Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 3, 2013

Research Article

ELECTROCHEMICAL DETECTION OF FLUOXETINE USING A BORON-DOPED DIAMOND ELECTRODE

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Received: 21 Mar 2013, Revised and Accepted: 06 May 2013

ABSTRACT

This study aims to develop an electrochemical method for the detection of fluoxetine (FXT) in the aqueous media using a commercial boron-doped diamond (BDD) electrode. The electrochemical behaviour and detection of FXT at BDD electrode were studied using cycling voltammetry (CV), differential-pulsed voltammetry (DPV), square-wave voltammetry (SWV) and chronoamperometry (CA) allowed to detect the fluoxetine using BDD electrode. The best performance in relation with the lowest limit of detection (0.037μgL^{-1}) was reached using differential-pulsed voltammetry, and the sensistivity (244.1 μAμM^{-1}) was obtained using square-wave voltammograms operated at 0.2 V modulation amplitude, 0.05V step potential and 100 Hz frequency. The accuracy of the applied method was proved by comparison the detection results with the conventional UV-VIS spectrophotometric method.

Keywords: Fluoxetine, BDD electrode, Electrochemical detection

INTRODUCTION

In the last years, the presence of pharmaceuticals compounds has been revealed in the surface waters, groundwater, seawater, drinking water, influents and effluents from sewage treatment plants (STPs). The most common sources of environmental contamination with pharmaceuticals have been reported, *e.g.*, the post-consumption metabolism, the diagnostic compounds, the household disposal and the impacts due to the anthropogenic activities. Several classes of drugs have been subjected to the research investigations, in the relation with the environmental consequences, *e.g.*, the non-steroidal anti-inflammatory drugs, the blood lipid lowering agents, the antibiotics and sex hormones [1]. In the environmental context, the class of antidepressants drugs shows very high interest regarding its detection and removal.

Fluoxetine (FXT), most commonly known as Prozac, is a potent highly specific serotonin uptake inhibitor (SSRI), released on the market in 1987. It is used to treat major depression, obsessive compulsive disorder, bulimia nervosa and panic disorder [2]. It is metabolized in the liver by N-demethylation, resulting norfluoxetine, its active metabolite. However, about 10% of the parent drug is eliminated unchanged through kidneys. Taking into consideration the large number of people who suffer a behavioral disorder [3, 4] the main important pathway for this drug to discharge in the environment is human ingestion, followed by excretion and then disposal via wastewater [5].

Several methods have been developed in order to detect fluoxetine in biological matrices, *e.g.*, high performance liquid chromatography (HPLC) and gas chromatography (GC). The limit of detection is ranging between 0.5 μg/L in human plasma, 33.6 μg/L in human urine and 67 μg/L in human blood [6].

The world wide use of this drug made it to be detected in surface water [7], sewage treatment plants [8], downstream sewage treatment plants [9, 10], wastewater treatment plant effluent [11-13] in US, Canada and Northern and Western Europe. The higher concentrations detected in wastewater treatment plant influent were ranged from 91 ngL^{-1} up to 175.5 ngL^{-1} [14, 15]. Because this drug does not biodegrade rapidly in wastewater treatment plants, it is recalcitrant to hydrolysis, photolysis and microbial degradation, and it can be adsorbed by sediments, its presence being detected even in the first 30 cm of soil [16, 17]. In the environment, the life cycle of the organisms is influenced by this drug, and several potential health risks have been reported [18-20].

Beside chromatography methods coupled with mass spectrometry for better detection results, the electroanalytical techniques have been also developed in order to quantify the fluoxetine in pharmaceutical formulations. The results obtained were in good agreement with the pharmaceutical formulations and respected the regulation from the official pharmacopeias. A better sensitivity was obtained for the dropping mercury electrode (LOD about 0.099 μM) than for the glassy carbon electrode (LOD=1μM) [21, 22]. Also, good results were obtained in the case of chemical sensors (LOD> 5μM) [23-25]. However, taking into account that the potential toxicity of mercury limits its use as the electroanalytical tool and no very good sensitivity was reached using GC electrode, a fast electroanalytical method involving a stable, environmental and health friendly electrode material is desired, which allows to detect FXT in the aqueous media.

