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# Electrochemical Behaviour of Ofloxacin in Pharmaceutical and Biological Samples Using a Boron-Doped Diamond Electrode in Using Anionic Surfactant

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**Abstract**

This paper examined use of a boron doped diamond electrode (BDDE) for the electroanalysis of ofloxacin (one of the fluoroquinolone compounds) by cyclic voltammetry (CV) and square wave voltammetry (SWV) in the presence of anionic surfactant (sodium dodecyl sulfate, SDS). The current signal due to the oxidation process was a function of the amount of ofloxacin, pH of the medium, effect of SDS and scan rate. Cyclic voltammetric studies indicated an irreversible behaviour of ofloxacin in phosphate buffer solution at pH 2.0 with well-defined oxidation peak at +1.24 V (absence SDS) and +1.21 V (presence of SDS) vs. Ag/AgCl, respectively. With optimized experimental parameters, the current response of ofloxacin was proportionally linear in the concentration range from $1.0\times10^{-7}$ to $3.5\times10^{-6}$ M. A detection limit of $1.76\times10^{-8}$ M was observed anodically electrochemical surface pretreatments. The practical applicability of the developed method was demonstrated on the determination of ofloxacin in human urine and pharmaceutical samples. In this way, BDD electrode may represent an efficient alternative to widely used modified electrodes in the determination of fluoroquinolone compounds.

## 1. INTRODUCTION

Fluoroquinolones are very important antibacterial agents advanced in the 1980s, and have many applications in veterinary and human medicine. The pharmaceuticals have a broad spectrum of activity and good oral absorption. In this work, ofloxacin (+/−)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (Figure 1) was investigated and quantitatively analysed by voltammetric methods.

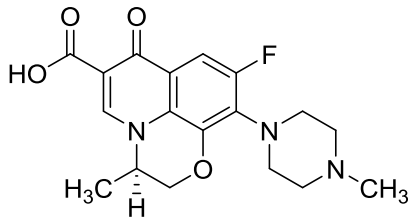


***Figure 1.*** *The structure of ofloxacin*

This agent belongs to a group of broad spectrum antibiotics called the fluoroquinolone. This antibiotic drug prevents the bacterial reproduction and their growth is stopped. Ofloxacin is effective against several types of bacteria that tend to be resistant to other commonly used antibiotics. It is used to treat a wide range of infections, urinary tract, pneumonia, bronchitis and venereal disease. It is also used as a single dose treatment for gonorrhea [1-3]. Several methods have been reported for determination of ofloxacin, such as high performance liquid chromatography [4-11], spectrophotometry and flow injection spectrophotometry [12-16], capillary electrophoresis [17-19], fluorimetric methods [20,21], and

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chemiluminescence [22]. However, most of these methods need more complicated procedures, costly instrumentation, over analysis time, because they need derivatization or combination with various detection methods when compared to electroanalytical methods. Electroanalytical methods (such as voltammetry, amperometry) are characterized by such as low cost, low background current, wide range of potential ranges, good sensitivity, selectivity, precision, accuracy and speed, quick surface renewal, easy fabrication. Nowadays, the use of boron-doped diamond (BDD) electrode is very attractive in electroanalytical chemistry. Boron-doped diamond is member of carbon-based materials and this electrode has several unique properties such as high thermal conductivity, good mechanical and electrochemical stability in both alkaline and acidic media, low background current, wide potential range (up to 3.5 V) and low sensitivity on dissolved oxygen in aqueous solutions. However, for many analytes, these properties of BDD electrode are extremely dependent on its surface termination (oxygen or hydrogen), which can be modified by appropriate electrochemical pretreatment (anodic or cathodic pretreatment. Compared to classical carbon electrodes and other metallic electrodes, boron-doped diamond electrodes differ by their excellent chemical inertness and chemical stability that enable their use in extreme chemical environments such as strongly acidic media. [23-27]. Several methods have been investigated for the electrochemical methods of ofloxacine such as graphene oxide and ionic liquid modified carbon paste electrode [28], β-cyclodextrin modified carbon paste electrode [29], molecularly imprinted polymer/mesoporous carbon composite nanoparticles [30], cycteic acid modified carbon paste electrode [31], poly(serine) film modified glassy carbon electrode [32], PSS/nano-ZnS film modified electrode [33], cuprous oxide/nitrogen-doped graphene nanocomposites [34], and hanging mercury drop electrode [35-39].

As a result of this research, no electrochemical oxidative assay has been performed on ofloxacin using boron-doped diamond electrode and using anionic surfactant. Surface active agents otherwise known as 'surfactants' are generally amphiphilic organic compounds (normally possessing a hydrophobic tail and a hydrophilic head), which allow them to change the interfacial properties of liquids in which they are present. There are four types of surfactants, according to the formal charge present in their hydrophilic head: anionic, cationic, nonionic and amphoteric. Surfactants were commonly used in electroanalytical chemistry to enhance the sensitivity and selectivity [40-45].

