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Sensitive Electrochemical Determination of Oxcarbazepine using Polymer Film Modified Glassy Carbon Electrode

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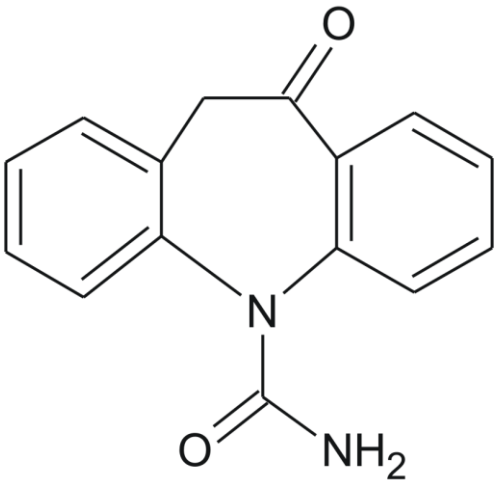
A glassy carbon electrode (GCE) is modified with electropolymerized film of *p*-aminobenzene sulfonic acid (*p*-ABSA) in pH 7.0 phosphate buffer solution (PBS). A poly(*p*-ABSA) modified glassy carbon electrode was used for the voltammetric determination of oxcarbazepine. The modified electrode exhibited excellent electrocatalytic activity for the reduction of oxcarbazepine. The voltammetric response of oxcarbazepine at this polymer film modified electrode increased significantly when compared with that at a bare glassy carbon electrode. The proposed method was applied to the quantification of oxcarbazepine in pharmaceutical formulations. The proposed method exhibits good recovery and reproducibility. The mechanisms of electropolymerization of *p*-ABSA and reduction of oxcarbazepine are also suggested.

Keywords: *p*-Aminobenzene sulfonic acid; Modified-glassy carbon electrode; Electropolymerization; Electrocatalytic-reduction; Determination of oxcarbazepine.

1. INTRODUCTION

Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide) (Fig. 1) is the keto form of 10-hydroxycarbamazepine. As a blocker of pre- and postsynaptic voltage-dependent sodium channels in the central nervous system, it has been in therapeutic use for a few years in the treatment of partial and generalized seizures, trigeminus neuralgia, affective disorders and spasticity [1,2].

It is quickly absorbed after oral administration and undergoes rapid and almost complete reductive metabolism to form the pharmacologically active 10-monohydroxy derivative [3].



Scheme 1. Chemical structure of oxcarbazepine.

Several analytical methods have been reported titrimetric and spectrophotometric [4], high-performance liquid chromatography [5,6,7], liquid chromatography [8], for its determination in pharmaceutical formulations. Most of the reported methods required a long time for sample pretreatment, expensive reagents and equipment, which are not usefull for routine analysis studies.

Voltammetry is a practical analytical technique that offers high sensitivity, precision, and accuracy, wide linear range and low-cost instrumentation and time. A few electrochemical studies have been conducted on the electrochemical behavior and determination of oxcarbazepine in pharmaceuticals by voltammetric techniques. The electrochemical behavior of acyclovir was studied using different electrodes such as hanging mercury drop electrode [9], glassy carbon electrode [10], silver nanoparticle-modified carbon screen-printed electrodes [11].

Research on surface modified electrode has involved studies of the electrochemistry of the attached molecules, the catalysis and inhibition of various electrochemical processes and specific applications to such videly varying areas as photoelectrodes and analytical determinations [12]. One of the methods used for the modification of electrode surfaces is electropolymerization. Electropolymerization can accelerate transmission of electrons onto the surface of the electrode, it has high selectivity and sensitivity due to the film homogeneity in electrochemical deposition, and it has strong adherence to the electron surface and large surface area [13,14].

The aim of this work was electrochemical investigation of oxcarbazepine and to develop a sensitive electrochemical methodology for the quantification of oxcarbazepine in pharmaceutical formulations at modified electrode using voltammetric techniques.

Oxcarbazepine have not been studied determination from its drug forms and electrocatalytic-reduction behavior at poly(*p*-ABSA)-modified glassy carbon electrodes. In this study, we prepared the poly(*p*-ABSA) modified GCE [15,16] and studied the electrochemical properties of oxcarbazepine on modified glassy carbon electrode. Quantitative analysis was performed on the drug active substance in tablet dosage form at modified GCE electrode. It showed excellent electrocatalytic activity for oxidation of oxcarbazepine in 0.1 mol L^{-1} PBS (pH 7.0).

