Microchemical Journal 193 (2023) 109125

Contents lists available at ScienceDirect

Microchemical Journal

journal homepage: www.elsevier.com/locate/microc

Voltammetric determination of sulfamethoxazole using commercial screen-printed carbon electrodes

Elena Alberto [a], Julio Bastos-Arrieta [a,b], Clara Pérez-Ràfols [a,b], Núria Serrano [a,b], M. Silvia Díaz-Cruz [c], José Manuel Díaz-Cruz [a,b,*]

[a] Department of Chemical Engineering and Analytical Chemistry, Universitat de Barcelona (UB), Martí i Franquès 1-11, 08028 Barcelona, Spain
[b] Water Research Institute (IdRA), Universitat de Barcelona (UB), Martí i Franquès 1-11, 08028 Barcelona, Spain
[c] Department of Environmental Chemistry, Institute of Environmental Assessment and Water Research (IDAEA), Spanish Council of Scientific Research (CSIC), Jordi Girona 18-26, 08034 Barcelona, Spain

ARTICLE INFO

Keywords:
Antibiotics
Differential pulse voltammetry (DPV)
Metabolites
Screen-printed carbon electrode (SPCE)
Sulfamethoxazole (SMX)
Sulfonamides

ABSTRACT

A differential pulse voltammetric (DPV) method using commercial screen-printed carbon electrodes (SPCE) is developed for a fast and cost-effective determination of the antibiotic sulfamethoxazole (SMX). Optimal measurements are carried out at pH 5.5 in acetate buffer and yield a detection limit of 15 μg/L and a linearity range of 50 – 600 μg/L with good repeatability (1.1%) and reproducibility (2.5%). The method is successfully applied to the analysis of a spiked tap water sample with very high reproducibility (0.4%) and good trueness (Recovery 95.2%).

Additional considerations are made about the irreversible electrochemical oxidation of SMX, which is notoriously pH-dependent according to a process involving $2e^-$ and $2H^+$, in agreement with several reported mechanisms in the literature. Besides, the analysis of other sulfonamide antibiotics is discussed, showing the key role of the free terminal amino group in oxidation, which makes almost undistinguishable voltammetric signals from different molecules sharing this moiety. In contrast, the acetylation of the mentioned group (e.g., in sulfonamide metabolites) drastically reduces the sensitivity of voltammetric measurements.

1. Introduction

Recent advances in the field of analytical methodology have allowed the study of a large number of substances that are potentially harmful to different ecosystems and were previously undetected or not considered a risk. These so-called contaminants of emerging concern (CECs) are not necessarily new, but of recent concern due to their potential consequences, since very little is known about their medium- and long-term effects on the environment and human health. Despite that, CECs are not regulated yet and demand urgent research to determine their maximum allowed concentrations in the environment based on reliable ecotoxicological information. A common characteristic of CECs is that they are introduced into the environment at generally low concentrations, of the order of ng/L–μg/L, but continuously, thus behaving as persistent pollutants [1–3].

CECs include many chemicals widely and daily used by modern society, such as personal care products (creams, perfumes, make-up, etc.), household products (detergents, degreasers, window cleaners, etc.), industrial products (plasticizers, paints, preservatives, etc.), perfluoroalkyl compounds, pesticides, and pharmaceuticals used in the treatment and prevention of diseases in both humans and animals [4]. Among them, pharmaceuticals generate great scientific and social concern, mainly due to their daily use and biological activity, which results in a concerning environmental threat [5–9]. Moreover, the consumption of pharmaceuticals is constantly increasing as a direct consequence of a larger human population and a longer life expectancy on a global scale. At the same time, the increase in food demand has resulted in a greater number of livestock activities, thus generating a growing consumption of veterinary medicines [6].

The main routes of contamination by pharmaceuticals are related to the excretion in feces and urine of compounds not assimilated by the body and the corresponding metabolites, which can also be bioactive. These substances are accumulated in wastewater (including urban, hospital, industrial and agricultural wastes) and ultimately reach

* Corresponding author at: Department of Chemical Engineering and Analytical Chemistry, Universitat de Barcelona (UB), Martí i Franquès 1-11, 08028 Barcelona, Spain.
E-mail address: josemanuel.diaz@ub.edu (J. Manuel Díaz-Cruz).

https://doi.org/10.1016/j.microc.2023.109125
Received 14 June 2023; Received in revised form 20 July 2023; Accepted 21 July 2023
Available online 22 July 2023

wastewater treatment plants (WWTPs). The conventional wastewater treatment carried out in WWTPs consists of a primary treatment (degreaser and solids filter) followed by a biological or secondary treatment using commonly activated sludge, but also membrane bioreactors. The elimination of most contaminants during these treatments is usually incomplete since the determination of CECs is not considered among the parameters for controlling the efficiency of WWTPs, essentially designed to eliminate pathogens, suspended solids, and in many cases, also species with nitrogen and phosphorus [10]. Thus, WWTP effluents are usually considered the main sources of discharge of pharmaceuticals into the environment [11]. The concern regarding the environmental occurrence of pharmaceuticals into the natural ecosystems is particularly important for the antibiotics class, based on the formed antibiotic-resistant bacterial (ARBs) strains and antibiotic resistance genes (ARGs) spread [7,8].

