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A glassy carbon electrode modified with boron-doped graphene oxide/ polyaspartic acid for electrochemical determination of oxazepam

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ABSTRACT

In this study, the electrochemical determination of oxazepam in plasma samples was studied. The composite of graphene oxide/boron (B-RGO) was synthesized via the hydrothermal method and it was cast on the glassy carbon electrode (GCE). The polyaspartic acid (poly(ASP)) was deposited on the B-RGO by electropolymerization to prepare the modified electrode named B-RGO/ poly(ASP)|GCE. The B-RGO and B-RGO/poly ASP were characterized using scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR). Electrochemical studies were performed by cyclic voltammetry (CV), linear sweep voltammetry (LSV) and differential pulse voltammetry (DPV) methods. The experimental parameters affecting the reduction of oxazepam such as pH, preconcentration time, scan rate and other analysis conditions, and instrumental parameters were optimized. Under the optimal conditions, the linear range was obtained from 0.001 to 800 μM with a correlation coefficient of 0.998. The repeatability of the method for the electrode to electrode and one electrode were 4.3% and 4.9%, respectively. The limit of detection (LOD) of 0.3 nM and the limit of quantitation (LOQ) of 1 nM were obtained. The high efficiency of the developed electrode in the determination of oxazepam in the plasma sample was proved by using acceptable results and satisfactory relative recovery percentage (>90%). Based on our calculation, the heterogeneous electron transfer rate constant (k_s) was 1.92 s^{-1}. The interaction between oxazepam and modifier was single-layer and multi-layer adsorption, respectively in low and high concentrations.

***Keywords**: Aspartic acid, Boron, Differential pulse voltammetry, Glassy carbon electrode, Graphene oxide, Oxazepam*

1. Introduction

Oxazepam (**Fig. 1**), a short- and medium-acting benzodiazepine, is exploited in the treatment of insomnia and used as a sedative to mitigate alcohol withdrawal symptoms and anxiety [1, 2]. There are diverse side effects associated with the use of oxazepam, like other benzodiazepines, such as being dizzy, drowsy, memory impaired, addicted, and paradoxically excited; however, transient amnesia is not affected by oxazepam. Some side effects arise because of the abrupt withdrawal or quick dose reduction of oxazepam as it happens in the case of alcohol and barbiturates withdrawal, including cramps in muscles and abdomen, depression, paroxysm, sweating, vomiting, problems related to falling and staying asleep. It is better to mention that the risk of these undesirable withdrawal symptoms occurs to a great extent in cases of longer medication time and/or the application of higher doses. Therefore, short-term usage and gradual reduction of oxazepam treatment should be considered. [3]. Oxazepam is not prescribed for patients suffering from myasthenia gravis, severe liver disease, and disease related to the lung including limited lung storage and chronic obstructive pulmonary. Benzodiazepines require special precautions when used in the elderly, pregnant women, children, alcohol and substance abusers, and people with comorbid psychiatric disorders. Benzodiazepines use in late pregnancy, particularly in high doses, may lead to neonatal flap syndrome. Therefore, measurement of

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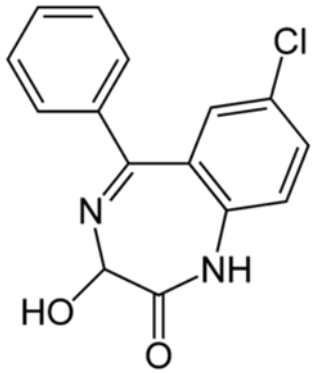

Fig. 1. Structure of oxazepam

benzodiazepines in biological samples takes the attention of researchers. Analytical methods such as chromatography [4-6] and spectroscopy [7, 8] have been reported to measure oxazepam. Despite the availability of good analytical results, most of these methods face limitations such as long response time, the need for pure and toxic solvents, expensive equipment, and the need for skilled experts.

Among the different analytical methods, the electrochemical methods have some advantages such as low cost, being fast, high dynamic range, no need for an internal standard, stable response, user-friendly and precise instruments without needing high knowledge, which makes them preferred for the analysis of pharmaceutical and biological compounds [9-13]. In electrochemical sensors, electrodes are the heart of the sensors but directly electrochemically oxidizing many materials is irreversible on the surface of bare electrodes, which results in the need for applying high voltage for their oxidation [14]. To overcome these problems, the electrodes must be modified by adding different materials [15, 16]. A good modifier should facilitate the transfer of electrons between electroactive species and electrodes [17, 18].