2. EXPERIMENTAL

2.1. Reagents and Materials

Oxcarbazepine and Trileptal were kindly supplied by Novartis (Turkey). Their stock solutions (0.01 mol L^{-1}) were prepared with water. *p*-aminobenzensulfonic acid (Sigma Aldrich) solution was prepared with 0.1 mol L^{-1} PBS and used without any further purification. Phosphate buffer solutions were prepared with 0.1 mol L^{-1} NaH_2PO_4-Na_2HPO_4 and by adjusting the pH with 0.1 mol L^{-1} H_3PO_4 and 0.1 mol L^{-1} NaOH. All aqueous solutions were prepared in twice-distilled de-ionized water and used analytical grade chemicals. To remove oxygen in experimental solutions argon gas (99% purity) was used.

2.2. Apparatus

A Model Metrohm 757 VA Trace Analyzer (Herisau, Switzerland) and Metrohm Autolab PGSTAT 101 (Netherlands) were used for the voltammetric measurements, with a three-electrode system consisting of glassy carbon working electrode (GCE) [surface area (ϕ) 7 mm; disc diameter (R) 2 mm, Metrohm], a platinum wire auxiliary electrode and Ag/AgCl (KCl 3 M, Metrohm) reference electrode. The bare GCE was polished successively with 0.3, 0.1 diamond suspension and 0.05 μm Al_2O_3 slurry on a polishing cloth before electrochemical modification. Firstly, the deoxygenating process of the supporting electrolyte solutions was carried out with argon gas for 5 min before all experiments. Then, the argon gas was also passed through the solutions for 60 s after the addition of each sample solution in the experiments. Monomer solutions were purged with argon gas for about 30 min before polymerization and the solution was blanketed with the same gas during electropolymerization. In each new experiment, a new bare electrode surface was used. All pH measurements were made with Model Metrohm 744 pH meter (Herisau, Switzerland). All measurements were carried out at ambient temperature of the laboratory (15-20 °C). Wise Clean model sonicator was used to clean the surface of electrodes. The 0.055 μS/cm ultra pure water (UPW) was used throughout the experiments.

For analytical application, the following parameters were employed: pulse amplitude (pulse amplitude of the voltage pulse superimposed on the direct voltage) 50 mV; pulse time (time interval during which a voltage pulse is superimposed on the direct voltage) 0.04 s, voltage step (voltage step for direct voltage ramp) 0.009 V, voltage step time (time interval after which the voltage in the sweep is increased or decreased by the amount of the voltage step) 0.04 , potential step 10 mV (DPV); and scan rate (display of the ramp slope calculated as voltage step/voltage step time) in the range 30-300 mV s^{-1} (CV).

2.3. Preparation of poly(p-Aminobenzene Sulfonic Acid)-modified GCE

Prior to electrochemical modification, the bare GCE was polished successively with 1 μm diamond paste, 3 μm diamond paste and 0.05 μm Al_2O_3 slurry on a polishing cloth. Then it was rinsed

with double-distilled water, and sonicated in 1:1 nitric acid, acetone and double-distilled water for 10 min, respectively. After being cleaned, the electrode was immersed in 2.0×10^{-3} mol L^{-1} *p*-ABSA solution and was conditioned by cyclic sweeping between −1.5 to +2.4 V at 200 mV s^{-1} for 10 scans (Fig. 1). In order to get a stable response prior to measurements, the resultant modified electrode was also continuously cycled from 0.5 to 1.5 V in pH 7.0 PBS for another few scans. Finally, the modified electrode was carefully rinsed with distilled water, and used for analysis of oxcarbazepine and stored in air for later use. We studied the reduction of oxcarbazepine at modified-GCE (0.1 M of pH 5-8 PBS). Best results were obtained at 0.1 mol L^{-1} PBS (pH 7.0). Therefore PBS (pH 7.0) was selected for detection of oxcarbazepine by modified GCE.

3. RESULTS AND DISCUSSION

3.1. Electropolymerization of p-aminobenzene sulfonic acid at the GCE surface

The electropolymerization of *p*-ABSA on GC electrode surface was performed by repetitive cyclic voltammetry (Fig. 1).

