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Degradation of Antihypertensive Hydrochlorothiazide in Water from Pharmaceutical Formulations by Electro-Oxidation Using a BDD Anode

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The electrochemical oxidation (EO) of hydrochlorothiazide (HCTZ) in water has been carried out at applying constant current in an electrochemical cell containing a boron-doped diamond (BDD) anode and a stainless steel cathode. The effect of initial pH of the solution and the applied current density were evaluated in the HCTZ concentration decay and total organic carbon abatement during the electrolysis. A qualitative analysis of the degradation by-products was made by chromatography and photometric assays. Finally, EO was applied for the HCTZ degradation from commercial formulations. Thus, HCTZ can be degraded by EO at neutral pH, applying low current densities due to the attack of $^{\bullet}$OH electro-generated on the BDD surface. Aromatic intermediates, aliphatic carboxylic acids, and inorganic anions were detected as main products during the mineralization of HCTZ to CO_2. Solutions prepared from commercial formulations of HCTZ were completely mineralized by EO, which can be an interesting step towards the applicability of the EO processes for the treatment of wastewater containing these kinds of drugs as raw materials or pharmaceutical formulations.

Keywords: hydrochlorothiazide, electro-oxidation; boron-doped diamond electrode; hydroxyl radical; mineralization.

1. INTRODUCTION

Since they have existed, pharmaceutical products have been introduced into the environment in various ways, from production centers, after excretion of drugs administered to humans and animals, through direct removal of excess household medicines, and treatment of fish and other animals [1]. That is why it is likely for most urban wastewater to contain pharmaceutical wastes, and for them to reach natural water courses, water, or soil. The presence of these contaminants in water has existed for decades, but the difference is that their levels in the environment have been studied and quantified recently as a potential danger [2]. An example of this is pharmaceuticals that have been detected in effluent treatment plants and sewage, and they have been reported in numerous publications referring to countries like Germany, Greece, Italy, France and Canada, among others [3]. Besides, the presence of trace pharmaceuticals in drinking water has been reported in 24 major US cities according to a study by the Associated Press [4].

Pharmaceuticals have received much attention during the last fifteen years due to their potential presence in the environment in the form of by-products (metabolites), considered as emerging contaminants because they still remain unregulated or are in the process of being regulated [5,6]. In addition to this, it is important to mention that their effects on the environment are not sufficiently known [7].

In terms of the production of medicines, according to data from the Agencia Nacional de Medicinas del Instituto de Salud Pública (ISP) of Chile, to date there are 29 laboratories producing drugs, five laboratories distributing pharmaceuticals, and 219 companies or individuals registered as importers of medicines in Chile [8]. The generation of liquid waste by the pharmaceutical industry occurs primarily in the production of syrups, creams and ointments and the reactors in which medicines are prepared. Another source of generation of liquid waste is the discharge of liquids expired drugs to the sewer system [9,10].

Among the drugs whose production has increased in Chile we find antihypertensives, because hypertension is the leading chronic disease found in the Chilean population [11]. Among the range of antihypertensive drugs, hydrochlorothiazide (HCTZ) is one of the most widely used in Chile according to the National Health Survey 2009-2010 on antihypertensive agents [12]. Hydrochlorothiazide belongs to the family of thiazides, which act as diuretics in the treatment of hypertension; increasing renal excretion of water and electrolytes [13,14]. The high consumption of antihypertensive drugs at the national and international levels, together with their increased production, leads to the generation of wastewater containing pharmaceutical wastes from (i) the production of the drug, (ii) excretion by humans, (iii) drugs and/or discarded materials, etc. It is therefore important to have effective methods for treating wastewater containing pharmaceuticals, such as those of the antihypertensive type like HCTZ.

Since the late 20th century, electrochemical technologies have been developed to efficiently decontaminate wastewater containing organic pollutants. These technologies are based on classical industrial oxidation methods, and among them there is electrochemical oxidation (EO), the electro-Fenton process (EF), electrocatalysis (EC), and photoassisted systems like photoelectron-Fenton (PEF) and photoelectron-catalysis (PEC). All of them are so-called electrochemical advanced oxidation processes (EAOPs) [15-19].

EAOPs are based on the in situ generation of $^{\bullet}OH$, which reacts with most organics producing dehydrogenated or hydroxylated derivatives up to conversion into CO_2, H_2O and inorganic ions due to its high standard redox potential ($E°(^{\bullet}OH/H_2O) = 2.80$ V/SHE). The most popular EAOP is anodic oxidation or (EO) [20-23], where organics are oxidized to CO_2 at high current by physisorbed $M(^{\bullet}OH)$ formed during the anodic water discharge:

$$M + H_2O \rightarrow M(^{\bullet}OH) + H^+ + e^- \quad \textbf{(1)}$$

The electrochemical generation and the chemical reactivity of heterogeneous $M(^{\bullet}OH)$ depend strongly of the electrode material. According to Comninellis [24], the use of a non active anode in electro-oxidation process allow the direct reaction of organics with $M(^{\bullet}OH)$ to give fully oxidized reaction products such as CO_2 according to Equation 2. A non active anode interacts very weakly with $^{\bullet}OH$.

$$aM(^{\bullet}OH) + R \rightarrow aM + mCO_2 + nH_2O + xH^+ + ye^- \quad \textbf{(2)}$$

where R is an organic compound with m carbon atoms and without any heteroatom, which needs (2m + n) oxygen atoms to be totally mineralized to CO_2.

Different authors have proposed the use of a boron-doped diamond (BDD) thin film to treat wastewater containing different organic pollutants by EO [25-28] provides a total mineralization with high current efficiency in synthetic and real wastewater. Depending on the applied potential, the oxidation of organics on BDD electrodes can follow two mechanisms: direct electron transfer in the potential region before oxygen evolution (water stability) producing a partial , and indirect oxidation via electrogenerated hydroxyl radicals, in the potential region of oxygen evolution (water decomposition) [29]. Moreover, highly boron-doped diamond exhibits several technologically important properties that distinguish it from conventional electrodes, such as: (i) an extremely wide potential window in aqueous and non-aqueous electrolytes (from −1.25 V to +3.0 V versus SHE), (ii) corrosion stability even in very aggressive or strongly acidic media, (iii) an inert surface with low adsorption properties, and (iv) very low double-layer capacitance and background current [30,31].

