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FFTSW Voltammetric Sensor based on $Eu_2(CO_3)_3$ Nanoparticles for Sulfadiazine Determination

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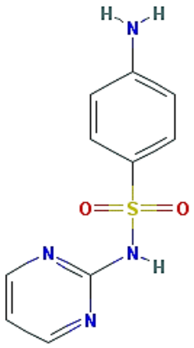
Abstract- In this work, a new sensitive sensor based on the application of fast Fourier transform square wave voltammetry (FFTSWV) for the determination of sulfadiazine is described. The developed sensor is a modified carbon paste electrode with $Eu_2(CO_3)_3$ nanoparticles. The characterization of the used materials was done through transmission electron microscopy (TEM) and FT-IR spectroscopy. The cyclic voltammogram of sulfadiazine showed a well-resolved irreversible oxidation peak at around 0.85 V vs. Ag/AgCl. After optimization of experimental conditions, such as pH, percentage of modifier, amplitude, number of cycles, and frequency a linear calibration curve was obtained in the concentration ranges of 1.0×10^{-6}-250.0×10^{-6} M with a limit of detection of 0.4×10^{-7} M. The proposed sensor was successfully applied for the determination of sulfadiazine in pharmaceutical samples with the RSD range of 0.7 to 1.7.

Keywords- Sulfadiazine; Carbon paste electrode; $Eu_2(CO_3)_3$ nanoparticles; Fast Fourier transform square wave voltammetry

1. INTRODUCTION

Sulfadiazine is a sulfonamide antibiotic. Sulfonamide compounds or sulfa drugs have a place with an extensive gathering of engineered antibacterial compounds [1]. In spite of the disclosure and wide utilization of different anti-microbials, sulfonamides are one of the most generally utilized antibacterial drug for human and veterinary [2] because of their inexpensive and high effectiveness in the treatment of bacterial diseases. As a systemic antibacterial drug sulfadiazine (4-amino-N-2-pyrimidinylbenzenesulfonamide) has numerous applications. For example, in ophthalmology, it is utilized as a part of treatment of trachoma and ocular toxoplasmosis. Nonetheless, the broad utilization of sulfadiazine can prompt issues as far as human wellbeing, contemplating that unfavourably susceptible and poisonous responses have been seen in patients treated frequently with Suflas. Consequently, techniques which are precise, simple and prudent regarding time and price for drug residue monitoring and control processes should be created. The structure of sulfadiazine amides is shown in Scheme 1.



Scheme 1. Structure of sulfadiazine

A number of analytical techniques have been reported for the monitoring sulfadiazine, such as spectrophotometry [3], different chromatographic methods (HPLC, LC/MS, GC) [4-9], capillary electrophoresis using various detectors [10,11] and electrochemical methods [12-20]. Where in electrochemical methods, the NH_2 and the SO_2NH are the groups that could be oxidized and reduced, respectively [11]. However, such techniques can undoubtedly be an answer for several problems in the filed of pharmaceutical sciences having a high degree of accuracy and precision, sensitivity and selectivity.

Among the various working electrodes be used for determination of sulfonamides, modified carbon paste electrodes have gotten widespread attention, due to some superiorities to other type of electrodes including simple preparation, inexpensiveness, renewable electrode surface, high mechanical stability and a wide operation potential window. Additionally, integration of modifiers into the paste material gives opportunity of improvement of signal/noise in the electroanalysis [21-23].

The lanthanide series of chemical elements comprises the fifteen metallic chemical elements with atomic numbers 57 through 71, from lanthanum to lutetium [24]. Five elements of all lanthanides are electroactive which are Ce, Sm, Eu, Tb and Yb, which are suitable to use as modifier in modified carbon paste. In this direction modifier lanthanides nanostructures were chosen.

Application of the fast Fourier transform methods with electrochemical method offer the advantages of trace detection of numerous materials [25-27]. In this work, a fundamentally different approach to SWV measurement is introduced. By this way the limit of detection can be seriously enhanced. In this method, the voltammetric signals and background signals are separated in frequency domain using discrete fast Fourier transformation (FFT) process [28].

In this work, successful attempts have been made towards the fabrication of carbon paste electrode with the $Eu_2(CO_3)_3$ nanostructure to construct the pharmaceutical sensor for the first time. Attempts were made in applying the $Eu_2(CO_3)_3$ in the detection of trace amounts of sulfadiazine in complex matrixes. The application of the proposed electrode in monitoring of sulfadiazine in pharmaceutical formulations was considered by the fast Fourier transform square wave voltammetry system (FFTSWV). FFT techniques, a highly sensitive electrochemical method that significantly reduces the noise and increase the signal to noise ratio, has been utilized as recognition method in designing sensors [29,30].

