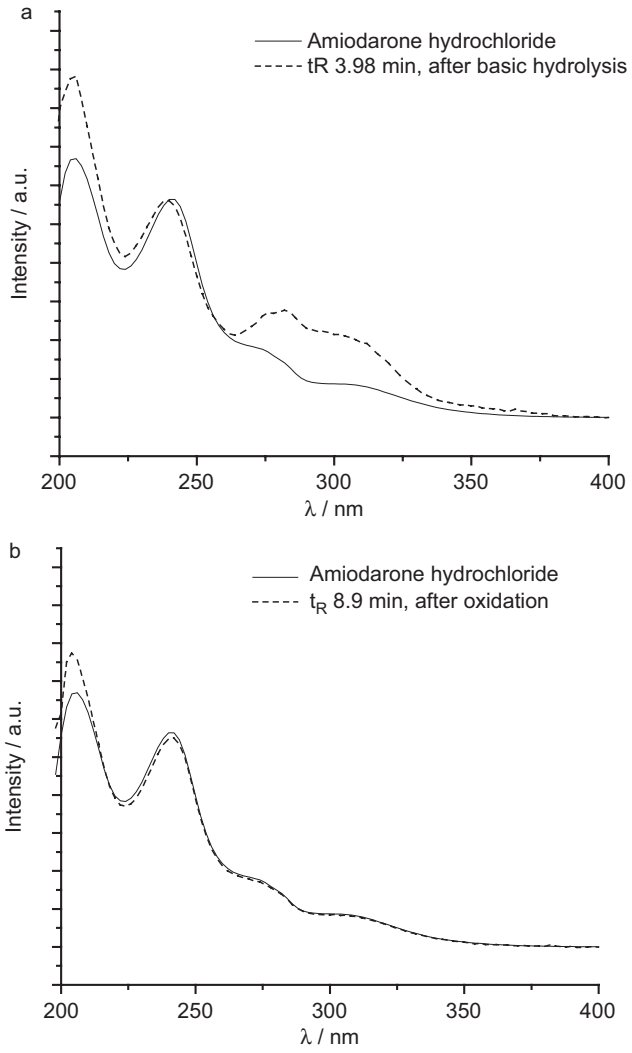

Figure 4. Overlay of UV spectra of amiodarone hydrochloride (t_R 18.4, k′ 22.9) before (—) and after stress conditions (---) obtained for degraded solutions under: (A) basic hydrolysis (t_R 3.9, k′ 4.2) and (B) oxidation (t_R 8.9, k′ 10.6).

HPLC/MS-MS was performed using the same conditions as that used for the HPLC/UV-DAD analysis validation method by adjusting the pH with ammonium hydroxide. AMI, an haloaryl, degraded under basic hydrolysis via nucleophilic substitution with the formation of the degradation product 2-butyl-3-benzofuranyl-3,4-dihydroxy-5-iodophenyl ketone, which was identified by the main peak, m/z (M^* +1) 436.24 in the mass spectrum (Figure 5). Figure 6 shows the degradation mechanism suggested for the drug in two steps. Figure 6A suggested a reaction of nucleophilic aromatic substitution with replacement of ether for the hydroxide group. The reaction is favored by the presence of the ketone group in *para* position; this produces resonance structures that favor the reaction. Figure 6B represents a substitution based on the benzyne mechanism with the exchange of iodine for the hydroxide group. Sodium hydroxide, a strong nucleophile, is present in excess in the reaction, thus favoring the formation of the compound. This degradation product has the same chromophore structure

