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Methodology for decentralized analysis: Detection, quantification and *in situ* monitoring of pharmaceutical formulations removal by electro-Fenton

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ABSTRACT

Water quality is essential to both human and ecosystem health, and a fast detection of emerging pollutants is claimed, along with effective wastewater treatment plants to eliminate these types of substances. The goal of this study was the development of a sensitive and selective methodology to customize a handle device that meets this demand. Clozapine and its pharmacological formulation, Leponex®, were used as a model. The results obtained from the studies by differential pulse voltammetry (DPV) demonstrated that this methodology allows a simpler and cheaper decentralized analysis without losing sensitivity, performing electrochemical measurements *in situ*, in real-time and directly without sample treatment, with a good precision (RSD 3.7 %) and excellent accuracy (recoveries between 97.6 and 99.9 %). Moreover, the methodology was successfully used for direct follow-up the medicine removal in real samples by electro-Fenton (EF) treatment. The results gathered showed a relative error of less than 2 % concerning the measurements made with the conventional potentiostat. Bearing this in mind, the effectiveness of these electrochemical techniques used in tandem with the comfort and high specificity offered by the portable device, a more exhaustive control of water quality can be achieved, thus improving the quality of life in the planet.

1. Introduction

Clozapine (CLZ) is a tricyclic dibenzodiazepine derivative that belongs to the second-generation antipsychotic drugs, indicated for the treatment of schizophrenia and the psychotic disorders that appear in the course of Parkinson's disease when standard treatment has failed. There are complex cases and particular situations in which the use of CLZ shows clear advantages over other drugs due to its characteristics derived from its physicochemical properties [1–5]. Until the present day, CLZ is considered the prototype of atypical antipsychotics and its use is highly widespread [6].

Over time, different methodologies have been developed for the analysis of these compounds, such as voltammetric [7–12], spectroelectrochemical [13] and, the most popular, chromatographic as well [14–18]. Due to the intensive use of these drugs, it is necessary to develop methodologies for analysis, monitoring and quality control by pharmaceutical companies. Electrochemical techniques are the main used because of their high sensitivity and selectivity, with the support of very specific working electrodes and, in this sense, different studies confirm the effective detection of CLZ by these techniques at ultra-trace level (Table 1).

The widespread use of this type of drug around the world constitutes an important fact because it supposes a serious pollution problem, mainly of water, as they are thrown directly as residues in nature, and when human excretions become part of wastewater as well [32]. Water quality is essential to both human and ecosystem health, and wastewater treatment plants are not equipped at all to eliminate this type of substance, so they can become part of the water cycle, which leads them to get incorporated into the life cycle of many species, including humans. The effects of these drugs in the environment are just beginning to be studied and the acceptable concentrations for not producing a negative impact on humans and/or other organisms are unknown [33,34]. Physical, chemical and biological methods of elimination of the different types of drugs in wastewater have been

Abbreviations: DPV, Differential Pulse Voltammetry; EF, electro-Fenton; SEC, Spectroelectrochemistry; CLZ, Clozapine; Leponex®, Leponex®.

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Table 1
Comparison of different electrodes used for determination of CLZ by voltammetry.

Technique*	Electrode**	Linear Interval (μM)	Sensitivity ($\mu A \cdot \mu M^{-1}$)	LOD (nM)	LOQ (nM)	Reference
Ads. AV	GCE	0.18×10^{-3}–1×10^{-3}	–	0.022	0.073	[19]
	CPME	1×10^{-3}–0.79×10^{-3}		0.104	0.346	
CV	HR-PRX	1.0–100	–	0.17	0.566	[20]
DPV	EPGCE	0.1–1	2.313	8.0	26.64	[21]
LSV		1–10	1.159			
		10–100	0.492			
CV	Au-MER	1.0–50	–	7.0	23.31	[22]
CV	GCE-SDS-CPE	1×10^{3}-3.5×10^{3}	–	1×10^{6}	3.33×10^{6}	[23]
DPV	ILCPE	0.2–1	0.0572	0.9	3.0	[24]
		1–10	0.5455			
Ads. DPV	TiO_2NP-CPE	0.5–45	0.6594	61	203.1	[25]
CV	SNTs	0.3–50	–	30	99.9	[26]
LSV	MWCNT-PPY-GC	0.01–5	–	3.0	9.99	[27]
SWV	MWWT	2.0–150	0.69	30	99.9	[28]
DPV	Fe_3O_4/Ala/Pd/GCE	0003–0.070	0.043	1.53	5.095	[29]
CV/DPV	NiO/GQD/GCE	0.003–1.00	42.2	0.55	1.831	[30]
CV/DPV/CA	RuO_2 NP/SPE	0.2–500	0.076	70	233	[31]
DPV	RegoPt/nafion/PGE	0.05–10	9.16	50	166,5	[10]
SWV	Ru-TiO_2NPs/CPE	0.9–40	5.714	0.43	1.43	[12]

* Adsorptive Anodic Voltammetry (Ads. AV); Cycle Voltammetry (CV); Differential Pulse Voltammetry (DPV); Adsorptive Differential Pulse Voltammetry (Ads. DPV); Linear Sweep Voltammetry (LSV); Chronoamperometry (CA)

** Glassy Carbon Electrode (GCE); Carbon Paste Electrode Modified with sepiolite (CPME); Horseradish Peroxidase Enzyme Electrode (HR-PRX); Electrochemically Pretreated Glassy Carbon Electrode (EPGCE); Au Electrode modified with 16-Mercapto-hexadecanoic Acid (Au-MER); Glassy Carbon Electrode Nanotubes with Sodium Dodecyl Sulfate modified Carbon Paste Electrode (GCE-SDS-CPE); Ionic Liquid modified Carbon Paste Electrode (ILCPE); Carbon Paste Electrode chemically modified with TiO_2 Nanoparticles (TiO_2NP-CPE); Novel Silicate Nanotubes (SNTs); Glassy Carbon Electrode modified with Multiwalled Carbon Nanotubes/New Coccine Doped Polypyrrole (MWCNT-PPY-GC); Glassy Carbon Electrode modified with WO_3 Nanoparticles hydride by α − terpineol (MWWT); Fe_3O_4/β-Ala/Pd immobilized on the surface of a Glassy Carbon Electrode (Fe_3O_4/Ala/Pd/GCE); Nickel Oxide Nanoparticle decorated Graphene Quantum Dot modified Glassy Carbon Electrode (NiO/GQD/GCE); Ruthenium (IV) Oxide Nanoparticle modified Screen-Printed Electrode (RuO_2 NP/SPE); Reduced Expanded Graphene Oxide-Pt nanocomposites with Nafion modified Pencil Graphite Electrode (RegoPt/nafion/PGE); Ruthenium doped TiO_2 Nanoparticles modified Carbon Paste Electrode (Ru-TiO_2NPs/CPE).

studied and, in this sense, Advanced Oxidation Processes (AOPs) have been revealed as one of the most effective treatments for the elimination of organic contaminants [35]. These processes are based on the generation of powerful oxidants which can degrade organic and organometallic compounds. Fenton reaction, specifically, is an AOP in which hydroxyl radicals, $^{\cdot}OH$, are generated because of the reaction between H_2O_2 and Fe^{2+} in an acidic medium, and it constitutes an effective and environmentally friendly method for the treatment of wastewater containing different organic compounds that are difficult to degrade by conventional biological treatments.