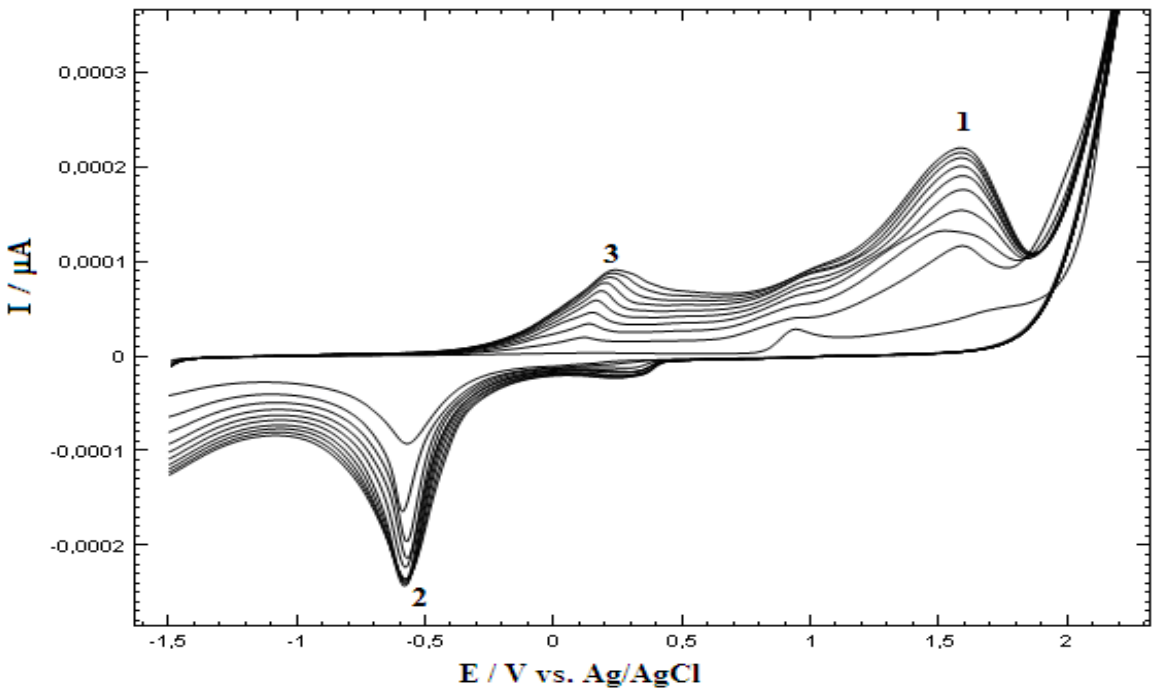
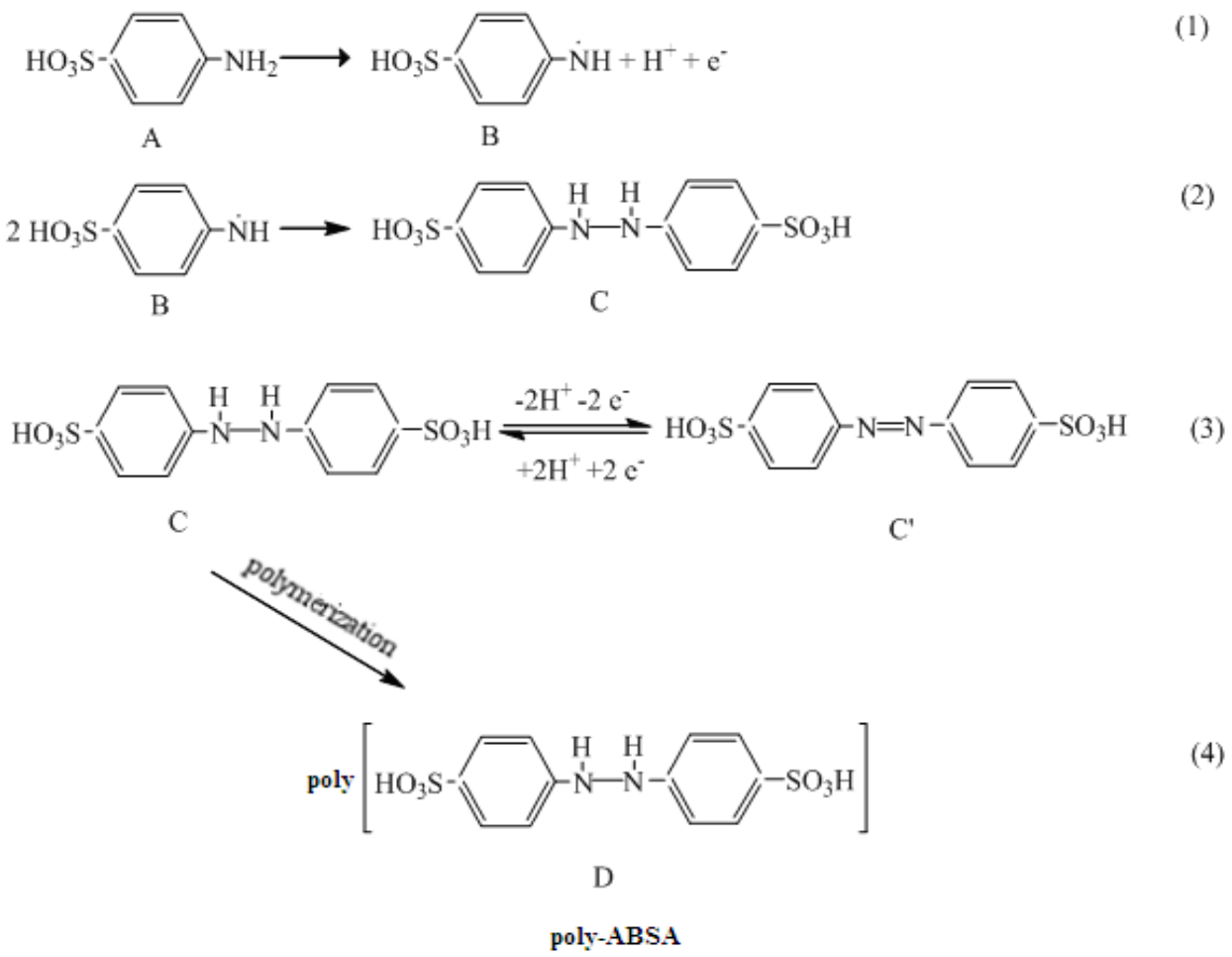