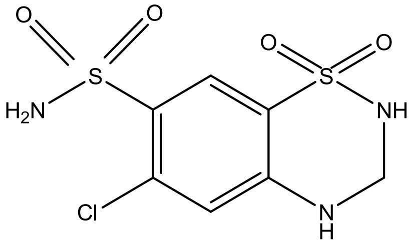
In order to increase the knowledge about the possible application of electro-oxidation for the treatment of wastewater containing different pharmaceutical pollutants, the aim of this work was to study the elimination of the antihypertensive drug HCTZ in water by EO at constant current using a BDD/stainless steel electrochemical system. The analytical determination of the organic by-products or intermediates formed during the abatement process was carried out. The best operating conditions founded were used for the application of EO to the mineralization of HCTZ from commercial formulation.

2. EXPERIMENTAL

2.1. Chemicals

Hydrochlorothiazide (HCTZ, Table 1, 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, 99.9%) were supplied by Laboratorio Chile and was used as received. Analytical grade carboxylic acids: fumaric, maleic, oxalic and oxamic were from Sigma-Aldrich. Solutions of anhydrous sodium sulfate (Merck analytical grade) prepared with previously deionized distilled water and with its pH adjusted with 1.0 M sulfuric acid or sodium hydroxide analytical grade (both from Merck) were used as supporting electrolyte. Organic solvents and other chemicals used in the analysis procedure were either HPLC or analytical grade from Merck or Sigma-Aldrich.

Table 1. Chemical structure and characteristics of HCTZ compound.

Commercial name	Hydrochlorothiazide
Chemical name	6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide
Chemical structure	
Molecular formula	$C_7H_8ClN_3O_4S_2$
Molecular weight	297.73 g/mol
CAS Number	58-93-5

2.2. Electrochemical system

A volume of 0.1 L of HCTZ solution was introduced into a single compartment electrolytic cell with constant stirring at 35 ºC. A BDD thin film (on Si) electrode from Adamant Technologies was used as anode and an AISI 304 stainless steel (SS) plate as cathode, both of 5 cm^2 geometric area, with 1.0 cm of interelectrode gap. Solutions containing 353 mg L^{-1} of HCTZ (corresponding to 100 mg L^{-1} of total organic carbon, TOC) were prepared in 0.05 M Na_2SO_4 at initial pH 3.0, 7.0 and 10.0 and then were treated by EO. The effect of the applied current density (j) was tested at 10, 30, 50 and 80 mA cm^{-2}, resulting in average cell voltages of 5.3, 7.1, 10.6 and 14.0 V, respectively, for the HCTZ solutions. The electro-oxidation of commercial pharmaceutical tablets was examined for 100 mg L^{-1} of HCTZ tablets from two pharmaceuticals: Labomed and Laboratorio Chile. All these solutions were prepared in 0.05 M Na_2SO_4 to provide enough ionic strength.

2.3. Apparatus and analytical procedures

Constant current electrolyses were performed with an EHQ Power model PS3010 power supply, which also displayed the cell voltage. The pH was measured with a HANNA HI 8424 pH-meter. During the electrolysis, samples were withdrawn at regular time intervals from the solution kept in the cell and then refrigerated until performing the analytical procedures. The degree of mineralization was monitored from total organic carbon (TOC) determined with a Vario TOC Select (Elementar) analyzer. Reproducible TOC values with an accuracy of ±1% were always found injecting 500 μL aliquots in the analyzer. From these data, the mineralization current efficiency (MCE) for each treated solution was then calculated from Eq. (3):

$$\%\text{MCE}= \left(\frac{nFV_s(\Delta TOC)_{exp}}{4.32\ x10^7\ m\ I\ t}\right) \text{x } 100 \qquad \textbf{(3)}$$

where n is the number of electrons consumed in the mineralization of HCTZ, F is Faraday's constant (96487 C mol^{-1}), V_s is the solution's volume (L), $\triangle(TOC)_{exp}$ is the experimental TOC decay (mg L^{-1}) evaluated as the difference between the initial value and that analyzed at time t, 4.32×10^7 is a conversion factor (3600 s h^{-1} × 12000 C mol^{-1}), I is the applied current (A), t is the electrolysis time (h), and m corresponds to the number of carbon atoms present in the HCTZ molecule (7 C atoms). The n-values were taken according the mineralization reaction as 46 (reaction 4), considering complete mineralization to CO_2, and inorganic ions determined in this work as NH_4^+, SO_4^{2-}, Cl^- and NO_3^- from the following reactions:

$$C_7H_8ClN_3O_4S_2 + 24\ H_2O \rightarrow 7\ CO_2 + 52\ H^+ + 2\ SO_4^{2-} + NH_4^+ + 2\ NO_3^- + Cl^- + 46\ e^- \qquad (4)$$

We also monitored the COD decay as a function of time with a multiparameter HANNA photometer COD-HI 839800. The samples were previously digested with reactive HI 93754A- 25LR.

The decay of HCTZ with electrolysis time was followed by reversed-phase HPLC using a Hitachi LaChrome Elite chromatograph fitted with a Kromasil C-18 (4.6 mm (i.d) x 250 mm) chromatographic column at room temperature, and coupled with a Hitachi L-2455 Elite LaChrome photodiode array detector set at λ = 272 nm. The analyses were carried out isocratically using 70:30 (v/v) phosphate buffer 0.1 M at pH 6.8/acetonitrile as mobile phase, at a flow rate of 1.0 mL min^{-1}. The aliphatic carboxylic acids obtained as intermediary products were identified and quantified by ion-exclusion chromatography using the same equipment mentioned before, but fitted with a Bio-Rad Aminex HPX 87H, 30 cm x 7.8 mm (i.d.), column at 35 ºC, at λ = 210 nm. The mobile phase was 4.0 mM H_2SO_4 at 0.6 mL min^{-1}. The corresponding calibration curves were constructed using samples of pure acid. Absorption peaks with retention times (t_R) of 3.1 min for HCTZ, 9.1 min for oxalic, 9.9 min for malic, and 13.1 min for oxamic acids were obtained in the corresponding chromatograms.