The aim of this study was to establish the experimental conditions, to investigate the voltammetric behavior and possible oxidation mechanism of ofloxacin at boron-doped diamond electrode in anionic-surfactant media by cyclic and square wave voltammetric techniques. This work was also aimed development of new, fully validated, rapid, selective and simple voltammetric methods for the direct determination of ofloxacin in raw materials, pharmaceutical dosage forms and spiked human urine samples without any time-consuming extraction, separation, evaporation or adsorption steps prior to drug assay.

## 2. EXPERIMENTAL

### 2.1. Reagent and Chemicals

Ofloxacin hydrochloride, sodium dodecyl sulfate were obtained from Sigma or Aldrich. Other reagents used were of analytical grade, and their solutions were prepared with deionized water further purified via a Milli-Q unit (Millipore). All experiments were carried out at the room temperature of the laboratory. For the preparation of stock solutions ($10^{-2}$ M), appropriate amounts of the ofloxacine hydrochloride were dissolved in water, and stored in dark bottles at 4 $^{0}$C when not in use. Working solutions were prepared before use by diluting the stock solution with a selected supporting electrolyte. After due investigation, as reported further below, the following supporting electrolyte solutions were chosen for the ofloxacine determination: phosphate buffer (pH 2.0-12.0, 0.1 M), and Britton–Robinson buffer (BR, pH 2.0–12.0, 0.1 M).

### 2.2. Instrumentation

Cyclic (CV) and square-wave (SWV) voltammetric curves at boron-doped diamond electrode was recorded with the aid of a Autolab type III electrochemical analyser with GPES 4.9 software package (EcoChemie, The Netherlands). The raw data were also treated in all SWV and CV measurements by using Savitzky and Golay filter (level 2) of the GPES software, followed by the moving average baseline correction with a peak width of 0.01 V. In all measurements, the reference electrode was an Ag/AgCl (3 M NaCl) (Model RE-1, BAS, USA) and the auxiliary electrode was a platinum wire. The working electrode was BDD (Windsor Scientific Ltd.; *Ø*: 3 mm, diameter) electrode. The pH values of solutions were measured using a WTW inoLab pH 720 meter with a combined electrode (glass-reference electrodes). The measurements were carried out in a standard 10-mL one-compartment voltammetric cell, at a laboratory temperature ($20 \pm 5$ °C). Anodic and cathodic pretreatment procedures consisted of the polarization at +1.6 V and −1.6 V of the BDD electrode, respectively, in 0.5 M $H_2SO_4$ for 180 s in an independent electrochemical cell. Once the anodic pretreatment was shown to lead to a better electroanalytical response of the BDD electrode, this pretreatment was carried out at the beginning of each working day. Between individual measurements, an activation program was applied for 60 s under the same conditions.

### 2.3. Preparation and Analysis of Pharmaceutical Samples

#### *2.3.1. Tablet Assay Procedure*

The proposed method was tested to determine ofloxacin in pharmaceutical formulation, Tarivid® tablets labeled as containing 200 mg ofloxacin were used for the present analytical applications, using the following procedure: ten tablets were accurately weighed and powdered. The average mass per tablet was determined. An accurate weight of this powder equivalent to one tablet content was weight and transferred into a 100-mL calibrated dark flask, which was completed to the volume with water and dissolved ultrasonic bath for 20 min. The non-dissolved excipients were waited to precipitate completely. An aliquot of the supernatant liquid was transferred to a calibrated flask and a series of dilutions were prepared with the selected buffer solution (in the presence of surfactant, selected buffer solution containing SDS at the final concentration of $1\times10^{-3}$ M). Quantifications were performed by means of the calibration curve method from the related regression equation.

#### *2.3.2. Analysis of Human Urine Samples*

Blank urine sample is collected from healthy female voluntary (female, age 30 years) immediately before the experiments. The 5 mL of urine sample was mixed with an equal volume of acetonitrile in the sample tube. The tube was tightly capped and vortex-mixed for 1 min and then centrifuged for 5 min at 5000 rpm to remove the unknown endogenous chemicals. A 50-µL aliquot of upper layer was mixed with the selected SDS-containing buffer solution (pH 2.0) in the voltammetric cell. Small aliquot volumes of concentrated ofloxacin standard solution were then added to this mixture, and analyzed immediately.

## 3. RESULT AND DISCUSSION

### 3.1. Electrochemical Response of Ofloxacin at Boron-Doped Diamond Electrode and Effect of Surfactant

In order to understand the electrochemical response of ofloxacin on BDD with regard the morphology and peak potential, initial experiments by means of CV and SWV were performed in aqueous and aqueous-surfactant media at different pHs. The voltammetric behaviour of ofloxacin with different concentration of SDS was examined and it was found that ofloxacin with 1 mM SDS solution gave single, well defined oxidation peak with maximum peak height (Fig. 2).