Thus, in this study was selected an AOP method based on Fenton´s process denominated electro-Fenton (EF), in which H_2O_2 is electrogenerated *in situ* from 2-electron reduction of dissolved O_2 generated by the aeration on the cathode (Eq. (1)). Fe^{2+}, which is used in the process as a catalyst, reacts with the generated H_2O_2 producing Fe^{3+} and $^{\cdot}OH$ in the bulk solution (Eq. (2)) and then, the Fe^{3+} formed is regenerated to Fe^{2+} by direct reduction on the cathode (Eq. (3)) [36,37].

$$O_2 + 2H^+ + 2e^- \rightarrow H_2O_2 \quad (1)$$

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + \dot{O}H \ + -OH \quad (2)$$

$$Fe^{3+} + e^- \rightarrow Fe^{2+} \quad (3)$$

The $^{\cdot}OH$ generated is a highly oxidizing agent with a formal potential of 2.8 V *vs* Normal Hydrogen Electrode (NHE), reacting with organic compounds until their mineralization (i.e. their conversion into CO_2, H_2O and inorganic ions).

Several studies are found in the literature using EF process to degrade a wide range of organic pollutants [38–40]. As far as pharmaceutical pollutants are concern, studies mainly refer to a variety of antibiotics and anti-inflammatories [41], with very few studies referring to anxiolytic and antipsychotic drugs, in a situation of increasing consumption worldwide [42].

The goal of this work is the development of an electroanalytical methodology based on Differential Pulse Voltammetry (DPV), combined with Cyclic Voltammetry (CV) and SpectroElectroChemical (*SEC*) studies to better understand the electrochemical processes, all focussed on the analysis of CLZ and its determination in its pharmacological formulations (Leponex®). Moreover, a cheap electrode material, graphite or carbon, was used for this purpose. Once validated, this methodology has been applied for monitoring its degradation performed by the EF process. In addition, the results obtained from these studies were customized to manufacture a portable device that allows performing electrochemical measurements *in situ*, in real-time and directly without sample treatment.

To get reliable results after following the methodology described below, the chemometric study is essential to data processing statistically, being able to express the results with their associated uncertainty exactly and plainly. Furthermore, the electrochemical reaction on the electrode surface has to be studied in-depth and the results have to be interpreted in detail to be sure that the developed portable device is working properly at any time.

2. Materials and methods

2.1. Reagents and solutions

Clozapine (3-chloro-6-(4-methylpiperazin-1-yl)-11*H*-benzo[b][1,4]benzodiazepine, $C_{18}H_{19}ClN_4$, MW 326.823 $g\cdot mol^{-1}$, standard grade) and its commercial formulation Leponex® were supplied by Sandoz. Other drugs used were supplied by Kali-Chemie Pharma (Tifluadom), Sandoz (Clothiapine) and European Pharmacopoeia (Alprazolam). $FeSO_4\cdot7H_2O$ (≥99 %, catalyst) and Na_2SO_4 (electrolyte) were acquired by Sigma-Aldrich. H_2SO_4 obtained by Fisher Chemical was used in 1:10 and 1:50 dilution to adjust pH to a convenient value. Ethanol Absolute (density 0.79 $kg\cdot L^{-1}$) and NaOH were supplied by VWR Prolabo. For $^{\cdot}OH$ analysis, disodium terephthalate (99+ %, Alfa Aesar)

was used. CLZ standard solution (696 mg·L^{-1}, 2.13 mM) was prepared in hydroalcoholic solution, with an ethanol percentage of 50% to help solubilize CLZ due to its low solubility in water. It must be taken into account that the percentage of ethanol must not exceed 5% in the dilutions that will be measured afterwards. All chemicals are of analytic grade and were used without further purification, and both working solutions and suspensions were prepared with Milli-Q grade water as a solvent (Reverse Osmosis RO1-Compact/C system, 18 MΩ cm, Peter Taboada, Spain).

All the experiments were performed at room temperature. Furthermore, all working solutions were stored at +4 °C.

2.2. Instrumentation and procedures

2.2.1. Voltammetric analysis

Cyclic Voltammetry (CV) and Differential Pulse Voltammetry (DPV) measurements were performed with a potentiostat-galvanostat PGSTAT12 (Autolab), connector DSC (Metrohm-Dropsens) for SPCE (DRP-C110 and DRP-110, DropSens) and controlled by General Purpose Electrochemical Experiments Software (GPES 4.9.05). The electrochemical cell configuration consists of a Screen-Printed Carbon Electrode (SPCE) composed of a graphite working electrode (4 mm diameter), a carbon counter electrode and an Ag pseudoreference electrode. The sample volume used to cover the electrodes in all measurements was 50 μL. CV is the technique used in order to carry out the electrochemical process study attending to the following conditions: potential range from −0.5 to 0.8 V and scan rate between 10 and 500 mV·s^{-1} for scan rate study. A scan rate of 100 mV·s^{-1} was selected for number of cycle's studies. For DPV technique, the conditions were as follows: step potential of 5 mV, modulation time of 0.05 s, interval time of 0.5 s, modulation amplitude of 50 mV and scan rate of 9.9 mV·s^{-1}, with an initial and end potential of −0.5 and 0.8 V, respectively. SPCEs were subjected to a process of "cleaning/regeneration" of electrode surface known as activation before each measurement as described in other articles, in which a drop of H_2SO_4 50 mM solution is placed on the electrode and is submitted to 5 scans from −1.2 to 1.2 V with the purpose of homogenizing the functionality of the electrode and also eliminating possible adsorbed impurities. [43–45].

For pH measurements, a pH-meter 744 Metrohm was used, and the calibration was checked against two commercially standard buffer solutions at room temperature, pH 4.01 (Potassium Acid Phthalate) and pH 7.00 (Potassium and di-sodium phosphates), both supplied by Crison.

2.2.2. Spectroelectrochemical analysis

Spectroelectrochemical experiments were carried out with VIS-NIR UV–VIS SPELEC instrument (DropSens), a measuring instrument which combines in only one box a Light source (UV-VIS-NIR wavelength range; 215–400 nm Deuterium, 360–2500 nm Tungsten halogen), a Bipotentiostat/Galvanostat (±4 V DC potential range, ± 40 mA maximum measurable current) and a Spectrometer UV-VIS whose wavelength range is from 350 to 1050 nm, allowing electrochemical and spectroscopic simultaneous measurements. DropView SPELEC Software (3.2.2 18AZ2) is the spectroelectrochemical software tool that controls the instrument.

The SPCEs were connected to the instrument using a DRP-CAST wire and inserted into a Teflon cell (TRANSCELL). For reflection experiments, a Reflection Probe (RPROBE-VIS-UV) was incorporated into this cell and reflection measurements with SPCE (DRP-110) were done. All experiments were performed with a volume of 100 μL of Leponex® suspension in 10 mM Na_2SO_4 electrolyte, with an ethanol content of 2.9 % at pH 3. The voltammetric and spectroelectrochemical measurement parameters were −0.5 and 0.9 V for initial and end potential, respectively, a step potential of 5 mV, an interval time of 50 ms for reflection experiments (average of 3 scans) and 3 s of equilibration time. As far as scan rate is concerned, the optimal value for reflection studies was 20 mV·s^{-1}. Before the electrode was inserted into the cell, two drops of the sample were placed on the working electrode surface so that the three electrodes were covered, to then dispense the rest of the volume once the assembly had been carried out. In this case, the electrodes were not subjected to the "cleaning/regeneration" process. The spectra were smoothed by Savitzky-Golay filter, selecting 20 points and 3 degrees on the software window.