Sulfonamides (SAs) are low cost synthetic antibiotics with a bacteriostatic effect and a broad spectrum of action against a large number of microorganisms. As shown in Fig. 1, SAs are structural analogues of p-aminobenzoic acid (PABA) and act as its competitive counterpart in the synthesis of folic acid, which interrupts DNA production in bacteria [12]. All SAs are sulfanilamide derivatives that can be released to the environment via several routes, mostly from animal farms and human consumption. However, emergence of antibiotics resistance poses a great threat to their efficiency in medical treatments [12–14]. In particular, sulfamethoxazole (SMX), whose chemical structure is shown in Fig. 1d, is one of the most prescribed SAs [15,16]. The excretion in urine of unchanged sulfamethoxazole is about 20% [16], thus constituting an important pathway to the environment. SMX is usually detected in wastewater, surface water, and groundwater and international studies have reported concentrations up to 49.7 μg L^{-1} in waters [17].

The growing interest in the environmental presence of SAs has been the main driver of the great advance in analytical methodologies intended for their determination. The combination of the high separation capacity of liquid chromatography (LC) with the high sensitivity and specificity of mass spectrometry (MS), even more in the case of tandem mass spectrometry (MS/MS), and the coupling of on-line preconcentration systems like solid phase extraction is today the best strategy in the detection of SAs in environmental matrices [18–20].

Nevertheless, LC-MS/MS techniques use expensive, non-portable equipment located in centralized laboratories and require highly specialized analysts. Thus, it is interesting to complement these powerful tools with simple, fast and cost-effective strategies based on electrochemical sensors for screening purposes and on-site monitoring of pollutants. In recent years, electrochemical sensors based on carbon materials and nanomaterials have become very popular in the detection of pharmaceuticals and bioactive substances due to their simplicity, low cost, disposable character and versatility, which is especially true for screen-printed electrodes (SPE) [21–27].

Although the interest of electrochemists in SAs is relatively old [28], the mechanism of its electrochemical oxidation is not clear yet. It appears to involve two protons and two electrons in an irreversible electrochemical process and different mechanisms have been proposed [29], such as these shown in Fig. 1f and g.

There are few studies on the electroanalytical determination of SAs [29–42], and they are mostly based on modified solid electrodes. Regarding SPEs, such devices are scarcely used for the voltammetric determination of SAs and, in most cases, they are lab-made or modified from the bare commercial units [43–47].

Considering the good results obtained with carbon-based commercial SPEs for the determination of other pharmaceutical products [48–50], in this work we evaluate the performance and applicability of a commercial screen-printed carbon electrode (SPCE) in the voltammetric determination of SMX as a proxy sulfonamide antibiotic. We believe that an electrochemical detection strategy based on the use of the simplest and less expensive type of commercially available SPEs would be especially useful in the design of sensing platforms for the in-situ monitoring of antibiotics like SMX in WWTPs. It is important to evaluate the