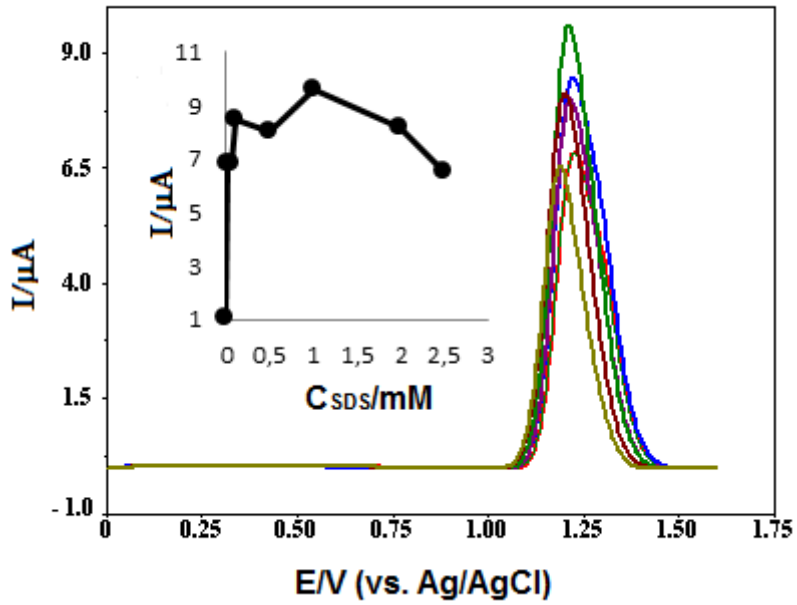


***Figure 2.*** *Square-Wave voltammograms of 0.1 mM ofloxacin at pH 2.0 of 0.1 M phosphate buffer on BDD electrode at different sodium dodecylsulfate concentration levels: (1) 0, (2) 0.01, (3) 0.05, (4) 0.1, (5) 0.5, (6) 1.0, (7) 2.0, (8) 2.5. (inset: Curve of the oxidation peak current on the SDS concentration).*

Fig. (3A;a) shows cyclic voltamogram of $1x10^{-4}$ M ofloxacin in pH 2.0 phosphate buffer recorded within the potential window from 0 to 1.8 V. The ofloxacin exhibits an anodic peak potential and peak current at 1.312 V and 1.63 µA at the BDD electrode without surfactant.

In order to understand the effect of anionic surfactant the ease of the oxidation of ofloxacin, SDS was added to pH 2.0 phosphate buffer solution having a final concentration of 1mM. It is important to stress out that, SDS is electrochemically inactive in the potential range under investigation. When the solution contains SDS, CV curves showed in the form a peak, being sharper and easily measurable. Furthermore, its peak potential shifted to less positive values, indicating that the oxidation process of the compound becomes easier in the presence of SDS than in its absence. As shown in Fig. (3A;b), it exhibits an anodic peak potential and peak current at 1.214 V and 3.302 µA at the BDD electrode with surfactant. It is well known that surfactants can be adsorbed on a hydrophobic surface to form surfactant film, which may alter the over voltage of the electrode and influence the rate of electron transfer. In the presence of SDS, the electrode surface may form a hydrophilic film with positive charge. This hydrophilic layer increases the concentration of ofloxacin on the electrode surface. On the scan, no corresponding cathodic peak was observed, indicating the irreversible character of electrode reaction of ofloxacin on BDD electrode.

The electrochemical responses of ofloxacin were also investigated in various types of electrolyte solutions, including phosphate and Britton-Robinson buffers over the pH range of 2.0-10.0. The oxidation of ofloxacin produced one oxidation step depending on pH and composition of the supporting electrolyte. As shown in Fig.3B, It shows the square-wave voltammograms obtained at the BDDE electrode in the potential range from 0 to 1.6 V in the 0.1 M phosphate buffer solution at pH 2.0. The oxidation peak potential and peak current occur at +1.29 V; 1.05 µA (without SDS, a) and +1.21 V; 5.96 µA (with SDS, b), respectively. The peak current was lower for without SDS when compared with presence SDS at the BDD electrode. As seen clearly from the fig. 3, the highest peak current of ofloxacin was obtained in the presence of SDS. Therefore, this medium was chosen for the subsequent analytical experiments.

