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Electroanalytical Study of Metronidazole and its Interaction with Sodium Dodecyl Sulfate in Aqueous Medium

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Abstract. From electrochemical techniques, it was shown that a carbon paste electrode (CPE) served as depositing substrate for molecular aggregatess of sodium dodecyl sulfate, SDS, termed hemimicelles, that adsorb metronidazole, MTZ, molecules selectively from a water-based dissolution containing the protonated species of MTZ. The manner in which both molecules react SDS–MTZ is indeed relevant since it leads to a different electrochemical MTZ reduction mechanism from one where matter transfer controls the reaction rate through difussion with $D = (2.991 \pm 0.106)\ x10^{-6}\ cm^2s^{-1}$ (when there is no SDS), to a mechanism where adsorption is the rate controlling stage.This leads to implementation of a novel methodology used for single quantification purposes of said MTZ in varied aqueous media or even synthetic urine. This is, analytically speaking the work presented here proves that it can function better, or even just as well as methods comprising other seemingly sophisticated and expensive techniques that can be found elsewhere.
Keywords: Metronidazole; sodium dodecyl sulfate; cyclic voltammetry; carbon paste electrode.

Resumen. A partir de técnicas electroquímicas, se demostró que un electrodo de pasta de carbón (CPE) servía como sustrato de depósito para agregados moleculares de dodecilsulfato de sodio, SDS, denominados hemimicelas, que adsorben moléculas de metronidazol, MTZ, de forma selectiva a partir de una disolución a base de agua que contiene las especies protonadas de MTZ. La manera en que ambas moléculas reaccionan SDS-MTZ es de hecho relevante ya que conduce a un mecanismo de reducción electroquímico de MTZ diferente de uno donde la transferencia de materia controla la velocidad de reacción a través de difusión con $D = (2.991 \pm 0.106)$ x10-6 cm^2s^{-1} (cuando no hay SDS), a un mecanismo donde la adsorción es la etapa de control de la velocidad. Esto conduce a la implementación de una novedosa metodología utilizada para propósitos de cuantificación única de dicha MTZ en variados medios acuosos o incluso orina sintética. Es decir, analíticamente hablando, el trabajo presentado aquí demuestra que puede funcionar mejor, o incluso tan bien como métodos que comprenden otras técnicas aparentemente sofisticadas y costosas que se pueden encontrar en otros lugares.
Palabras clave: Metronidazol; dodecilsulfato de sodio; voltamperometría cíclica; electrodo de pasta de carbón.

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Introduction

Metrodinazole (MTZ), see Fig. 1, it's a synthetic antibacterial and antiparasitic agent. It is classed along nitroimidazoles, with substitution at carbon -1, -2 and -5 with 2-hydroxyethyl, of nitro and methyl groups. The solubility is of 1 mg mL^{-1} at 20° C. It is considered useful with treatments dealing with infections due to harmful anaerobic microorganisms and protozoa. Due to its medical properties, it is widely prescribed and administered, however, 60 to 80 % is discarded in the urine and 6 to 15 % in the feces [1]. Once administered, it can be excreted without undergoing transformation. Thus it is present, and even accumulates in wastewater because of increasing human consumption, thereby giving rise to deleterious effects in humans (associated to bacterial resistance) and the environment at large. Is notable that hospital and wastewater treatment plants bear concentrations of the order (40 to 112) ng L^{-1} of MTZ [2].

It is alarming that the International Agency for Research on Cancer (IARC) stated that animals can undergo lethal mutations, carcinogenicity and genotoxicity of metronidazole although carcinogenicity has not been proven for humans, so far. [3, 4]. The United States enforced legislation against the use of metronidazole in food – producing species [5]. The lack of a reference point to act on nitroimidazoles [6], has impelled publishing guidelines (authored by the community Reference Laboratories) to recommend sensitivity of an analytical method capable of detecting and confirming the presence of nitroimidazole residues in samples [7]. The recommended sensitivity of these methods is 3 mKg^{-1} (or mL^{-1}) in all matrices. On consideration of the above, it's important to develop methodologies that allow their determination and quantification quickly, efficiently and economically. Since Sodium dodecyl sulfate (SDS), an anionic surfactant, is commonly used to solubilize and stabilize some drugs, as well as to improve analytical quantification parameters [8, 9], thus in this work it is reported the electrochemical characterization and quantification of MTZ by means of cyclic voltammetry (CV) in aqueous solution, using a modified carbon paste electrode, CPE, with hemimicelles of SDS.