2.2.3. Electro-Fenton treatment

EF experiments were performed with a constant current of 200 mA applied between two electrodes connected to a direct power supply DC Power Supply Agilent, model E3611A. In this process, Boron-Doped Diamond (BDD) supplied by DIACHEM® Germany (4–5 lm diamond film thickness and doping level around 2500 ppm) was used as an anode, while the cathode was carbon felt (Carbon Lorraine, France). The last one was placed on the inner wall of the cell covering the total internal perimeter. In contrast, BDD (16 cm^2 surface) was centred in the reactor. Experiments were carried out in a 0.25 L open cylindrical glass reactor with a working volume of 0.20 L consisting of 0.125 mM CLZ (Leponex® suspension), with a content of 5 % ethanol and Na_2SO_4 10 mM as the electrolyte to increase the conductivity of the medium. Furthermore, $FeSO_4{\cdot}7H_2O$ 0.25 mM was added as a catalyst and the pH was adjusted to 3 with H_2SO_4. The resulting solution was continuously stirred with a magnetic bar (250 rpm) to avoid concentration gradients·H_2O_2 was electrochemically generated *in situ* on the cathode surface through the continuous aeration (0.5 L·min^{-1}) with a Tetra APS50 air pump. This aeration started over 20 min before the treatment in order to reach a stationary O_2 concentration. To monitor the degradation process, aliquots of 50 μL of the EF reaction mixture were transferred to the SPCE (DRP C-110), at convenient intervals of time, using one electrode for each measurement.

2.2.4. Fluorometric hydroxyl radical analysis

The ·OH generated at the EF process was quantified using terephthalic acid (TA), which reacts in its anionic form with ·OH resulting in the formation of the 2-hydroxyterephthalic acid (TAOH), which exhibits fluorescence [46]. EF solution samples, taken at determined times, were added into 3 mL of TA/NaOH aqueous solution, where the concentration of TA and NaOH were 0.67 mM and 2 mM, respectively. TAOH fluorescence was measured, previously filtered through a 0.45 μm filter, by a spectrofluorimeter FP-6500 (Jasco) with an excitation wavelength of 315 nm and emission wavelength of 425 nm. The amount of ·OH generated was determined from the calibration curve whose equation is I_F(a.u.) = (3 ± 1) (a.u.) + (2245 ± 7) (a.u. μM^{-1})·[TAOH](μM) (R^2 = 1), where a.u. is arbitrary units.

2.2.5. Portable device development

A Portable Electrochemical Reader was configured to analyse the concentration of CLZ in complex samples without any previous sample treatment. The technique was validated to custom configure the device under the conditions described in Section 2.2.1. *Voltammetric analysis*. It is therefore necessary to include the Birke's criterion [47], essential for developing the analytical method in the DPV technique, that also allows to characterize the CLZ process as by CV and to optimize the potential window where the oxidation peak of CLZ can be located. The portable device automatically measures the peak height and, according to the calibration curve, displays the corresponding analyte concentration in the LCD display. The procedure was very simple: an SPCE (DPR-110) was inserted into the instrument, directly, without the aid of a connector, a sample volume of 50 μL was dispensed covering the electrode surface and the concentration measurement was done. Measurements were taken simultaneously with the EF experiment (Section 2.2.3. *Electro-Fenton treatment*) and obtained concentration data were collected on the LCD screen directly as well.

The device is a product manufactured by the company Metrohm-Dropsens (under the customized specifications described in this work), which is certified in the UNE EN ISO 9001 quality standard.

2.2.6. Sample preparation

Leponex® stock suspension was prepared with 72.6 mg of pharmaceutical product in pills, previously finely powdered using an agate mortar and accurately weighed afterwards. Then, it was dissolved in the minimum content of ethanol absolute, adding bit by bit and shaking by hand until it was completely dissolved, for which it was necessary to use 25 mL before diluting to a final volume of 100 mL with Milli-Q water. The addition of water makes the sample opaque, achieving a homogeneous suspension that was kept at 4 °C in the dark.

The analysis of CLZ content in Leponex® was performed by external standard and also by standard addition in order to evaluate matrix effects, maintaining the electrolytic medium Na_2SO_4 at 10 mM, 5 % of ethanol and a pH value around 3.

Tap water samples were collected in a 1000 mL beaker directly from the laboratory water supply, unfiltered. The sample collection was done after the following protocol: opening the tap and allowing the water to run for 2 min, then rinsing the beaker with a small volume of water. That procedure had to be repeated in triplicate. For EF experiments, it is required a total volume of 200 mL approximately, so the necessary volume of tap water was taken and mixed with a stirring rod to achieve a homogeneous medium.

3. Results and discussion

A comprehensive study of electrochemical behavior is performed in the following sections. This is done on unmodified graphite SPEs (SPCE) to reduce costs when tuning the methodology to use as decentralized analysis that allows a simpler and cheaper detection and quantification way without losing sensitivity.

3.1. Cyclic Voltammetry and reflection SpectroElectroChemistry studies on SPCE of Clozapine

Firstly, it is necessary to study the nature of the electrochemical process that takes place on SPE when applying a potential scanning to a CLZ solution. Based on the chemical structure, the CLZ's secondary amine is expected to oxidize in an acid medium, releasing two electrons during the process. Given that CLZ is an organic molecule, the electronic exchange is linked to a proton exchange, which can be observed in the loss of the two protons of the seven-membered heterocycle [12]. This process is shown in Fig. 1:

In order to visualize this phenomenon, CV voltammetric studies were performed (Fig. 2). By using CV it is also possible to obtain more detailed information on the electrochemical process. For this purpose, the effect of the number of scans was studied by subjecting a CLZ standard solution to a potential scanning for 25 consecutive cycles, and the results are collected in Fig. 2a.

In the first scan (blue line), the main oxidation and reduction peaks were located at a potential of +0.340 V (peak 1) and +0.276 V (peak 2), respectively. Two secondary peaks at lower potentials appear, being centred at +0.091 V in anodic direction (peak 4) and at −0.022 V in cathodic direction (peak 3). The study of the number of cycles also shows how the position and intensity of the peaks are modified after being subjected to several scans. Therefore, the obtained results show that after the first scan, the height of both anodic and cathodic main peaks decreased (peaks 1 and 2 in Fig. 2a). The additional anodic peak 4 shows the same tendency, but on the contrary, the height of cathodic peak 3 increased. Moreover, as the number of scans progresses, all peaks shift towards more negative potentials and from scan 22 onwards, the graphs practically overlap. All of this fact can be due to the strong adsorption of the already oxidized CLZ on the working electrode surface during its reduction in the backward scan [19,48] which means the accumulation of adsorbed product on SPCE electrode surface happens with the increase of the number of scans. This adsorption process minimizes the active surface available for the drug to be oxidized, which explains the mentioned decrease of the peaks during the course of the number of scans. But contrary to what might be expected, this will not be a problem during the analysis since DPV will be used for this purpose, a more sensitive technique in which the backward scan does not take place, thus avoiding the physisorption process.

Moreover, in Fig. 2a (peaks 1 and 2 in the first scan, blue line), it can be seen that the reaction looks like a quasi-reversible process since an anodic and a cathodic peak with similar morphology but different intensity appears in the voltammogram. The process is not reversible since the anodic peak intensity/cathodic peak intensity ratio (i_{pa}/i_{pc} ratio) is not equal to 1. Furthermore, although the peak separation is very close to the 59 mV·number of electrons exchanged^{-1} criteria (59 mV·n^{-1}), it can be observed that the separation, in this case, is 64 mV·n^{-1}, thus confirming that the electrochemical process is not reversible but quasi-reversible. This behaviour was as a consequence of ECE mechanism involved on electrode surface [12,29,49], where a chemical reaction of CLZ^+ cleavage (c in Fig. 1) and degradation of the piperazine ring assumed as the electroactive products resulted from the electrochemical reaction.

