



# Differential Pulse Voltammetry as an Alternative Method for Tracking Hydrochlorothiazide Electrolytic Degradation

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## Abstract

This study aims to compare differential pulse voltammetry as a tracking method with chromatography and photometry. The three methods were used to track the degradation of the model compound hydrochlorothiazide (HCT) where 250ml of 0.50mM HCT solution (pH of 3.50 and ionic strength of 0.010M) was electrolyzed with 50.0mA constant current. The degradation process demonstrated great fit ( $R^2 > 0.99$ ) with pseudo-first-order kinetics when the three tracking methods were utilized. However, different rate constants were reported for these methods:  $0.032\text{min}^{-1}$ ,  $0.016\text{min}^{-1}$ , and  $0.0052\text{min}^{-1}$  for the chromatographic, photometric, and voltammetric techniques, respectively. The observed variation was attributed to the nature of the utilized probing methods. The differential pulse voltammetry is promising as an electrolytic decomposition tracking method; however, the working probe to target pollutants needs to be improved.

**Paper type:** Research paper

**Keywords:** Anodic oxidation, differential pulse voltammetry, hydrochlorothiazide, electrolytic degradation.

**Citation:** Khanfar, M., T., Kopti, N., Gharaibeh, and Z. Abu El-Rub "Differential Pulse Voltammetry as an Alternative Method for Tracking Hydrochlorothiazide Electrolytic Degradation", *Jordanian Journal of Engineering and Chemical Industries*, Vol. 4, No.3, pp:70-77 (2021).

## Introduction

Population growth and the associated increase in production and industrialization led to increased potential sources of environmental pollution to water. Inorganic elements (such as heavy metals) and organic compounds (such as pesticides and pharmaceuticals) are significant environmental pollutants (Obinna *et al.*, 2019; Yadav *et al.*, 2019; Nie *et al.*, 2020). These pollutants lead to toxic effects such as mutagenicity, carcinogenesis, and many other related diseases (Ashok *et al.*, 2020). Therefore, there is a great demand to find viable techniques that remove these pollutants. Many physical techniques have been developed to remove pollutants from water, most notably coagulation-flocculation, filtration, membrane separation, reverse osmosis, and adsorption (Huang *et al.*, 2020; Ma *et al.*, 2017; Khanzada *et al.*, 2017). However, these methods' main challenges are equipment cost, energy consumption, limited efficiency of metals removal, non-generation of toxic sludge, limitation to specific pollutants, eco-friendliness, and ease of operation. In addition, standard physical water treatment methods have significant shortcomings, such as the inability to remove water-soluble pollutants or contaminants with nano-scale dimensions. Chemical water treatment methods could be alternatives (Atkinson *et al.*, 2019; Cai *et al.*, 2019; Kim *et al.*, 2021). These methods focus on waste removal by interacting the target contaminant with short-lived chemical species in the absence or presence of an external form of energy. Advanced oxidation processes represent a group of chemical methods based on potent oxidizing agents such as hydroxyl radicals. These dynamic species oxidize organic pollutants into carbon dioxide, water, and other smaller molecules.

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Received on September 8, 2021.

*Jordanian Journal of Engineering and Chemical Industries (JJECI)*, Vol.4, No.3, 2021, pp. 70-77.

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Accepted on October 4, 2021.



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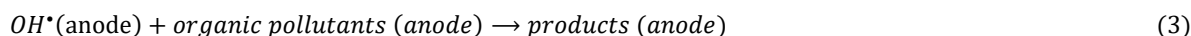
Furthermore, the forms of advanced oxidation incorporate electrochemical oxidation, Fenton process, photocatalysis,  $O_3$ /UV radiation, and cavitation (Sillanpää *et al.*, 2018; Miklos *et al.*, 2018; Matafonova *et al.*, 2018). Anodic oxidation presents the simplest form of advanced oxidation processes. Being efficient, clean, and quick are the main advantages of anodic oxidation processes. In these processes, the pollutants diffuse from the bulk of the treatment vessel to the anode surface, followed by oxidation of the pollutants on the anode surface with the electrically generated hydroxyl radicals. Production of these radicals at the anode could be presented by equation (1);