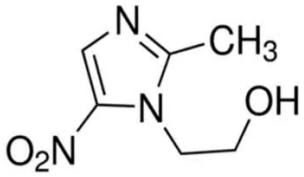

Fig. 1. Metronidazole molecule.

Experimental

Materials and chemicals

The reactants used were classed as analytical grade; the metronidazole (Sigma) was purchased as the sodium salt and acid respectively, phosphate salts and sodium hydroxide (J. T. Baker) and SDS (Aldrich). Deionized water from a Milli-Q (Millipore) served to prepare all dissolutions supplied with 18.0 MΩU cm resistivity. The MTZ was mixed with real samples, from Flagyl® I.V., solution 500 mg /100 mL. The synthetic urine was prepared following Deroco et al. [10], and the resulting samples comprised: 0.73 g NaCl, 0.40 g KCl, 0.28 g $CaCl_2 \cdot H_2O$, 0.56 g Na_2SO_4, 0.35 g KH_2PO_4, 0.25 g, NH_4Cl, and 6.25 g of urea. These were placed in a 250 mL volumetric flask: subsequently, the volume mark was reached with water thus readying the samples to be used right after. Also, the sample was added with 60 mM MTZ (from Flagyl ®).

Electrochemical measurements

A potentiostat AUTOLAB served to do the electrochemistry study, with a conventional three-electrode cell where the working electrode was a bare CPE with a geometric area of 0.071 cm^2), a Pt wire worked as auxiliary electrode (BASi MW-1032) and Ag/AgCl (BASi MF-2021) as the reference electrode, to which all

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potentials must be quoted. Graphite powder (Johnson Matthey 1 mm, 99.9%) and mineral oil (Nujol) from Sigma-Aldrich in a 1 : 1 w/w ratio are the basic ingredients to prepare the CPE. The required conductive mix is placed in a polyethylene tube (10 cm long and 3 mm in diameter) and pushed by a piston. Further relevant details must be found elsewhere in Ramírez et al. [11, 12].

The pH measurements were carried out, through a potentiometer pH/Ion Analyzer (HACH) equipped with a glass electrode (HACH series 5010T) suitable for working in the 0–14 range. A nitrogen protective shroud was used throughout the experiment. Also, the direct incidence of light over the cell was curtailed, with the measurements carried out at 25 ºC.

Results and discussion

Electrochemical characterization

Fig. 2 shows a linear predominance zones diagram constructed following the method reported elsewhere by Rojas-Hernández et al. [13-16], for MTZ. Fig. 2**(a)**, using the respective pKa value [4]; it is possible to observe that at pH values less than 2.55 the protonated species, MTZ^+, does predominate whereas at higher pHs, the neutral species, MTZ, does so.

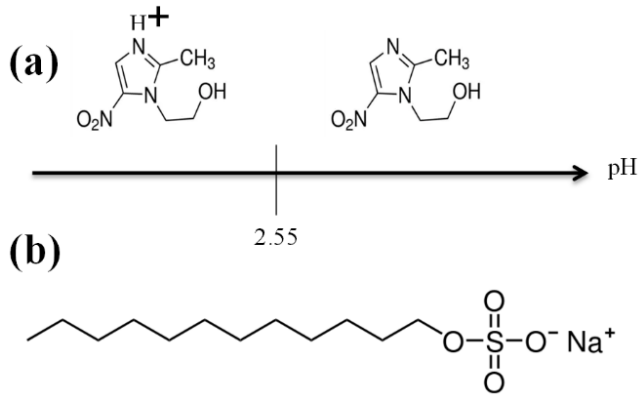

Fig. 2. (a) Linear predominance zones diagram for MTZ constructed following the method reported by Rojas-Hernández et al. [13-16]. **(b)** sodium dodecyl sulfate´s molecule.