On the other hand, the effect of scan rate on the main oxidation/reduction peaks was also studied by CV (peaks 1 and 2 in Fig. 2b). This study makes it possible to know if the electrochemical process is controlled mainly by diffusion or with an adsorption contribution. The obtained voltammograms can be observed in Fig. 2b, and these results agree with the hypothesis raised during the study of the number of cycles: at fast scan rates, the CLZ does not have time to get adsorbed, which leads to a drastic reduction of the intensity on the peak associated with the adsorption process (peak 3) with the increasing of scan rate.

For electrochemically electron transfer processes by diffusion, the Randles − Sevcik equation (Eq. (4)) describes how the peak current, ip, increases linearly with the square root of scan rate ($v^{1/2}$), where n is the number of electrons transferred in the redox event, A is the electrode surface area in cm^2, C is the bulk concentration of the analyte in mol·cm^{-3} and D, in cm^2·s^{-1}, is the diffusion coefficient of the oxidized analyte.

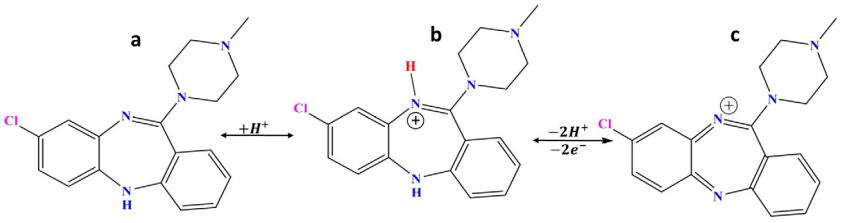

Fig. 1. Oxidation of CLZ in acidic medium [25]. The positive charge on the N of seven-member ring (c) can also be located on the N of the piperazine ring as conjugate structure.

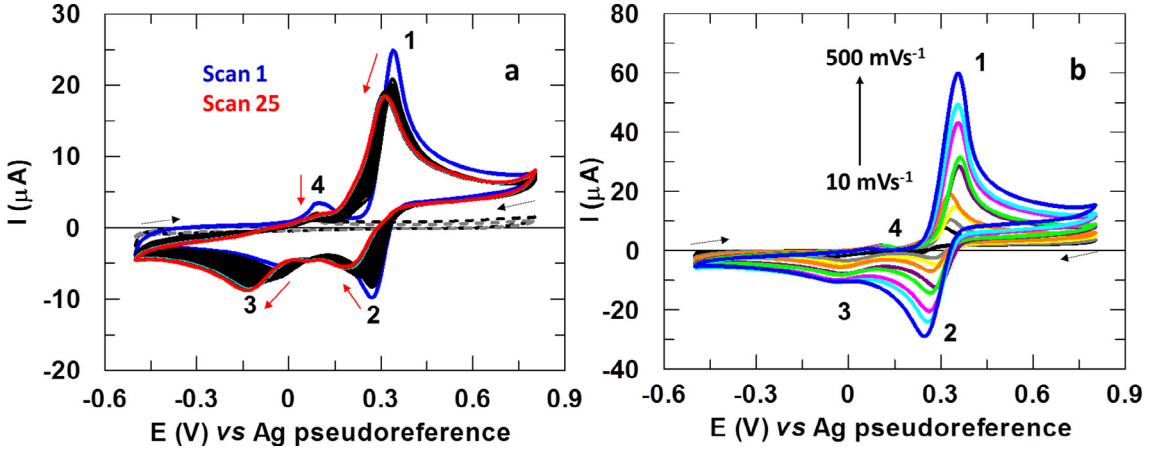

Fig. 2. (a) Voltammograms obtained for 25 scans by CV at scan rate 100 mV·s^{-1} and potential range of −0.5 to 0.8 V. CLZ suspension 0.256 mM, in 10 mM Na_2SO_4 electrolytic medium at pH 3 and 5 % ethanol. (b) Voltammograms obtained during the 1st scan for the scan rate study (CLZ 0.256 mM, in 10 mM Na_2SO_4 electrolytic medium at pH 3 and 5 % ethanol, potential range from −0.5 to 0.8 V) at 10, 25, 50, 75, 150, 200, 300, 400 and 500 mV·s^{-1} scan rates.

$$i_p = \left(2.69x10^{-5}\right)n^{3/2}ACD^{1/2}v^{1/2} \quad (4)$$

In this study, the faster the scan rate is, the higher the peak current is. Therefore, in a range from 10 to 500 mV·s^{-1}, the peak current of both anodic (peak 1) and cathodic (peak 2) main peaks is directly proportional to the square root of scan rate, following the equations $i_p(\mu A) = (-2.3 \pm 0.5)\ \mu A + (2.59 \pm 0.03)\ \nu^{1/2}$ (ν, mV·s^{-1}) ($R^2 = 0.9993$) for oxidation reaction and $i_p(\mu A) = (4.9 \pm 0.3)\ \mu A + (-1.57 \pm 0.02)\ \nu^{1/2}$ (ν, mV·s^{-1}) ($R^2 = 0.9993$) for reduction reaction, respectively, indicating the processes were diffusion-controlled.

To get insight into something more about the electrochemical reaction of CLZ on SPCE, the reflection spectroelectrochemical technique was applied (Fig. 3).

The evolution of UV-VIS reflection spectra obtained during the 1st scan by CV (at scan rate 20 mV·s^{-1} and a potential range of −0.5 to 1.0 V) shows one broad absorbance band centered at 392 nm and a small band at 582 nm. These two bands can be attributed to a $\pi \rightarrow \pi^*$ and to a $n \rightarrow \pi^*$ transitions, respectively, related to simultaneous protonation of amine group (b in Fig. 1) and formation of the oxidized product (c in Fig. 1) where both amine groups in the seven-member ring were involved, reaching higher conjugation on the structure (the positive charge can also be located on the N of the piperazine ring) with the corresponding bathochromic effect. The voltabsorptograms obtained at both wavelengths are shown in Fig. 3b. From the beginning of the scan, absorbance changes with a similar trend for both wavelengths. At 392 nm, the absorbance decreases until a potential close to −0.3 V, keeping constant until around −0.2 V and, thereafter, it starts to increase rapidly until around 0 V, indicating that a slow reaction or adsorption can be taken place at this potential range [13]. Absorbance at 392 nm does not decrease in the backward scan. In the case of 580 nm, the absorbance variation was lower than at 392 nm with a small increase in absorbance close to −0.4 V. As illustrated in Fig. 2a, all these phenomena took place at a window potential where appear the peak 3, ascribed to the adsorption of the product generated in the electrochemical reaction of CLZ. Hence, these results were clear evidence of ECE mechanism described before for CLZ electrochemical reaction and the confirmation of the observed adsorption phenomena on the electrode surface by CV as well.