At the cathode, oxygen is reduced to hydrogen peroxide as per equation (2);

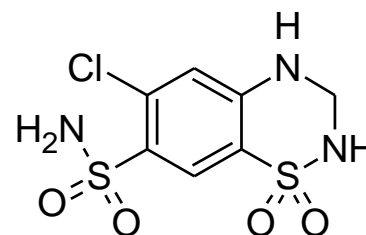


Oxidation of the pollutants occurs in the proximity of the anode surface as per equation (3);



The oxidation adsorbed products then diffuse away to the bulk of the solution.

From the reduced concentration, one could recognize the elimination of a target contaminant during the treatment. Therefore, an analytical method is required for probing the concentration of the degraded pollutant. Consequently, evaluating the performance of the utilized decomposition conditions, such as pH, ionic strength, and the type of the used electrolysis electrodes. Estimation of the efficiency of water treatment methods could be performed with the assistance of vital instrumental methods such as total organic carbon analysis (TOC), high-performance liquid chromatography (HPLC), spectrometry (mainly UV-Visible), and gas chromatography (GC). The selection of the proper tracking method depends on the nature of the target pollutant and how a signal correlated to its structure is obtained. Electro-analytical methods such as voltammetry could be employed, for tracking purposes, as they are cheap, relatively sensitive, and straightforward. However, less attention has been paid to voltammetry as a tracking tool, mainly since not all suspected pollutants are electro-active (Gao *et al.*, 2020; Ganiyu *et al.*, 2019; Yang *et al.*, 2018). Like many pharmaceuticals, hydrochlorothiazide (HCT) and its metabolites enter main water streams such as rivers, water supply networks, and municipal aquatic reservoirs. The complete removal of the drug and its metabolism products cannot be achieved by conventional means of water purification because HCT is chemically stable. The activation of its bonds requires specific forms of energy such as electricity, sonic energy, photo energy, or a combination of these sources (Yao *et al.*, 2019; Mussa *et al.*, 2018; Monteil, *et al.*, 2019). HCT is chemically designated as 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide by IUPAC nomenclature with five main functional groups: an aromatic ring, halide group, secondary amino group, cyclic and acyclic sulfonamide groups. The chemical structure of the compound is illustrated in **Figure 1**. Using HPLC, HCT has been analyzed by different practical scenarios as an individual component in human fluids, pharmaceutical formulations, or combined with other drugs such as irbesartan and metoprolol (Kurbanoğlu *et al.*, 2020; Srinivasu *et al.*, 2018; Kumar *et al.*, 2021). Spectrometry has also been used for the quantification of HCT as a combination extracted from human plasma or bulk tablets (Shah *et al.*, 2017; Sharma *et al.*, 2020; Binh *et al.*, 2021). The HCT was quantified in the presence of accompanying ingredients such as valsartan, amlodipine, and telmisartan. Voltammetric methods such as potential sweep and potential step techniques have been utilized to detect hydrochlorothiazide as well since it could be oxidized to the corresponding imine. Many research groups have investigated the electrochemical behavior of HCT and employed the reported detection conditions- after optimization- for the quantitative analysis of the drug in its matrices. For detection purposes, different modified working electrodes in low pH working solutions were employed for HCT analysis (Hudari *et al.*, 2018; Rezaei *et al.*, 2019; Valezi *et al.*, 2017). Electrolytic degradation of HCT has been performed using different electrolytic methods such as UV/solar-assisted, UV/ $H_2O_2$  catalyzed, and electro-Fenton processes. Conventional methods such as photometry and chromatography have tracked the concentration of the degraded hydrochlorothiazide (Fernández-Perales *et al.*, 2020; Paniagua *et al.*, 2019; Monteil *et al.*, 2019). To the best of our knowledge, our previous published work is among the few examples on the utilization of voltammetry as a tracking method of pharmaceuticals electrolytic degradation (Khanfar *et al.*, 2019). In this work, the electrolytic degradation of HCT was tracked by voltammetry, and the obtained results were compared with those generated from two key methods; HPLC and



**Fig. 1** Chemical structure of HCT.

spectrometry. HCT was selected in this study as a model compound to evaluate the efficiency of voltammetry as a tool for tracking purposes like that of spectrometry and chromatography.