NO_3^- ions were quantified by ionic chromatography by injecting 50 µL aliquots in a Waters 600 chromatograph equipped with a 600 controller pump and a Waters 431 conductivity detector. An IC-Pak AHR, 75 mm × 4.6 mm (i.d.), anion column at 35 ºC and a mobile phase of borate/gluconate at 1.0 mL min^{-1} was used. The quantification of NH_4^+ and Cl^- was performed by colorimetric analysis using a multiparameter HANNA photometer COD-HI 839800 with reactive HI93715-01 and HI93711-01 for NH_4^+ and Cl^-, respectively.

Aromatic intermediates were detected by HPLC-MS. Solutions under different experimental conditions were electrolyzed at short and long electrolysis times. They were collected and then mixed until 500 mL were obtained, which were extracted three times with 50 mL of CH_2Cl_2 each time with the purpose to identify as many reaction intermediates as possible. Finally, a volume of 150 mL of organic phase was obtained). The collected organic solution was dried with anhydrous Na_2SO_4, filtered and completely evaporated in a rotary evaporator, yielding a pale yellow solid. Liquid chromatography-electrospray ionization mass spectrometry (LC-ESI–MS) was performed using an LTQ XL linear ion trap (Thermo Scientific) interfaced with a Thermo Scientific UHPLC system equipped with a quaternary pump (UltiMate 3000 High-Speed LC System). Sample separation was conducted on a Thermo Scientific MS C18 Hypersil Gold column (50 mm×2.1 mm) with 1.9 μm particle size. Chromatographic analyses were carried out using isocratic elution with 5 mM ammonium acetate (A) and Acetonitrile (B), A:B = 60:40. The flow rate was 0.1 mL min^{-1} and the column temperature was kept at 30 ºC. Volumes of 20 μL of extracted samples were injected. The ESI source was set in negative and positive ion detection modes with the following ionization parameters: spray voltage 3 kV; spray current 1 μA; capillary temperature 350 °C, and tube lens voltage 30.00 V. Full scan MS data were collected for a mass range of 100–1000 amu. The identified products or intermediates were compared with standards.

Energy consumption per volume of electrolyzed solution was obtained from:

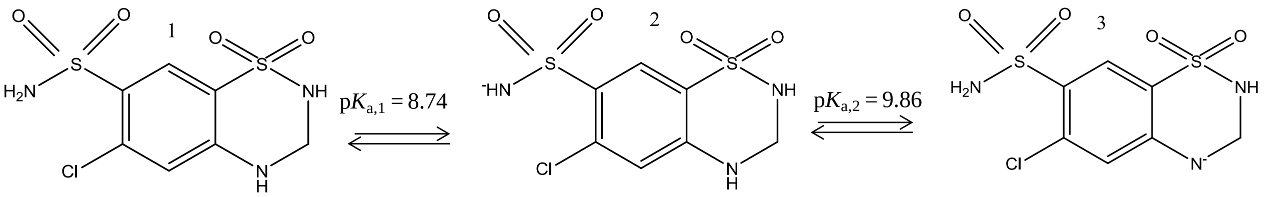
$$\text{Energy Consumption (kW h m}^{-3}\text{)} = \frac{IE_{cell}t}{1000\,V_s} \qquad \textbf{(5)}$$

where I is the applied current (A), E_{cell} is the average cell voltage (V), t is the electrolysis time (h), and V_{s} is the volume of the treated solution (m^3) [32].

3. RESULTS AND DISCUSSION

3.1. Effect of the experimental parameters on the mineralization of HCTZ

The effect of the experimental parameters in the decay of absorbance maximum and mineralization, during the EO treatment of HCTZ were evaluated, to find the best operational conditions and then apply them to the degradation of HCTZ from commercial tablets. In a first stage, the influence of the initial pH of the solution was evaluated, as this significantly influences the generation of hydroxyl radicals on the electrode surface. Thus, HCTZ solutions with 353 mg L^{-1} (= 100 mg L^{-1} TOC) were electrolyzed at initial pH of 3.0, 7.0 and 10.0, with a current density of 50 mA cm^{-2}. Fig. 1(A) shows the spectra of HCTZ at pH 3.0 during the electrolysis. At the three pH values (3.0, 7.0 and 10), HCTZ shows the same spectrophotometric profile, with two maximum wavelengths at 272 and 317 nm. The presence of an acidic sulfonamide moiety ($\text{-SO}_2\text{NH}_2$) in the chemical structure of HCTZ allows HCTZ to be present in its neutral and deprotonated form in aqueous media (Scheme 1) [24].



Sheme 1. Acid-base equilibrium of HCTZ.

As shown in the acid-base equilibrium in Scheme 1, in the experiments performed at pH 3.0 and 7.0 the neutral species (1) is predominant in solution ($\text{pK}_{a,1}$ = 8.74), while at pH 10.0 the active species is the deprotonated one (3), considering the value of $pK_{a,2} = 9.86$, but as described above, there are no substantial differences in the UV-Vis spectrum before electrolysis.