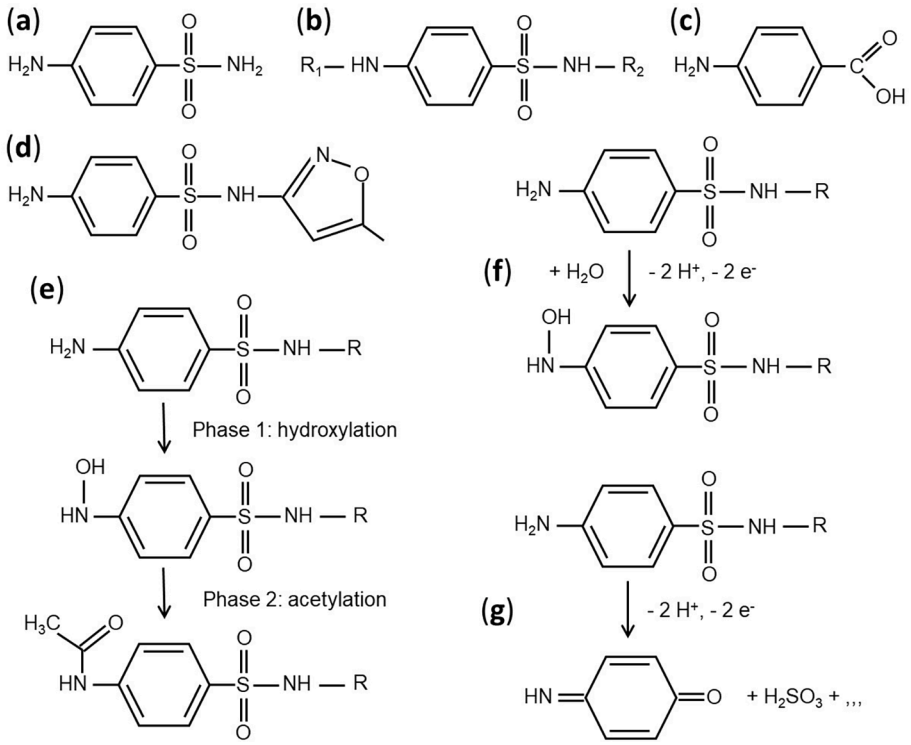

Fig. 1. Chemical structure of sulfanilamide (a), generic family of sulfonamides (b), p-aminobenzoic acid (PABA) (c) and sulfamethoxazole (SMX) (d). Generation of typical metabolites of sulfonamides (e), and two alternative mechanisms proposed for the oxidation of sulfonamides, one involving hydroxylation (f) and the other a fragmentation of the molecule (g). For more information, see refs. [13] and [26].

capability of voltammetry using these bare devices and be able to reach low concentration levels without the need of costly and time-consuming modifications. In the event of high detection limits, preliminary on-line concentration systems could be used in combination with other in-situ detection and/or sampling systems installed in the same platform.

In addition, a comparative study on the electrochemical behavior of SMX and other SAs has been carried out to assess the extent in which voltammetric measurements refer to a specific compound or a group of them, and also to identify which functional groups are involved in the detection mechanism. Table S1, in the supplementary information, summarizes the structure and main properties of the substances considered.

2. Materials and methods

All chemicals employed were of analytical grade. Sulfamethoxazole (SMX), sulfapyridine (SPY), sulfadiazine (SDZ), sulfamerazine (SMR), sulfamethazine (SMZ), N-acetyl sulfamerazine (acSMR), N-acetyl sulfadiazine (acSDZ), sodium acetate and sodium hydrogen carbonate were acquired from Sigma Aldrich (St. Louis, USA). Acetic acid was purchased from Merck (Darmstadt, Germany), whereas sodium dihydrogen phosphate, ethanol and formic acid were provided by Panreac (Barcelona, Spain). Purified water was obtained from Milli-Q Reference A+ Water Purification System by Millipore (Burlington, Massachusetts, USA) and employed to prepare buffer solutions.

Stock standard solutions of SMX, SPY, SDZ and SMZ were prepared in 0.1 mol/L acetic acid/acetate buffer solution at pH 5.5, whereas stock standard solutions of acSMR and acSDZ were dissolved in acetic acid / acetate buffer solution pH 5.5 with 2.5 % of ethanol. pH measurements were carried out with a pH-meter Crison basic 20 (Barcelona, Spain).

Voltammetric measurements by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) were carried out using a μAutolab potentiostat System type III purchased from Ecochemie (Utrecht, Netherlands) and attached to a 663 VA Stand Metrohm (Herisau, Switzerland) and a personal computer with GPES software 4.9 version (Ecochemie) to control the system. GPES software was also used for data acquisition and visualization. The experiments were performed in a glass cell with a three-electrode arrangement: Ag/AgCl/KCl (3 mol/L) as reference electrode (to which all potentials are referred), a Pt wire as an auxiliary electrode and a commercial SPCE ref. DRP-110 from Metrohm-Dropsens (Oviedo, Spain) as a working electrode. The working electrode of the SPCE was connected to the potentiostat using a flexible cable (ref. CAC) acquired from Metrohm-Dropsens. All experiments were carried out without deaeration and at room temperature (20 °C). Unless otherwise indicated, pulse heights of 50 mV, pulse durations of 50 ms and scan rates of 50 mV s^{-1} were applied in DPV measurements.

3. Results and discussion

3.1. Preliminary electrochemical studies

The first goal of the study was to characterize the electrochemical behavior of SMX using CV. Considering previous studies in the literature [34,36,38], initial experiments were carried out at pH 7.0 using a phosphate buffer solution (PBS). Successive CV scans were performed in a solution containing 2 mg L^{-1} of SMX using a SPCE as a working electrode and considering a potential window between 0.4 and 1.1 V at different scan rates (Fig. 2). The scans were very reproducible when repeated at the same scan rate, thus demonstrating the absence of electrode fouling. The anodic peak at *ca.* 0.75 V and the absence of the corresponding cathodic peak (Fig. 2a) confirm the irreversible oxidation of SMX under these experimental conditions, in line with previous results reported in the literature [28]. Moreover, the good linearity between the peak height (I_p) and the square root of the scan rate (v) (Fig. 2b) evidences that the electrochemical process is controlled by diffusion. This is confirmed by the linear plot of log I_p vs. log v observed (data not shown), which provides a slope of 0.57 (pretty close to ½), an intercept of 0.11 and an r^2 value of 0.9999. The results described so far are qualitatively similar to those reported in the study by Chen *et al.* [32] with a SPCE modified with reduced graphene oxide (rGO-SPCE) and in the study by Arvand *et al.* [35] by using a carbon-nanotube paste electrode (CNTPE).