Boron-doped diamond (BDD) electrode has received increasing attention for the electroanalysis based on some advantages, including its wide potential window in both aqueous and organic solutions, low background currents, chemical and mechanical stability, resistance to fouling, lack of a surface oxide film and controllable surface termination [26, 27].

To the best of our knowledge, there is no information about the fluoxetine (FXT) detection on BDD electrode. This study aimed to demonstrate that the BDD electrode can be used as a very easy electroanalytical tool characterized by the enhanced properties for the FXT determination in the aqueous media. The electrochemical oxidation and determination of FXT on a BDD electrode was investigated by cyclic voltammetry (CV), differential-pulsed voltammetry (DPV), square-wave voltammetry (SWV) and chronoamperometry (CA) techniques. Some considerations regarding the mechanistic aspects of FXT electrooxidation have been suggested. The optimization of DPV and SWV experimental conditions, *e.g.*, pulse amplitude, step potential and frequency, for FXT determination using BDD have been determined.

MATERIALS AND METHODS

The electrochemical studies were performed using an Autolab potentiostat-galvanostat PGSTAT 302 (Eco Chemie, The Netherlands), controlled by a PC using the GPES 4.9 software and a three-electrode cell. The cell structure included a 3 mm boron-doped diamond electrode (BDD) working electrode, a platinum counter electrode and a saturated calomel electrode (SCE) reference electrode. For comparison, glassy-carbon (GC) was used as working electrode for FXT detection by cyclic voltammetry. The BDD

electrode supplied by Windsor Scientific Ltd. for electroanalytical use was a mirror polished doped polycrystalline industrial diamond (microcrystalline; doping degree about 0.1% boron) and GC working electrodes was purchased from Metrohm, Switzerland. All measurements were performed at room temperature without further temperature control.

The working electrode was cleaned mechanically by polishing on 0.2 μm Al_2O_3 powder, washed in water and then, in ethanol. Before the electrochemical measurements, an electrochemical pre-treatment by ten repeated cycling in a potential range between 0 and +1.5 V vs. SCE in 0.1 M Na_2SO_4 supporting electrolyte was performed. The electrochemical behaviour/performance of the electrode was studied by cyclic voltammetry (CV), linear-scan voltammetry (LSV), square-wave voltammetry (SWV), differential-pulsed voltammetry (DPV), and chronoamperometry (CA).

Fluoxetine (FXT) was provided by Lilly (Pantheon, France). The stock solution was prepared using ethanol (PAM Corporation, Romania) and 0.1 M NaOH solution (Merck, Germany) in a volume ratio of 1:1 to obtain 0.1 mM FXT solution.

The supporting electrolyte was 0.1 M Na_2SO_4 solution, prepared using Na_2SO_4 of analytical purity (Merck, Germany) with distilled water.

RESULTS AND DISCUSSION

Cyclic voltammetry measurements

The electrochemical characterization of BDD electrode in the presence of various fluoxetine (FXT) concentrations was conducted by CV. Figure 1 shows the cyclic voltammograms (CVs) recorded at the BDD electrode in 0.1 M Na_2SO_4 supporting electrolyte within potential range of 0 to 1.5 V / SCE in the presence of various concentrations ranged from 0.05 to 0.5 μM FXT. An oxidation peak at the potential value of +1.35 V/ SCE on forward scan corresponding to the electrooxidation of FXT on the BDD was noticed, which increased direct proportionally with FXT concentration (see Inset of Figure 1). In comparison with GC electrode, for which the FXT oxidation process occurred at the potential value of +1.13 V/SCE (the results are not shown here), the sensitivity for FXT detection on BDD electrode using CV was better (15.87 $\mu A \mu M^{-1}$ versus 4.36 $\mu A \mu M^{-1}$ reached for GC electrode).