3.2. Electroanalysis of Clozapine by Differential Pulse Voltammetry

CLZ concentration effect was quantitatively analysed by DPV under optimized conditions collected in the experimental section, due to the sensitivity and simplicity that this technique offers while working with complex samples. The DP voltammograms at different concentrations

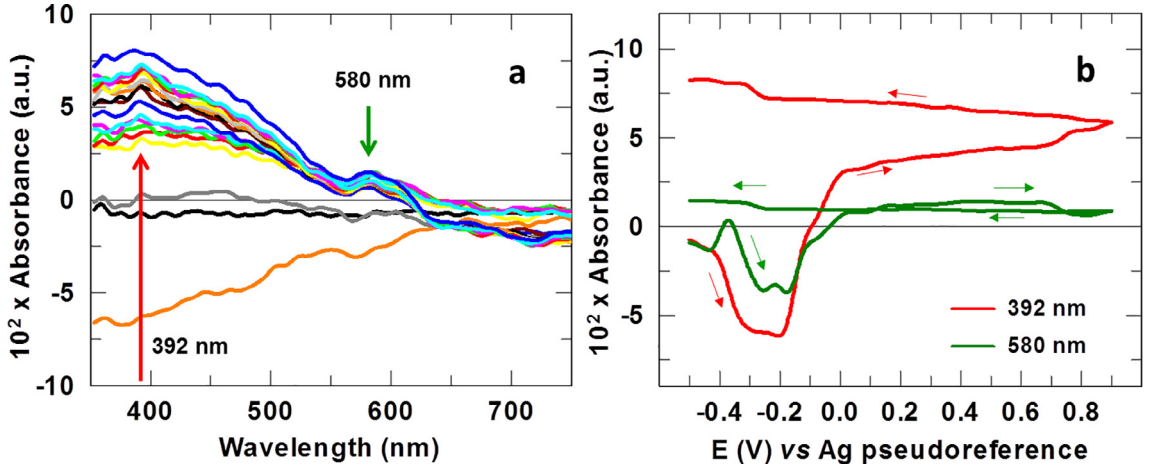

Fig. 3. (a) Evolution of UV–VIS reflection spectra obtained during the 1st scan by CV at scan rate 20 mV·s^{-1} and a potential range of −0.5 to 1.0 V. CLZ 122,7 μM, in 10 mM Na_2SO_4 electrolytic medium at pH 3 and 2.9 % ethanol. (b) Voltabsorptograms obtained from spectra at 392 nm and 580 nm. The arrows indicate the direction of the potential scan at both wavelengths.

are shown in Fig. 4a. The calibration curve (Fig. 4b) was generated from Fig. 4a to check the analytical parameters, such as linearity, sensitivity, precision, and both limits of detection (LOD) and quantification (LOQ) as well. LOD is defined as the lowest analyte concentration that can be distinguished, while LOQ is said to be the lowest concentration at which the analyte can be quantified. Fig. 4a (inset in Fig. 4a) illustrates the voltammograms at concentrations close to both LOD and LOQ.

Acceptability of linearity was examined by the correlation coefficient (R^2) of the linear regression line for the response *versus* concentration plot. The variation of anodic peak current with CLZ concentration shows a linear tendency between both variables in the range from 2.045 to 122.7 μM (Fig. 4c). As a result, the analytical parameters collected in Table 2 (located in the next section) were obtained. Sensitivity is given by the slope of the calibration line, 0.137 $\mu A \cdot \mu M^{-1}$; while precision can be expressed as the relative standard deviation, RSD, with an acceptable value of 3.7 % (n = 6). No significant changes in analytical signal were observed as long as the ethanol content in the solution was below 5 %.

In addition, selectivity was also evaluated by mixing the CLZ in the presence of other three widespread drugs, Tifluadom (TFL), Clothiapine (CLT) and Alprazolam (ALP), whose respective chemical structures together with their cyclic voltammograms are collected in Fig. 5. Concentrations of 0.25 mM were chosen for TFL and CLT, while the concentration of the ALP suspension was 0.15 mM. TFL oxidation peak appears at 0.876 V in the voltammogram, and the peak related to CLT is observed at 0.955 V (both *vs* Ag pseudoreference), attributed to the thiol group in both structures. In the case of ALP, an oxidation peak does not even appear since the compound is preferably reduced due to the presence of azomethine groups (>C=N-) in its chemical structure. Therefore, ALP was studied by applying cathodic potentials, and its peak was found at −0.965 V. Bearing in mind that the CLZ oxidation peak does not overlap with the peaks related to the other three drugs, the selectivity of the DP voltammetric method is good enough.

3.3. Determination of CLZ in pharmaceuticals (Leponex® formulation)

In order to know the accuracy of this method, the theoretical concentration expected by the drug pharmaceutical company's specifications was compared with the concentration measured at the laboratory. After taking eight measurements of CLZ in Leponex® of different concentrations, and by interpolation of those data in the CLZ calibration curve, a value of 99.94 ± 0.01 mg was obtained. Comparing this result with the declared quantity of CLZ in the medicine, which was 100 mg of CLZ per tablet, it is achieved a recovery of 99.9 %. Therefore, the quality control of the medicine can be performed, and the obtained result is consistent with the product specifications. Moreover, the analysis demonstrates that the methodology perfectly works in complex samples without any pre-treatment (in suspension and in presence of excipients).

In addition to that, to check the existence or absence of a significant matrix effect that could influence the analytical signal, both CLZ standard and Leponex® suspensions (with CLZ content in both samples around 125 μM) were measured and the voltammograms were compared afterwards. In Fig. 6a, a slight matrix effect is found comparing the active ingredient with its medicine. Although the difference between both signals is not too significant, a standard addition method was performed to evaluate the DP methodology when the content of the analyte in the sample is below LOQ (ultra-trace level) and to compensate the possible matrix effect.

Increasing volumes of the pure analyte suspension were added to a constant sample volume. Furthermore, it was necessary to add determined volumes of pure ethanol in order not to vary its percentage in the suspensions measured afterwards. Then, by plotting the experimental signal against the “added” analyte concentration (Fig. 6b), the parameters collected in Table 2 were obtained. From this linear equation, the real concentration of the active ingredient in the medicine can be extracted by extrapolation.

Finally, a value of 97.56 mg of CLZ in Leponex® was obtained. As expected, the amount found is somewhat lower than that declared as a consequence of two reasons: the first one, the error made with extrapolation is greater than in interpolation (a minimal variation in the slope translates to a large change in the cut-off point with the abscissa) and, the second one, the analysed sample was below the LOQ (ultra-trace level). Comparing this result with the extracted by interpolation, it can be seen that there is a relative error of 2.4 %. As far as the drug company’s specifications are concern, a recovery of 97.6 % is achieved in this case, proving again the adequate accuracy of this methodology. Moreover, a relative error of 2.4 % is found between both methods, demonstrating again that the matrix effect is almost negligible. In any case, the methodology developed offers good precision and excellent accuracy, using a very cheap electrode material and achieving LODs similar to those listed in Table 1.