Cyclic voltammetry (CV) was used to assess the electrochemical response of MTZ^+. Fig. 3 shows the typical CV of MTZ^+ in the solution prepared. A reduction peak at -0.44 V becomes apparent whereas when inverting the potential sweep no oxidation peaks could be observed, thus it is an irreversible reduction process.

Fig. 4**(a)** shows the experimental CVs obtained during the electrochemical reduction of MTZ^+ by applying different potential sweep speeds; the cathodic peak current of the CVs set obtained evolves linearly with the square root of the potential scan rate, see Fig. 4**(c)**. This indicates that this process is limited by the diffusion of MTZ^+ to the surface of the electrode. Further, Fig. 4**(b)** shows the log-log plot of the cathode peak current as a function of the potential sweep speed (v) displaying a linear trend represented by the log i_{cp}= (0.520 ± 0.011) log ν + (2.831 ± 0.056) equation with r^2 = 0.997. The slope 0.520 corroborates that the charge transfer process is controlled by diffusion [17].

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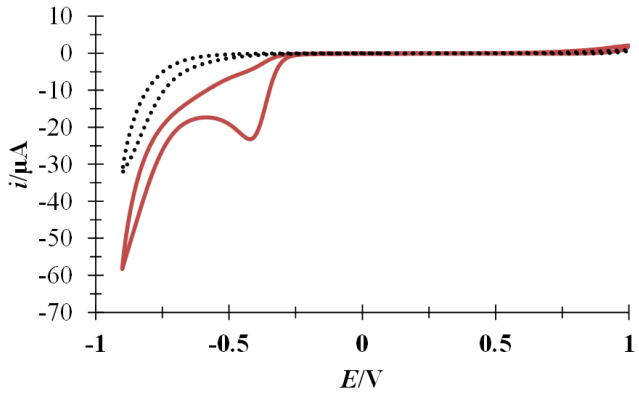

Fig. 3. Experimental CVs recorded in the system CPE / $HClO_4$ 0.1 M MTZ 141.23 (pH 1.1) in the absence (broken black line), and in the presence of MTZ 141.23 mM (solid red line). In both cases the potential sweep started at -0.1 V (zero current potential) in the cathodic direction at 0.1 Vs^{-1} potential sweep rate of, at 25 ºC.

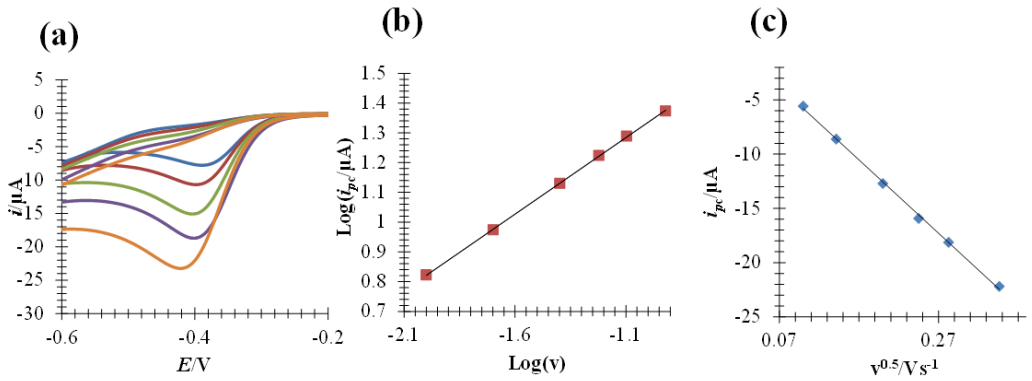

Fig. 4. (a) Experimental CVs recorded in the system CPE / MTZ 141.23 mM, $HClO_4$ 0.1 M (pH 1.1), the potential sweep was started at -0.1 V (zero current potential) in the cathodic direction at different potential sweep speeds (0 - 0.16) Vs^{-1} and 25 ºC. Graphs $\log(i_{cp})=f(\log v)$ **(b)** and $i_{cp}=f(v)^{0.5}$ **(c)** of the CVs in (a).