Figure 1. Repetitive cyclic voltamograms of 2.0×10^{-3} mol L^{-1} *p*-ABSA at bare GCE. Initial potential: -1.5 V; terminal potential : +2.4 V. Scan rate: 200 mVs^{-1}; supporting electrolyte: 0.1 mol L^{-1} PBS (pH 7.0).

As can be seen in Fig. 1, in the first scan, anodic peak 1 and cathodic peak 2 were observed with peak potential value at about +1.5 V and −0.65 V, respectively. From the second cycle on, anodic

peak 3 appeared with potential at about +0.15 V. Then larger peaks were observed upon continuous scanning, reflecting the continuous growth of the film. These facts indicated *p*-ABSA was deposited on the surface of GCE by electropolymerization. A uniform adherent blue polymer film was formed on the GCE surface. After modification, the poly(*p*-ABSA) film electrode was carefully rinsed with doubly distilled water, then stored in pH 7.0 PBS and for later use.

The electropolymerization behavior of *p*-ABSA at GCE was similar to the references reported [15,16,17]. The reaction mechanism may be similar to that proposed in Scheme 2.



Scheme 2. Suggested electrochemical polymerization of *p*-ABSA at GCE.

As can be seen from Scheme 2, *p*-ABSA (A) was first oxidized to free radical (B) (Fig.1, peak 1); the free radical (B) combined together rapidly to form hydrazobenzene sulfonic acid (C); then hydrazobenzene sulfonic acid (C) was oxidized to azobenzene sulfonic acid (C′) (Fig.1, peak 3), and azobenzene sulfonic acid (C′) was reduced to hydrazobenzene sulfonic acid (C) (Fig.1, peak 2) and finally the electrode surface was covered by the formed polymer (D).

3.2. Electrochemical response of oxcarbazepine at poly(p-ABSA)-modified GCE

Fig. 2 shows CV curves of $5.0x10^{-5}$ mol L^{-1} oxcarbazepine at bare GCE (b) and poly(*p*-ABSA)-modified GCE (c) in 0.1 mol L^{-1} PBS (pH 7.0), respectively.

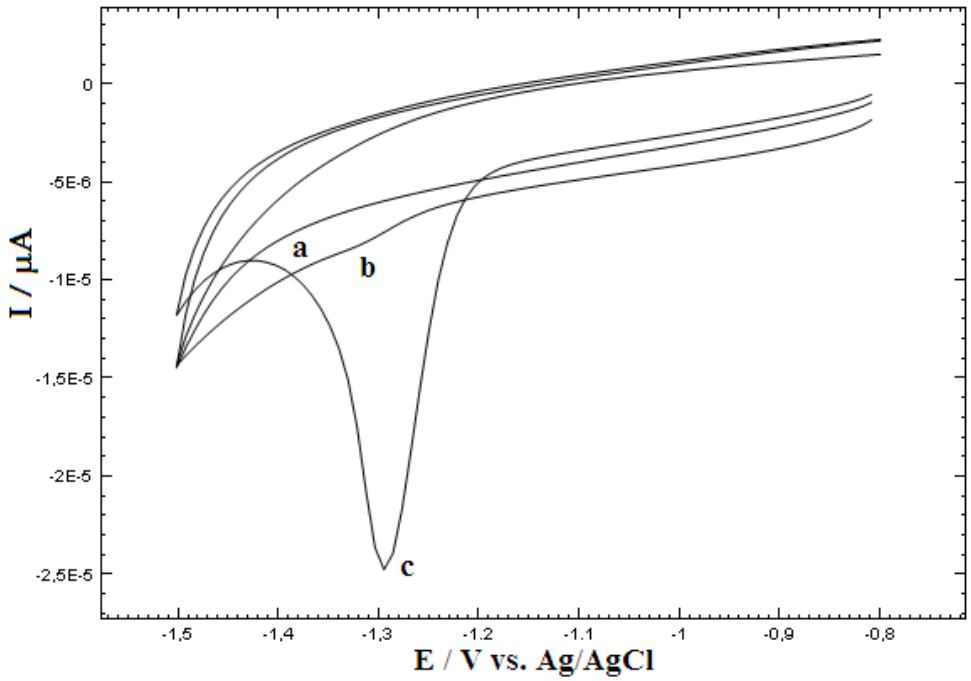


Figure 2. CV voltamograms of $5.0x10^{-5}$ mol L^{-1} oxcarbazepine a) blank, b) at bare GCE c) at poly (*p*-ABSA)-modified GCE. Scan rate: 100 mVs^{-1}; supporting electrolyte: 0.1 mol L^{-1} PBS (pH 7.0)