pH plays a key role in the optimization of the voltammetric determination of SMX, as different protonation states of SMX result in either cationic, anionic or neutral SMX species. SAs present two pK_a values and an isoelectric point between pH 4 and pH 5. At low pH, cationic species occur, since the amino group is protonated (pK_{a1}); at slightly acidic pH values neither group is ionized and neutral species predominate; finally, at high pH the amide group (pK_{a2}) is deprotonated, producing anionic species. Fig. S1 shows the species distribution diagram as a function of

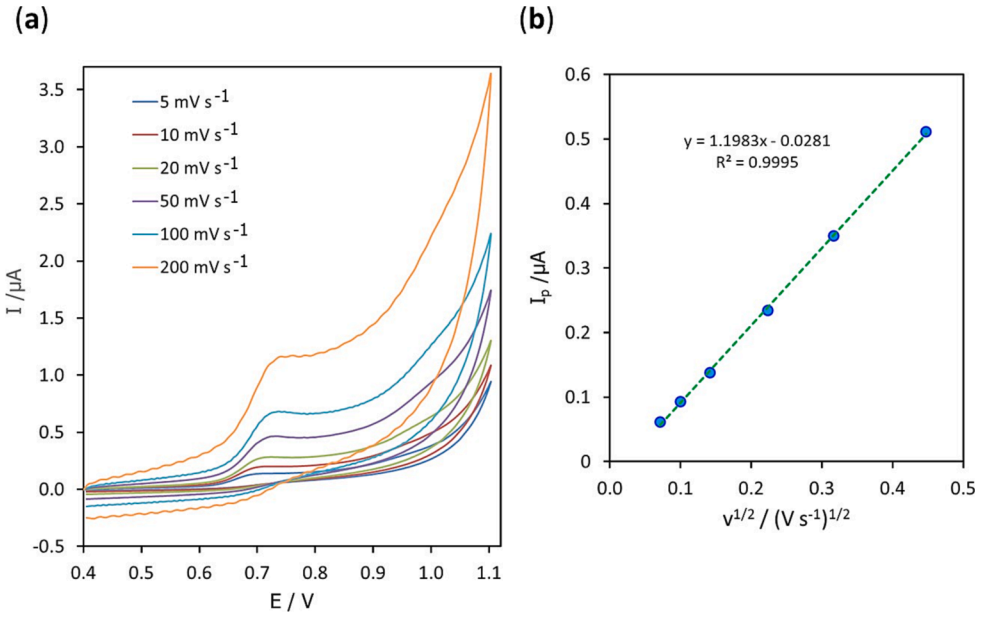

Fig. 2. (a) Cyclic voltammograms measured with a SPCE in a solution containing 2 mg/L of SMX in PBS buffer 0.1 mol/L at pH 7.0 and at different scan rates; and (b) plot of the height of the anodic peak, I_p, as a function of the square root of the scan rate, v. The parameters of the regression line are shown in the graph.

pH for SMX ($pK_{a1} = 1.9$; $pK_{a2} = 5.7$).

To assess the influence of pH on the oxidation signal of SMX, a series of DPV scans were registered for a concentration of SMX of 0.6 mg L^{-1} at different pH values, using 0.1 mol/L buffer solutions of acetic acid/acetate at pH 4.0, 4.5, 5.0 and 5.5, and PBS at pH 6.0, 6.5, 7.0, 7.5 and 8.0 (Fig. 3).

As Fig. 3a shows, decreasing pH causes a progressive shift of the peak toward more positive potentials, thus hindering the oxidation process. However, peaks obtained at acidic pH are higher than those measured under neutral or basic conditions. Fig. 3b depicts the evolution of the peak current as a function of pH. As can be seen, the peak current increases from pH 4.0 to 5.0, reaches a maximum between pH 5.0 and 5.5 and then starts to decrease at higher pH values, especially above 6.0. It must be noticed that this last decrease concurs with the disappearance of the neutral form of SMX (Fig. S1). A plausible explanation for such behavior is that thermodynamic and kinetic factors are interacting with each other. It seems that basic pH values stabilize the oxidized form of SMX and/or destabilize the reduced form, so that the oxidation is easier and takes place at lower positive potentials. However, both proposed mechanisms (Fig. 1f and g) include H^+-ions in the electrochemical reaction and, therefore, such ions are supposed to play a key role in the electrode kinetics (high concentrations of protons lead to increased oxidation rates). Considering both aspects, we could explain the presence of a maximum in the current at pH *ca.* 5.5 as a compromise between thermodynamic and kinetic contributions to the SMX oxidation: at lower pH values, the presence of abundant H^+-ions improves kinetics, but is thermodynamically unfavorable, whereas at higher pH thermodynamics is more favorable but the low concentration of H^+-ions makes kinetics slower. Nonetheless, without a doubt the optimal pH value for achieving a good sensitivity in the determination of SMX is around 5.5. Hence, pH 5.5 was selected for further experiments.