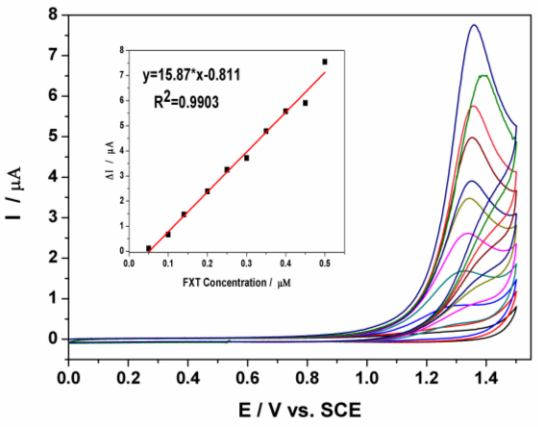

Fig. 1: It shows cyclic voltammograms recorded at BDD electrode in 0.1 M Na_2SO_4 supporting electrolyte in the presence of 0.05;0.1; 0.15; 0.2; 0.25; 0.3; 0.35; 0.4; 0.45; 0.5 μM FXT, potential scan rate:0.05 Vs^{-1}; potential range: 0 to +1.5 V/SCE; Inset: the calibration plot of the current vs. FXT concentration of the CVs recorded at E= +1.35 V vs. SCE.

Taking into account the literature data regarding the mechanistic aspects of fluoxetine oxidation on GC electrode, it can be assumed also that on BDD electrode, FXT oxidation should occurred based on the reaction (1) [28]:

$$RNHCH_3+H_2O \rightarrow RNH_2+HCHO+2e^-+2H^+ \quad (1)$$

Where, R is represented in Figure 2.

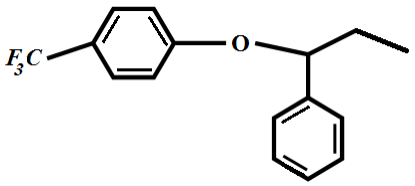

Fig. 2: It shows the molecular structure of radical R.

The fluoxetine oxidation process involved mainly its secondary amine group oxidation from the molecule structure. Also, it must be considered that it is very well-known that the presence of the aromatic ring-based organics represents a very complex oxidation process on the carbon-based electrodes involving both the adsorption of the reactant/intermediate or oxidation products and the formation of passive, nonconductive layers of oligomer products of the oxidation process on their surface by electropolymerization [29].

This aspect was noticed only for GC carbon, when starting with the second scan, the oxidation peak decreased and the background current as capacitive component increased (an undesired aspect) due to the formation of the nonconductive layer on the electrode surface. No similar behavior was found for BDD electrode, for which no significant decreasing of the oxidation peak height was noticed after the first scanning.

The effect of the scan rate on the electrooxidation of 0.5 μM FXT on the BDD electrode was studied to elucidate some mechanistic aspects. In Figure 3 are presented CVs recorded for 0.5 μM FXT using the BDD electrode in 0.1M Na_2SO_4 supporting electrolyte at various scan rates (0.01-0.2 Vs^{-1}). Inset a of Figure 3 shows the dependences of the anodic peak currents versus the square root of the scan rates. The anodic current corresponding to FXT oxidation increased linearly with the square root of the scan rate ($v^{1/2}$), indicating that the oxidation reaction of FXT is a diffusion-controlled process at the BDD electrode. The FXT oxidation starting potential shifted towards positive potential when increasing scan rate indicating that the electrooxidation process is irreversible (Inset b of Figure 3), which is supported also, by the lack of the cathodic peak corresponding to the anodic one.

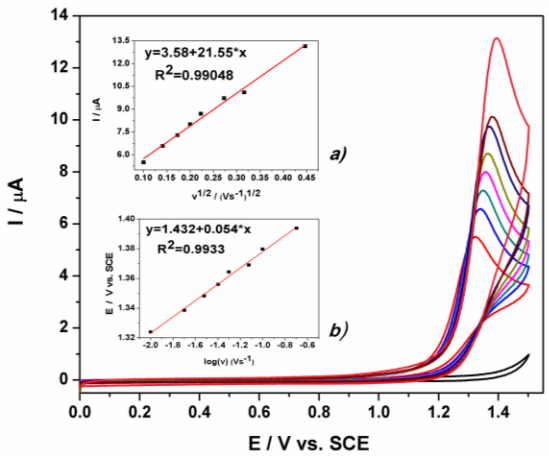

Fig. 3: It shows cyclic voltammograms of 0.5 μM FXT at BDD electrode in 0.1 M Na_2SO_4 supporting electrolyte with different scan rates 0.01, 0.02, 0.03, 0.04, 0.05, 0.075, 0.1, 0.2 V/s; Inset a) The calibration of the anodic peak current vs. the square root of the scan rate; Inset b) The calibration plot of the peak potential E vs. log (v).