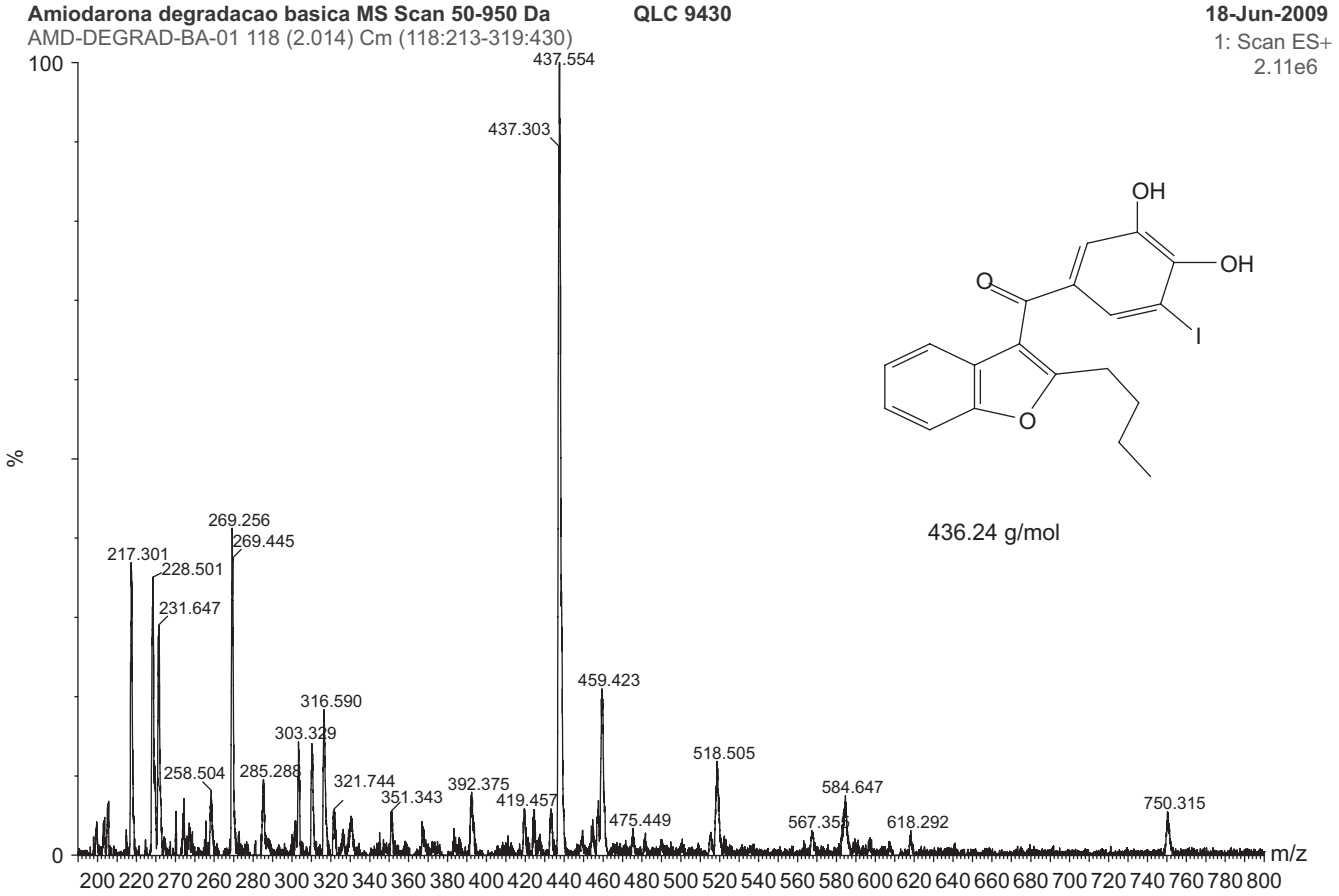

Figure 5. Mass scan obtained after elution by HPLC/MS-MS of product degradation in t_R 3.986 min, after basic hydrolysis.

as AMI; therefore, it presented a similar spectrum in the analysis performed using HPLC/UV-DAD.

The oxidation of the drug occurs by means of the oxidation of the side chains of alkylbenzenes. However, the MS/SCAN graph of the degradation product peak showed several mass peaks. As such, it was impossible to identify the major degradation product. This fact may well be due to the formation of adducts and subsequent molecule oxidation.

The attempt to identify AMI polymorphism began with a search by means of DSC analysis at different temperature rates. Heating rates of 2 and 20 K/min under a nitrogen atmosphere, from room temperature to 453 K, showed no crystalline transition events and no double melting peaks, which rules out the presence of AMI polymorphisms.