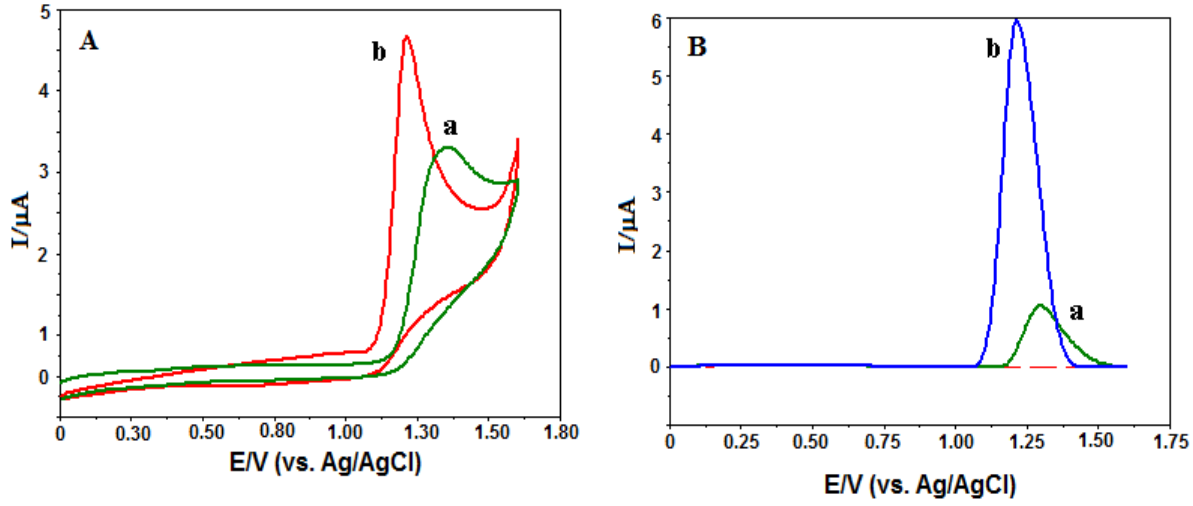


***Figure 3.*** *(A) The cyclic voltammograms at the BDD electrode in phosphate buffer solution (pH 2.0) of 0.1 mM ofloxacin, scan rate 0.1 Vs*$^{-1}$*. (B) Square-wave voltammograms at the BDD electrode in phosphate buffer solution (pH 2.0) of 0.1 mM ofloxacin. (a; non-surfactant, b; with surfactant)*

### 3.2. Effect of Scan Rate on The Cyclic Voltammetry

In order to understand whether the electrode process is diffusion or adsorption controlled, scan rate influence on peak current was investigated. The effects of scan rate (υ) in the range 10-1000 mV s$^{-1}$ on the oxidation of ofloxacin at the BDD electrode were investigated by CV in phosphate buffer, pH 2.0. A plot of logarithm of oxidation peak current (log*ip*) vs. logarithm of scan rate (logυ) showed a straight line relationship within the range of 30–800 mV/s with the regression equations of log*i*p (µA) = -0.969 + 0.60 log*v* (mV/s), ( *r* =0.998), close to the theoretical value of 0.5. This fact indicates that the electrochemical reaction of ofloxacin is controlled by diffusion under influence of adsorption. The linear relationship existing between oxidation peak current (*i*p) and the square root of the scan rate (√υ) showed with the regression equations of *i*p (µA) = -0.91 + 0.29 √*v* (mV/s), ( *r* =0.995), that the oxidation process is diffusion-controlled in the whole scan rate range studied (Fig. 4).

In order to ascertain the electron number (n) involved in ofloxacin oxidation process at BDD electrode, the n value was determined by CV voltammogram using the equation $Ep - Ep/2 = 47.7\text{mV}/\alpha n$ [46,47], where Ep is peak potential, Ep/ 2 is half-peak potential, α is the charge transference coefficient (generally, assumed as 0.5 for totally irreversible system) and n is the number of electrons. Using the cyclic voltammogram obtained for ofloxacin oxidation at 100 mV s$^{-1}$ the value of $Ep - Ep/2$ was 41.0 mV, so n value was found to be 2.33 (≈2). This result indicates that the irreversible oxidation of ofloxacin involves two electrons per molecule at BDD electrode in phosphate buffer solution (pH 2.0). The reaction pathway for this step can be written as in Fig. 5.