2. EXPERIMENTAL SECTION

2.1. Chemicals

Sulfadiazine and its tablets were gotten from a local pharmaceutical factory (Soha Co.). Paraffin oil, graphite powder with a < 50 µm particle size, 2.2 g/cm^3 density and about 20–30 g/100 mL bulk density, V_{total} 0.35 cm^3/g and SBET 4.5 m^2/g; and other chemicals and solvents in analytical grade were provided by Merck Co. A standard stock solution (1.0 mM) of sulfadiazine was made daily in phosphate buffer solution (PBS). Phosphate buffers of 0.01 M were prepared by mixing stock standard solutions of NaH_2PO_4 and Na_2HPO_4 and adjusted to the required pH with NaOH solution and used as supporting electrolyte. All aqueous solutions were made with doubly distilled water.

2.2. Apparatus

Voltammetric measurements including cyclic voltammetry (CV) and fast Fourier transform square wave voltammetry (FFTSWV) were carried out with a homemade electrochemical system. The electrochemical system (ultra-voltammetry system) designed in Centre of Excellence Electrochemistry at University of Tehran. The homemade potentiostate was connected to a PC equipped with an analogue to digital (A/D) data acquisition board (PCL-818H, Advantech Co.). The generated analogue waveform and acquiring current data was done by A/D board. Figure 1, shows the applied potential waveform to the working electrode. The electrochemical software was developed using Delphi 6.0. A three-electrode cell configuration was used with bare or modified carbon paste electrodes (CPE, 3 mm diameter) as working electrode, a graphite as an auxiliary electrode and a saturated Ag/AgCl electrode as a reference electrode.

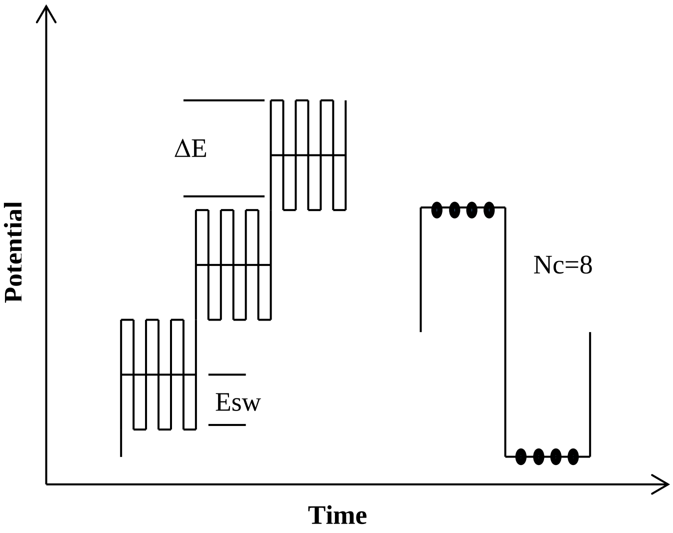


Figure 1. Diagram of potential wave form of square-wave voltammetry

2.3. Modification of the electrodes

For preparation of the carbon paste electrode, 0.1 g paste was made by mixing paraffin oil with graphite powder carefully in a ratio of 70/30 (w/w). The prepared carbon paste was then filled into the end of a tube (3-mm in diameter) of a plastic electrode body equipped with a copper wire over the paste. The electrode surface was delicately smoothed by rubbing on a piece of paper only preceding use. The modified carbon paste electrodes were made in a similar way, except for adding 3% to 10% of the $Eu_2(CO_3)_3$ to the graphite powder.

2.4. Real sample preparation

The commercially available sulfadiazine with the labelled value of 500 mg was obtained. Ten tablets of sulfadiazine were grounded. Then, the powder was weighed in the required amount for preparation the solutions, dissolved in phosphate buffer (pH 10.0) and was sonicated for 5 min. Other calibration series were prepared by serial dilution technique.

3. RESULTS AND DISCUSSION

3.1. Characterization of $Eu_2(CO_3)_3$ nanoparticles

Europium(III) carbonate were prepared by precipitation method. Different concentrations of Eu^{3+} reagent was added to carbonate reagent solutions, at certain flow rates under strong stirring and at a certain reactor temperature. The resulted material was then filtered and washed with distilled water and ethanol two times, and then dried at 80 °C for 3 h. The optimization of the reaction parameters was performed by applying an experimental design on the variables. Figure 2A depicts SEM image of as-prepared nanoparticles. As shown, the synthesized particles are about 33 nm. The transmission electron microscopy (TEM) analysis (Figure

2B) confirmed the size and morphology of the nanomaterial and the shape of the particles is spherical with average diameters in good agreement with SEM image. The FT-IR spectrum of the synthesized nanomaterial is shown in Figure 3. The peak at 3421.1 cm^{-1} is related to the stretching and bending vibrations of O–H and H–O–H of water molecules absorbed on the surface of the dried nanoparticles. The bands at 1499.2 and 1400.7 cm^{-1} also are corresponded to the υ_3 mode of the carbonate group. It is split because of the inhomogeneity of the locations of the carbonate ions in the crystal structure of the product. Additional bands at 1077, 842.5, 751.8 and 699.7 cm^{-1} can be given the υ_2, υ_8, υ_3 and υ_6 modes of CO_3^{2-}, respectively [31].