Recrystallization was performed under different conditions, such as different solvents, temperatures, and solution saturations. No detection of the formation of different crystalline forms after the evaluation of the crystals by XRD and DSC could be observed.

As for drug recrystallization in acetone, XRD analysis demonstrated that there is no difference in the crystallinity among the crystals before (default) and after recrystallization, given that the peaks contain defined angles (2θ) and intensities (Figure 7A). DSC curves (Figure 7B) showed a slight shift in the T fusion onset of crystals that recrystallized in acetone, a thinning of the melting peak, and a better symmetry, which is characteristic of a drug purification process. Through the van't Hoff equation, using a software to determine the purity via DSC, a peak purity of 96.1% for the AMI standard and a peak purity of 98.2% for crystal found in acetone were obtained. By light microscopy, it could be observed that the crystal habit of the drug is prismatic.

The isothermal degradation kinetics was performed to assess the stability of the drug and pharmaceutical formulation as well as to predict their shelf lives at 298 K. Figure 8 shows the dynamic TG curves of the drug and the pharmaceutical formulation in which the onset of degradation within the same temperature range can be observed.

TG isothermal curves were obtained in heating times ranging from 2 to 4 h and were conducted at the beginning of the degradation process, at 433, 438, 448, 453, and 458 K. The isotherms were fitted according to the second-order model for both the drug and the pharmaceutical formulation. Table 1 shows the values of correlation linear coefficients (r) and rate constants (K) for each evaluated isotherm.

The kinetics data for the drug and pharmaceutical formulation were carried out according to the second-order model, which presented a better fit. The activation energy (E_a), the rate constants, and the shelf life at 298 K were calculated by isothermal degradation kinetics.

