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Thermal decomposition of tetracycline and chlortetracycline

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ABSTRACT

The thermal behavior of tetracycline hydrochloride (TC) and chlortetracycline hydrochloride (CTC) antibiotics was evaluated using thermoanalytical techniques TGA-DTA, DSC and evolved gas analysis by TGA-FTIR, providing information regarding thermal stability, decomposition steps and melting. TGA-FTIR revealed hydrochloric acid, water, isocyanic acid, dimethylamine, methane as main decomposition products for both antibiotics. Ammonia and carbon dioxide from the decomposition of the isocyanic acid have also been detected. According to DSC data the melting process occurred just before decomposition at 220.9 °C for TC. Tentative mechanisms for the thermal behavior of TC and CTC are presented.

1. Introduction

The tetracycline antibiotics (TCAs, Fig. 1) were discovered in the 1940's while their therapeutic use for human health began in the 1950's [1]. These antibiotics exhibit activity against infections caused by both *Gram (+)* and *Gram (−)* microorganisms as well as protozoan parasites, among others. [2]. Clinical studies of tetracyclines [3] demonstrated that this group of antibiotics presented an auxiliary treatment of some tumors, inhibit the activity of collagen enzyme and promote bone absorption. They are also one of the primarily antibiotic groups used for veterinary purposes and in animal growth facilities as feed additive, as well as in human therapy [4], due to their relatively low cost and broad range of antimicrobial activity. Among tetracycline antibiotics, chlortetracycline (CTC), oxytetracycline (OTC) and tetracycline (TC) were the most often used throughout the world [5]. TC is one of the most frequently used antibiotics in aquaculture and veterinary medicine [6], whereas CTC and OTC are two of the ten antimicrobials licensed as growth promoters in the United States [7].

An increasing concern issue regards in what extension tetracycline antibiotics residues and wastes can promotes in the development or evolution of antibiotic resistant microorganisms and the consequences to human health [8]. Although extensive studies have been conducted on these antibiotics, the fate and effect of its metabolites is still unknown. So, the development of techniques for the determination and removal of TCAs from environment has been studied [9].

The papers presented in the literature between 2010–2015 describe the TC and/or CTC determination in several kind of samples, by different methods, as electrochemical [10–17], electrochemiluminescence [18], spectroscopy [19], spectrophotometric [20–22], chemiluminometric [23–27], chromatographic [28–40] and chromatographic/tanden mass spectrometric [41–47]. Some works present the TC extraction from milk [48–52], soil [53,54], fermented broth [55] and honey [50].

However, few works described the thermal analysis of these antibiotics. These include the thermostability of oxytetracycline, tetracycline and doxytetracycline at high and ultrahigh temperatures (110–140 °C), showing a first order reaction kinetic [56]. Gratacos-Cubassi et al. [57] observed that the formation of TC degradation in chicken and pig meat under different thermal processing conditions followed a first order kinetic.

A differential scanning calorimetry study of TC repressor was made to observe the thermal denaturation of TC repressor in the absence and presence of TC. The results showed that in the absence of TC, the thermally induced transitions of TC repressor can be described as an irreversible process, indicating that the protein denaturation is under kinetic control, while in the presence of TC repressor undergoes co-operative unfolding, characterized by enthalpy and entropy changes [58].

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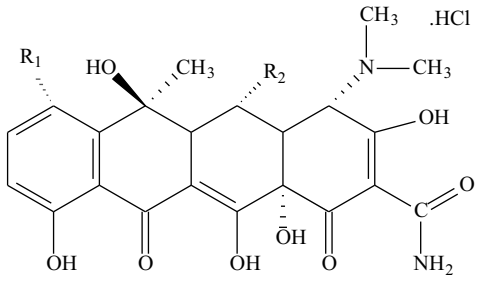


Fig. 1. Structural formulae of tetracycline (R1 = R2 = H) and chlortetracycline (R1 = Cl, R2 = H).

The sorption and intercalation of tetracycline from water onto rectorite, a regular interstratified clay mineral was investigated by Changa et al. [59]. Thermogravimetry showed a decomposition temperature of 230 °C for crystalline TC, which increased to 410–420 °C after intercalation in rectorite. The thermal behavior of TC hydrochloride was evaluated, using TGA and DSC [60]. TGA curves showed mass losses in three consecutive steps between 200 and 650 °C. In the DSC curve of TC the sharp exothermic peak at 235 °C was attributed to the oxidation of the evolved products corresponding to the first mass loss observed in the TG curves. The exotherm between 250 and 600 °C was ascribed to the thermal decomposition and pyrolysis of the carbonaceous product corresponding to the second and third mass losses of the TG curve.

However, no reports concerning the analysis of the volatile products formed during the decomposition of these drugs were found, being pyrolysis an option for environment remediation or destruction of drug out of use.

Thus, this paper aims to investigate the gases evolved during heating of tetracycline and chlortetracycline by TG-FTIR, proposing a tentative mechanism of its thermal behavior and decomposition.

2. Material and methods

Tetracycline and chlortetracycline hydrochlorides pharmaceutical grade (min. 99.0%, Sigma–Aldrich) was used without further purification, and stored in a refrigerator before analysis.