Looking at the plot of peak potential as a function of pH (Fig. 3c), we realize that there are two well-defined linear ranges. At pH between 4.0 and 5.5, just in a range where the neutral form of SMX predominates (Fig. S1), there is a linear relationship ($r^2 = 0.9999$) with a slope of −0.059 V, fully coincident with a proton-to-electron ratio of 1.0 in the electrochemical reaction [33]. This agrees with both oxidation mechanisms proposed for SMX in Fig. 1f and 1g, since both involve $2H^+$ and 2 e^-. In contrast, at pH values higher than 5.5, when the deprotonated form of SMX starts to predominate (Fig. S1), the slope suddenly decreases and approaches the value of −0.042, corresponding to a proton-to-electron ratio of 0.7. Indeed, the intersection of both lines takes place at pH 5.35, close to the tabulated value of $pK_{a2} = 5.7$, suggesting that the electrochemical reaction suddenly changes depending on the degree of protonation of SMX. In the studies of refs. [32] and [35], such evolution of the slope is not so clear and overall values of −0.039 V and −0.032 V, respectively, are obtained along the whole pH range considered. Nevertheless, in both cases, a slight sigmoidal shape of the plot is perceived with a noticeable higher slope between pH 3 and pH 6. In contrast, the use of a silver-filled carbon nanotube composite in ref. [37] produced a slope of −0.052 (very similar to ours) in a relatively wide pH range, from 2.0 to 8.0. Likewise, in ref. [38] a glassy carbon electrode modified with a graphitic carbon nitride and zinc oxide nanocomposite generated a slope very close to our value (-0.0575). All this suggests that the electrochemical oxidation of SMX may be quite similar regardless of the nature of the electrode.

Finally, some attempts at electrochemical preconcentration of SMX were made at different potentials in the range of −0.5 – 0.5 V, but they were unsuccessful. Similar results were reported by Aryand *et al.* [35]. Indeed, preconcentration by oxidation was highly improbable considering the irreversible character of the oxidation, but these experiments have also shown that there is not a remarkable affinity between SMX molecules and the electrode surface, hindering an effective preconcentration by adsorption (which is consistent with the good linearity observed between I_p and $v^{1/2}$ in CV measurements). Although these facts do not contribute to increasing the sensitivity of the method, they would probably assure a low degree of electrode fouling and good repeatability and reproducibility.

3.2. Calibration and figures of merit

Once experimental conditions were optimized, calibration curves for SMX at the optimal pH of 5.5 were recorded by DPV in triplicate (Fig. 4). As can be seen in Fig. 4b, the obtained linearity was good and it extends up to 600 μg/L (0.6 ppm). At higher concentrations, the standard deviation of the measurements notoriously increased and the peak current started to deviate from linearity. Sensitivity, determined from the slope of the calibration plot, was 0.328 nA μg^{-1} L. By using the values below 600 μg/L, a detection limit (LOD) of 15 μg/L was computed as 3 times the standard deviation of the intercept of the regression line divided by

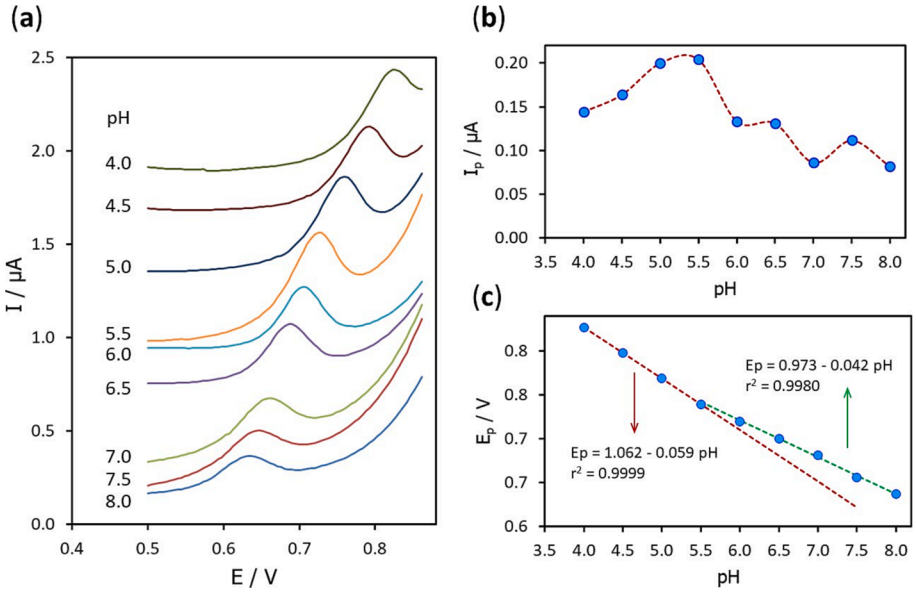

Fig. 3. (a) Differential pulse voltammograms measured with a SPCE in solutions containing 0.6 mg/L of SMX at different pH values, which are indicated in the graph, and evolution of the peak height (b) and the peak potential (c) of the oxidation signal of SMX as a function of pH. The parameters of the regression lines of (c) are also shown.