In this work, modification of the glassy carbon electrode (GCE) was conducted by focusing mainly on the preparation of boron-doped graphene oxide (B-RGO) and the layer covered by poly aspartic acid (Poly (ASP)) for the determination of oxazepam. The unique structural and electrochemical properties of GO make it an ideal material for the fabrication of electro sensors [19]. Reduced GO (RGO) can be changed to n-type or p-type materials as a result of doping with nitrogen or boron, respectively. For example, due to the good electron-donor properties of N-doped RGO, it has versatile applications such as heterojunction nano photocatalysts, lithium-ion batteries, water electrolysis, fuel cells, and supercapacitors [20-23]. Boron doping enhances the conductivity of GO and creates several defect sites during the reduction process, which can play a vital role in achieving the high-sensing performance of electrochemical sensors. In addition, the high adsorption affinity of boron towards oxygen atoms can help analytes to adsorb on the electrode surfaces. Poly amino acids, as conductive polymers, show great electrocatalytic properties. Take aspartic acid ($C_4H_7NO_4$) as an example of hydrophilic poly amino acid with carboxyl and amine functional groups which induces a negative charge on the surface of the electrode. This electrochemically polymerized synthetic polymer includes some features of easily synthesizability, biodegradability, easy accessibility, biocompatibility and low toxicity. Until now, diverse studies about the application of poly aspartic acid in sensors have been reported, two of which are using graphene quantum dots- modified poly (ASP) and poly (L-Aspartic Acid) modified GCE for the determination of taurine and Ibuprofen, respectively [24-26].

2. Experimental

2.1. Materials and devices

Graphite, potassium permanganate, hydrogen peroxide 30%, phosphoric acid, sulfuric acid, ethanol, hydrochloric acid, sodium nitrate, and hexacyanoferrate were purchased from Merck (Germany). Briton-Rubinson solution was used not only as a supporting electrolyte but also used for adjustment of pH in the range of 2 to 8. All the reagents purchased from Sigma Company or Merck were in the analytical grade. Distilled deionized water was used for the preparation of aqueous solutions. Autolab PGSTAT-302 (Eco Chemie B. V.) potentiostat/galvanostat was utilized as the experimental apparatus for voltammetry. A conventional three-electrode system was utilized consisting of the bare or modified GCE, an Ag/AgCl (3 M KCl), and a Pt wire as the working, reference and counter electrodes, respectively. Also, the pH meter of Metrohm (model: 691, Switzerland) was used.

2.2. RGO and B-RGO synthesis

The modified hummer method was applied to synthesize GO from graphite [27], and the conventional hydrothermal process was employed for the boron-doped product. Briefly, 54 mL of sulfuric acid was added to 6 mL of phosphoric acid and stirred for 1 hr. Then 0.45 g of graphite powder was added to the solution and mixing was continued for several minutes. Subsequently, 2.64 g of potassium permanganate was slowly added to the solution and stirred for 6 hours. After that, 1.35 mL of H_2O_2 was added slowly and stirred for 10 minutes. Finally, 20 mL of hydrochloric acid and 60 mL of deionized water were added and

centrifuged. The obtained residuals were rewashed several times with hydrochloric acid and deionized water. The product was dried in an oven at 90 °C for 24 hours.

Then, 0.5 g of GO was dispersed ultrasonically in 100 mL of a mixture of water and ethanol for 15 min, and then 0.5 g of H_3BO_3 was added to the dispersed GO under vigorous stirring (2h). The mixture was transferred to a Teflon-lined stainless-steel autoclave and was heated at 180 °C for 12 h. The acquired suspension was centrifuged for 15 min at 12000 rpm. The solid product was dried at 60 °C after repeated washing with distilled water [28].

2.3. Modified electrode preparation by B-RGO/Poly (ASP)

First, the GCE was polished with alumina powder and ultrasonicated in water and ethanol for 10 min to remove surface contaminants. The electrode surface was cast using 2 µL of B-RGO at a concentration of 1 mg/mL. An oven of 50 °C was used to dry the electrode named GCE/B-RGO. GCE/B-RGO was then placed in a 1 mM solution of aspartic acid and the electrochemical polymerization was performed by a 20 cycles cyclic voltammetry (CV) in the range of -2 to 2 V at a scan rate of 100 mV/s. The electrode was then washed with water and dried at ambient temperature. GCE|B-RGO/Poly(ASP) was the resulting electrode [29].

2.4. Plasma sample preparation

The plasma sample for the oxazepam determination was gained from a middle-aged man (Tehran blood transfusion organization, Iran). 1 mL of plasma sample was diluted until 10 mL using the buffer at the optimal pH. The concentration of oxazepam content in plasma was quantified by the standard addition method. It is better to mention that spiking the specific amounts of standard solution into the samples was done before dilution for performing the standard addition method.