For an electrochemical process at 25 °C controlled by diffusion, it has the Randles−Ševčík Eqn. 1 [17].

$$i_{cp} = (2.99x10^5)n^{3/2}AC_0^*Do^{1/2}v^{1/2} \quad (1)$$

where i_{cp} is the cathodic peak current in Amperes, n is the number of electrons, A is the area of the working electrode in cm^2, *C*o is the concentration of the analyte in mol/cm^3 and *D*o is the diffusion coefficient.

From the plot of Fig. 4**(c)** the equation obtained is i_{cp} = (-6.753 ± 0.121)x10^{-5} A(Vs^{-1}) + (9.46 ± 2.84)x10^{-7} A, r^2 = 0.998. Using the value of the slope obtained from the linear regression and the number of electrons (4) that are involved in the proposed reduction mechanism reported by Edward [18], it is possible to obtain the diffusion coefficient (D) from equation 1 giving a value D = (2.991 ± 0.106) x10^{-6} cm^2s^{-1}. This value obtained is consistent with others reported using glassy carbon working electrodes modified differently [18].

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Electrochemical study of the MTZ–$(SDS^-)_n$ interaction

Given that SDS is an anionic surfactant, see Fig. 2**(b)**, it will be present as ionic SDS^- molecules in aqueous solution when the SDS concentration values are lower than the respective critical micelle concentration, CMC, and as micelles $(SDS^-)_n$ for [SDS] > CMC. To determine the CMC of SDS in the experimental system, a CV study was carried out. Fig. 5**(a)** exhibits a family of CV for MTZ^+ reduction at different SDS concentrations. Note that in the absence of SDS, the MTZ^+cathodic peak potential shifts from -0.55 V, toward more positive potentials forming a new well resolved peak at -0.3 V as the SDS concentration increases. Fig. 5**(b)** shows the plot of E_{cp} = f ([SDS]) where it would be possible to see the two slopes intersecting, which indicates that the value of the critical micelle concentration (CMC) is above 0.9 mM.

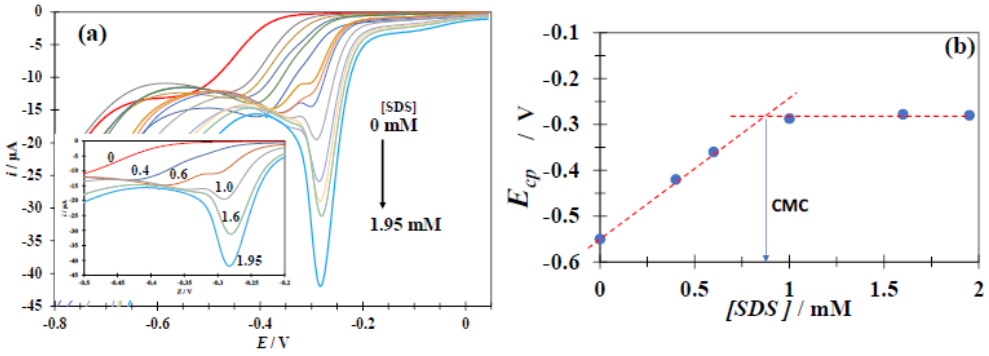

Fig. 5. (a) Family of linear sweep voltammograms, LSV, recorded in the system CPE / MTZ 141.23 mM, $HClO_4$ 0.1 M (pH 1.1) added with different SDS concentration (0-1.95) mM. In all cases the potential sweep started at -0.1 V (zero current potential) in the cathodic direction at 0.1 V s^{-1} and 25 ºC. **(b)** Graph i_{cp}= f [SDS] of some of the LSV in **(a)**.

Once the CMC is found, the electrochemical characterization of MTZ^+ is carried out in the presence of SDS. Fig. 6 shows a comparison of the experimental CVs recorded in a solution containing 1.39 mM SDS in the absence and presence of MTZ 141.23 µM. It is possible to observe that within the potential region where MTZ^+ is reducing, it forms a well-defined cathodic peak with negligible SDS electroactivity. However for more negative potentials than that of this peak, the SDS becomes electroactive (see broken line in Fig. 6).