## 1 Materials and Methods

### 1.1 Chemicals and reagents

HCT was provided by Sigma-Aldrich Chemie GmbH, Darmstadt, Germany. Sodium hydroxide, potassium chloride, boric acid, and phosphoric acid were all provided by VWR chemicals, NY, U.S.A. Glacial acetic acid was purchased from S D Fine-Chem Ltd., Mumbai, India. The measurements were carried out using Britton-Robinson pH=3.50. To prepare the buffer solution, the appropriate amounts of phosphoric, boric, and glacial acetic acids were dissolved in ultrapure water (Ultra Max 372, Yong Lin Instrument Co., Ltd, Anyang, Korea). The pH of the buffer solution was adjusted by the addition of the required amount of 0.100M NaOH. The pH values were determined by Symphony SB90M5 pH meter supplied by VWR, PA, U.S.A.

### 1.2 Instruments

The voltammetric experiments were performed in a three-compartment glass cell using Ag/AgCl and platinum as the reference and the counter electrodes, respectively. Pine Research Instrumentation, NC, U.S.A provided the glassy carbon working electrode (3.0mm i.d.). PGSTAT101 Autolab (Metrohm, Utrecht, The Netherlands) operated by NOVA 2.2 and connected to a PC used to perform the electrochemical experiments. For the photometric measurements, model 1800 double beam spectrophotometer provided by Shimadzu Corp., Kyoto, Japan was employed. Chromatographic experiments were performed using Dionex Ultimate 3000 HPLC/UPLC, ThermoFischer Scientific, Karlsruhe, Germany. The elution was performed with water: acetonitrile (3:1) mobile phase at 1.000mL/min rate. The eluted HCT was detected at 270nm. C<sub>18</sub> column, 250mm, Fortis Technologies Ltd. Neston, Cheshire, UK, was used in the performed isocratic separation.

### 1.3 Experimental conditions

The electrolytic degradation of HCT was performed using 100×50×2mm boron-doped diamond (BDD) electrodes (Neocoat, La Chaux-de-Fonds, Switzerland). The degradation was performed in a 250ml Teflon cylindrical homemade cell with a cover that has slots for the cathode and the anode. Tektronix PWS4305, DC power supply (Tektronix, Inc., OR, U.S.A.) was used for HCT degradation. The applied current was kept constant at 50.0mAmp. At different time intervals, the electrolysis was stopped, and portions of the electrolyzed solution were pipetted and used for the voltammetric, photometric, and chromatographic measurements. The voltammetric measurements were performed using the differential pulse mode with the following parameters; 0.001 V potential Step, 0.025V modulation amplitude, 0.05s modulation time, 0.5s Interval time, and 0.01007V/s scan rate.

## 2 Results and Discussion

HCT is a diprotic acid with  $pK_{a1}=7.0$  and  $pK_{a2}=9.2$ . Therefore, all experiments were performed in pH of 3.5 buffered solutions to secure the presence of the HCT in its most acidic form. The dependence of the HCT structure on the pH of the working solution is shown in **Figure 2**. Under the employed experimental conditions, HCT oxidation to the corresponding imine, as shown in **Figure 3**, generates a well-defined oxidation peak around 1.2V.