3.4. Electrochemical applications

The advantages of electrochemical techniques have already been, not only mentioned but also demonstrated with the different studies

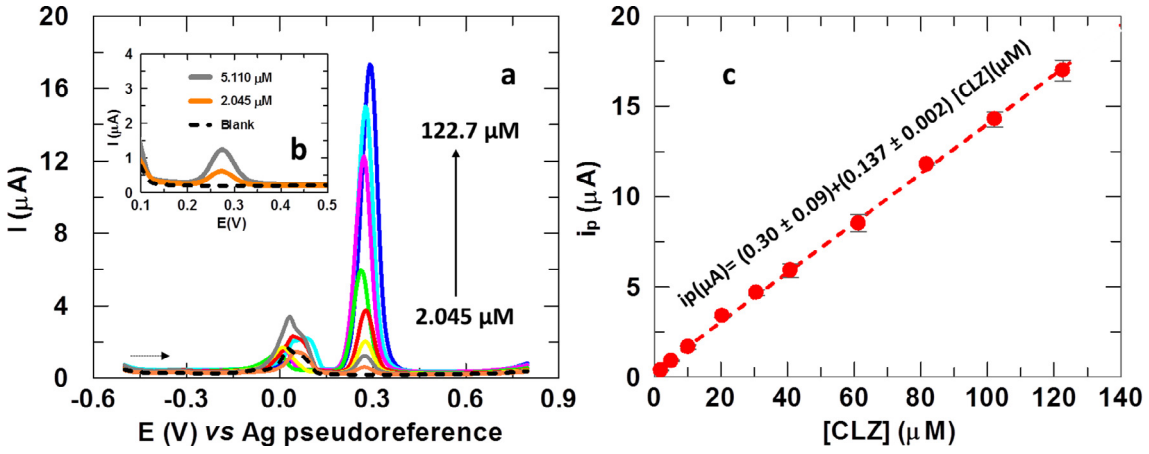

Fig. 4. (a) DP voltammograms obtained by DPV at scan rate 9.9 $mV \cdot s^{-1}$, step potential 5 mV, modulation time 50 ms, modulation amplitude 50 mV and potential range from −0.5 to 0.8 V. Suspension prepared in 10 mM Na_2SO_4 electrolytic medium at pH 3 and 5 % ethanol. (b) Voltammograms at concentrations close to instrumental LOD and LOQ. (C) Fitted curve for CLZ standard with a concentration range from 2.045 to 122.7 μM (n = 6).

Table 2
Analytical parameters and statistical data for CLZ's calibration curve and standard addition analysis of Leponex®.

External standard	Intercept (μA)	Sensitivity (μA·μM^{-1})	Correlation Coef., R^2	Linear range (μM)	LOD (μM)	LOQ (μM)	RSD (%) (n = 6)
$CLZ_{std.}$	0.30 ± 0.09	0.137 ± 0.002	0.9996	2.045 – 122.7	1.69	5.63	3.7
Standard addition CLZ in Leponex®	Intercept (μA) 1.59 ± 0.09	Sensitivity (μA·μM^{-1}) 0.193 ± 0.001	Correlation Coef., R^2 0.9999	CLZ declared (mg/tablet) 100	CLZ found (mg/tablet) 97.56		Recovery (%) 97.6

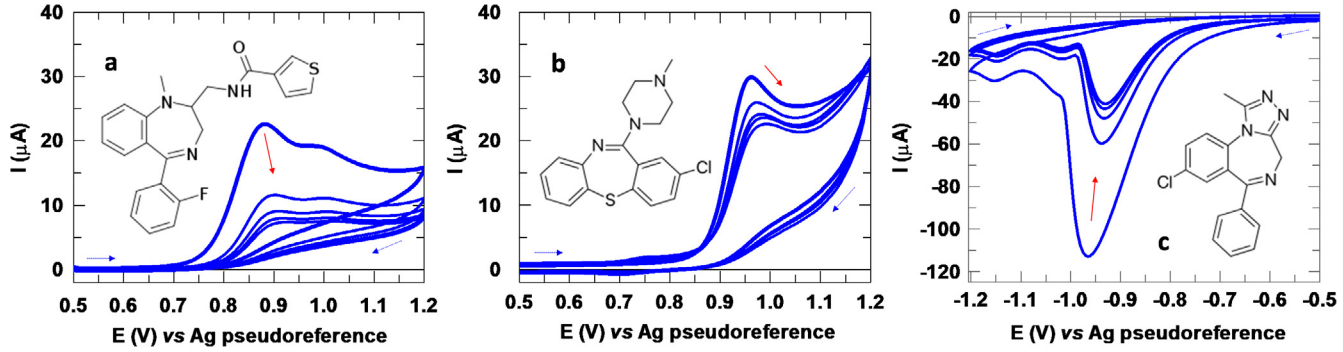

Fig. 5. Cyclic voltammograms (5 scans) and chemical structures of (a) TFL, (b) CLT and (c) ALP.

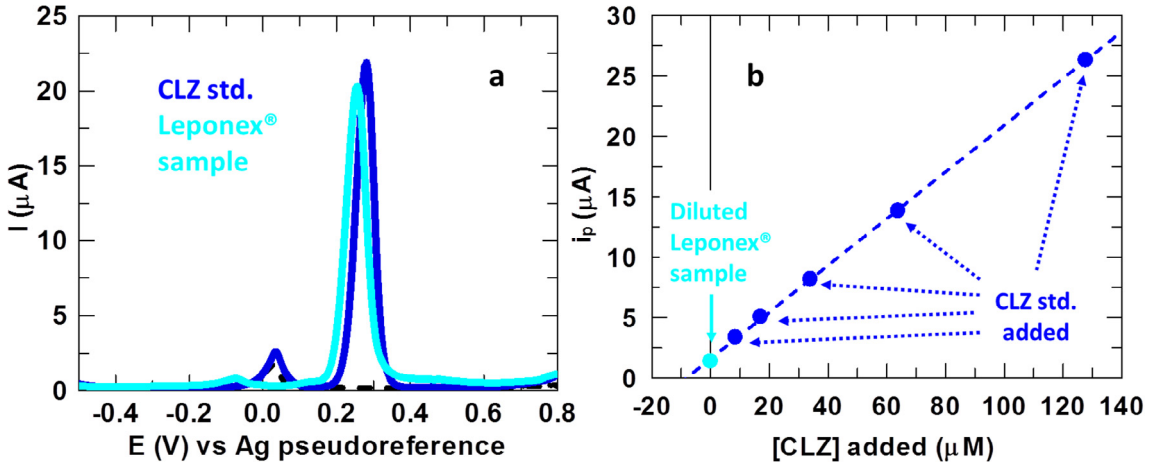

Fig. 6. (a) Both CLZ (standard concentration 125 μM) and Leponex® (with content around 125 μM in CLZ) voltammograms obtained under identical conditions by DPV at scan rate 9.9 mV·s^{-1}, step potential 5 mV, modulation time 50 ms, modulation amplitude 50 mV and potential range from −0.5 to 0.8 V, in 5 % of ethanol and at pH 3. (b) Standard addition plot in the analysis of Leponex® formulations.

collected in the previous sections. Therefore, the next step is to verify the feasibility of this group of techniques when dealing with real problems. Since the aim of this work is to apply these methodologies to prevent environmental pollution, EF process is put in the spotlight. In this way, the study of the degradation of stable active principles is performed using CLZ as a reference.

Moreover, because of the interest generated by the methodology described for its speed and the absence of sample treatment, a portable device was fabricated by Metrohm-Dropsens for the specific analysis of CLZ in complex samples. To verify the performance of the device and also demonstrate that its reliability is comparable to the voltammetric method, measurements in real samples are carried out, as well as the EF process described below.

3.4.1. Monitoring electro-Fenton degradation of pharmaceuticals (Leponex®) in Milli-Q and tap water

As it was previously mentioned, the high stability of this type of drug makes them difficult to get eliminated from the environment. To degrade them, EF is carried out. Throughout this process, the drug is fragmented by the highly reactive ˙OH in a series of successive reactions until total mineralization is achieved. By monitoring the evolution of the anodic peak current of CLZ during the process, it is possible to follow its removal in real-time until its complete degradation, taking DPV measurements at specified time intervals for 24 h. Two different experiments were performed; one with Milli-Q water and the other one with tap water, both under identical conditions. The obtained voltammograms for both experiments can be observed in Fig. 7.