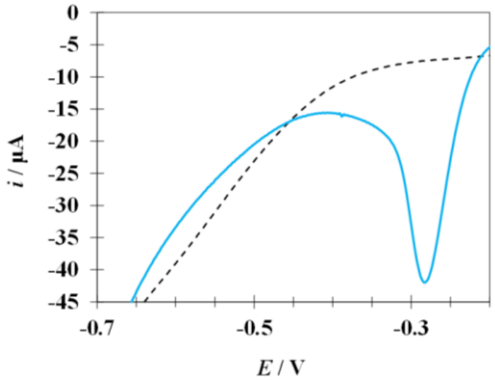

Fig. 6. Comparison of LSVs recorded in the system CPE / SDS 1.95 mM, $HClO_4$ 0.1 M (pH 1.1) in the absence (broken line) and presence (solid line) of MTZ 141.23 mM. In both cases the potential sweep started at -0.1 V (zero current potential) in the cathodic direction at 0.1 V s^{-1} and 25 ºC.

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To know about which is the limiting step during MTZ^+ reduction process, in the presence of SDS micelles, a family of CVs, recorded at different potential sweep rates with the CPE immersed in an aqueous solution containing both MTZ^+ and SDS micelles are reported in Fig. 7**(a)**. The log-log plot of (i_{cp}) as a function of the (ν), from this CVs, see Fig. 7**(b)**, a linear response was obtained, indicating in this case that the process is controlled by adsorption [17] opposite to the diffusion-controlled process observed in the absence of SDS micelles, see above. To further corroborate this outcome, the CVs in Fig. 7**(a)** were analyzed with the theoretical model developed by Laviron [19], see equation (2), of the experimental i-E curves of electrochemical adsorption-controlled processes, that in this case was successfully used to describe the dopamine-SDS micelle interaction in aqueous media [20] and that of dopamine [21,22] and ascorbic acid [23] supramolecular complex formation with β-Cyclodextrin in aqueous media. Fig. 7**(c)** depicts a comparison of an experimental CV, in Fig. 7**(a)**, with a theoretical CV generated by non-linear fit of eqn. (8) to the experimental data. From this figure it is concluded that the model on which is based, eqn. (2), can adequately describe the experimental evidence and that when SDS is present in the system in concentrations grater that the CMC the reduced form of MTZ^+, is strongly adsorbed. Furthermore, from P_3 best fit parameter and eqn. 11 it was obtained the number of electrons involved in this reduction process, being is practically 1.

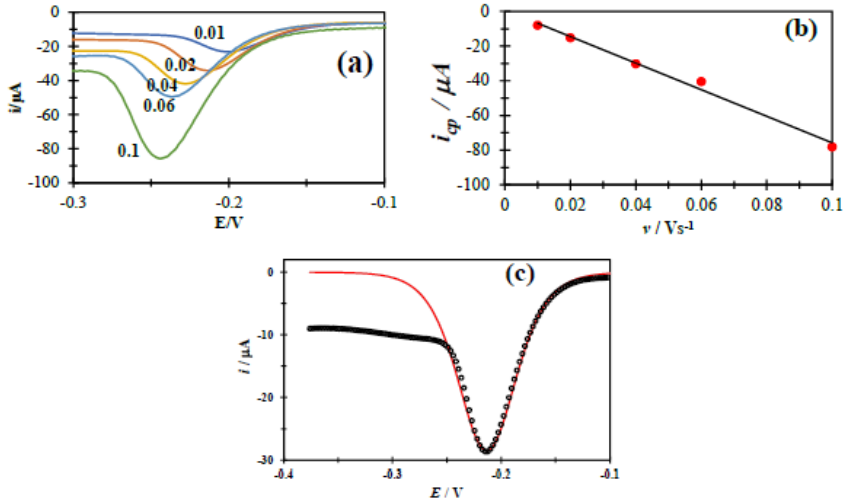

Fig. 7. (a) Set of CVs from the system CPE / MTZ 141.23 mM, 1.39 mM SDS, $HClO_4$ 0.1 M (pH 1.1). In all cases the potential sweep started at -0.1 V (zero current potential) in the cathodic direction at the potential scan rates mentioned in the figures in V s^{-1} and 25 ºC. **(b)** i_{cp} dependence with the potential scan rate, *v*, of the CVs in **(a)**. **(c)** Comparison of the CV reported in **(a)** for 0.01 V s^{-1} (markers) with the theoretical CV (red line) generated by non-linear fitting of equation (2) to the experimental points. The best fit parameters were: P_1 = -114 mA, P_2 = 1.2, P_3 = 52 V^{-1}, P_4 = -0.21 V.