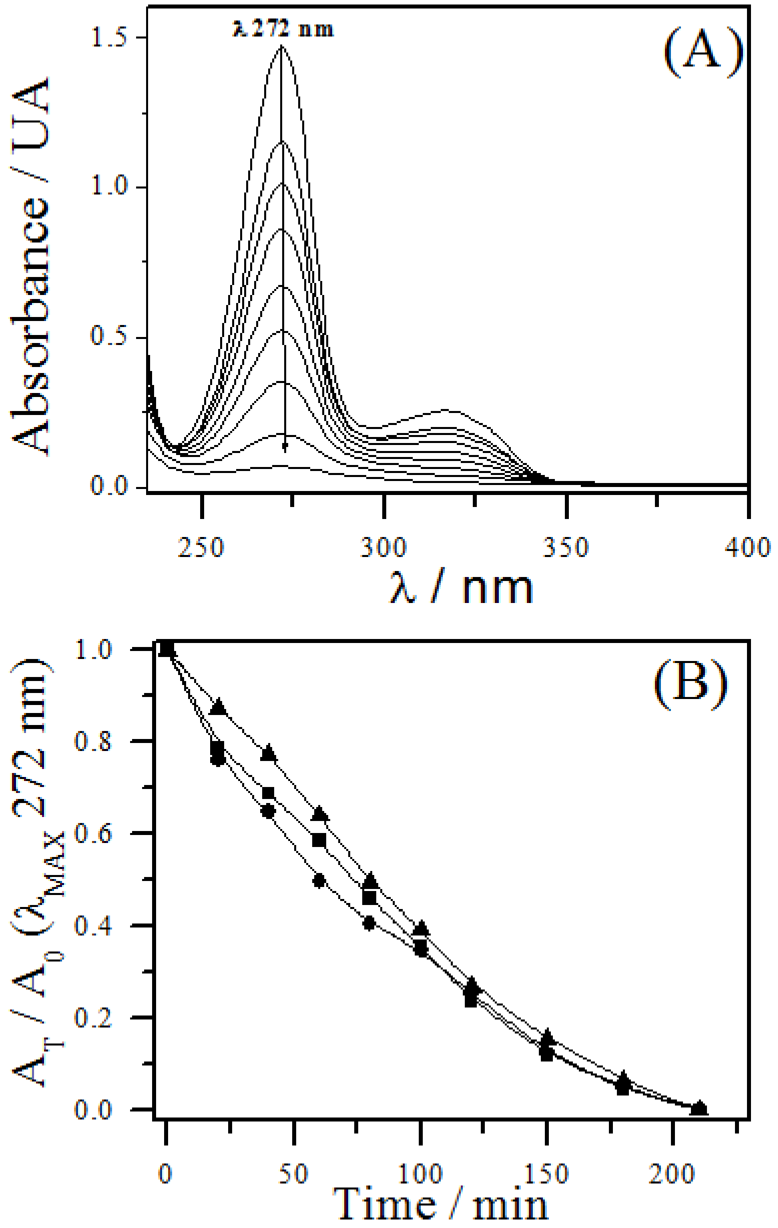


Figure 1. (A) Spectral decay during the electro-oxidation of 0.1 L of 353 mg L^{-1} of HCTZ at pH 3.0 in 0.05 M Na_2SO_4 at 35 ºC using the BDD/stainless steel system. (B) Time course of the normalized absorbance at 278 nm for the EO of 0.1 L of HCTZ at pH 3.0 (●), 7.0 (■) and 10.0 (▲). Applied current density: 50 mA cm^{-2}.

A marked decay of the bands was observed during the course of electrolysis applying 50 mA cm^{-2}. In all these trials the pH of the solution remained almost unchanged, with variations of ± 0.17 pH units. Considering λ_{MAX} of HCTZ at 272 nm, the ratio between the absorbance during the electrolysis time (A_T) and the absorbance before starting the electrolysis (A_0) was obtained for each initial pH, and the results are shown in Fig. 1(B). As can be seen, the absorbance at 272 nm decreases as the electrolysis proceeds, to disappear completely after 200 min, regardless of the initial pH of the solution. These changes in the UV-Vis spectrum of HCTZ during the course of the electrolysis is due to the attack of the hydroxyl radicals formed on the anode surface BDD($^{\bullet}$OH). Moreover, no new bands were observed during the electrolysis, supporting the complete degradation of HCTZ in the solution and the formation of intermediates or oxidation products in very low concentrations.

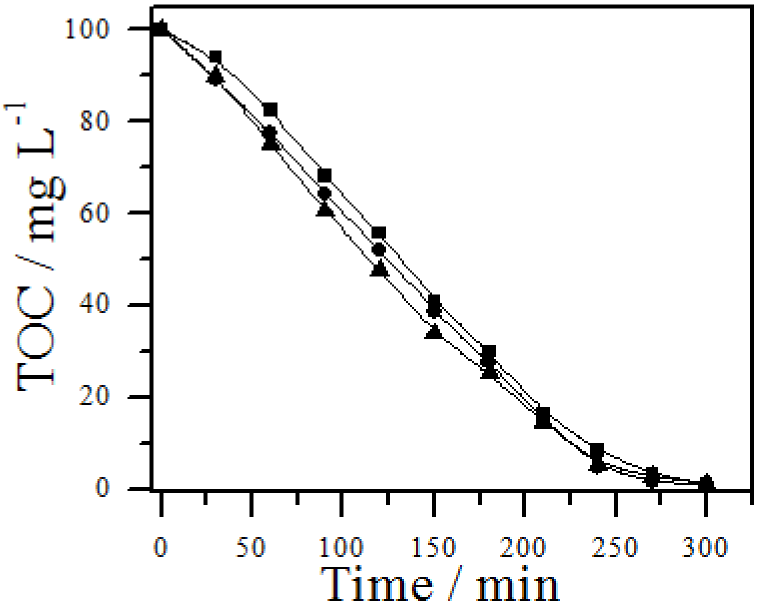


Figure 2. TOC abatement for the EO of 0.1 L of 353 mg L^{-1} HCTZ solutions in 0.05 M Na_2SO_4 at 35 °C using the BDD/stainless steel system at pH 3.0 (●), 7.0 (■) and 10.0 (▲). Applied current density: 50 mA cm^{-2}.

A similar profile to that obtained by spectrophotometric experiments was seen for the mineralization of HCTZ (Fig. 2). A continuous and quick TOC abatement was observed for HCTZ at the three initial pH values (3.0, 7.0 and 10), reaching >90% mineralization after 240 min of electrolysis (q = 10 A h L^{-1}), confirming that as in the Absorbance decay, the pH does not play any role in the process. These results indicate that HCTZ and its organic by-products are destroyed by electro-oxidation at a similar rate at the three pH values using a BDD electrode. This could be because a similar production of $^{\bullet}$OH by reaction (1) is taking place in our electrolytic system. In the literature, the results are diverse and even contradictory with respect to the best pH conditions of different organic pollutants by EO. Some authors have reported that the oxidation process of pharmaceuticals on BDD (or other) anode surface is more favorable in acidic media, others in alkaline media [34-37]. However, the effect of pH strongly depends on the electrode surface, the nature of the organic species (and its intermediates) to be degraded, and the supporting electrolyte. Therefore, the possibility of degrading HCTZ in a pH range of 3 - 10, is an important finding considering the potential industrial applications of this technology, as this may avoid a stage of self-adjusting the pH in during an industrial wastewater process, decreasing the total cost of treatment. Therefore, subsequent experiments were performed at pH 7.0.