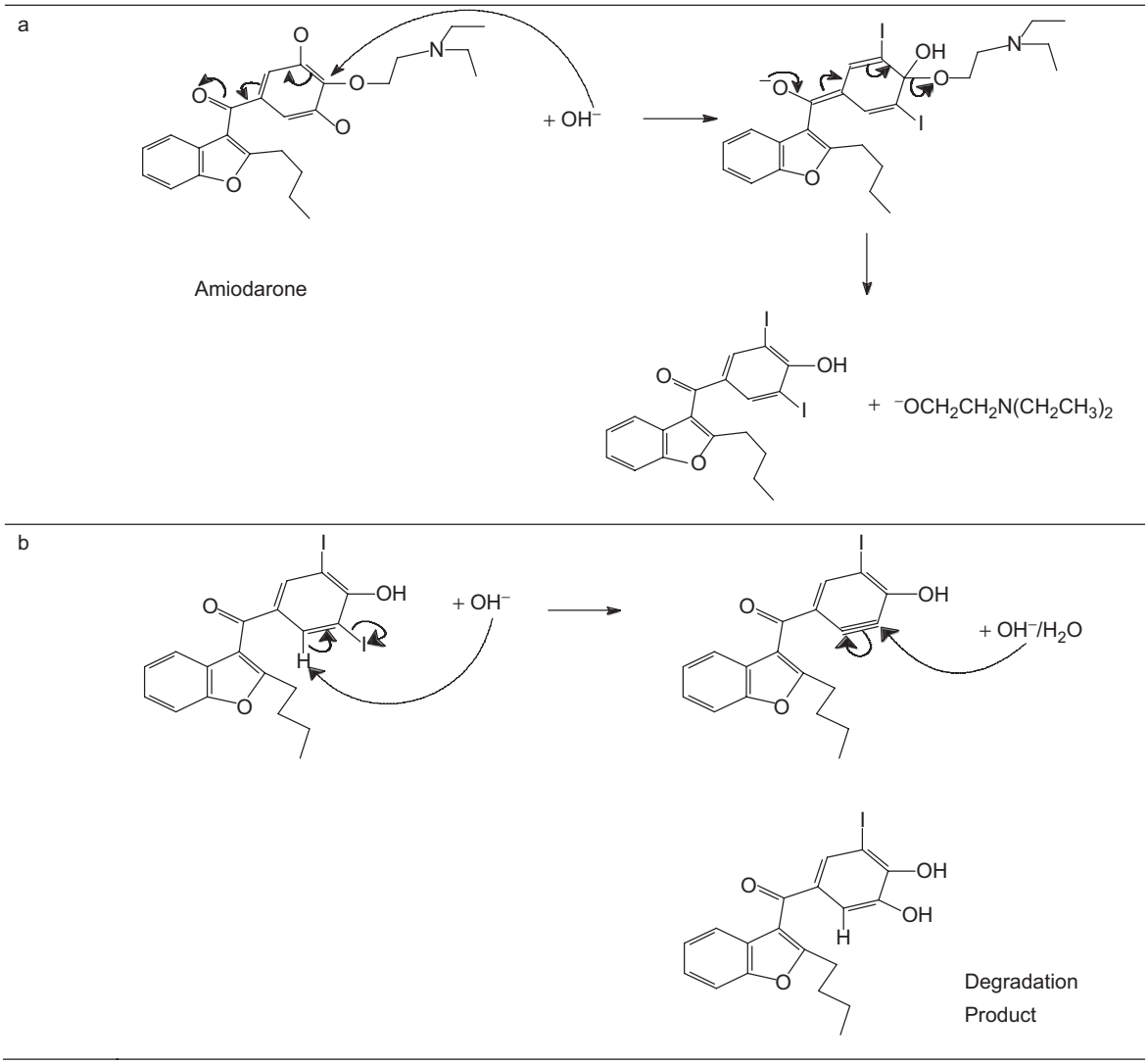

Figure 6. Schematic reaction of amiodarone hydrochloride under basic hydrolysis. (A) Nucleophilic aromatic substitution and (B) benzyne mechanism.

The graph of the Arrhenius equation, $1/T$ versus log K, is shown in Figure 9. The slope of the line is defined by $E_a/(2.303 \times R)$, where the activation energy can be calculated by multiplying the slope value by the gas constant R (8314 J/mol/K) and by 2.303. The linear regression calculated for the kinetic data of the drug led to Equation (1) with the correlation coefficient of 0.9927 (r). The activation energy calculated for AMI was 102.7 KJ/mol.

$$\log K = 5362.7 \times 1/T + 5.91 \quad (1)$$

Where K = rate constant (sec^{-1}), T = temperature (Kelvin).

For the pharmaceutical formulation, the linear regression calculated using kinetic data is shown in Equation (2) with a correlation coefficient of 0.9506 (r). The activation energy calculated for the formulation was 64.3 KJ/mol.

$$\log K = -3357.5 \times 1/T + 0.8887 \quad (2)$$

Where K = rate constant (sec^{-1}), T = temperature (Kelvin).

It was possible to calculate the constant rate of reaction (K) at 298 K by extrapolation (highlighted, Figure 9) for both the drug and the pharmaceutical formulation, as follows:

$$K_{298}\ \text{drug} = 8.2658 \times 10^{-13} \text{sec}^{-1}$$

$$K_{298}\ \text{pharmaceutical formulation} = 4.1872 \times 10^{-11} \text{sec}^{-1}$$

Given the K_{298} value, the shelf life and t_{90} were calculated according to Equation (3) at 298 K, whereas the degradation follows the second-order model. The concentration of AMI in the tablet formulation was considered to be 50% of the C_0 (initial concentration), since the average weight for a tablet containing 200 mg of the drug was ~400 mg. A value of 43.2 years of shelf life was obtained for the drug, and 1.7 years for the pharmaceutical formulation, which was consistent with the incompatibility problems of the pharmaceutical formulation discovered through DSC analysis.