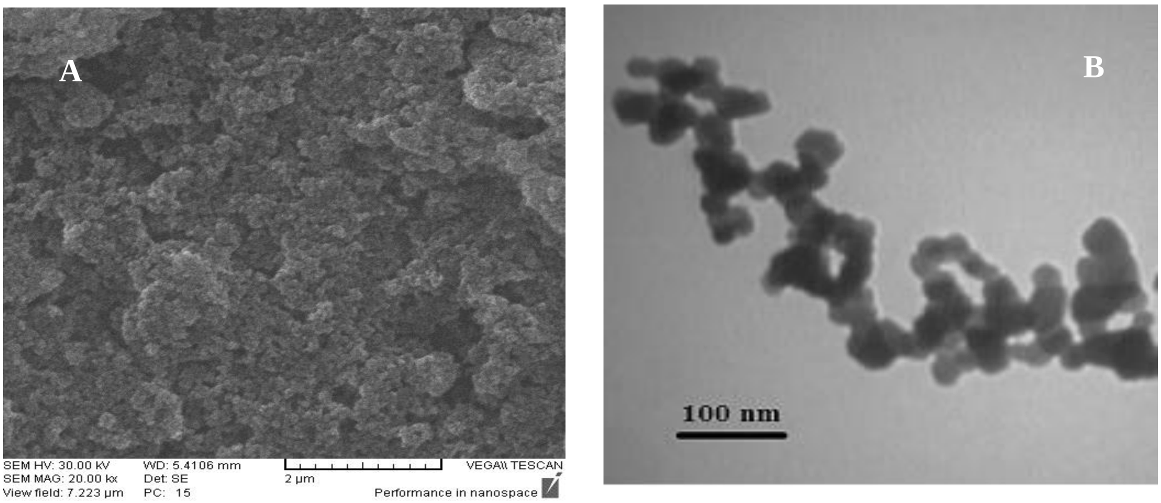


Figure 2. SEM image (A) and TEM image (B) of $Eu_2(CO_3)_3$ nanoparticles

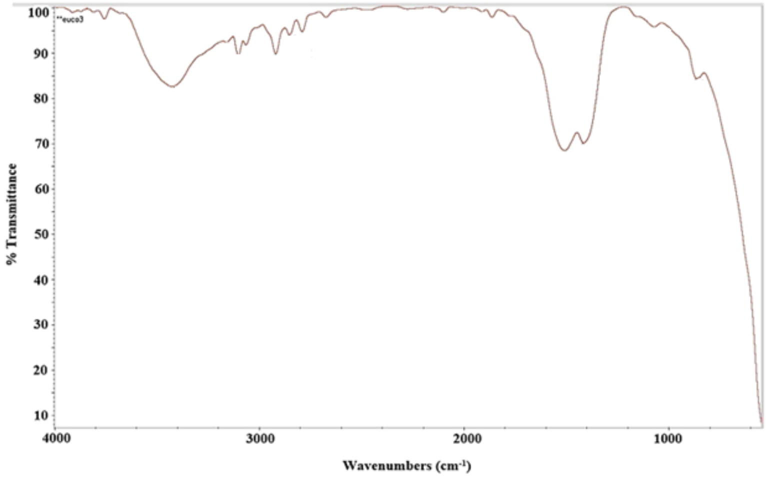


Figure 3. FT-IR spectrum of the $Eu_2(CO_3)_3$ nanoparticles

3.2. Electrochemical characterization of the sensor

To verify the role of the $Eu_2(CO_3)_3$ in the modified electrode toward electrochemical measurement of sulfadiazine, the cyclic voltammogram of the bare and 7% $Eu_2(CO_3)_3$ modified carbon paste electrode were recorded in 1.0 mM sulfadiazine and 0.01 M PBS of pH 8.0 at the scan rate of 100 mV/s. In Figure 4, curves (a) and (b) show an oxidation peak around 0.87 and 0.85 V, respectively, with no cathodic peak on the reverse scan at both electrodes. Also, for $Eu_2(CO_3)_3$/CP electrode the peak current increase near to 93% compared to the bare electrode. Such current enhancement could be attribute to electrocatalyst effect of the $Eu_2(CO_3)_3$ nanoparticles.