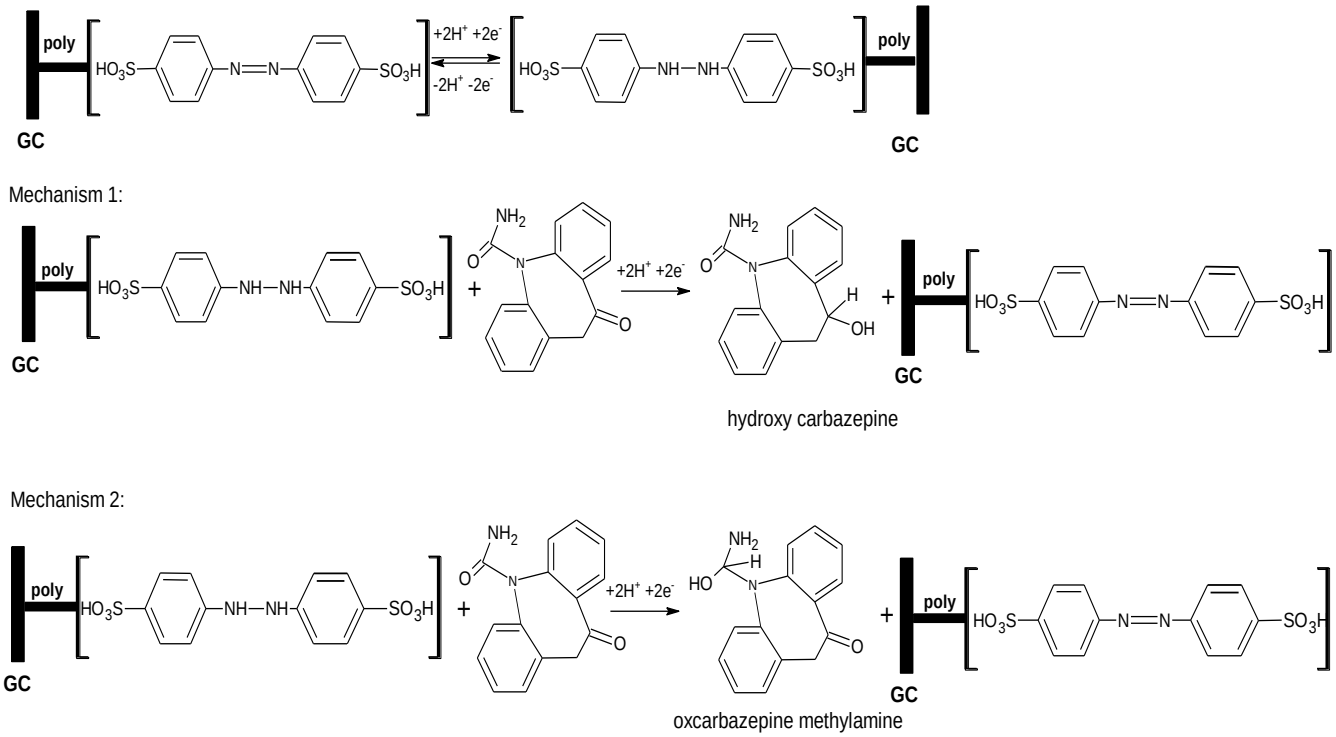
In blank buffer solution, no obvious peaks were observed at both bare GCE and poly(*p*-ABSA)-modified GCE. As can be observed from Fig. 2, oxcarbazepine cathodic peak showed about -1.29 V at bare GCE and -1.31 V at the modified-GCE. Reduction peak potential of oxcarbazepine was shifted 0.02 V positively and peak current increased about 128 times at the modified-GCE. Essentially modified electrode reduced the over potential for the reduction of oxcarbazepine by 0.2 V. The high conductivity of modified electrode is due to the presence polymer film. poly(*p*-ABSA)-modified GCE exhibit electro-catalytic behaviour towards the electrochemical reduction of oxcarbazepine due to its fast electron transfer capability. As result, modified electrode can be effectively used to detect oxcarbazepine at lower potential with high sensitivity.

3.3. Proposed Electrochemical Reduction Mechanism at poly(p-ABSA)-modified GCE

The electrochemical reduction mechanism of oxcarbazepine at poly(*p*-ABSA) modified GCE is proposed in Scheme 3.