CLZ oxidation peak in Leponex® suspensions appears at 0.280–0.335 V in Milli-Q water (Fig. 7a) and at 0.311–0.354 V in tap water, (Fig. 7b). Two secondary peaks appear in Milli-Q water, one at −0.095 V and another at 0.096 V. These two secondary peaks are also observed in tap water, the first one at −0.085 V and the last one at 0.188 V. All of them may be due to the formation of electroactive polyhydroxylated intermediates generated during the process, which can be oxidized to quinone functionalities. On the other hand, a flattened peak with low intensity located between 0.1 and 0.2 V is associated with iron. The intensity of this peak increases as the CLZ

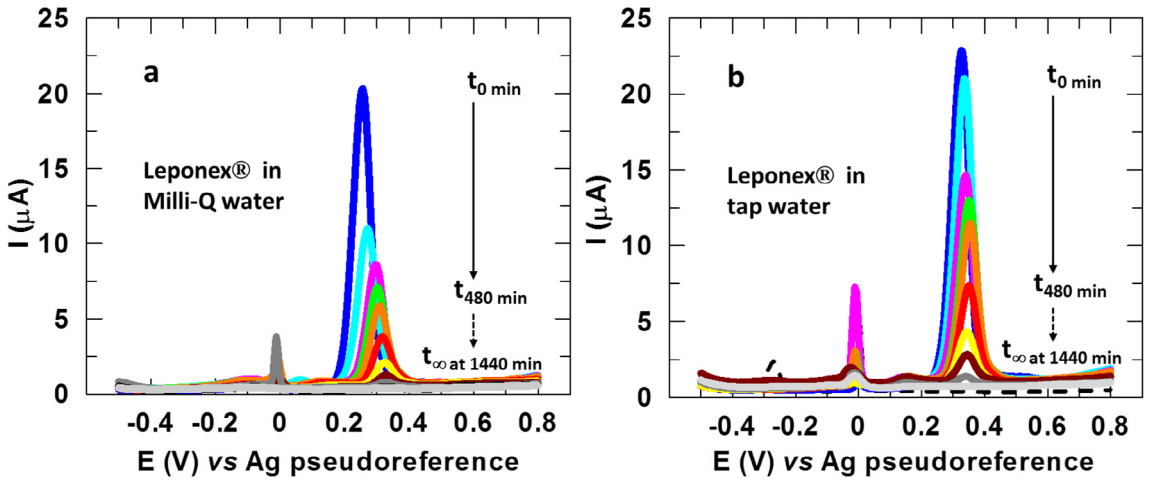

Fig. 7. Monitorization of EF degradation of Leponex® (around 0.123 mM in CLZ, 5 % EtOH) obtained by DPV at scan rate 9.9 mV·s^{-1}, step potential 5 mV, modulation time 50 ms, modulation amplitude 50 mV and potential range from −0.5 to 0.8 V (Fe^{2+} 0.2653 mM, in Na_2SO_4 10 mM medium at pH 3) in (a) Milli-Q (b) and tap water.

peak disappears due to the formation of stable complexes with the organic acids derived from the degradation process. Furthermore, comparing these voltammograms with the already shown in Fig. 6, it can be seen that the peak of the CLZ is not affected by the presence of iron since neither its potential nor its intensity show significant differences with regard to the mentioned experiment in which the drug is found alone.

On the other hand, it can be seen that the drug is degraded faster (around 50 %) during the first 15 min, reaching around 85 % after 2 h of EF treatment, and it completely disappears after 6 h, which means that the degradation process is relatively fast. In contrast, the degradation of Leponex® in tap water shows to be 30 % slower. To verify this in a quantitatively way, the observed kinetic constants, k_{obs}, are obtained both by non-linear fit for the exponential curve, and by linear regression of the logarithmic fit.

The graphics are shown in Fig. 8. In Milli-Q water, a value of 0.0123 ± 0.0003 min^{-1} was obtained from the linearization of the exponential curve, proving that fast degradation kinetics is followed. As far as tap water is concerned, the value decreases to 0.0110 ± 0.0004 min^{-1} because of the presence of intrinsic organic matter, which reduces the availability of ˙OH in the medium and therefore the yield of the reaction.

To determine the variation of ˙OH concentration during the EF process, the reaction of these radicals with terephthalic acid (TA) was used. When TA reacts with ˙OH, it can be obtained the 2-hydroxyterephthalic acid (TAOH) derivative, a highly fluorescent compound which can be analyzed by fluorimetry, from which an excellent calibration curve can be obtained that follows the regression I_F(a.u.) = (3 ± 1) + (2245 ± 7) · [TAOH] (μM) (R^2 = 1). Being able to quantify the amount of ˙OH, it is possible to study the influence of certain parameters which could modify the presence of ˙OH in the reaction during the EF (Fig. 9).

Firstly, the effect of aeration on ˙OH during the EF process in tap water was evaluated. In all three experiments (Milli-Q and tap water with air, and tap water without air) the highest ˙OH concentration was reached approximately at 2 h after starting the process. The higher response was achieved in the case of Milli-Q water, while the lowest was found with tap water without aeration (Fig. 9a) due to the lack of O_2 available in the medium capable of being reduced to H_2O_2 from which the ˙OH are obtained afterwards. On the other hand, the possible effect of the percentage of ethanol (0, 0.25 and 2.5 %) in the EF process was studied, both in Milli-Q water and in tap water (Fig. 9b).

According to the results shown in Fig. 9b, it can be deduced that the ethanol percentage affects the amount of ˙OH generated since the organic solvent acts as a ˙OH scavenger. This effect is highly noticeable in Milli-Q water, while in tap water the intrinsic presence of organic compounds leads to a lower quantity of ˙OH because of that scavenger effect [50,51], as already mentioned above. It is precisely due to this

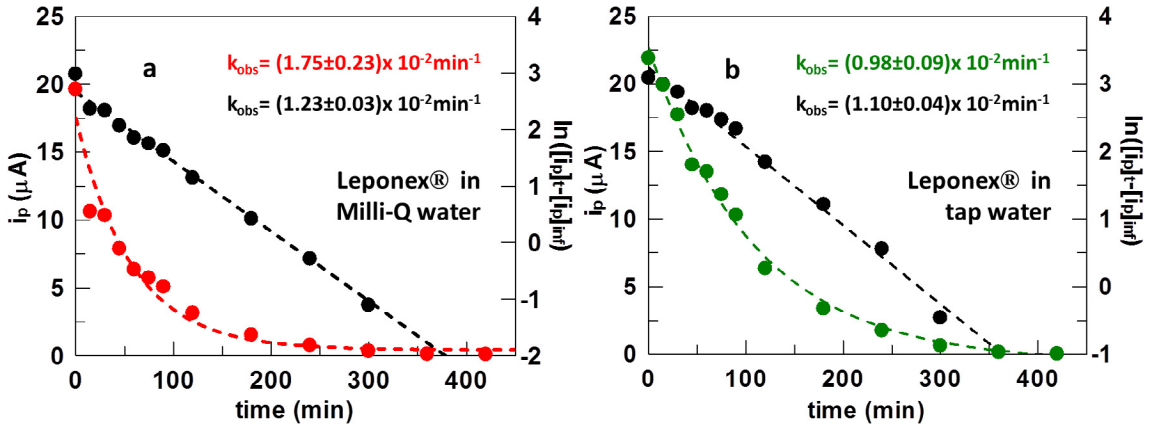

Fig. 8. Determination of k_{obs} from the data of Fig. 7; DPV voltammograms at (a) 276 mV for Milli-Q water and (b) at 325 mV for tap water, with the corresponding linear plot.