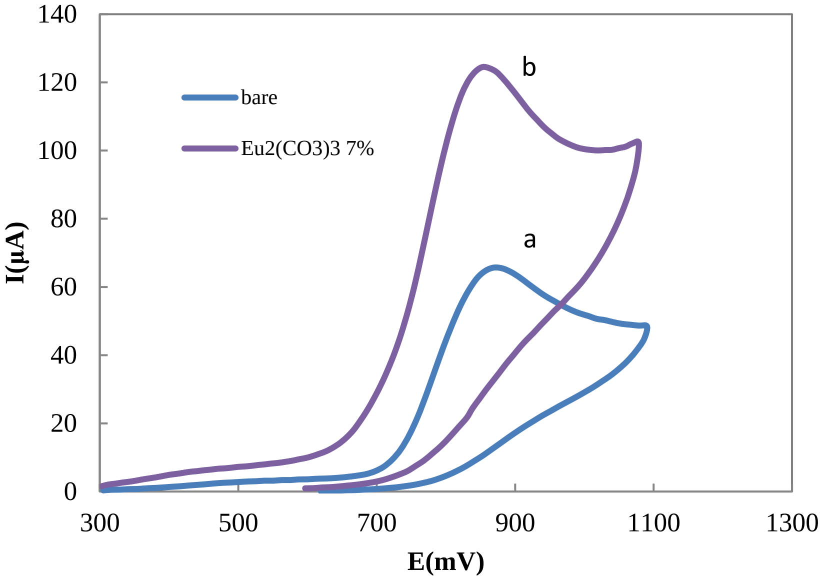
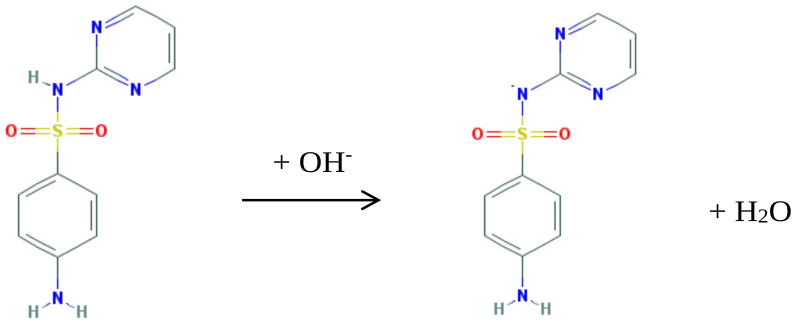


Figure 4. Cyclic voltammograms of electro-chemical oxidation of sulfadiazine (1.0 mM) in PBS (pH 8.0) at bare and 7% $Eu_2(CO_3)_3$/CPE with the scan rate of 0.1 V/s

3.3. pH effect study

The effect of pH on the $Eu_2(CO_3)_3$ modified carbon paste electrode performance in solution of 1.0 mM sulfadiazine and 0.01 M PBS is shown in Figure 5. According to the scheme 2, to solve the active ingredient of sulfadiazine, alkaline rezones were needed. To ponder the impact of pH on sensor response, pH 8, 9, 10 and 11 were picked.



Scheme 2. The suggested reaction for the solvation of sulfadiazine in alkaline solution

The oxidation peak potential shifted to more negative values with the increase in pH, while the current density increased from pH 8.0 to 10.0 and after 10-value reduced. According to Scheme 3, the negative shift in the potential (Figure 5) shows the effect of modifier in the electrode reaction process and that the oxidation of sulfadiazine is thermodynamically favored with the increase in pH. The maximum peak currents of sulfadiazine occurred at pH 10.0. For this reason, pH 10.0 was picked as the best pH for further studies.

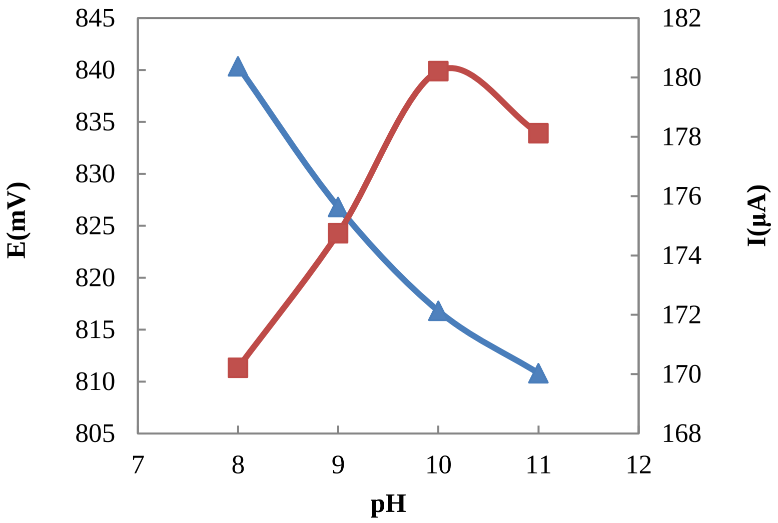
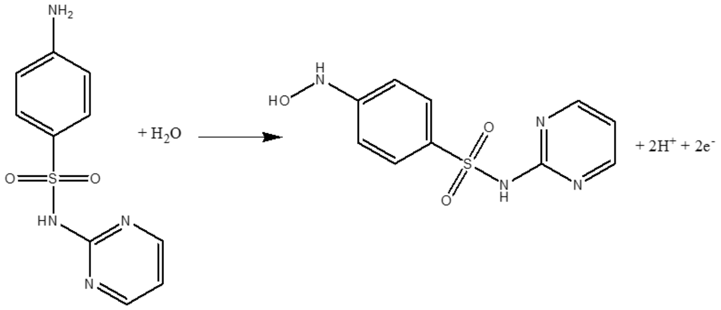