Detection measurements

Differential-pulsed voltammetry

Differential-pulsed voltammetry (DPV) has been employed as technique for the evaluation of the performance of the BDD

electrode for the FXT assessment, in order to improve the electroanalytical parameters.

In order to achieve the best performance of this technique, the operating parameters, *i.e.*, modulation amplitude (a), step potential (ΔE_s) and scan rate(v) were varied and the useful signal determined as the difference between the anodic peak current and the background current was recorded for the detection of 0.2 µM FXT. The results are presented in Table 1, and it can be noticed that the optimal conditions were a=0.2V, ΔE_s= 0.05V and v= 0.025 Vs^{-1}.

Table 1: It shows the useful signal recorded for 0.2 µM FXT detection at various operating DPV variables

a (V)	ΔE_s (V)	v (Vs^{-1})	ΔI_u (µA)
0.025			0.39
0.05	0.05	0.05	1.05
0.2			22.938
	0.01		4.334
0.2	0.025	0.05	5.619
	0.05		22.938
		0.025	27.182
0.2	0.05	0.05	22.938
		0.1	26.576

Figure 4 depicts the DPVs recorded with the BDD electrode under optimized conditions, and as it is expected for pulsed voltammetry technique, the oxidation peak appeared at the potential value lower versus CV (1.25 V vs. 1.35 V/SCE). Also, better sensitivity was achieved, about five times higher than in the case of CV (81.21 $\mu A \mu M^{-1}$ versus 15.87 $\mu A \mu M^{-1}$).

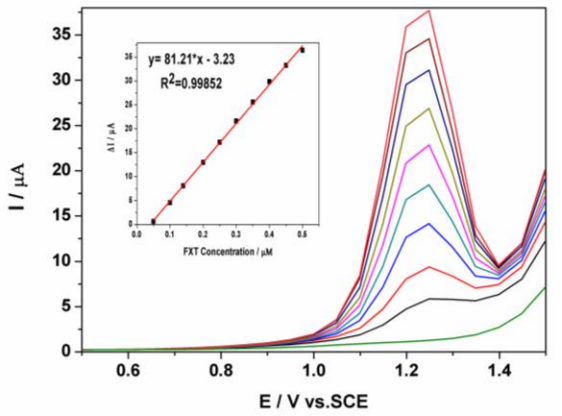

Fig. 4: It shows differential-pulsed voltammograms recorded on BDD electrode under optimised conditions: modulation amplitude of 0.2V, step potential of 0.05V and potential scan rate of 0.025 Vs^{-1} between 0 and +1.5V vs SCE in 0.1 M Na_2SO_4 supporting electrolyte in the presence of different FXT concentrations: 0.05;0.1; 0.15; 0.2; 0.25; 0.3; 0.35; 0.4; 0.45; 0.5 µM; Inset: the calibration plot of the currents recorded at E = 1.25 V/SCE vs. FXT concentration.

Square-wave voltammetry

The optimal operating conditions previously determined for DPV regarding the modulation amplitude of 0.2V and step potential of 0.05V were also applied for square-wave voltammetry (SWV). A very important operating parameter of SWV is the frequency that is directly related to the intensity of the analytical signal and the sensitivity. By varying frequency from 10 to 100 Hz the scan rate is also varied and different values of the sensitivities were achieved (Table 2). The best sensitivity was achieved for the frequency of 100 Hz and no reproducible signal was obtained for the frequency higher than this value.

Figure 5 shows the square-wave voltammograms obtained for the oxidation of FXT at different concentrations on BDD electrode in 0.1 M Na_2SO_4 supporting electrolyte within the potential range between 0 and +1. 5V vs. SCE under the optimised working conditions. Inset of Figure 5 corresponds to the analytical curve, that is, the linear dependence of I_p with FXT concentration under investigated conditions (0.05 µM to 0.5 µM).