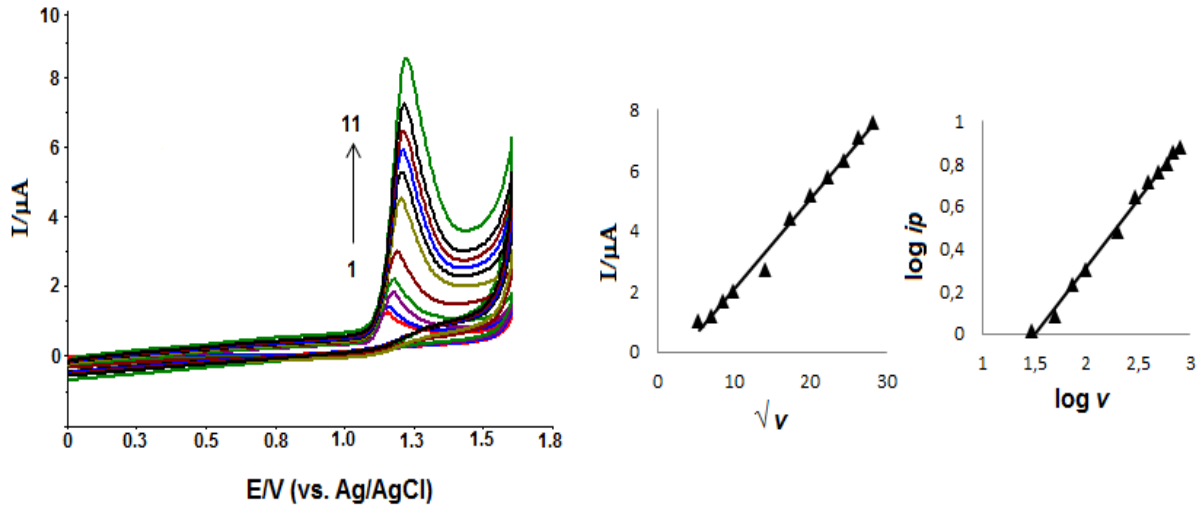


***Figure 4.*** *Influences of scan rate on the electrochemical oxidation peak current of 0.1 mM ofloxacin at the BDD electrode in phosphate buffer solution (pH 2.0) in presence of 1 mM SDS: (1) 30, (2) 50, (3) 75, (4) 100, (5) 200, (6) 300, (7) 400, (8) 500, (9) 600, (10) 700, (11) 800 mV/s. Inset: a plot of the peak current vs. the square root of scan rate and a plot of the logarithm of the peak current vs the logarithm of the scan rate for ofloxacin.*

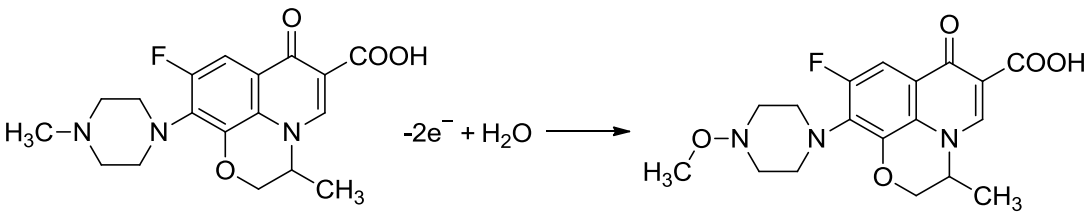


***Figure 5.*** *The proposed mechanism of ofloxacin*

### 3.3. Effect of pH

The electro-oxidation of 0.1 mM ofloxacin in presence of 1 mM SDS was also studied over the pH range 2.0 to 9.0 in phosphate buffer solution by square-wave voltammetry. For a solution with pH between 2.0 and 9.0, ofloxacin oxidation peak potential did not depend practically on pH (from +1.222 V at pH 2.0 to +1.198 V at pH 10.0).As shown is Fig.6. the maximum anodic peak current was obtained at pH 2.0. Therefore, this pH was chosen as an optimal pH for the sensitive determination of this compound.

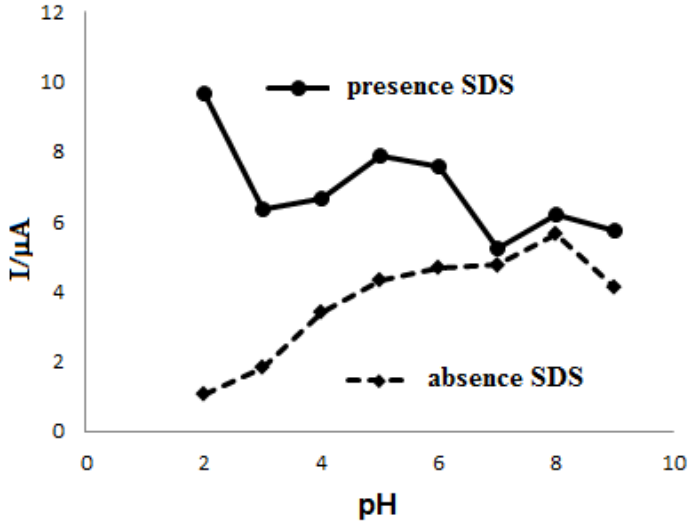


***Figure 6.*** *Influence of pH on the oxidation peak current of 0.1 mM ofloxacin in absence and presence SDS at BDD electrode in phosphate buffer (pH 2.0-9.0)*