Figure 5. Plot of pH *vs.* peak current for $Eu_2(CO_3)_3$/CPE at different pH values, scan rate 100 mVs^{-1}



Scheme 3. The electro-oxidation mechanism for sulfadiazine

3.4. $Eu_2(CO_3)_3$ nanoparticles amounts optimization

For getting maximum amount of the current of the sensor, the percentage of $Eu_2(CO_3)_3$ was optimized. Four electrodes with diverse percentages of $Eu_2(CO_3)_3$ was constructed. The change of the peak current of sulfadiazine at different electrodes vs. percentage of $Eu_2(CO_3)_3$ is illustrated in Figure 6. As shown, the oxidation peak current intensifies with the amount of $Eu_2(CO_3)_3$ in the carbon paste up to 7%, and then it decreases. This may due to weakening the conductivity of the electrode. Thus, the 7% (w/w) of $Eu_2(CO_3)_3$ in graphite composition was chosen as suitable amount of the paste.

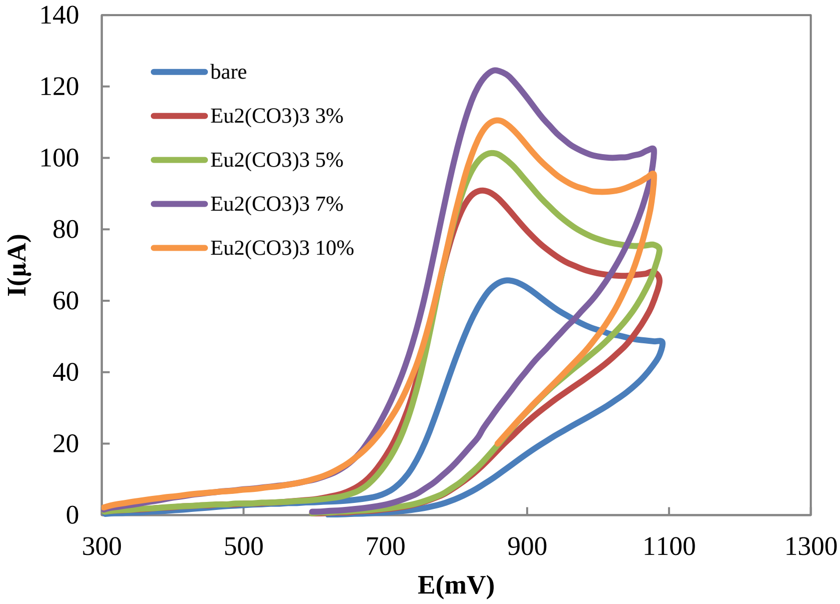


Figure 6. Cyclic voltammograms of different electrodes; Bare CPE (dark blue line), 3% $Eu_2(CO_3)_3$/CPE (red line), 5% $Eu_2(CO_3)_3$/CPE (green line), 7% $Eu_2(CO_3)_3$/CPE (violet line) and 10% $Eu_2(CO_3)_3$/CPE (orange line)electrodes in 1.0 mM sulfadiazine and 0.01 M PBS solutions (pH 10.0). Scan rate: 100 mVs^{-1}

3.5. Scan rate study

The impact of the potential scan rate on the sensor response was studied over scan range of 10 to 1000 mV s^{-1} in solution 1.0 mM sulfadiazine and 0.01 M PBS at pH 10.0. Figures 7 A to C, display the cyclic voltammograms with different scan rates, changes of peak current respect to square root of scan rates and the changes of E_p with the logarithm of the scan rates, respectively. As can be seen in curve B, peak current (I_p) is linearly increases with $\nu^{1/2}$ at scan rates 10 up to 1000 mV s$^{-1,}$ which indicate the electrochemical processes is diffusion controlled.

By using the variation of anodic peak potentials with logarithm of scan rate and according to the Laviron equation [32], the charge transfer coefficient (α) of a reaction is obtained. The kinetic parameters α_a (anodic transfer coefficient) can be extract from the slopes of plot shown in Figure 7C. The slope of the linear segment is equal to 2.303RT/ (1 – α) nF for the anodic peaks. Based on a report [14], the number of electron transfer for oxidation of sulfadiazine was 2. The anodic transfer coefficient (α_a) was 0.99.