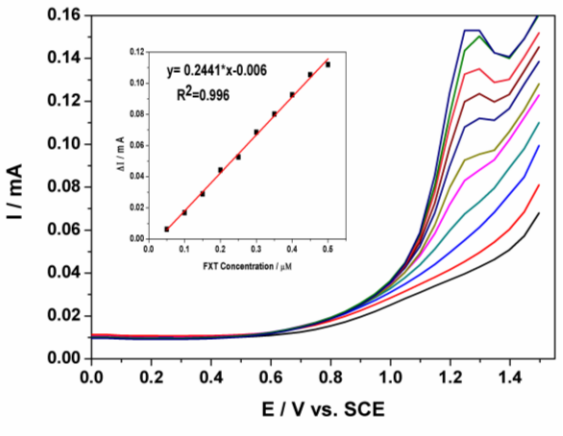

Fig. 5: It shows the square- wave voltammograms recorded on BDD electrode with a modulation amplitude of 0.2V, a step potential of 0.05V, a scan rate of 5 Vs^{-1} and a frequency of 100 Hz in a potential range between 0 and +1.5V vs SCE in 0.1 M Na_2SO_4 supporting electrolyte in the presence of different FXT concentrations: 0.05; 0.1; 0.15; 0.2; 0.25; 0.3; 0.35; 0.4; 0.45; 0.5 µM; Inset: the calibration plot of the currents recorded at E = 1.271 V/SCE vs. FXT concentration.

For all the studied frequencies (10, 50, 75 and 100 Hz) it was observed a liniarity between the anodic peak current and the FXT concentration, which supported also the difussion-controlled process for FXT electrooxidation. In Figure 5 are presented only the voltammograms recorded for the frequency of 100 Hz. Applying this technique, the results led the best sensitivity of the voltammetric determination of FXT on BDD electrode.

Table 2: It shows the electroanalytical parameters of FXT detection at BDD electrode using SWV at different frequencies

Frequency (Hz)	Sensitivity (µA/ µM)	LOD (µg/L)	LQ (µg/L)
10	83.435	0.71	2.37
50	170.79	0.124	0.416
75	203.7	0.163	0.54
100	244.11	0.53	1.78

In comparison with CV and DPV, SWV technique operated at 100 Hz frequency allowed to achieve the best electroanalytical performance regarding the improvement of the sensitivity, the relative standard deviation, the lowest limit of detection and the limit of quantification of FXT on BDD electrode (Table 3).

Chronoamperometry

However, for practical working applications the optimum analytical procedure should involve the recording of the chronoamperogram, which represents the easiest electroanalytical technique. The operating conditions for chronoamperogram recording are based on the existing well-established essential point of reference provided by the voltammograms. Thus, a series of chronoamperograms was recorded at the potential value of + 1.4 V/SCE within a FXT concentration ranged between 0.05 and 0.4 µM.

The current response of FXT oxidation increased linear with FXT concentration, but lower sensitivity was reached, probably due to the electrode fouling. This behavior suggested that the chronoamperometry technique is not suitable for enhanced detection of FXT.

The electroanalytical parameters for the concentration ranges where a linear dependence was obtained at the various potential values in relation with the applied electrochemical techniques

are gathered in Table 3. The limit of detection (LOD) and the limit of quantification (LQ) was evaluated based on $3S_B/b$ and respective, $10S_B/b$ [28], where S_B is the standard deviation of the mean value of three voltammograms/amperograms of the blank and b is the slope of the straight line in the analytical curve by using each electrochemical technique.