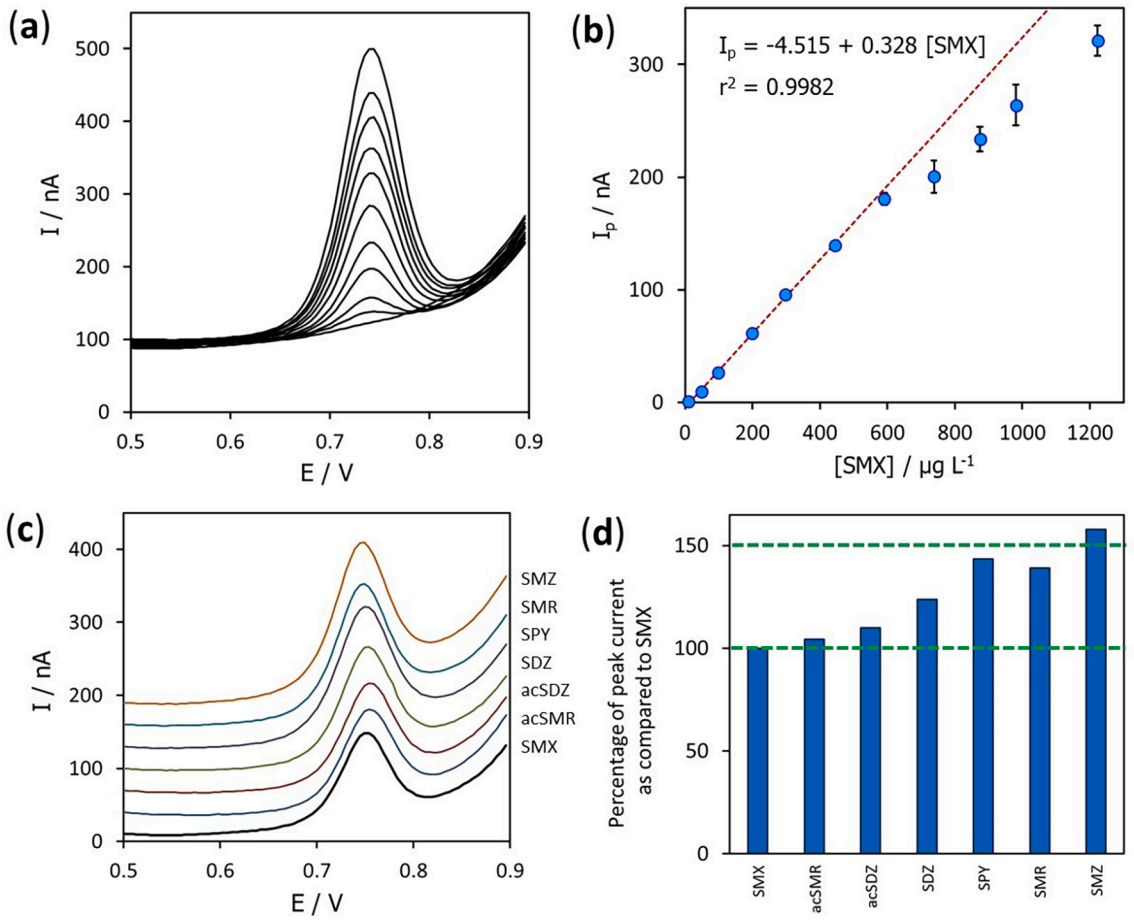

Fig. 4. (a) DP voltammograms measured along a calibration experiment in the range 10 – 1200 µg/L of SMX at pH 5.5. (b) Calibration curve of SMX obtained from DPV peak currents. Each point is the average of three measurements obtained along three independent calibration curves. The standard deviation of each point is denoted by the error bars and the equation of the regression line (marked in red color) is given in the graph. (c) Comparison of the DP voltammogram measured in a SMX solution of 400 µg/L (in black) and in solutions which, besides 400 µg/L of SMX, also contain 200 µg/L the indicated sulfonamides. (d) Comparison of the peak heights of the signals referred as a percentage of the SMX signal. Green lines denote two limiting situations: the additional sulfonamide does not contribute to the current (100%) and it contributes with the same sensitivity as SMX (150%).

the slope. Similarly (10 times instead of 3 times), a quantification limit (LOQ) of 50 µg/L was calculated, thus defining a linearity range of 50 – 600 µg/L.

Repeatability and reproducibility were evaluated with successive DPV measurements carried out in solutions containing 400 µg/L of SMX at pH 5.5. For this purpose, three series of 10 measurements were performed with three different SPCE units. Repeatability was computed in each series as the relative standard deviation of the peak heights, and ranged between 1.1 and 2.5%. As for reproducibility, calculations were done in the same way but considering together all measurements of the three series, and a value of 3.8% was obtained.