As mentioned above, electrogenerated hydroxyl radicals are responsible for oxidation of organics. The production rate of physisorbed •OH on the BDD surface is regulated by the current density applied. The influence of this parameter in the TOC abatement is shown in Fig. 3(A), for 353 mg L-1 of HCTZ, corresponding to 100 mg L^{-1} of TOC at pH 7.0. A gradual TOC decay was obtained at 10 and 30 mA cm^{-2}, achieving a complete mineralization after 300 minutes of electrolysis. The oxidation process is faster at higher applied current density, with a TOC reduction of >90% after 240 min of electrolysis applying 50 mA cm^{-2} (q = 10 Ah L^{-1}), and >90% mineralization is achieved after 150 – 180 min applying 80 mA cm^{-2} after higher q consumptions of 10 - 12 A h L^{-1}.

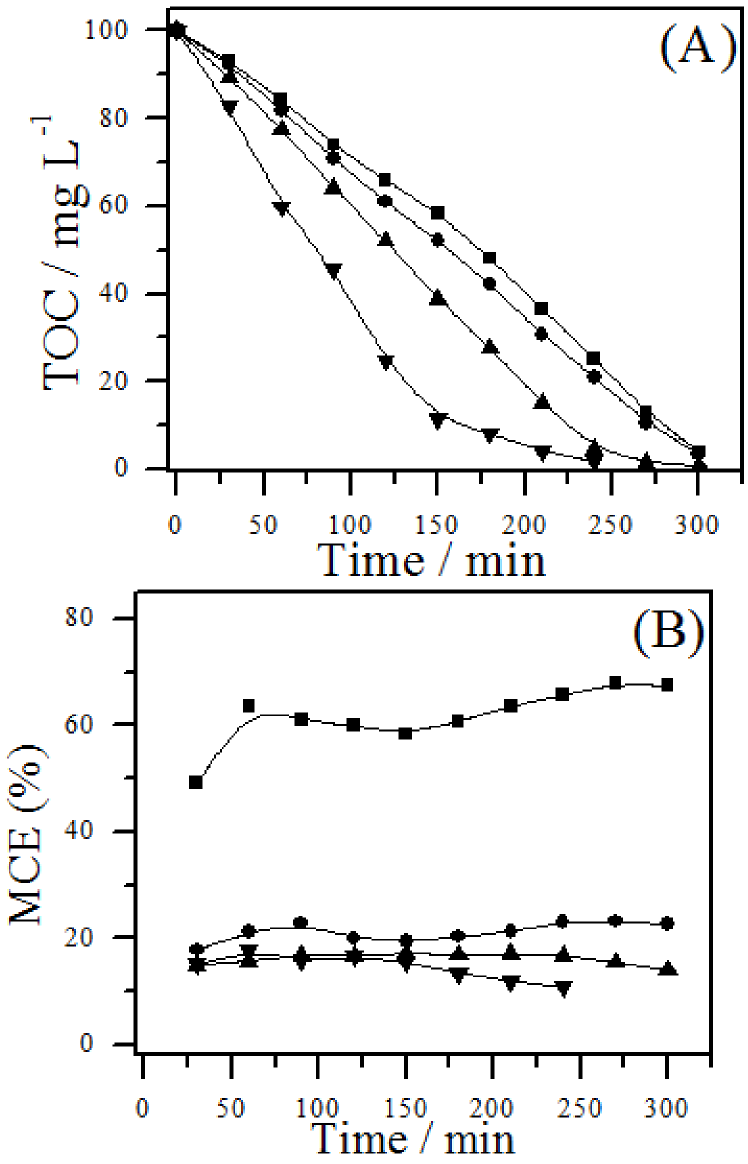


Figure 3. (A) TOC abatement and (B) Mineralization current efficiency (%) with respect to electrolysis time for the EO of 353 mg L^{-1} HCTZ solutions in 0.05 M Na_2SO_4 at 35 ºC using the BDD/stainless steel system at pH 7.0. Applied current density: 10 (■), 30 (●), 50 (▲) and 80 (▼) mA cm^{-2}.

It is seen that increasing the applied current density decreases mineralization times, making faster the transformation of the HCTZ to CO_2. However, this current increase caused a progressive consumption of electric charge, decreasing the efficiency of the process. Thus, by applying a lower current density (10 mA cm^{-2}), complete mineralization of the drug is obtained with longer electrolysis time (300 min), but with lower consumption of electric charge (2.5 A h L^{-1}), making the process energetically more efficient, and this is supported by the percent MCE values. As can be seen in Fig. 3(B), the highest MCE values are achieved applying 10 mA cm^{-2} (MCE > 60%), while the other current densities applied have a mineralization efficiency of ~20%. According to literature, a series of parasite reactions can be occurring in the Na_2SO_4 medium at higher current densities, increasing the electric charge consumption, *q*, with loss of %MCE of the organic pollutant [38]. The oxygen evolution reaction (OER), the oxidation of BDD ($^{\bullet}OH$) to O_2, the generation of ozone, the formation of peroxodisulfate ion [39], and the generation of H_2O_2 could cause a decrease in the MCE at higher current densities, yielding a relatively smaller number of organic oxidation events.