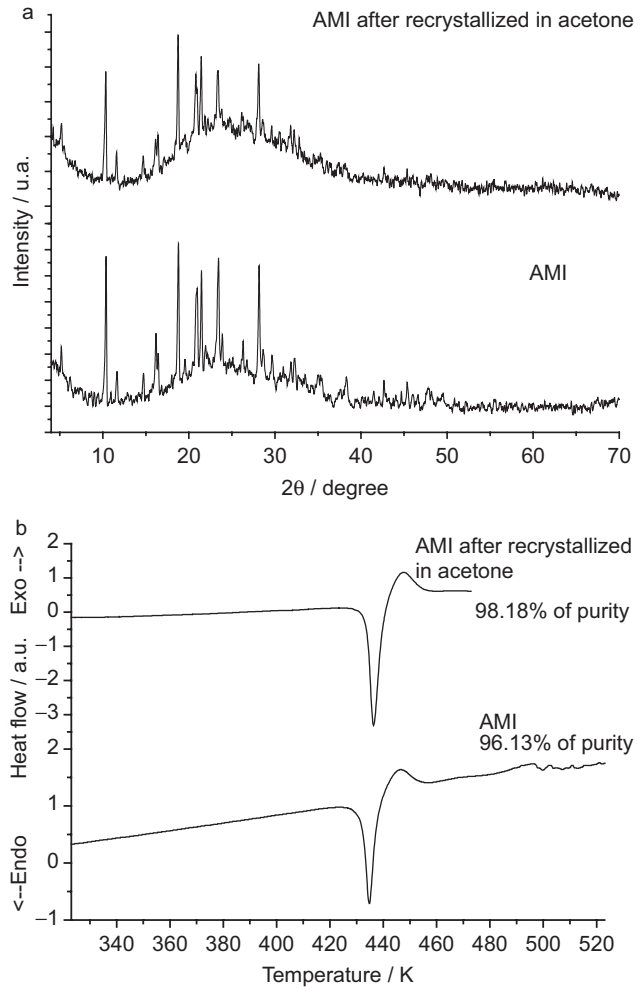

Figure 7. Crystallinity profile of amiodarone hydrochloride before and after recrystallization in acetone. (A) XRD curves and (B) DSC curves.

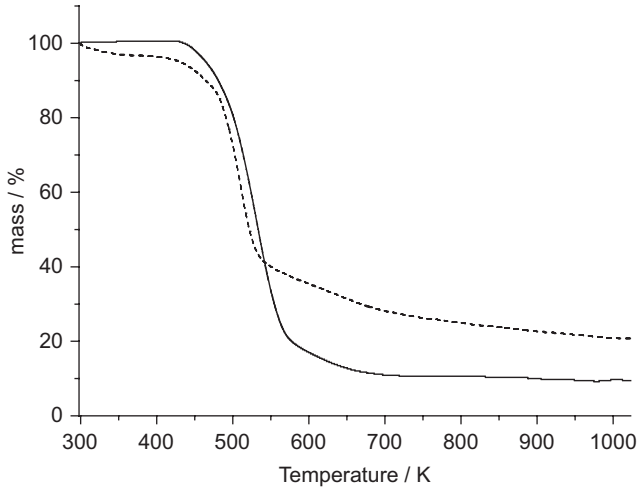

Figure 8. TG curves. Amiodarone hydrochloride (—); and pharmaceutical formulation (---) containing amiodarone hydrochloride.

The E_a (activation energy) was 102.7 KJ/mol and 64.3 KJ/mol for the drug and the pharmaceutical formulation, respectively. The drug is less stable when associated with excipients in the pharmaceutical formulation.

Table 1. Results of the mathematical models adjustment of zero, first, and second order, with values of r (correlation coefficient) and K (reaction rate).

		Order		
Temperature (K)		Zero	First	Second
a				
433	r	0.9807	0.9870	0.9920
	K	0.002783	3.42308×10^{-5}	4.2316×10^{-7}
438	r	0.9778	0.9862	0.9926
	K	0.002783	3.42308×10^{-5}	4.2316×10^{-7}
448	r	0.9849	0.9911	0.9956
	K	0.005935	7.36449×10^{-5}	9.1775×10^{-7}
453	r	0.9870	0.9925	0.9965
	K	0.008263	0.000102679	1.2812E–06
458	r	0.9859	0.9919	0.9962
	K	0.009683	0.000119975	1.4931×10^{-6}
b				
433	r	0.9705	0.9758	0.9806
	K	0.001025304	1.19901×10^{-5}	1.40368×10^{-7}
438	r	0.9594	0.9659	0.9717
	K	0.001225515	1.45957×10^{-5}	1.74065×10^{-7}
448	r	0.9296	0.9400	0.9494
	K	0.001297639	1.60311×10^{-5}	1.98416×10^{-7}
453	r	0.9509	0.9611	0.9700
	K	0.002120921	2.68929×10^{-5}	3.41968×10^{-7}
458	r	0.9455	0.9570	0.9671
	K	0.002231546	2.86651×10^{-5}	3.69366×10^{-7}

(a) Drug and (b) pharmaceutical formulation.