$$i = \frac{n^2F^2}{RT}\frac{vA\Gamma_O^*\left(b_O / b_R\right)\exp\left[\left(nF / RT\right)\left(E - E^{0'}\right)\right]}{\left\{1 + \left(b_O / b_R\right)\exp\left[\left(nF / RT\right)\left(E - E^{0'}\right)\right]\right\}^2} \qquad (2)$$

where the reduction potentials refer to the unabsorbed species and Γo* is the surface coverage. b_O an b_R are related to the adsorption free energy through eqns. (3) and (4) respectively.

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$$b_O = \exp\left(-\Delta G^0_{ads,O}\right) \tag{3}$$

$$b_R = \exp\left(-\Delta G^0_{ads,R}\right) \tag{4}$$

The peak's potential and current are:

$$E_p = E^{0'} - \left(\frac{RT}{nF}\right)\ln\left(\frac{b_O}{b_R}\right) \tag{5}$$

$$i_p = \frac{n^2F^2}{4RT}\nu A\Gamma^*_O \tag{6}$$

Substituting eqns. (5) and (6) in (2) yields eqn. (7)

$$i = \frac{4i_p\left(b_O / b_R\right)\exp\left[\left(nF / RT\right)\left(E - E^{0'}\right)\right]}{\left\{1 + \left(b_O / b_R\right)\exp\left[\left(nF / RT\right)\left(E - E^{0'}\right)\right]\right\}^2} \tag{7}$$

A parameterized form of eqn. (7) is eqn. (8)

$$i = \frac{P_1P_2\exp\left[P_3\left(E - P_4\right)\right]}{\left\{1 + P_2\exp\left[P_3\left(E - P_4\right)\right]\right\}^2} \tag{8}$$

where

$$P_1 = 4i_p \tag{9}$$

$$P_2 = \frac{b_O}{b_R} \tag{10}$$

$$P_3 = \frac{nF}{RT} \tag{11}$$

$$P_4 = E^{0'} \tag{12}$$

MTZ electrochemical quantification

Figure presents the LSVs obtained after the MTZ electrochemical reduction without, Fig. 8**(a)**, and with, Fig. 8**(b)**, MTZ concentrations; see the insets in Fig. 8. These calibration plots allow estimation, with and without SDS micelles and salient analytical characteristics, namely: the limits of detection (LOD) and

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quantification (LOQ) and the respective sensitivity, using the methodology reported by Swartz and Krull [24]. Both plots of the insets in Fig. 8 display a linear trend. Table 1 shows the equation of the straight line obtained for each curve [25].

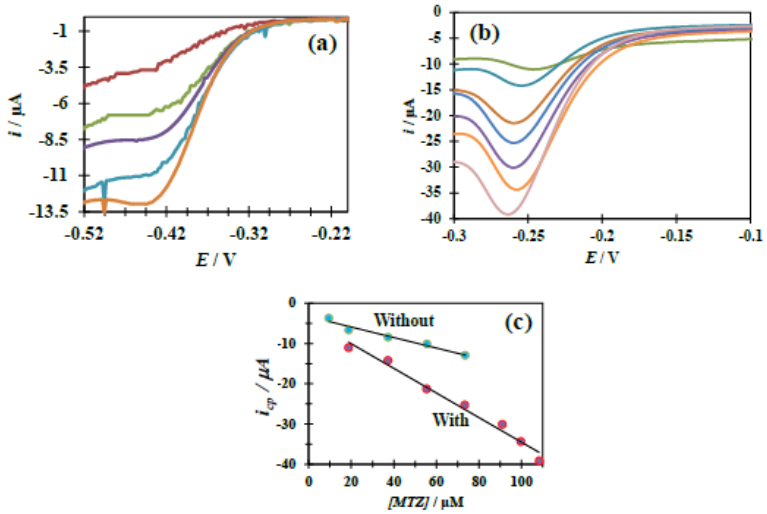

Fig. 8. Set of CVs from the system CPE / $HClO_4$ 0.1 M (pH 1.1) added with different MTZ concentrations without **(a)** and with **(b)** of 1.39 mM SDS. The potential sweep shown started at -0.1 V (zero current potential) in the cathodic direction at 0.1 Vs^{-1} potential scan rate and 25 ºC. **(c)** Calibration plots obtained from their respective CVs (points) along with the corresponding regression line.