The process is associated with the production of two protons and the release of two electrons. The generated voltammogram is presented in **Figure 4-a**, which shows how the oxidation peak current decreases with dilution. On the other hand, **Figure 4-b** presents the obtained calibration curve based on the descending in the oxidation current with dilution. In this context, it is noteworthy

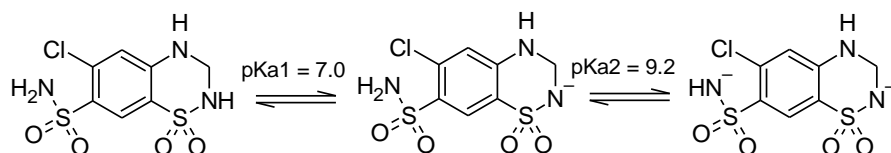


Fig. 2 pH dependence of HCT structure.

to mention a difference between analytical oxidation and electrolytic degradation. The former is related to the analyte's interfacial oxidation at the sensor electrode's surface that generates an analytical signal attributed to the analyte concentration. In electrolytic degradation, the decomposition of the analyte (or pollutant) to simpler forms such as water and carbon dioxide takes place entirely.

In this work, tracking the degradation of HCT by voltammetry, spectrometry, and chromatography was performed. Each of the employed methods generates an analytical signal that could be correlated to HCT concentration. Therefore, the kinetics of HCT decomposition could be deduced from correlating the pollutant concentration to the electrolysis time. The oxidation current presents the analytical signal required to follow the contaminant concentration (Bard *et al.*, 2000). For spectrometry and chromatography, the corresponding signal is the extent of light absorption, according to Beer's law, which states that at a specific wavelength, the extent of absorption of a light-absorbing compound is directly proportional to its concentration, the light pathway, and extinction coefficient of the absorbing compound (Skoog *et al.*, 2006). The corresponding mathematical formulation of Beer's law is given in equation (4);

$$A = \varepsilon.b.c \quad (4)$$

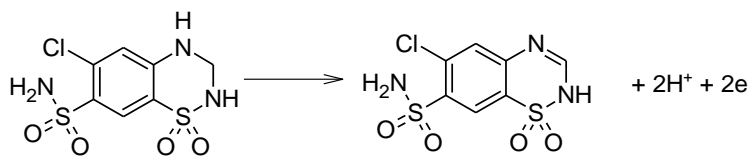


Fig. 3 Electrochemical oxidation of HCT.

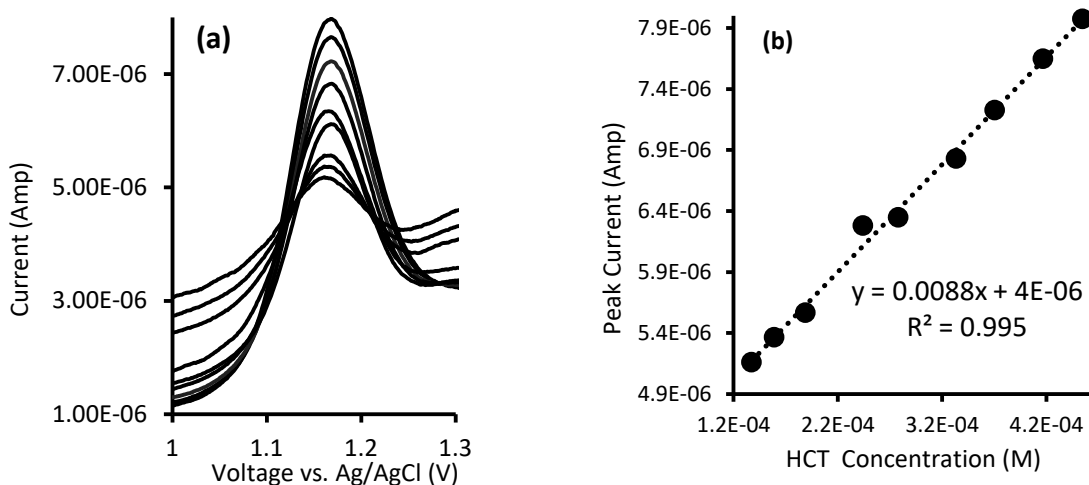


Fig.4 (a) Differential pulse voltammograms of carbon electrode in pH 3.50 Britton-Robinson buffer solution containing HCT. (b) Calibration curve for HCT as detected by differential pulse voltammetry.