Oxcarbazepine compound contains more than one reduced group. Thus, the compounds can be determined by performing more detailed analysis which group the reduction. This study attempted

reduction of the compound only. The above was given two possible mechanisms. In the first mechanism, carbonyl group in the compound is reduced by taking $2H^+$ and 2 electrons to hydroxycarbazepine compound. In the second mechanism, amide group in the compound by taking $2H^+$ and 2 electrons is transformed into oxcarbazepine metylamine compounds. All of these reactions occur on the modified electrodes. On the poly(*p*-ABSA) modified electrode GCE, the reaction is formed out of hydrazine-diaza conversion. Hydrazine poly(*p*-ABSA) is transformed to diaza poly(*p*-ABSA) by taking hydrogen and electron. Finally, oxcarbazepine products formed by taking hydrogen and electrons from oxcarbazepine [3,15].



Scheme 3. Suggested reduction mechanisms of oxcarbazepine at modified-GCE .

3.4. Effect of pH on reduction of oxcarbazepine

In order to obtain the optimum experimental conditions, some variables affecting the peak current and peak potential, which are pH and the species of supporting electrolyte, were studied for oxcarbazepine solution of $5.0x10^{-5}$ mol L^{-1} on modified-GC electrode by the proposed voltammetric techniques. When the effect of pH on the peak current was studied, the highest peak current was observed at pH 7.0 PBS (Figure 3a). Therefore, pH 7.0 PBS was preferred for further work. The voltammetric responce was strongly pH depended. The peak potential of the reduction peak shifted more negative values with increasing pH (Figure 3b) . These can also be explained by changes in protonation of the acid-base functions in the oxcarbazepine molecules (Scheme 3) [18-25].

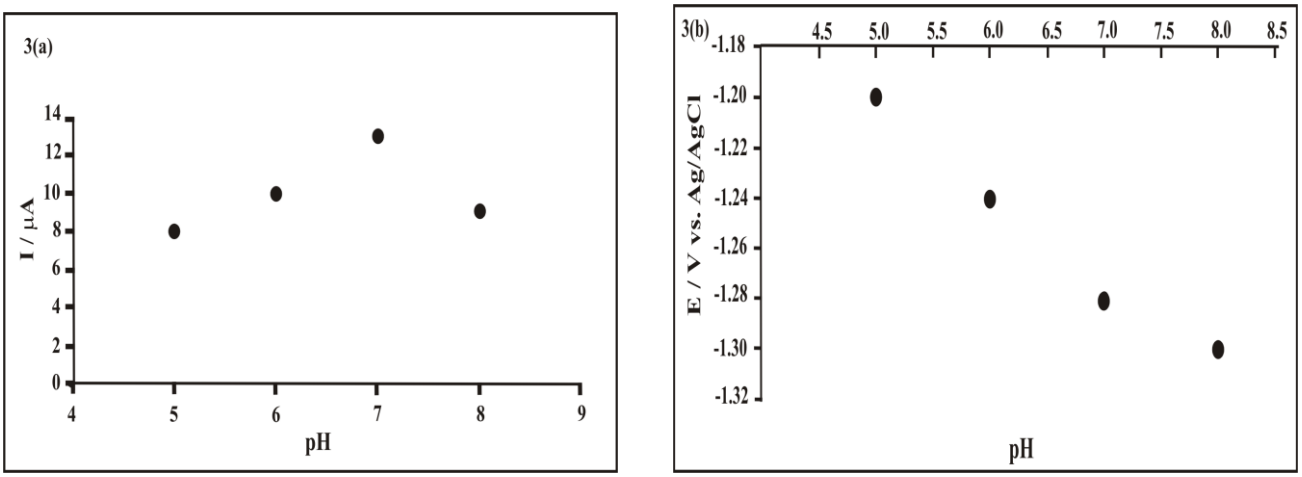


Figure 3. (a) Effect of pH on DPV peak current of $5x10^{-5}$ M oxcarbazepine. **(b)** Effect of pH on DPV peak potential of $5x10^{-5}$ M oxcarbazepine.

3.5. Effect of scan rate on reductin of oxcarbazepine

The effect of scan rate on the reduction peak current of $5.0x10^{-5}$ mol L^{-1} oxcarbazepine was studied. With increasing scan rate, the cathodic peak current increased. A good linearity between the square root of scan rate and peak current was obtained between the range of 30-300 mV s^{-1} (Fig. 4)..