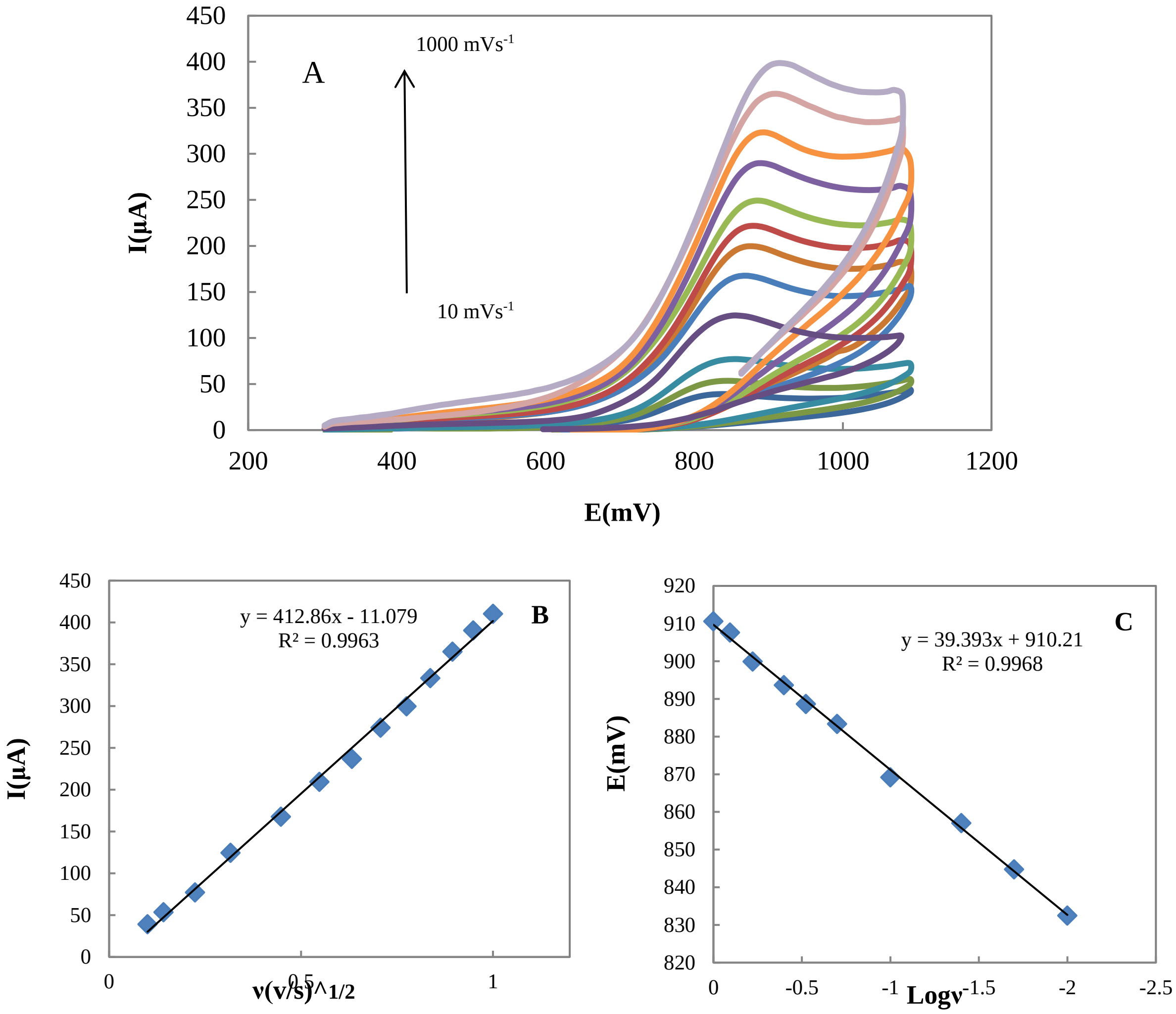


Figure 7. (A) Cyclic voltammograms of $Eu_2(CO_3)_3$/CPE in 0.1mM sulfadiazine and 0.01 M phosphate buffer (pH 10.0), at different scan rates, from 10, 20, 50, 100, 200, 300, 400, 500, 600, 700, 800, 900 and 1000 mVs^{-1} scan rates (B) variations of peak current versus square root of scan rates (C) Difference of E_p *vs.* the logarithm of the scan rate

3.6. Optimization of the FFTSWV parameters

The electroanalytical technique for determination of sulfadiazine was produced utilizing FFTSWV, which is an effective and well-established pulse voltammetric technique appropriate for detection of organic molecules. As is shown in Fig. 1, the obtained response is dependent on multiple SW pulse cycles with an amplitude of E_{sw} and frequency of f_o, which was changed by a small potential step of ΔE, superimposed on a staircase potential function. The values of potential pulse of SW (ESW) and ΔE were in a range of few mV (10–50 mV). Hence, in order to establish the optimum conditions in the determination, the peak current response of the senor was studied in solution of 0.1 mM sulfadiazine and PBS (0.01 M, pH 10.0). According to Figure

8 the optimized value for the number of cycles, frequency and amplitude were to be 32, 88 and 25, respectively.