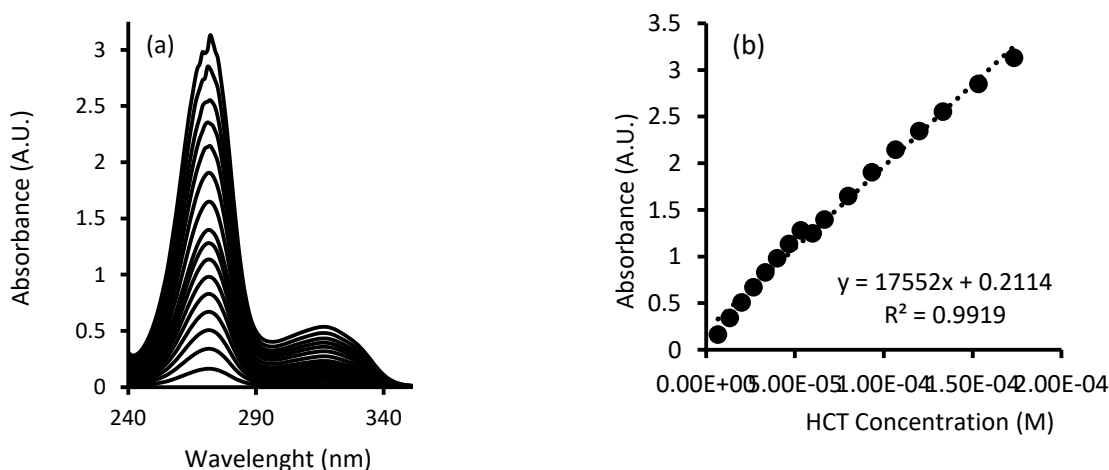


Fig.5 (a) UV absorption spectral profile of HCT in pH 3.50 Britton-Robinson buffer solution. (b) Calibration curve for HCT as detected by UV spectrometry.

Where  $\varepsilon$  is the extinction coefficient,  $b$  is the light pathway, and  $c$  is the concentration of the absorbing species. The main difference between chromatographic and spectroscopic measurements is the manner of photometric detection. In spectroscopy or spectrometry,

direct measurements of the target analyte are taking place. In chromatography, the corresponding measurements are obtained after separating the analyte from the other components of the test solution since chromatography involves two main steps: separation and then detection. Based on the conducted experiments, calibration curves based on the employed analytical methods were established, as shown in **Figures 4, Figure 5, and Figure 6**, when voltammetry, spectroscopy, and chromatography are utilized, respectively. The corresponding fittings to first-order kinetics are presented in **Figure 7, Figure 8, and Figure 9**. HCT degradation can be probed by voltammetry, and it was found that the results follow pseudo-first-order kinetics, as shown in **Figure 7**. The electrolytic degradation of HCT is a bimolecular reaction between the target pollutant, HCT, and the hydroxyl radical generated at the BDD anode. The degradation process could be described as shown in equation (5);

$$-\frac{dC_{HCT}}{dt} = k \cdot C_{OH^\bullet} \cdot C_{HCT} \quad (5)$$

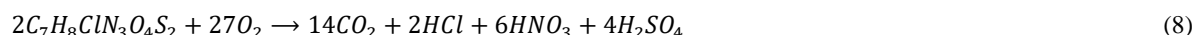
Due to the huge difference in concentration of the radical, when compared to that of HCT, the degradation process equation could be reformulated to equation (6);