Table 1. Calibration curve equations for MTZ quantification obtained from CVs in Fig. 8.

SDS	Equation	R^2
Absence	i_{cp}=(0.128 ± 0.002) µAµM^{-1} *[MTZ]*+ (0.176 ± 0.2) µA	0.997
Presence	i_{cp} = (0.233 ± 0.002) µAµM^{-1} *[MTZ]* + (0.032 ± 0.2) µA	0.998

The results displayed in Table 2, strongly suggest that use of this simple electrode leads to attain similar or better analytical advantages towards MTZ quantification, compared with more technically elaborated electrodes.

Table 2. Comparison of the analytical results of different electrodes towards MTZ quantification.

Electrode	Sensitivity / µA*µM^{-1}	LOD / µM	LOQ / µM	Ref.
CPE	0.128 ± 0.002	7.081 ± 2.476	23.606 ± 3.639	This work
CPE/$(SDS)_n$	0.233 ± 0.002	3.965 ± 1.459	13.219 ± 1.393	This work
Carbon fiber micro disc.	1.50 ± Not reported	0.5 ± Not reported	1 ± Not reported	[26]
Glassy Carbon / Bi film	0.388 ± Not reported	2.94 ± Not reported	Not reported	[27]

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Quantification of MTZ in real sample

Fig. 9 shows CVs recorded in with the CPE immersed in synthetic urine where the Flagyl® (MTZ) drug was dissolved in the absence (broken line) and presence (solid line) of SDS micelles. It becomes clear that the presence of this surfactant has an obvious influence over the voltammetry signal of the drug.

The determination in real samples was carried out using the curve of standard addition from the CVs recorded in the system CPE/MTZ (from Flagyl®). For the determination of MTZ from Flagyl® a calibration plot is to be used interpolating the drug signal. Details of this method are reported in Miller and Miller [28]. It was obtained (5.056 ± 0.119) mg $mL^{-1}$and the statistically estimated error with a 95 % confidence level is less than 1.11 %, which makes the method acceptable for the quantities of the drug obtained.

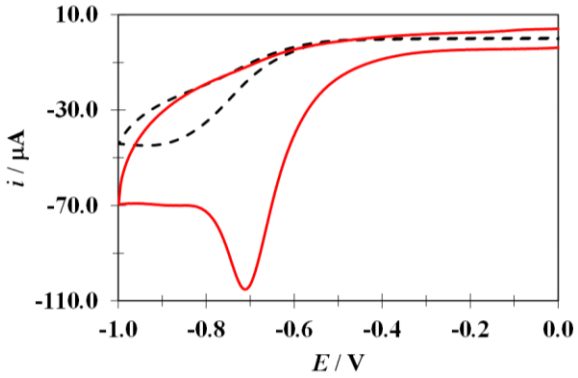

Fig. 9. Experimental CVs recorded in the system CPE / 27.0 mM MTZ (from Flagyl®) in synthetic urine, pH 5.3. with 0 (broken line) and 1.3 mM SDS (solid line) in both cases the potential scan rate started at 0.2 V, in the negative direction at 0.1 V s^{-1} and 25 ºC.

Conclusions

The previous results strongly support the fact that SDS hemimicelles, formed over a CPE, can be used advantageously, quicker and in a less expensive method for the electrochemical quantification of MTZ in aqueous solution. The supportive analytical criteria LOD, LOQ and sensitivity were attained by an inexpensive and simpler manufacture, where an SDS-modified CPE was evaluated, towards MTZ quantification that proved to display high selectivity and sensitivity even in real samples formed by commercial drugs and synthetic urine.

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