Table 1 compares the figures of merit discussed above with those achieved by other voltammetric methods in the literature. Considering that the proposed method uses an unmodified disposable commercial electrode, the obtained LOD is similar and sometimes lower than previously reported LODs using sensors for the determination of SMX, many of which involve complex modification processes. Moreover, if we compare the LOD achieved in this work with that obtained using another unmodified disposable commercially available electrode, such as the pencil graphite electrode (PGE) [42], SPCE provides a LOD value almost 1.5 times lower. Therefore, only works involving biosensors or some kind of preconcentration step with selective coatings on the electrode report lower LOD values.

Thus, the achieved results allow to conclude that the use of unmodified SPCE is fully suitable for the determination of SMX at low µg/L levels, with the additional advantage that SPEs can be used as commercially acquired, which represents a considerable reduction in the cost and the time dedicated to electrode preparation. Moreover, unmodified SPCEs can be safely stored at room temperature for long periods and are easily coupled to portable instrumentation, thus enabling in-situ analysis.

Finally, the voltammetric behavior of other substances of the family of SAs (Table S1) was also evaluated. For this purpose, solutions containing 400 µg/L of SMX were submitted to additions of 200 µg/L of the sulfonamides SDZ, SPY, SMR and SMZ, which, similarly to SMX, contain a free terminal amino group. The same experiment was done with the acetylated metabolites of the selected sulfonamides, i.e. acSDZ and acSMR, where such a group is conjugated in the form –NH-$COCH_3$. Fig. 4c and d show the obtained voltammograms and the corresponding peak currents, evidencing two main facts: i) all SAs tested are oxidized almost at the same potential, producing a severe overlapping of signals when they coexist in the same sample, and ii) the contribution of the acetylated SAs to the current is much lower than that of SAs with a free terminal amino group. On the one hand, these outcomes confirm the key role of amino groups in the oxidation of SAs, and, on the other hand, they shows that it is not possible to discriminate among the members of this family of antibiotics without a previous separation step. Therefore, although the present method would not be appropriate for the simultaneous determination of different SAs, the oxidation peak in DPV is a key indicator of the total amount of SAs with a terminal amino group in

Table 1
Comparison of the figures of merit of the proposed method with these of other voltammetric and amperometric methods for SMX determination found in the literature. All reported data have been converted from the original units to μg/L.

Technique	Electrode	pH	LOD (μg L^{-1})	Linearity range (μg/L) [a]	Ref.
DPV	SPCE-rGO	6.0	10	130 – 13000	[32]
DPV	ppMIP-MWCNT	2.4	105	500 – 2700	[33]
DPV	BDDE	7.0	16	65–9000	[34]
DPV	CNTPE	6.0	100	350–30000	[35]
DPV	PCE-MWCNT-SbNP	7.0	6.1	25.3–180	[36]
DPV	Ag-MWCNT-MTOAC	6.0	2.5	13–18000	[37]
AM	GCE-gC_3N_4/ZnO	7.0	1.7	5–280000	[38]
DPV	GO/ZnO	5.5	7.3	25.3–380	[39]
SWV	CPE	6.0	180	580–2500	[40]
DPV	AgNPs-PANI-NAs	6.0	0.02[b]	0.25–2500	[41]
DPV	PGE	8.0	1000	2500–63000	[42]
AM	TYR-AuNPs-SPCE	8.0	–	5000–50000	[44]
DPV	MWCNT/PBnc	7.0	9.6	250–2500	[45]
DPV	SPCE	5.5	15	50–600	This work

[a]In principle, the lowest value of the linearity range should be the quantification limit (LOQ), but this is not the case in some reported data.
[b]Doubtful value, computed by S/N ratio and much lower than the starting of the linearity range.
AM: amperometry; CPE: carbon paste electrode; DPV: differential pulse voltammetry; EIS: electrochemical impedance spectroscopy; GCE: glassy carbon electrode; GO: graphene oxide; MIP: molecular imprinted polymer; MNP: magnetic nanoparticle; MTOAC: methyltrioctyl ammonium chloride; MWCNT: multiwalled carbon nanotubes; NAs: nanowire arrays; NP: nanoparticle; PANI: polyaniline; PBnc: Prussian blue nanocubes; PCE: paraffin composite electrode; PGE: pencil graphite electrode; rGO: reduced graphene oxide; SPCE: screen-printed carbon electrode; TYR: tyrosinase.

its molecule.

3.3. Application to a spiked tap water sample

To evaluate the capabilities of the proposed methodology for the determination of SAs in natural waters, a tap water sample collected from the laboratory and part of the distribution network of Barcelona was spiked with 500 μg/L of SMX. For the voltammetric analysis, pH was adjusted to 5.5 with acetic/acetate buffer solution (dilution factor 1:1) and the standard addition calibration method was employed. This analysis was performed in triplicate (i.e., three standard addition series with three different samples and three new SPCE units) and consisted of measuring the sample before and after successive additions of a standard solution of SMX. Fig. 5 shows representative measured voltammograms and the corresponding standard addition plot. The concentration of SMX calculated by extrapolation and the obtained value was 476 μg/L with a standard deviation of 1 μg/L, thus achieving a satisfactory recovery of SMX in tap water (95.2%) and a good precision (0.4% relative standard deviation).