$$-\frac{dC_{HCT}}{dt} = k_{app} \cdot C_{HCT} \quad (6)$$

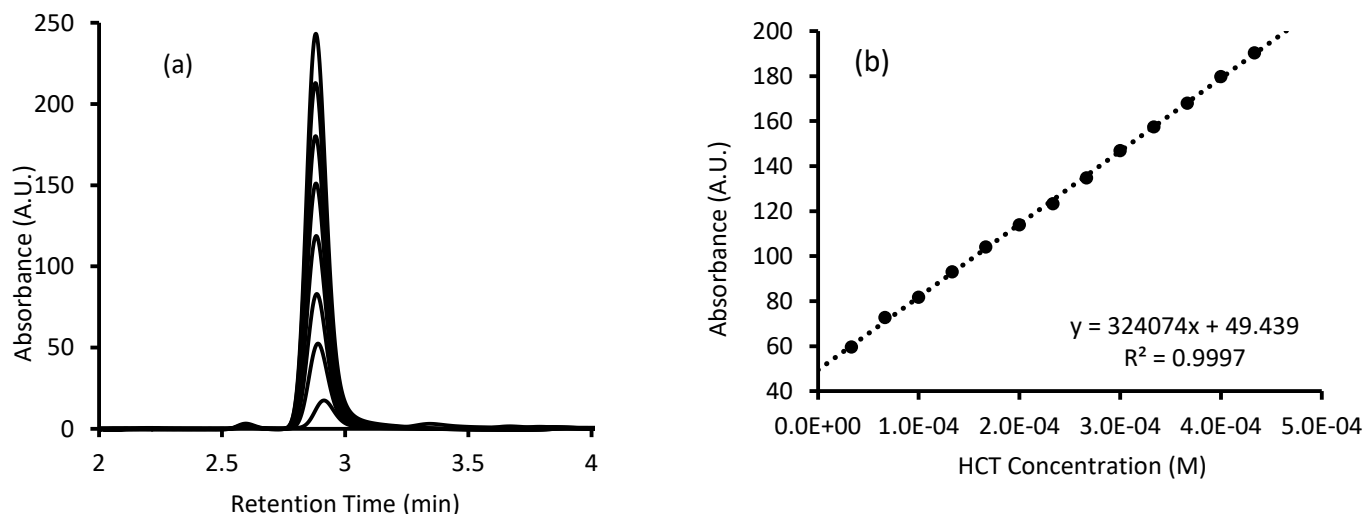
Where  $k_{app} = k \cdot C_{OH^\bullet}$ , and by integrating equation (6), equation (7) is obtained

$$\ln\left(\frac{C_0}{C}\right) = kt \quad (7)$$

Where  $C_0$  and  $C$  are the initial concentration and time-concentration, respectively. The overall degradation reaction could be formulated as given in equation (8);



As shown in the equation, carbon is converted to carbon dioxide, hydrogen to protons. While sulfur, chlorine, and nitrogen are transformed into their corresponding acidified ions.



**Fig.6 (a)** HPLC chromatogram of HCT in pH 3.50 Britton-Robinson buffer solution. **(b)** Calibration curve for HCT as detected by high-performance liquid chromatography.

Fitting the obtained data to a second or pseudo-second-order model leads to a linear curve with a correlation coefficient with a relatively lower magnitude ( $R^2=0.832$ ). Therefore, it is assumed that the degradation kinetics are pseudo-first-order. In aqueous solutions, hydrochlorothiazide responds to UV radiation by significantly absorbing around 270 nm, as shown in Fig. 5. The spectroscopic measurements were performed after dilution of the original solution to one-fourth of its initial concentration since the original solution exhibited an off-scale peak at 270nm. The decomposition of HCT is not accompanied by the production of light-absorbing intermediates, at least not in the scanned wavelengths range (results not shown). As reported in the voltammetric measurements, the electrolytic degradation of HCT tracked by photometry exhibits pseudo-first-order kinetics, as shown in Fig. 8.