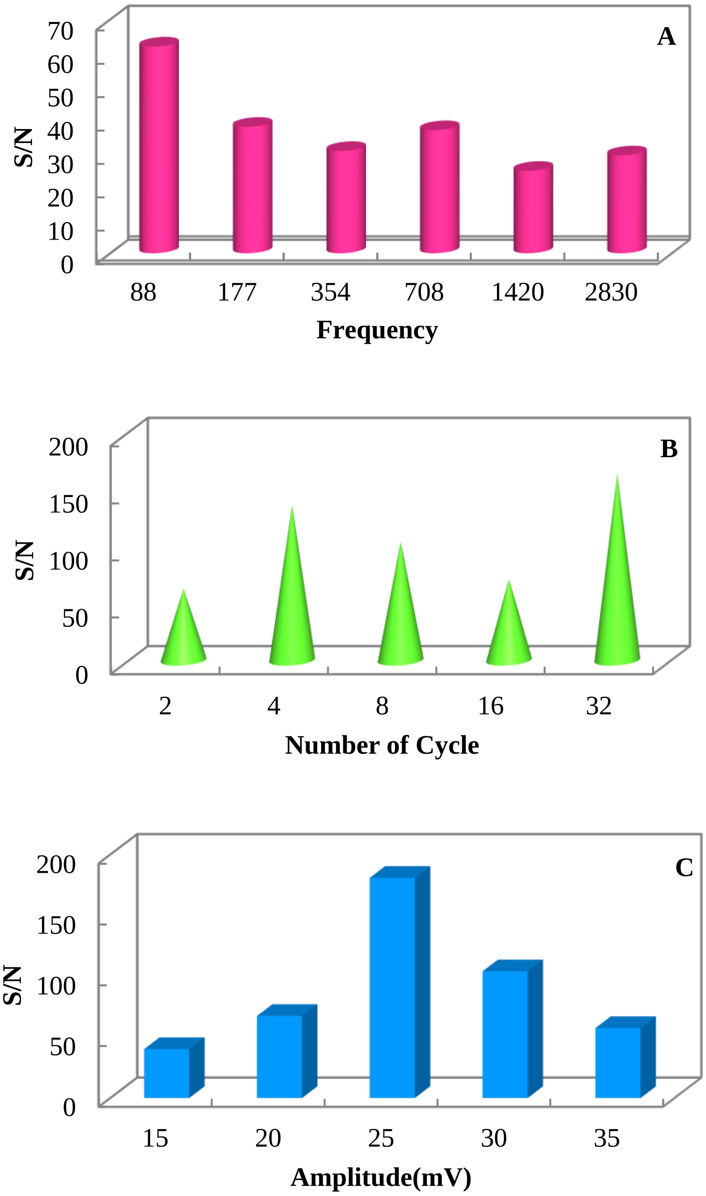


Figure 8. The optimization of frequency (A), number of cycles (B) and the amplitude (C) for 0.1 mM sulfadiazine in phosphate buffer, pH 10.0, at $Eu_2(CO_3)_3$/CPE

3.7. Reproducibility, Repeatability

To check the reproducibility of the proposed sensor, five electrodes were constructed during five days, checked their performance in a 0.1 mM solution of sulfadiazine and maximum response was recorded. The acceptable relative standard deviation (RSD= 5.6%), revealing good reproducibility. In order to obtain repeatability one constructed $Eu_2(CO_3)_3$/CPE was tested 5 times in a day and the RSD of maximum current was calculated 1.79%.

3.8. The analytical figure of merits

FFTSWV was used to evaluate the limit of detection (LOD), in which the peaks are sharper and better-defined as shown in Figure 9 (A). As mentioned above, the optimized parameters in FFTSWV were used to obtain the analytical curve for sulfadiazine in PBS (0.01 M, pH 10.0). Figure 9 (B) displays the obtained calibration curve for sulfadiazine which revealed a linear region from 1.0 to 250.0 µM. LOD of the method was obtained based on $3S_b/m$ principle. S_b was the standard deviation of the blank signal and m is the slope of the linear calibration curve. The LOD was calculated 0.04 µM of sulfadiazine which is significantly lower than the previously reports shown in Table 1.