3. Results and Discussion

3.1. Characterization

Based on the obtained FTIR spectra for B-RGO (**Fig. 2**), the main peaks are related to the following vibrations: 1040 cm^{-1}: the B-O stretching bond in asymmetric B–O–B among one tetrahedral and one trigonal B atom, 1050 to 1200 cm^{-1}: the B–C functional group, 1180 cm^{-1}: the B–C stretching vibration [30]. The improved frequency of B–C has been induced by the presence of higher content of C [31]. These peaks are the different peaks that individuate RGO from B-RGO. The main peaks related to the RGO structure are as follows: 3700–3000 cm^{-1}: hydroxyl group (H_2O and COOH), streaching vibrations of O–H, and water molecules adoption [32, 33], 1226, 1418, and 1743 cm^{-1}: epoxy (C–O–C), carboxylic (COOH/H_2O), and ketonic (C=O) groups [34, 35], 1620 cm^{-1}: (OH) bending vibration and (C=C) aromatic vibration [36], 1043 cm^{-1}: stretch vibration of C–O groups [37].

Fig. 3 presents the SEM images of B-RGO and B-RGO/Poly (ASP). As seen, GO nanosheets are clearly observed in **Fig. 3a** which proved the good synthesis of B-RGO. Also, **Fig. 3b** showed that the B-RGO surface was completely covered by Poly(ASP). As can be seen, the large specific surface area for electrochemical reactions was provided by the cover of the poly(ASP) layer on the RGO nanosheets. Also, the average particle size of B-RGO was calculated from remarkably intensive diffraction peaks at 2θ values of 25.81 and 27.70 in the XRD pattern and from Debye–Scherer formula. According to the result, the estimated B-RGO nanostructure size is 66 nm.