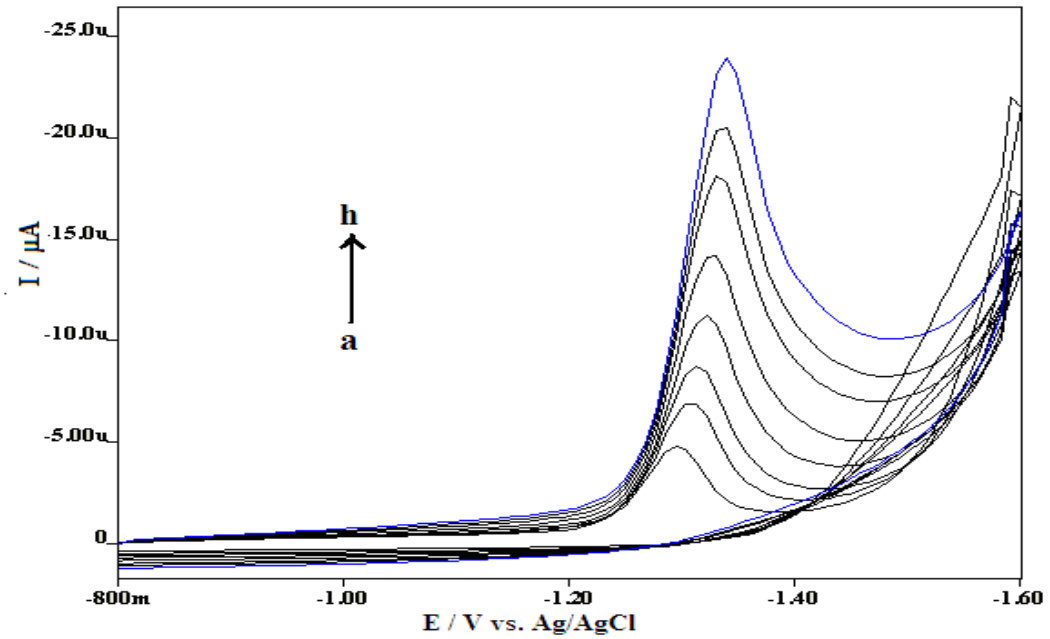


Figure 4. CV voltamograms of $5.0x10^{-5}$ mol L^{-1} oxcarbazepine at poly(*p*-ABSA)-modified GCE; Scan rates: a) 30, b) 50, c)100, d) 140, e)160 f) 200, g) 240, h) 300 mVs^{-1}; supporting electrolyte: 0.1 mol L^{-1} PBS (pH 7.0).

The linear regression equation was $I_p(\mu A)= 1.2537\upsilon^{1/2}$-3.4005 with correlation coefficient (r=0.99). A linear relationship was observed between peak current and square root of scan rate with a correlation coefficient of r=0.99. Correlation coefficient is very close to 1.0 showing that the reduction process is diffusion controlled. Also, the plot of logarithm of peak current versus logarithm scan rate has a slope of 0.68 which is almost close to the theoretical value of 0.5. The equation was log $I_p(\mu A)$=0.6853ogυ-0.4227 (r=0.99) on modified electrode. These indicate a diffusion controlled electron process of oxcarbazepine reduction at poly(*p*-ABSA)-modified GCE

3.6. Determination of oxcarbazepine

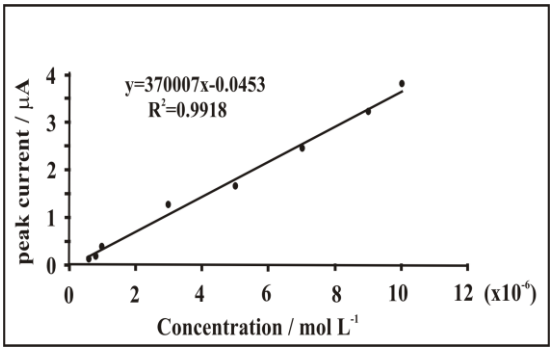


Figure 5. Plot of concentration versus current for oxcarbazepine.

The determination of oxcarbazepine concentration at poly(*p*-ABSA)-modified *GC* electrode was performed with differential pulse voltammetry (DPV). Under the optimum analytical conditions, the determination of oxcarbazepine at different concentrations was performed. A linear calibration curve (Fig**.** 5) was obtained for oxcarbazepine in the range $6x10^{-7}$ - $1x10^{-5}$ mol L^{-1} for 0.1 mol L^{-1} PBS supporting electrolyte **(**Fig. 6).