The effect of applied density current was studied following the decay of HCTZ (Fig. 4(A)) determined by HPLC experiments, as well as the EO experiment described above. The reversed-phase chromatograms of the electrolyzed solutions displayed a well-defined peak with a retention time (t_r) of 3.02 min for HCTZ. A faster removal using current densities of 50 and 80 mA cm^{-2} was observed, with total disappearance of the drug in ca. 180 – 200 min. During the same electrolysis time (180 – 200 min), 0.20 – 0.35 mM HCTZ still remain in the solution when applying low j of 10 and 30 mA cm^{-2}. Finally, complete decay of HCTZ is obtained after 300 min. The reaction of HCTZ with $^{\bullet}OH$ radical can be written as

$$\text{HCTZ} + {}^{\bullet}\text{OH} \rightarrow \text{Intermediates / Oxidation Products} \rightarrow \rightarrow \rightarrow CO_2 \quad \textbf{(6)}$$

The corresponding kinetic equation is

$$-\frac{dc_{HCTZ}}{dt} = k\, c_{^{\bullet}OH}\, c_{HCTZ} \quad \textbf{(7)}$$

where $c_{^{\bullet}OH}$ and c_{HCTZ} are the $^{\bullet}OH$ and HCTZ concentrations, and *k* is the intrinsic second order rate constant. By applying a constant current during the electrolysis, we can consider that $^{\bullet}OH$ concentration is constant because a quick and continuous production of hydroxyl radical by means of equation (1) occurs on the surface of BDD. In this way Eq. (7) becomes a pseudo-first order kinetics law, written as

$$-\frac{dc_{HCTZ}}{dt} = k_{app}\, c_{HCTZ} \quad \textbf{(8)}$$

where k_{app} is the experimentally determined rate constant. Integrating Eq. (8), we obtain the typical first order kinetic equation, which allows evaluating the rate constant from the slope of a plot of Ln (c_0/c_{HCTZ}) against electrolysis time. This kinetic analysis, assuming a pseudo-first order reaction for HCTZ, shows a linear correlation when the current range is 10 – 80 mA cm^{-2} (Fig. 4(B)). A three-fold increase in the rate constant value was observed increasing the j from 10 mA cm^{-2} to 80 mA cm^{-2}, as seen in Table 2.

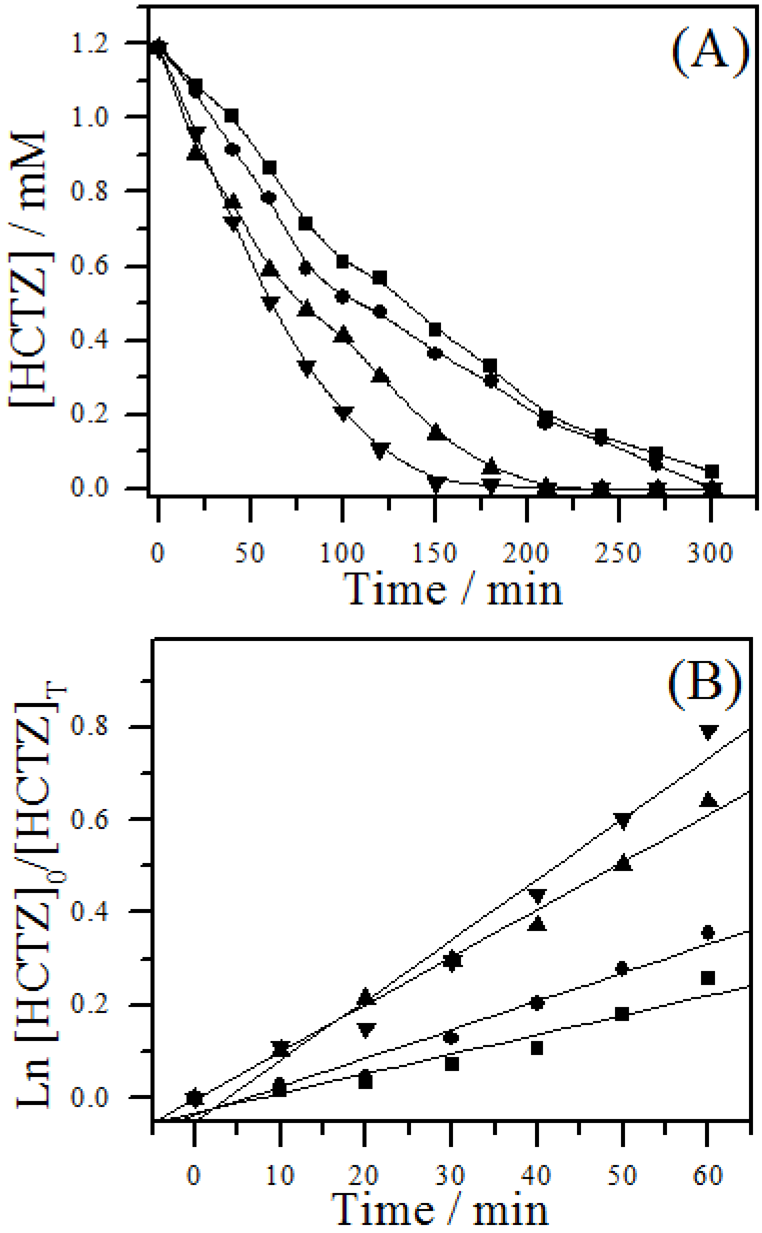


Figure 4. (A) Concentration decay with respect to the electrolysis time for the EO of 353 mg L^{-1} HCTZ solutions in 0.05 M Na_2SO_4 at 35 ºC using the BDD/stainless steel system at pH 7.0. Applied current density: 10 (■), 30 (●), 50 (▲) and 80 (▼) mA cm^{-2}. (B) Kinetic analysis assuming a pseudo-first order reaction.

Table 2. Apparent rate constant values considering a pseudo-first order kinetic analysis, obtained from Eq. (8) for HCTZ under the experimental conditions of Fig. 3. The data are the average of three independent experiments.