Table 1 shows that the constant rate (K) of degradation reaction is always higher in the pharmaceutical formulation, when compared with the drug, for each isothermal temperature.

$$t_{90} = 1/(9\times K\times C_0) \quad (3)$$

Where K = rate constant (sec^{-1}), C_0 = initial concentration (%).

Conclusions

AMI presented a T onset melting at 432 K. The drug proved to be incompatible with the excipients magnesium stearate, eskis red pigment, and yellow iron oxide. AMI degrades when subjected to basic hydrolysis and oxidation and commonly forms degradation products that contain structures that resemble drug chromophores. The degradation product under basic hydrolysis, 436.24 g/mol, is 2-butyl-3-benzofuranyl-3,4-dihydroxy-5-iodophenyl ketone. After recrystallization in acetone, a drug purification occurs but without the presence of polymorphism. By evaluating the degradation kinetic, it could be concluded that the drug is extremely stable, with a shelf life of 43 years. However, the drug does present incompatibilities with some excipients; thus, its pharmaceutical formulation tends to have a shelf life of only 1.7 years.

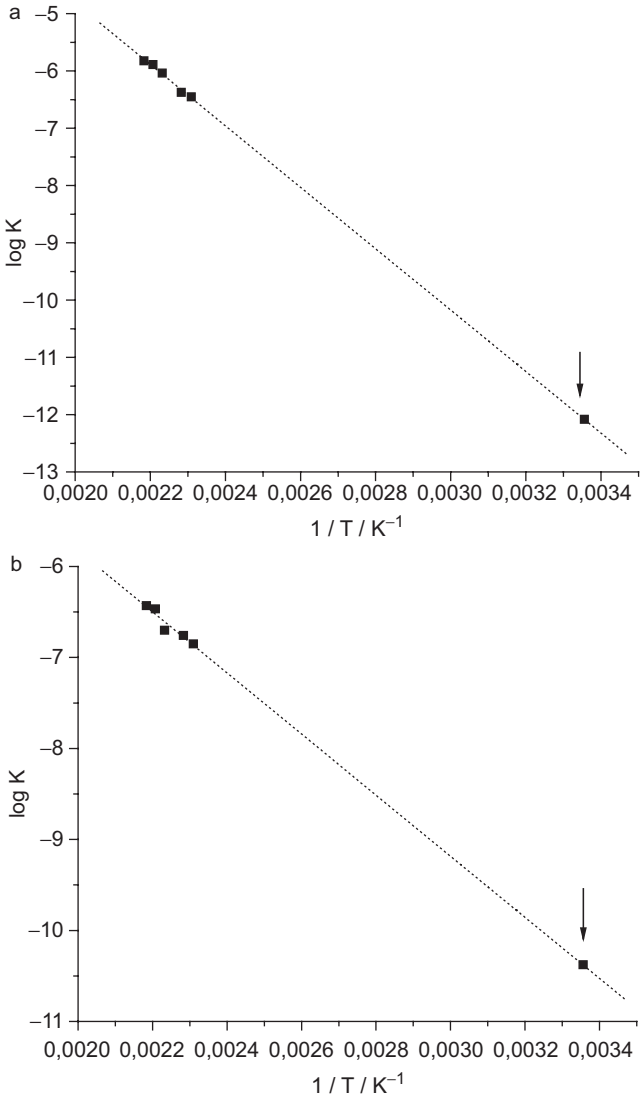

Figure 9. Graphic for Arrhenius equation with values extrapolated to 298 K for (A) amiodarone hydrochloride and for (B) pharmaceutical formulation.

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Declaration of interest

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