Simultaneous TGA/DTG and DTA analysis were carried out in α-alumina sample holders (90 μL) in simultaneous SDT-Q600 modulus controlled by the Thermal Advantage Q-Series software (v.5.4.0, both from TA Instruments). Experimental parameters for TGA curves were: sample mass of *c.a.* 10.0 mg (± 0.1 μg), heating rate of 10 °C min^{-1} under dynamic air atmosphere flowing at 100 mL min^{-1} from room to 1000 °C temperature. The apparatus was calibrated for mass and temperature with a zinc standard as recommended by the manufacturer.

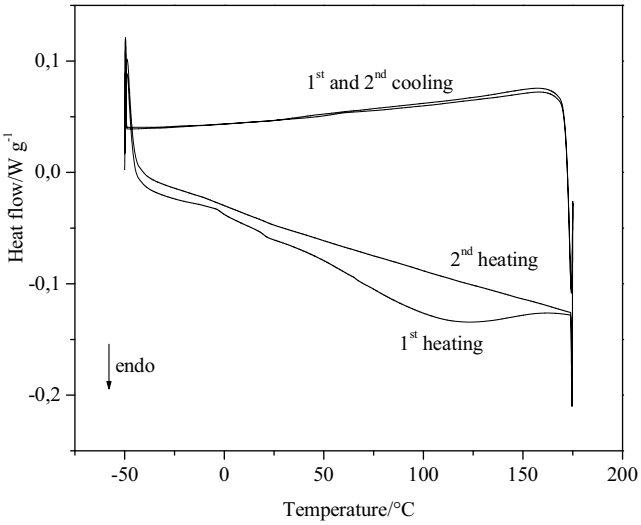
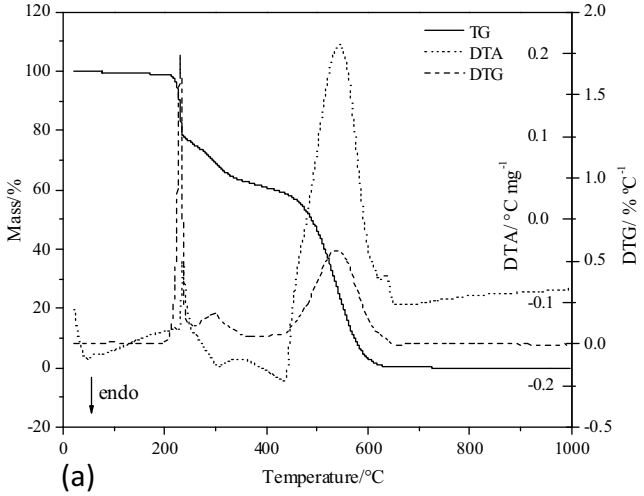


Fig. 3. Heat-cool-heat DSC curves of the tetracycline (*m* = 6.000 mg).

DSC curves were obtained using sample mass of *c.a.* 6.0 mg (± 0.1 mg), heating rate of 10 °C min^{-1} for TC and *c.a.* 11.0 mg (± 0.1 mg), heating rate of 20 °C min^{-1} for CTC, under N_2 dynamic atmosphere flowing at 50 mL min^{-1}, in a temperature interval of −50 to 175 °C and −50 to 220 °C for TC and CTC, respectively, in covered aluminum pans with a pinhole (φ = 0.7 mm) in the center of the lid. Curves were obtained in the heat-cool-heat successive cycles mode. Posterior measurement was made up to 230 °C for tetracycline, in order to better observe the melting phenomena. A TA DSC-Q10 unit controlled by the Thermal Advantage for Q-Series software (v.5.4.0, both from TA instruments) was used. Calibration of the equipment for temperature and enthalpy measurements were performed using the indium metal (99.99% purity) as a standard, according to the manufacturer's manual.

The analyses of the evolved gaseous products was carried out by connecting the exhaust of the TGA–DTA equipment to a Nicolet iS10 spectrophotometer (Thermo Scientific), with 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:



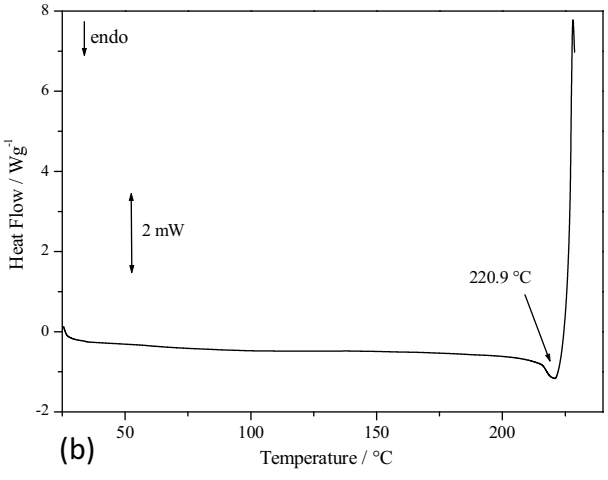


Fig. 2. TGA/DTG-DTA curves of the tetracycline (*m* = 10.713 mg) in air atmosphere. (b) DSC up to the decomposition start presenting an endothermic peak related to melting.