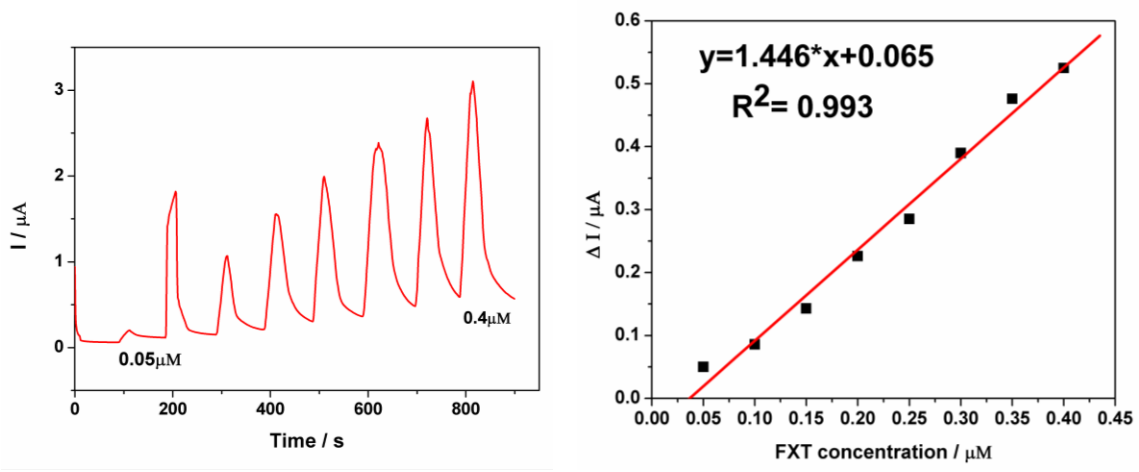

Fig. 6: It shows: up-the chronoamperogram recorded with BDD electrode in 0.1 M Na_2SO_4 supporting electrolyte and in the presence of different FXT concentrations (0.05; 0.1; 0.15; 0.2; 0.25; 0.3; 0.35; 0.4 µM) recorded at E = 1.4V vs. SCE; and down-the calibration plot of the currents vs. FXT concentrations.

Table 3: It shows the analytical parameters obtained at a BDD electrode using electrochemical techniques

Electroanal. techniques	E /V vs. SCE	Sensitivity (µA/ µM)	R^2	RSD (%)	LOD (µg/L)	LQ (µg/L)
CV	1.35	15.87	0.9902	6.54	0.982	3.27
DPV	1.25	81.21	0.9985	0.25	0.037	0.12
SWV	1.25	244.10	0.9967	0.34	0.530	1.78
CA	1.4	1.45	0.9930	5.10	4.680	15.61

The reproducibility of the electrode using the above-mentioned techniques was evaluated for three replicate measurements of FXT detection as relative standard deviation (RSD). The maximum value of RSD is 5.54 % informed about a good reproducibility.

A recovery test was performed by analyzing three parallel tap water samples, which contained 5 μgL^{-1} FXT. This test was run in 0.1 M Na_2SO_4 as supporting electrolyte and a recovery of 96 % with a RSD of 2.8 % was found for FXT determination using SWV operated with the optimum working variables above-presented. Finally, the results obtained by this method were compared with those obtained by means of a conventional UV-VIS spectrophotometrical method recorded at the wavelength of 263 nm. Based on the results obtained, it can be concluded that the two methods lead to very close results and that the accuracy of the proposed SWV method is good.

CONCLUSIONS

BDD electrode exhibited the useful peculiarities for the anodic oxidation and the voltammetric/amperometric detection of fluoxetine from the aqueous solutions. The anodic oxidation of fluoxetine on BDD electrode is a diffusion-controlled process, which is very desired in electroanalysis.

All tested electrochemical techniques, cyclic voltammetry, differential-pulsed voltammetry, square-wave voltammetry and chronoamperometry allowed to detect the FXT using BDD electrode.

However, it can be noticed that the best performance subjected to the sensitivity was obtained using square-wave voltammograms operated at 0.2V modulation amplitude, 0.05V step potential and 100 Hz frequency, and the lowest limit of detection was reached by differential-pulsed voltammetry at 0.2 modulation amplitude and 0.05 V step potential. .

The accuracy of the applied methods was excellent as compared to the detection results obtained using the conventional UV-VIS spectrophotometric method.

In comparison with the results reported in the literature for the FXT detection(Ganjali, 2011; Hussein, 2011; Lencastre, 2006; Nouws, 2007; Papas, 2010), the BDD electrode exhibited the superiority relating to the sensitivity and the lowest limit of detection.

These results indicate that BDD electrode is suitable for fluoxetine determination in real water sample and also, in pharmaceutical formulations, and that the proposed pulsed voltammetric-based methodology can be a valuable tool for the fluoxetine analysis.

ACKNOWLEDGEMENTS

Funding for this study was provided by the Romanian National Research Programs PN-II-ID-165/2011 and PNII-60/2012.

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