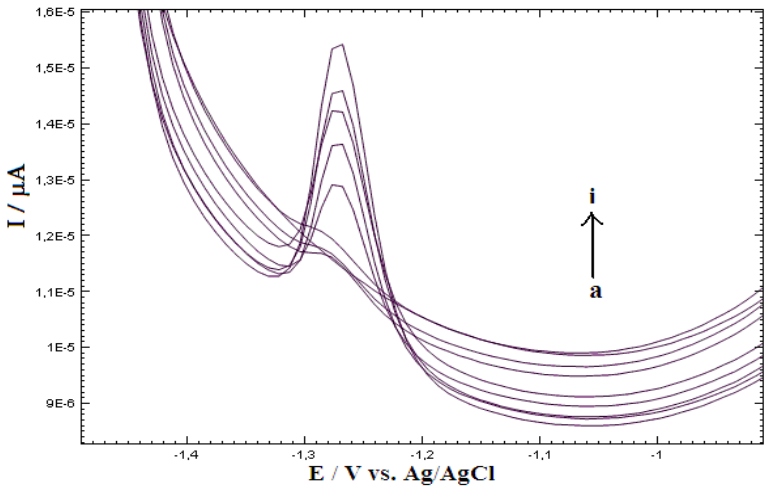


Figure 6. DPV voltamograms of oxcarbazepine at poly(p-ABSA)-modified GC electrode; a) blank; b) $6.0x10^{-7}$;c) $8.0x10^{-7}$; d) $1.0x10^{-6}$; e) $3.0x10^{-6}$; f) $5.0x10^{-6}$; g) $7.0x10^{-6}$; h) $9.0x10^{-6}$; i)$1.0x10^{-5}$mol L^{-1}; supporting electrolyte: 0.1 mol L^{-1} PBS (pH 7.0).

Limit of detection (LOD) and limit of quantification (LOQ) were calculated for the electro-reduction peak current using the following equations. LOD = 3 s/m, LOQ = 10 s/m; where, s is the standard deviation of the peak currents (for five runs) and m is the slope of the calibration curve. The achieved LOD and LOQ were $1.27x10^{-7}$ and $4.24x10^{-7}$ mol L^{-1} for poly(*p*-ABSA)-modified GCE, respectively. Validation of the procedure for the quantitative determination of oxcarbazepine was investigated via evaluation of the LOD, LOQ and recovery studies by DPV technique (Table 1).

Table 1. Regression data of the calibration curve for assay of oxcarbazepine by DPV.

Parameters	Results
Measuremed potential, V	-1.27
Linear concentration range, mol L^{-1}	$6x10^{-7}$ -$1x10^{-5}$
Slope, mA mol L^{-1}	370007
SD of slope	62621.2
Intercept, nA	-0.0453
SD of intercept	0.0148
Correlation coefficient,r	0.9918
LOD, mol L^{-1}	$1.27x10^{-7}$
LOQ, mol L^{-1}	$4.24x10^{-7}$

SD:Standart deviation; LOD:Limit of detection; LOQ:Limit of quantification

$5x10^{-6}$ mol L^{-1} oxcarbazepine was investigated repeatedly at an identical surface of poly(*p*-ABSA)-modified GCE for 20 successive times. The average currents were 1.65 µA with the relative standard deviation (RSD) of 3.54%. It indicated excellent reproducibility. Also, the stability of the modified electrode was investigated. Modified electrode was stored in PBS (pH 7.0) at 4 °C in a refrigerator. The peak current retained 97 % of its initial response after storage in air for 10 days. This indicates that the modified electrode has good stability.

3.7. Analytical Applications

Five tablets of Trileptal (Novartis Pharm Ind., İstanbul), containing 300 mg oxcarbazepine per tablet, were accurately weighed and ground to a fine powder. An adequate amount of this powder, corresponding to a stock solution of concentration $1x10^{-3}$ mol L^{-1}, was weighed and transferred into a 10 mL calibration flask and the volume was adjusted with distilled water. The contents of the flask were centrifuged for 20 min at 4000 rpm to affect complete dissolution. The non-dissolved excipients were settled on the bottom. Each solution was transferred into the voltammetric cell. The amount of oxcarbazepine in trileptal commercial tablets was calculated by reference to the appropriate calibration plots. For this reason, the proposed techniques were checked by performing recovery tests. The results obtained are given in Table 2. The proposed techniques could be successfully applied to oxcarbazepine assay in tablets without any interference.

Table 2. Detection of oxcarbazepine in commercial tablets and mean recoveries at poly(*p*-ABSA)-modified GCE by DPV.

Parameters	Results
Labeled oxcarbazepine, mg	300
Amount of oxcarbazepine found, mg	297
RSD, %	1.60
Bias, %	3
Spiked oxcarbazepine, mg	50
Found, mg	49.50
Recovery, %	99.00
RSD, %	1.51
Bias, %	1

RSD: Relative standart deviation

4. CONCLUSIONS

A poly(*p*-aminobenzene sulfonic acid)-modified GCE was fabricated by electropolymerization techniques in PBS using cyclic voltammetry method. The modified GC electrode showed good electrocatalytic activity for the reduction of oxcarbazepine. The modified electrode provides greater sensitivity and selectivity in the determination of oxcarbazepine. Moreover, the modified electrode showed easy regeneration, good reproducibility and stability. Proposed methods can be applied to the detection of oxcarbazepine in practical drug samples.

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