### 3.4. Analytical Applications and Method Validation

*3.4.1. Optimization of Parameters and Analytical Curve*

Square-wave voltammetric method was selected, because the peaks are better defined at low concentrations. The SWV parameters, frequency ( *f*,Hz), pulse amplitude (mV), and step potential (mV) were optimized for a $1\times10^{-4}$ M ofloxacin solution in 0.1 M phosphate buffer (pH 2.0). The studied ranges were 15 to 175 Hz for frequency, 10 to 60 mV for pulse amplitude, and 4 to 16 mV for step potential. The values were selected (frequency = 100 Hz, pulse amplitude = 40 mV, and step potential = 12.0 mV), taking into account repeatability, baseline stability, accuracy, and magnitude of analytical signal at the BDD electrode for ofloxacin determination (Fig.7). After optimization of the SWV parameters, the analytical curve for ofloxacin using BDD electrode was applied by adding, in the electrochemical cell, successive aliquots of ofloxacin concentrations ranging from $1\times10^{-7}$ to $3.5\times10^{-6}$ M, and the obtained SW voltammograms are shown in Fig. 8. The analytical curve (Fig. 8, inset) showed a linear dynamic range with the following linear regression equation for this range is $I$ (µA) = 0.042 + 1.04 C (µM); r = 0.997. The limit of detection (LOD) and limit of quantification (LOQ) were found to be as $1.76\times10^{-8}$ M and $5.3\times10^{-8}$ M, respectively. The LOD and LOQ values were calculated by using the following equations, LOD = 3.3s/m; LOQ = 10s/m, where 's' is the standard deviation of peak currents and 'm' is the slope of the working curve.

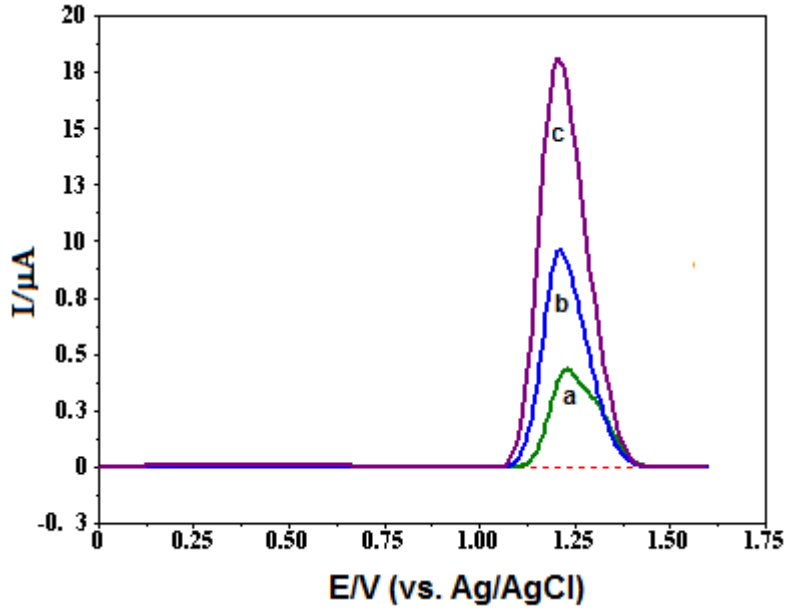


***Figure 7.*** *SW voltammograms in 0.1 M phosphate solution (pH 2.0) of 0.1 mM ofloxacin; (a) 0.1 mM ofloxacin, (b) 0.1 mM ofloxacin and 1.0 mM SDS (before optimization) (c) 0.1 mM ofloxacin and 1.0 mM SDS (after optimization)*

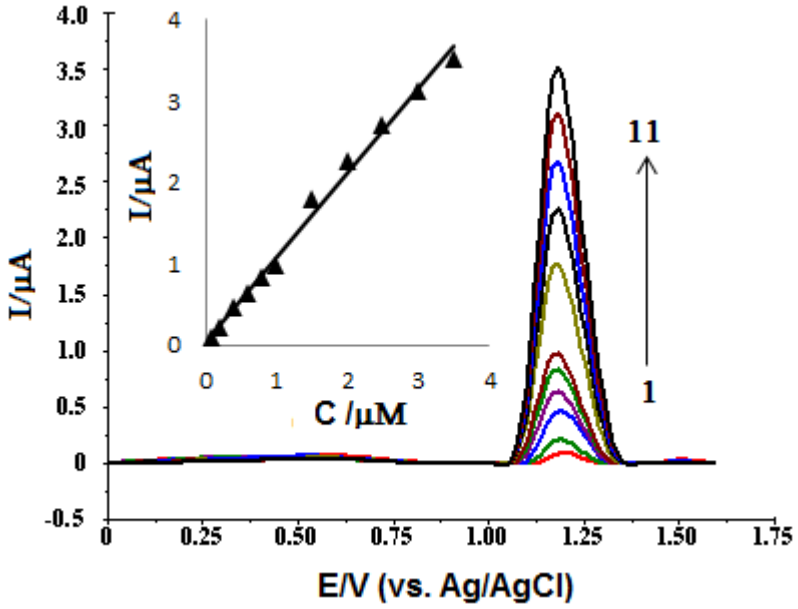


***Figure 8.*** *SW voltammograms in 0.1 M phosphate solution at pH 2.0 and presence of 1.0 mM SDS using a anodically pretreated BDD electrode at different ofloxacin concentration levels: (1) 0.1, (2) 0.2, (3) 0.4, (4) 0.6, (5) 0.8, (6) 1.0, (7) 1.5, (8) 2.0, (9) 2.5, (10) 3.0 and (11) 3.5 µM. (F = 100 Hz; A = 40 mV and $\Delta E_s$ = 12 mV). Inset: Analytical curve.*