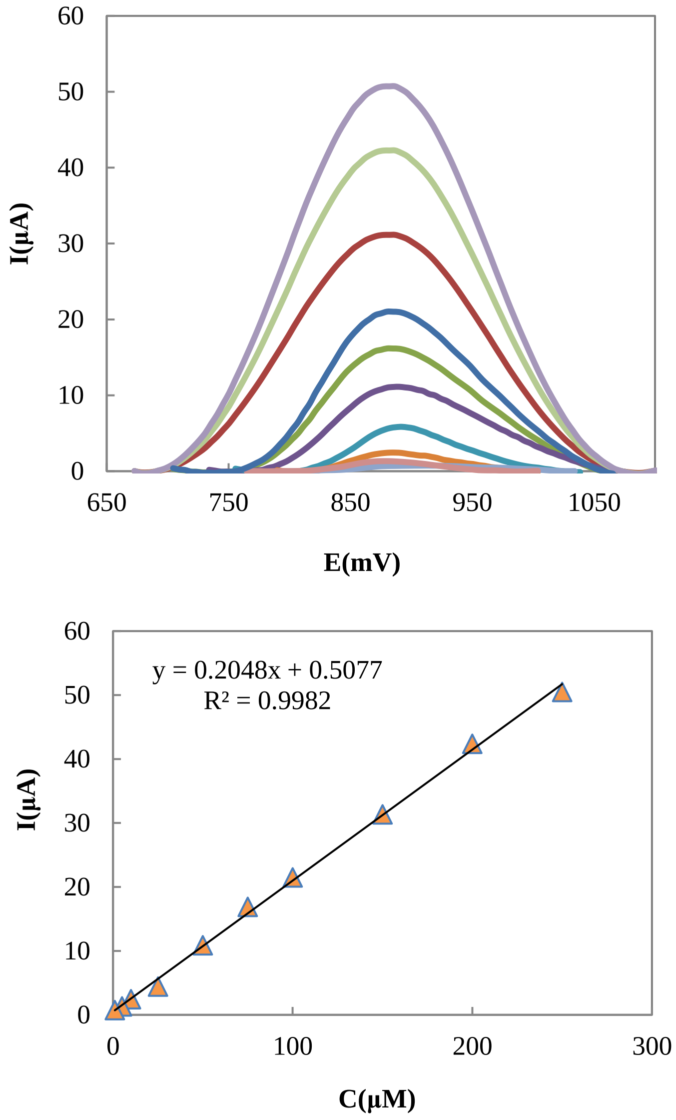


Figure 9. (A) Fast Fourier transform square wave voltammograms (B) Calibration plot observed for sulfadiazine in 0.01 M phosphate buffer (pH 10.0) at $Eu_2(CO_3)_3$/CPE electrode with various concentrations of sulfadiazine: 1.0-250.0 µM

Table 1. The reported electrochemical sensors used for the determination of sulfadiazine

Electrode	**Technique**	**E (mV)**	**LOD**	**Linear range**	**Ref.**
Boron-doped diamond (BDD)	Square-wave voltammetry	1100	2.19 µM	8.01 µM-1.19 mM	[20]
MIP modified carbon paste electrode	CV and DPV[a]	920	0.14 µM	0.2 µM-1.0 mM	[23]
DMF/carboxyl/MWCNTs/GCE	CV and EIS[b]	963	0.067 µM	0.5 µM-0.1 mM	[33]
PFR/CPE[c]	CV and EIS	990	1.47 µM	4.98 µM-47.6 µM	[34]

a. Differential pulse voltammetry, b. Eletrochemical impedance spectroscopy, c. Porphyran carbon paste electrode

3.9. Interference study

The potentially impact of a few coexistent substances, as the possible interference substances was investigated. An interferent concentration which make a relative error less than 5% in the current signal of sulfadiazine oxidation, was considered. 1000-fold excess of Mg^{2+}, Na^{+}, K^{+}, Ca^{2+}, CO_3^{2-}, H_2PO^{4-}, NO_3^{-}, I^{-}, Cl^{-}, 100-fold excess of glucose and maltose and 40-fold excess of uric acid and 20-fold ascorbic acid. The amounts are listed in Table 2 which demonstrates that the performance of the sensor is not significantly affected in the presence of interferences.

Table 2. Results of interference study for the detection of 0.01 mM sulfadiazine in pH =10.0 at $Eu_2(CO_3)_3$/CPE

Species	**Tolerance limits ($C_{species}/C_{naproxen}$)**
Mg^{2+}, Na^{+}, K^{+}, Ca^{2+} CO_3^{2-}, $H_2PO_4^{-}$, NO_3^{-}, I^{-}, Cl^{-}	1000
Glucose, Maltose	100
Uric acid	50
Ascorbic acid	30

3.10. Real sample analysis

The proposed $Eu_2(CO_3)_3$ sensor was applied for determination of sulfadiazine in some pharmaceutical tablets. The results are summarized in Table 3. A solution of specified amount of sulfadiazine tablets was analyzed using standard addition method. For this purpose, different concentrations of sulfadiazine were added to a 2.0 µM sulfadiazine tablet solutions. The results are shown in Table 3. As can be seen, the satisfactory recovery and RSD% were obtained.

Table 3. Determination of sulfadiazine in real sample by standard addition method

Sulfadiazine added(µM)	**Sulfadiazine found(µM)**	**Recovery (%)**	**(RSD %)[a]**
_	1.8	_	1.3
20.2	21.3	96.5	1.7
38.6	39.8	98.4	1.4
60.2	62.1	100.1	0.8
78.7	80.3	99.6	0.7

[a]RSD determined for n=4

4. CONCLUSIONS

The $Eu_2(CO_3)_3$ exhibited good electrocatalytic activity toward oxidation of sulfadiazine. The combination of $Eu_2(CO_3)_3$ modified carbon paste electrode and FFTSWV technique shows a promising tool for determination of sulfadiazine. The low detection limits obtained for sulfadiazine (0.4×10^{-7} M) demonstrate that the proposed electroanalytical method is attractive and also appropriate for trace analysis. The proposed sensor can be successfully applied for the detection of sulfadiazine in real sample with low RSD values. According to table 1 this method is at least 10-fold sensitive then the other detection methods. Beside the low detection limit and good sensitivity, the presented sensor has good reproducibility with advantages of fast response time, simplicity of preparation and renewable electrode surface that make the developed electrode a good electrochemical sensor in different systems.

Acknowledgements

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