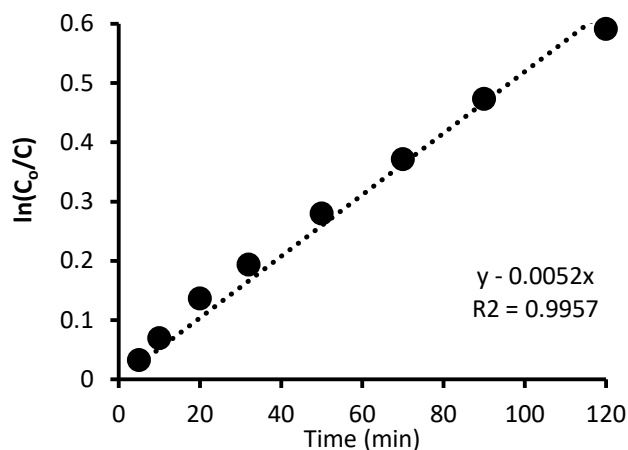


Fig. 7 Pseudo-first-order electrolysis of HCT in pH 3.50 Britton-Robinson buffer solution, tracked by differential pulse voltammetry.

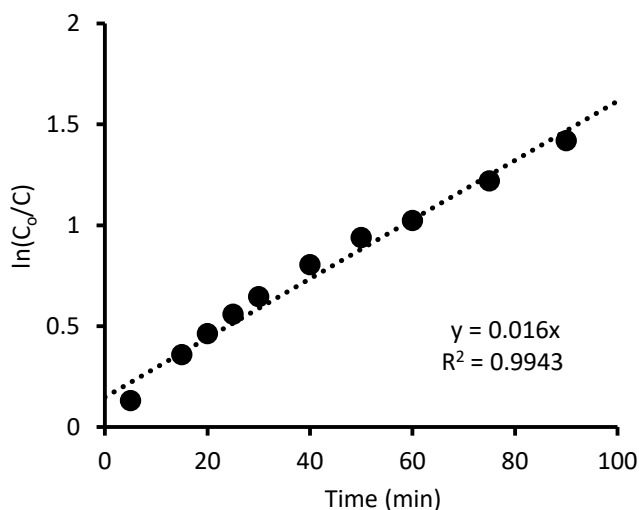


Fig. 8 Pseudo-first-order electrolysis of HCT in pH 3.50 Britton-Robinson buffer solution, tracked by UV spectrometry.

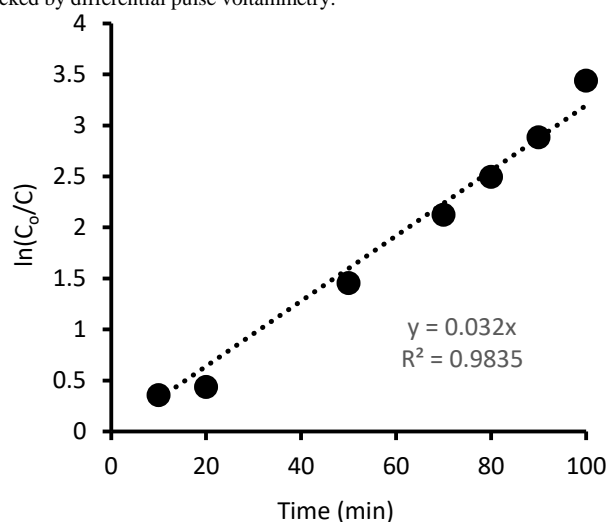


Fig. 9. Pseudo-first-order electrolysis of HCT in pH 3.50 Britton-Robinson buffer solution, tracked by high-performance liquid chromatography.

Under the utilized chromatographic separation conditions, HCT is separated with an elution time of 2.9 min., as shown in **Figure 6-a**. Whereas the corresponding calibration curve is demonstrated in **Figure 6-b**. HCT Degradation exhibited pseudo-first-order kinetics, as shown in **Figure 9**, with a decomposition rate constant of  $0.032\text{min}^{-1}$ . A summary of the found correlation coefficients and rate constants for the three techniques is given in **Table 1**. Degraded HCT, according to the utilized experimental conditions, does not produce any light-absorbing species. Two practical observations support this claim; in the spectral profile of HCT, one peak at 270 nm was reported. The peak height was decreasing as the electrolysis time proceeds, without the appearance of any other spectral features but the one reported at 270nm, which was attributed to HCT. In addition, the reported HPLC results support the photometric ones. No peaks were reported in the obtained chromatograms except the one at 2.9min. As shown in table 1, the magnitude of the rate constant depends on the utilized detection method, even if they are utilized under identical degradation conditions. The magnitude increases by going from voltammetry to spectrometry and then to chromatography. Voltammetry is an interfacial detection method where the analyte diffuses from the bulk of the solution and is then electrolyzed at the sensor electrode surface. The electrolysis process is highly affected by the presence of competing species that may block the electrode surface and leave less room for the target analyte. As a result, attenuation of the desired sensitivity and selectivity is reported.