Applied current density / mA cm^{-2}	k_{app}(s^{-1}) x 10^{-4}	R^2
10	0.703	0.9669
30	1.027	0.9484
50	1.718	0.9849
80	2.175	0.9825

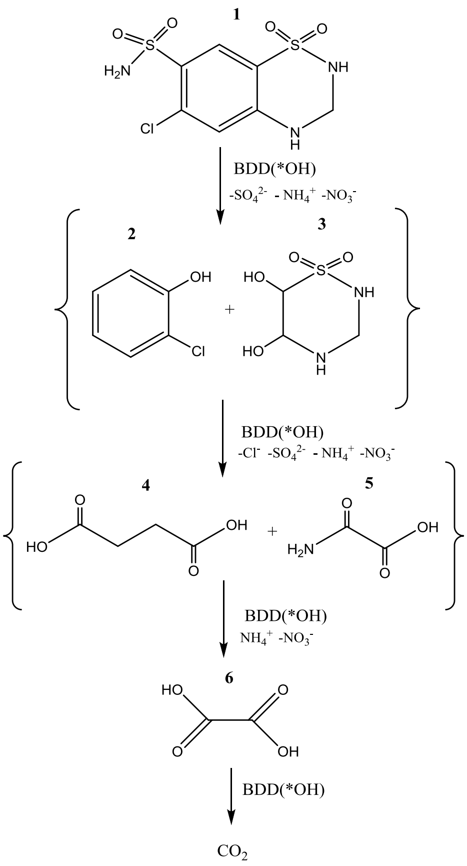
Another important point to note is related to the decay profiles of TOC (Fig. 3(A)) and concentration of HCTZ (Fig. 4(A)). Both profiles are similar, but for the same electrolysis time, the concentration decay is greater than the TOC abatement. This is due to the formation of organic intermediates and/or reaction products corresponding to compounds of lower molecular size than HCTZ. These intermediates provide mg of C to the solution prior to complete conversion to CO_2. In other words, the drug is eliminated at short time but a quantity of total organic carbon remains in solution, confirming the formation of organic by-products, which are also rapidly break down by hydroxyl radicals, reaching a total decay of organic compounds to achieve complete mineralization. Carboxylic acids, aromatic compounds, and inorganic ions correspond to the main by-products formed during EO of HCTZ using a BDD anode. All of them were detected by chromatographic assays to which.

The energy consumption associated with an electrochemical process is an important factor in any treatment system and depends on the applied current, electrolysis time and the potential difference generated. Thus, the energy consumption (kW h m^{-3}) associated with the electro-oxidation of HCTZ at different applied currents was estimated from Eq. (5). As mentioned earlier, applying different current densities (10 – 80 mA cm_{-2}), >95% mineralization is reached at different electrolysis times. Thus, applying 10 mA cm^{-2}, an energy expenditure of 0.013 kW h m^{-3} is obtained after 300 min of electrolysis. Considering an electrical energy cost of about CLP$ 106.4 (Chilean price, taxes excluded) per kWh (Compañía Chilena de Energia Eléctrica, Chile), the complete mineralization of HCTZ at pH 7.0 using a BDD anode has a cost close at CL$ 1.4 (0.0023 USD). At the same time, but applying 30 mA cm^{-2}, the energy consumption increases at 0.053 kWh m^{-3}. Finally, applying 50 and 80 mA cm^{-2}, complete mineralization of HCTZ is achieved at 210 – 240 min, with an energy expenditure of 0.127 and 0.196 kWh dm^{-3}, respectively, increasing more than 15 times the cost of the electrolysis process by applying 10 mA cm^{-2}.

3.2. Generated organic and inorganic products and by-products detected during the EO of HCTZ using a BDD anode.

Intermediates and/or reaction products formed during the electrolysis of HCTZ applying 10 mA cm^{-2} at pH 7.0 and 35 ºC, using the BDD/SS system, were detected by chromatographic techniques in order to identify and identify some of their main oxidation products. Thus, samples obtained at different electrolysis times were collected until an accumulated volume of 500 mL, then extracted with CH_2Cl_2, and finally concentrated by evaporation of the solvent. The resultant yellow solid was injected in a UHPLC-MS/MS apparatus. Only two aromatic intermediates were detected during the electrolysis of HCTZ. The identification of by-products was carried out based on the retention times of standards and their fragmentation patterns. MS spectra displayed the corresponding peaks associated with HCTZ (m/z = 298) at t_R = 2.9 min, together with two additional peaks associated with the presence of 4-chlorophenol (m/z = 128) at t_R = 8.8 min and for 5,6-dihydroxy-1,2,4-triazine-1,1-dione (m/z = 164) at t_R = 1.6 min, which correspond to the main aromatic intermediates found during electrolysis of HCTZ.

Moreover, the presence of linear short-chain carboxylic acids formed during the oxidation of HCTZ were determined by ion-exclusion chromatography, coinciding with previously described by other authors for the degradation of aromatic compounds [40]. To identify each carboxylic acid seen in the chromatogram, samples of the most probable pure carboxylic acid and their mixtures were used as standards under the same experimental conditions. Oxalic, oxamic, and malic acids were found during the mineralization of HCTZ to CO_2. Malic acid probably comes from the oxidation of the aryl moiety of the aromatics, and/or they could be formed by chlorophenol oxidation, detected by UHPLC-MS. Oxamic acid may be formed when a part of the triazine ring is opened by the attack of $^{\bullet}OH$. At the end of the electrolysis, oxalic and oxamic acids are the last carboxylic acids that are directly transformed into CO_2.



Sceme 1. Proposed reaction pathway for HCTZ by EO.

The mineralization of *N*-derivatives of organic compounds is usually accompanied by the loss of NH_4^+ and NO_3^- [41]. The concentration of both ions in the final HCTZ solutions treated by EO was determined by ionic chromatography (NO_3^-) and photometric atests (NH_4^+). The presence of NH_4^+ was confirmed in the final solution with a concentration of 20.98 mg L^{-1} (corresponding to 32.0% of initial N). On the other hand, a higher accumulation of 139.08 mg L^{-1} (62.8% of initial N) for the NO_3^- ion was found in the HCTZ solution. The remaining oxamic acid found was 10 mg L^{-1}, which correspond to 3.1% of initial N. It can infer therefore be inferred that a small portion of the initial N of the HCTZ (ca. 2 %) is lost as volatile N-species, probably NOx and N_2. The formation of Cl^- anions was also confirmed by photometric analysis. At the end of the electrolysis, a concentration of 0.04 mg L^{-1} of Cl^- was determined. Its concentration corresponds to the total initial Cl in the HCTZ (99.0 %), and it can mean that Cl^- does not undergo oxidation on the BDD anode at the applied density current (10 mA cm^{-2}).