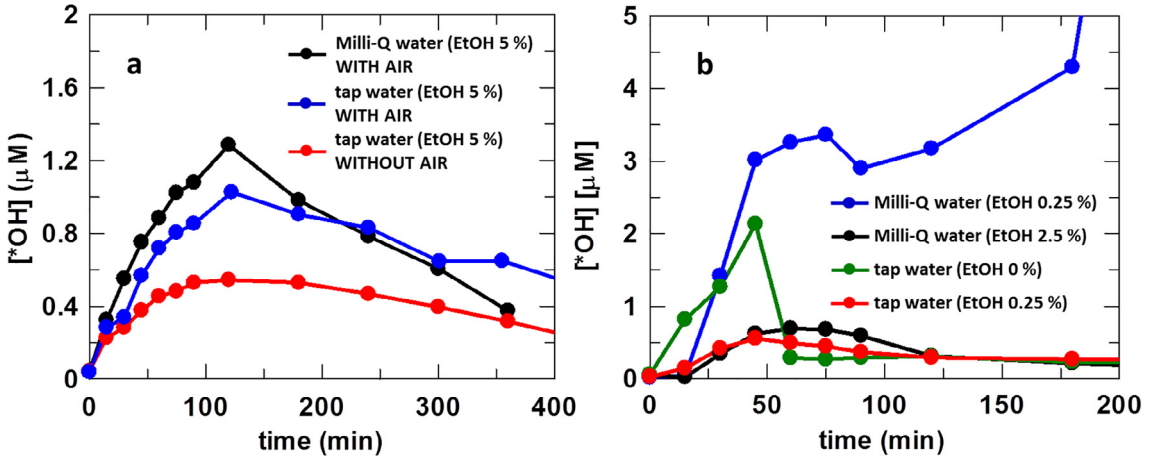

Fig. 9. (a) Hydroxyl radical formation during EF process in Milli-Q water and tap water with and without aeration. (b) Effect of the percentage of ethanol on ˙OH formation in Milli-Q water (0.25 and 2.5 %) and tap water (0 and 0.25 %).

fact that a higher response is achieved for Milli-Q water experiment when studying the aeration influence, since the absence of these intrinsic organic substances leads to a higher amount of radicals available in the medium.

3.4.2. Decentralized analysis and monitoring of medicine degradation in real samples

A portable device was fabricated for the specific determination of CLZ samples with the electrochemical data collected at our laboratory which enables *in-situ* measurements, being able to avoid transportation and storage costs while providing fast and reliable data even when working with complex samples such as pharmaceutical formulations or environmental suspensions. For this purpose, a form containing both optimal conditions and analytical parameters (Table 2) was sent to the manufacturing company so as to ensure the validation of the device. Apart from the statistical parameters studied in Section 3.2. *Electroanalysis of Clozapine by Differential Pulse Voltammetry*, it is necessary to verify if the method is acceptable for its intended purpose using Birke´s key criteria.

As a result, the portable device was sent to the laboratory afterwards in order to check its correct operation both for the quality control of the medicine and for the environmental application based on the EF process. Firstly, a series of Leponex® samples containing determined amounts of CLZ were prepared. The measurements were done using the device, incorporating the SPCE directly into the device. The concentration data is given in only a few minutes, and in this way, a CLZ found a value of 98.13 mg was obtained, which leads to a recovery of 98.1 %. Since the relative error compared to the voltammetric method (with conventional Autolab potentiostat) is 1.8 %, it can be concluded that the portable device is valid for the suggested purpose.

Once confirmed the validation of the portable device for analysis, the next step was to test it during the degradation process by EF. Thus, measurements were taken by the device for a tap water sample under identical conditions, as previously established, in order to compare these results with the obtained by DPV with the conventional Autolab potentiostat (Section 3.4.1, Fig. 7b and Fig. 8b). As it can be noticed from Fig. 10, the device provides the direct reading of the concentration, thus avoiding the intermediate step of interpolating and therefore speeding up the measurement process.

Fig. 10 shows the degradation kinetics of Leponex® in tap water using the portable device, and a value of 0.0010 ± 0.0006 min^{-1} was obtained from the linearization of the exponential curve, in good agreement with the case of tap water measurements with the conventional equipment (Fig. 7b). Attending to these data, it can be seen that

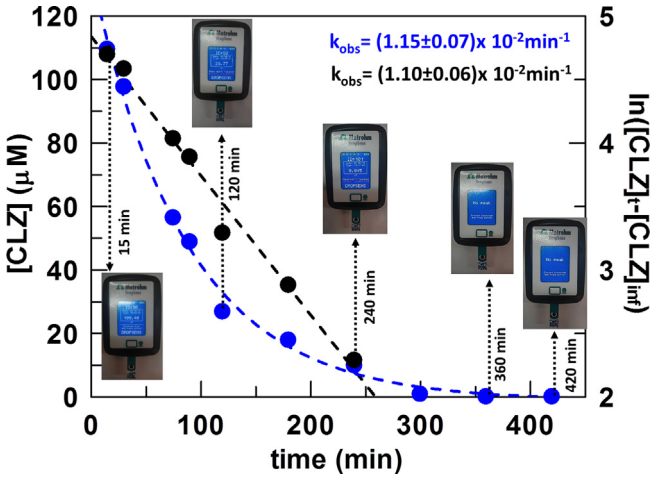

Fig. 10. Obtained k_{obs} with the handle device at 295 mV.

the difference between both methods is so slight that both of them are appropriate for the concerning purpose, thus confirming again the validation of the portable device with the proposed methodology.

4. Conclusions

Throughout this manuscript, electrochemical techniques have been deservedly praised as a means of early detection of environmental contamination, specifically water, whatever its nature. In recent years, drugs have been recognized as emerging pollutants due to their high stability, which allows them to accumulate in the environment. Growing concern about possible adverse effects has launched a race against time to find, not only how to detect these compounds at ultra-trace levels, but also how to efficiently remove them from water afterwards. For this purpose, a methodology has been tuned in which Fenton reaction stands out. Driven by a certain current intensity, EF has allowed the degradation of a specific drug, CLZ, to be achieved, proving to be a valid methodology for the proposed purpose.

Furthermore, the theoretical idea of developing a specific device for the detection of these emerging pollutants *in situ* has become a reality thanks to the developed methodology here and the miniaturized device development under our customized specifications. From the data collected in the laboratory after optimizing both experimental and instrumental conditions, a small, portable device was manufac-

tured by the company and sent to the laboratory afterwards in order to test it with real samples. In this way, water samples doped with the Leponex® medicine were measured, and the results gathered showed a relative error of less than 2 % concerning the measurements made with the conventional potentiostat in the lab. In addition, the EF was applied under the same conditions established for the Autolab equipment, obtaining comparable results in this case as well.

Bearing all this in mind, it can be said that electrochemical techniques, specifically the voltammetric ones studied in this work, do constitute a fast, sensitive and reproducible way of controlling the presence of small amounts of these pollutants in water. Moreover, combining the effectiveness of these techniques for detection and degradation of pollutants with the comfort and high specificity offered by the portable device, a more thorough control of water quality can be achieved, thus being able to improve our quality of life. It should be highlighted that the methodology described and the applicability of the device have been applied on a small scale as probe-of-concept, but due to the growing awareness about the potential danger constituted by these compounds, it is expected that these experiments will be studied on increasingly larger scales so that they can be implemented in water treatment plants in the near future. For this purpose, these investigations are in progress and will be part of a future report.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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