4. Conclusions

The investigations performed in this study show the promising role of commercial SPCEs in the determination of SMX in water samples. The LOD value achieved (15 μg/L) is in the order or even lower than those previously reported for other voltammetric and amperometric methods for SMX determination based on modified (bio)sensors. Certainly, this LOD value is still far from those provided by LC-MS/MS, which are in the low ng/L. However, the use of previous non-electrochemical preconcentration steps, for instance by solid phase extraction, could help approaching such low concentrations. Then, the disposable character, simplicity and low cost of SPCE units could be a great advantage for implementing this electroanalytical detection technique in integrated monitoring systems as a complement to the more accurate but also more complex and expensive HPLC-MS/MS methodology. The lack of selectivity of the voltammetric measurements towards the different members of the family of sulfonamides and its very low response when the terminal amino group is acetylated can be overcome if the method is

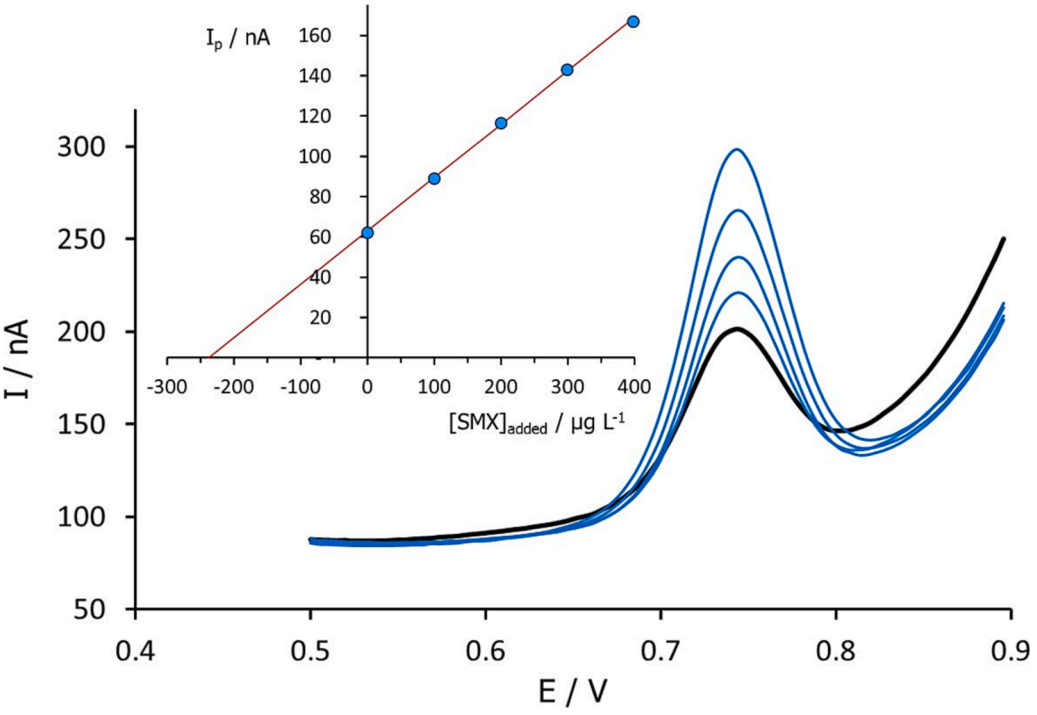

Fig. 5. DP voltammograms measured with a SPCE in the analysis of SMX in a spiked tap water sample at pH 5.5 and the corresponding calibration plot by standard addition (inset). The determination was carried out by triplicate. The voltammograms shown were measured in one of the series, whereas the peak currents of the calibration plot are the average of the three replicates (standard deviations are smaller than the radius of the points). The voltammogram of the sample prior to the standard addition is denoted by a thick black line.

intended as an indication of the overall amount of non-acetylated sulfonamides in the sample. The determination of the parent compound alone, without its metabolites, is useful, for instance, to determine the excretion rate of the pharmaceutical consumed, or as a control in the production of SAs in the pharmaceutical industry.

5. Author statement

Elena Alberto: experimental work and data treatment. Julio Bastos-Arrieta, Clara Pérez-Ráfols and Núria Serrano: experimental design, data treatment and revision of the manuscript. M. Silvia Díaz-Cruz and José Manuel Díaz Cruz: research funding, conceptualization and writing of the manuscript.

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.

Data availability

Data will be made available on request.

Acknowledgments

This work is supported by Project PID2019-107102RB-C22 funded by MCIN/AEI/10.13039/501100011033 and the Generalitat of Catalunya (Projects 2021 SGR 00006 and 2021 SGR 00753). Elena Alberto acknowledges the support of the Water Research Institute (IdRA) of the University of Barcelona for the acquisition of consumables.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.microc.2023.109125.

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