Scheme 1 presents a reaction sequence proposed for the mineralization of HCTZ by EO taking into account all the oxidation products detected. In this pathway, BDD(•OH) is considered the major oxidizing agent. The process is initiated either by the breaking of the aromatic ring or the thiazide ring of HCTZ 1 to yield 2 and 3 producing SO_4^{2-}, NH_4^+ and NO_3^-. Consecutive oxidation of the derivatives 2 and 3 yields a mixture of acids, 4 and 5, producing SO_4^{2-} and Cl^-. Malic acid 4 and oxamic acid 5, are subsequently oxidized to 6. This ultimate carboxylic acid together with 5, are converted to CO_2.

3.3. Degradation of HCTZ from the commercial formulation.

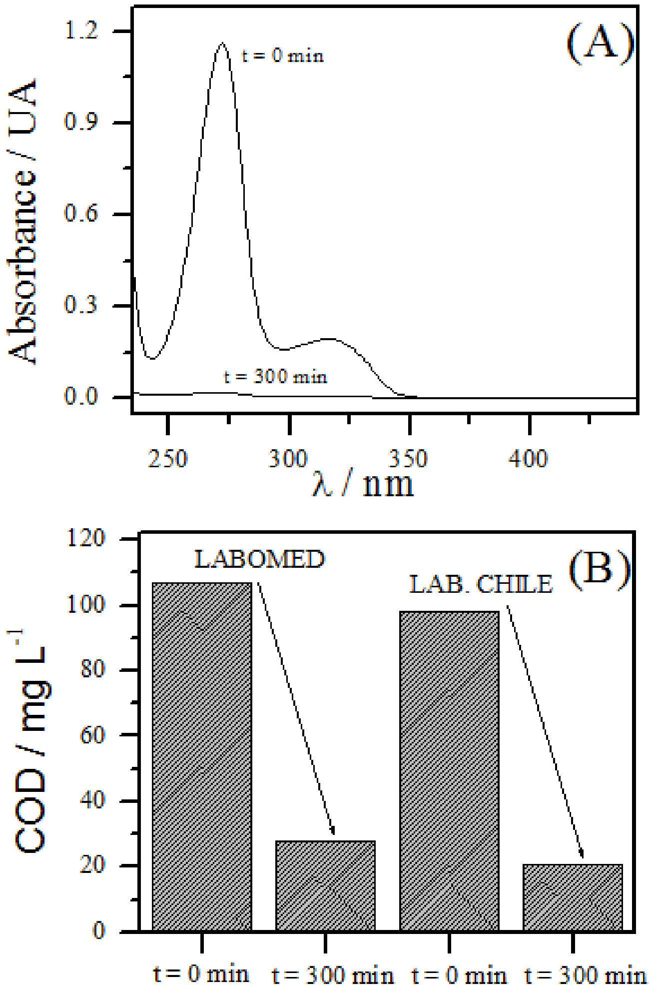


Figure 5. (A) Initial and final spectra of electrolyzed solution of 100 mg L^{-1} of HCTZ tablet from Labomed in 0.1 L of 0.05 M Na_2SO_4 at 35 ºC using the BDD/stainless steel system at pH 7.0 applying a current density of 10 mA cm^{-2}. (B) Chemical oxygen demand before and after electro-oxidation of 100 mg L^{-1} of tablets of commercial HCTZ under the same experimental conditions as (A).

Finally, the method of electro-oxidation using a BDD anode was applied for the degradation of HCTZ in two commercial tablets from two different pharmaceuticals, Labomed and Laboratorio Chile. Fig. 5(A) shows the spectra of a solution of HCTZ prepared from 100 mg L^{-1} of the Labomed tablet dissolved in 0.05 M Na_2SO_4 at pH 7.0. After 300 min of electrolysis applying 10 mA cm^{-2}, the bands of the HCTZ molecule disappear completely and no new bands are generate during the process. The presence of excipients in commercial tablets does not cause a significant difference when analyzing the decay of the absorbance of HCTZ.

The same behavior was observed for the electrolysis of HCTZ from Laboratorio Chile. The mineralization of the commercial drug was also evaluated by determining the chemical oxygen demand (COD) before and after electrolysis. For both pharmaceutical formulations it can be seen that there is more than 70% removal of COD. These results allow us to conclude that the method is applicable to the removal of HCTZ from waters containing it, under the experimental conditions applied. Thus, $^{\bullet}OH$ can attack HCTZ in the presence of excipients until its complete transformation into carbon dioxide.

4. CONCLUSIONS

It has been shown that an electro-oxidation process is able produce $^{\bullet}OH$ on the BDD surface in sufficient concentration to largely accelerate hydrochlorothiazide removal at low current density. Almost total mineralization of HCTZ was achieved under EO at different pH (3.0, 7.0 and 10.0) and different applied density currents. The most efficient degradation took place in a 353 mg L^{-1} HCTZ solution with 0.05 of Na_2SO_4 at pH 7.0 and at 10.0 mA cm^{-2}, atchieving 95% mineralization in 300 min with 60% current efficiency and an energy consumption of 0.013 kWh g^{-1}. Two intermediates produced from the hydroxylation/substitution of HCTZ were detected by HPLC-MS. Three linear short-chain carboxylic acids formed by cleavage of the product rings were quantified by ion-exclusion HPLC. Three inorganic ions are generated and remain in solution at the end of the electrolysis. HCTZ from pharmaceutical tablets was also oxidized by $^{\bullet}OH$ in the presence of excipients.

The results obtained for the wastewater treatment containing pharmaceutical compounds as HCTZ by electrochemical oxidation are promising from two standpoints: (i) a complete elimination of HCTZ without formation of recalcitrant compounds is obtained, and (ii) is possible to treat waters with high concentrations of this drug HCTZ. Finally, EO is an important alternative to treat wastes in the companies that manufacture or formulate this pharmaceutical.

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