The intra-day repeatability (n = 6) of BDD electrode was investigated for $1\times10^{-4}$ M ofloxacin solution in 0.1 M phosphate buffer (pH 2.0). Relative standard deviations (RSD) of 3.55 % were obtained, and indicating a good stability of the proposed electrode. Table 1 provides a comparison of the analytical parameters obtained for the proposed voltammetric method using a BDD electrode with those reported in the literature based on the polarographic determination of ofloxacin.

***Table 1*** *Comparison of the proposed method with previously reported electrochemical methods for determination of ofloxacin*

| Electrode | Method | Linearity range (M) | LOD (μM) | References |
|---|---|---|---|---|
| CDMCPE | DPV | $3.2 \times 10^{-8}$- $2.0\times10^{-5}$ | $2.4\times10^{-8}$ | [31] |
| MCNs@MIP | CV | $5.0 \times 10^{-7}$ – $1.0\times10^{-4}$ | $8.0\times10^{-8}$ | [32] |
| HMDE | SWV | $5.0 \times 10^{-7}$ – $1.7\times10^{-6}$ | $1.1\times10^{-8}$ | [36] |
| poly(L-serine)/GCE | DPV | $1.0 \times 10^{-5}$- $1.0\times10^{-4}$ | $1.6\times10^{-7}$ | [34] |
| BDDE | SWV | $1.0 \times 10^{-7}$ – $3.5\times10^{-6}$ | $1.76\times10^{-8}$ | Present work |

CDMCPE: β-Cyclodextrin-Modified Carbon-Paste Electrode, MCNs@MIP: Molecularly imprinted polymer/mesoporous carbon composite nanoparticles, HMDE: hanging mercury drop electrode, poly(L-serine)/GCE: poly(L-serine) film-modified glassy carbon electrode

*3.4.2. Interference Studies*

The possible interference of some compounds typically found in ofloxacin pharmaceutical formulations or biological fluid samples on the voltammetric determination of ofloxacin was investigated. To apply this objective, SWV measurements were performed for a 0.1 M phosphate buffer solution (pH 2.0) containing $1.0\times10^{-6}$ mol $L^{-1}$ ofloxacin in the presence and absence of each potential interferent. The chemical compounds tested in these studies were: NaCl, NaOH, HCl, KCl, CaCl2, NaI, glucose, uric acid, dopamine, at concentration ratios of 1:1 and 1:10 (analyte: potential interferent). Among those compounds analyzed, ofloxacin, dopamine, uric acid showed a measurable electrochemical response. As shown is fig. 9, the ofloxacin (OFL), dopamine (DA) and uric acid (UA) exhibit an anodic peak potential at 1.20 V, 0.82 V and 0.96 V, respectively.

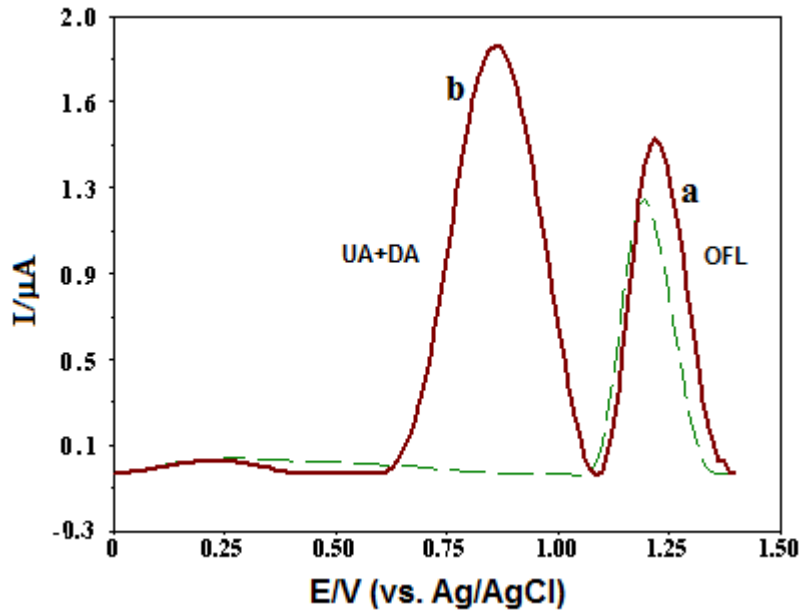


***Figure 9.*** *SW voltammograms in 0.1 M phosphate solution at pH 2.0 and presence of 1.0 mM SDS in mixture of (a) 0.001 mM ofloxacin and (b) 0.002 mM uric acid and dopamine. Dash line represent 0.001 mM ofloxacin at pH 2 phosphate solution.*