**Table 1** Comparison among the correlation coefficients ( $R^2$ ) and pseudo-first-order kinetic rate constants ( $k_{app}$ ) obtained by the different instrumental techniques.

Method	$R^2$		$k_{app} \times 10^3$ ( $\text{min}^{-1}$ )
	Calibration	Kinetics	
Chromatography	0.999	0.996	32
Spectrometry	0.992	0.994	16
Voltammetry	0.995	0.996	5.2

In ultraviolet spectrometry, a significant fraction of the test solution is irradiated with the incident electromagnetic beam, and the number of photons absorbed by the target molecules is controlled by Beer's law, as explained earlier. Therefore, the amount of absorbed light depends on the light pathway through the sample, which justifies why a higher rate constant was obtained when photometry was utilized for obtaining the kinetics measurements. Photometric measurements are affected by the matrix of the analyte solution and by the presence of light scattering objects that may attenuate light absorption. The effect of the matrix is minimized when performing chromatographic measurements. As a prerequisite for a chromatographic measurement and to avoid blockage of the HPLC column, the test samples were filtered by 0.22-0.45 micron filters. Therefore, most of the light scattering particulates and undesired contaminants are removed during the micro-filtration step. In addition, a small fraction of the test solution (ca 5-20 $\mu\text{L}$ ) per sample passes through the HPLC detector after its mixing with the mobile phase, which is a mixture of usually two ultrapure solvents with minimum amounts of contaminants or interfering species. The highest kinetic rate constant was found when HPLC was used due to the efficiency of this method that combines the separation with the subsequent detection. The voltammetric response could be enhanced by modifying the sensor used in HCT detection. The electrode could be modified with higher conductivity materials than the glassy carbon used in this work since conductive materials accelerate the charge transfer process across the electrode-surface interface. In addition, the working electrode could be modified with materials that have electron-deficient centers, which, in turn, has a higher affinity toward HCT oxidation. Transition metals modifiers usually have both higher conductivity and electron deficiency, especially if the metallic centers are in their 3+ or 4+ oxidation states, such as Fe(III), Zr(IV), or Mo(IV).

## Conclusions

In the present study, the electrolytic degradation of HCT was tracked successfully by three different instrumental methods; voltammetry, spectrometry, and chromatography. With all of the utilized methods, pseudo-first-order decay kinetics were reported. Variation in the reported kinetic constants was attributed to the matrix effect that has a higher impact on voltammetric measurements when compared to the spectrometric and chromatographic measurements. The conducted work demonstrates that the differential pulse voltammetry has promising potential as a method for probing the electrolytic degradation of electro-active pharmaceuticals and organic pollutants, especially after enhancement of the working electrode sensitivity toward the target contaminants.

## Nomenclature

HCT	=Hydrochlorothiazide	[mol/L]
BDD	=Boron-doped diamond	[-]
BRB	=Britton-Robinson Buffer	[-]
DPV	=Differential pulse voltammetry	[-]
HPLC	=High-performance liquid chromatography	[-]
pH	=Potential of hydrogen	[-]
UV-Vis	=Ultra violet-visible	[-]
b	=Light pathway	[cm]
c	=Concentration	[mol/L]
$K_a$	=Acid dissociation constant	[-]
$\epsilon$	=Extinction coefficient	[L/mol.cm]

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