*3.4.3. Determination in Pharmaceutical Formulations of Ofloxacin*

The proposed BDD electrode was applied to the voltammetric determination of ofloxacin in commercial pharmaceutical sample. The developed SWV technique for ofloxacin was applied to Tarivid® tablets. This commercial pharmaceutical sample was prepared as described in Experimental, was determined directly using the SWV technique. There is no need for any extraction procedure before voltammetric analysis. The results obtained using the BDD electrode and those obtained using an official method are presented in Table 2. The statistical calculations for the results presented in this table suggested good precision for the voltammetric method. Tarivid tablet also contain the inactive ingredients: corn starch, lactose, carboxymethyl cellulose, hydroxypropyl cellulose, magnesium stearate, titanium dioxide, hydroxypropylmethyl cellulose, talc and macrogol 8000. These excipients did not interfere with the assay.

***Table 2*** *Analysis of ofloxacin in commercial pharmaceutical dosage forms Tarivid®*

| Commercial preparation | Method | n | Found (mg) Mean±SD | Recovery | %RSD[a] |
|---|---|---|---|---|---|
| Tarivid (200 mg/tablet) | SWV | 6 | 198.33±1.5 | 99.2 | 1.94 |

*3.4.4. Determination of Ofloxacin in Human Urine Samples*

Lastly, the determination of ofloxacin in human urine sample was performed using the proposed method with the BDD electrode. As shown in Fig.10. The electroanalytical curves were obtained by using SWV, in the ranges $1\times10^{-7}$-$1\times10^{-6}$ M in the urine sample. It was observed that peak currents vs ofloxacin added into samples solution increased linearly. The statistical calculations for the assay results showed suitable precision of the proposed method (Table 3).

***Table 3*** *Characteristics of the calibration curves of determination ofloxacin in human urine using SWV at BDD electrode.*

| | method | Linearity range (M) | Slope±RSD% | intercept | Correlation coefficient |
|---|---|---|---|---|---|
| urine | SWV | $1\times10^{-7}$-$1\times10^{-6}$ | $0.65\times10^{6}$±0.15 | -0.044 | 0.999 |

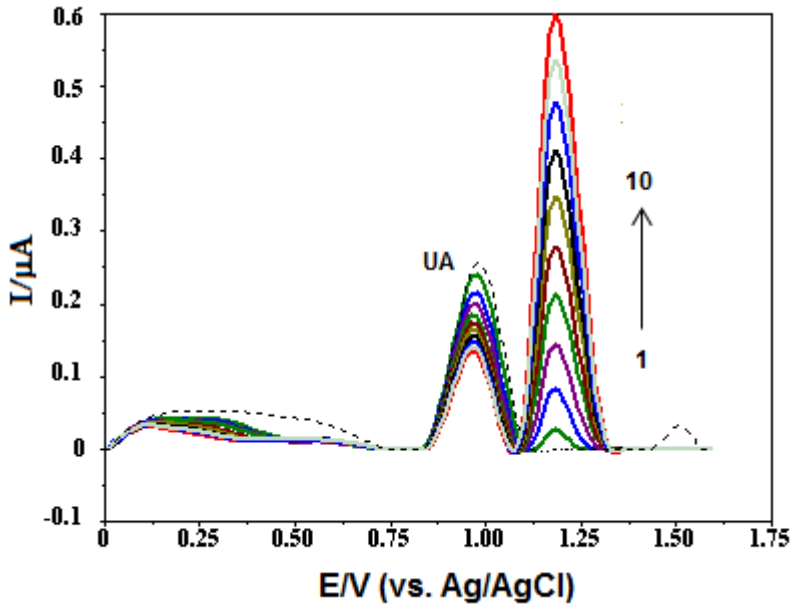


***Figure 10.*** *SW voltammograms for different concentrations of ofloxacin spiked in human urine sample in pH 2.0 (0.1 M phosphate buffer) and presence of 1 mM SDS. (1) 0.1, (2) 0.2, (3) 0.3, (4) 0.4, (5) 0.5, (6) 0.6, (7) 0.7, (8) 0.8, (9) 0.9, (10) 1.0.*

## 4. CONCLUSIONS

As far as it was searched from scientific literature, this paper is the first report describing a voltammetric studies for analysis of ofloxacin at boron-doped diamond electrode. The suitability of anodically pretreated BDD electrode assisted by SWV in aqueous/SDS solution was evaluated for electrochemical behavior of ofloxacin. Taking to the advantage of SDS effect on voltammetric response of ofloxacin, BDD electrode combined with high sensitive and precise and also accurate SWV could allow an attractive trace analysis of ofloxacin. A probable oxidation mechanism was proposed in this study and two electrons mechanism was optained for the oxidation of ofloxacin.

## CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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