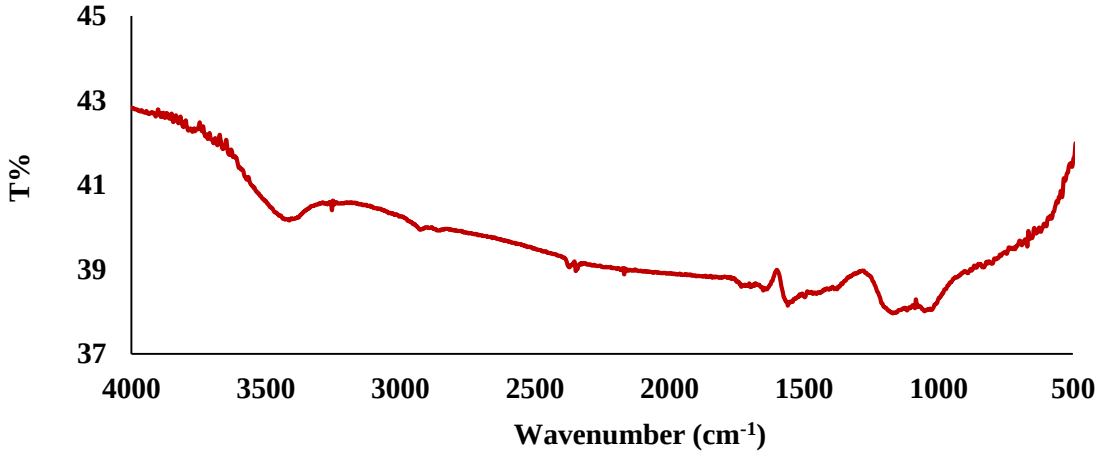

Fig. 2. FTIR spectrum of B-RGO

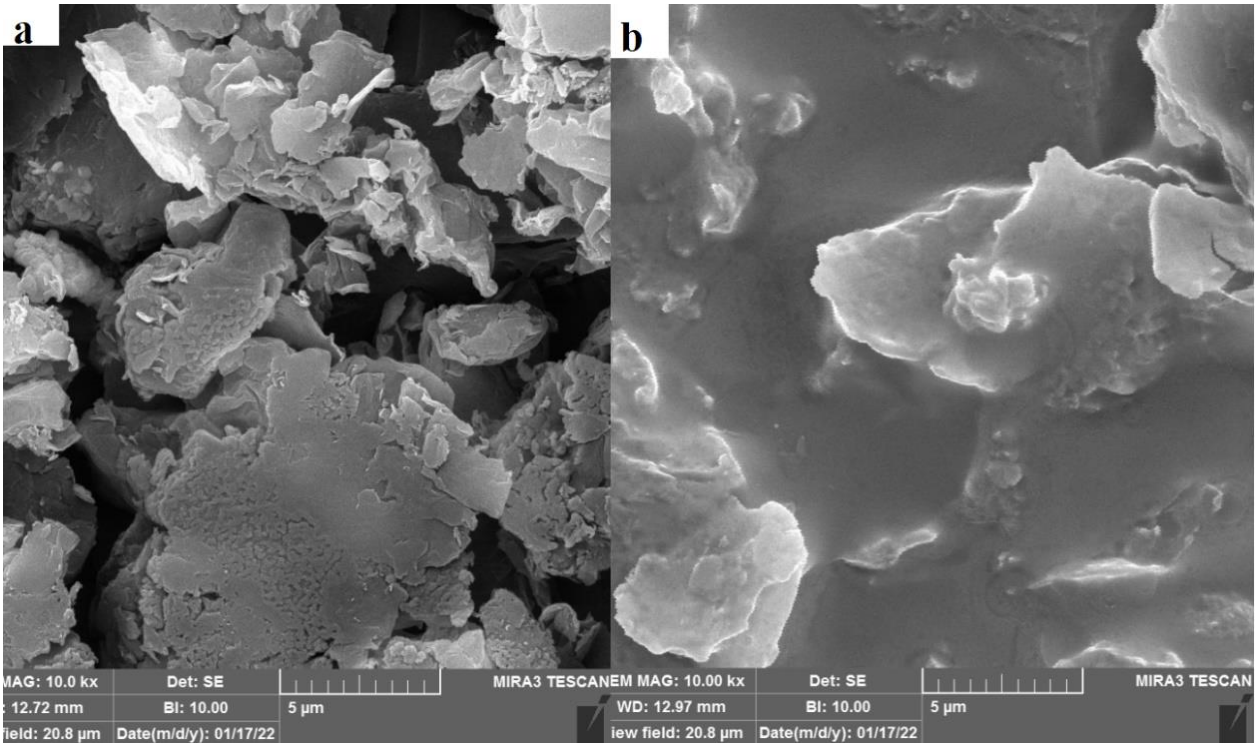

Fig. 3. SEM images of (a) B-RGO and (b) B-RGO/Poly(ASP)

3.2. The behavior of the redox probe and oxazepam on the surface of the modified electrode

Figs. 4a and **4b** show the CVs and LSVs of 15 µM oxazepam in buffer solution on the surfaces of electrodes. On the surface of bare GCE, oxazepam has a very weak cathodic peak at -1.05 V without an anodic peak that indicates an irreversible process. Modification of GCE with B-RGO and B-RGO/Poly(ASP) caused a big peak appearance in a lower potential with a significant current increase. These observations indicate that the modification was effective for sensing oxazepam

In the case of hexacyanoferrate probe redox, there are a pair of reversible peaks at the surface of unmodified and modified electrodes. When the GCE was modified by B-RGO and B-RGO/Poly(ASP) a reversible peak was noticed again with shifted redox peaks by increasing current compared to bare GCE. The closer the anodic current ratio to the cathodic current value to the unity, and the lower the value of ΔEpa-pc (GCE = 0.23 V, B-RGO/GCE = 0.18 V, B-RGO/Poly(ASP)|GCE (0.30 V). The obtained evidence is the indication of significant sensitivity, great catalytic activity, and fast electron transfer rate at the surface of B-RGO/Poly(ASP)|GCE. The surface area of GCE, GCE modified by B-RGO, and B-RGO/Poly(ASP), which was calculated according to the Randles-Swick equation, are equal to 0.027, 0.039 and 0.037 cm^2, respectively.

3.3. Scan rate and pH effect

Diverse pH ranges from 2 to 8 were set to study the pH effect on the electrochemical reduction of oxazepam. **Fig. 5** represents the results related to the LSV of oxazepam solution in buffer at this pH range. With the rise in pH to 8, the negative shift in the peak potential with a slope of 0.0511(close to the Nernst slope of 0.059 V) was observed as an indication of equal involvement of electrons and protons in the electrochemical process. The optimal pH was selected to be 7 since the high peak current was observed at pH 7 upon an increase of pH from 2 to 8, and the peak current dropped after pH 7. The structure of the analyte and modifier may change at lower and higher pHs. The oxazepam reduction mechanism is shown in **Fig. 6**.

Investigation of the scan rate effect on the electrochemical behavior of oxazepam is presented in **Fig. 7**. By increasing the scan rate from 10 to 150 mV/s, the oxazepam current was raised and this increase is linearly proportional to the scan rate and the square of scan rate. Therefore, adsorption/diffusion-controlled electron transfer is noted as the proposed electrochemical process.

3.4. Kinetic studies

Oxazepam reduction peak current increases significantly at the modified electrode surface due to its ability to be adsorbed by the B-RGO/Poly(ASP). Therefore, optimization of accumulation time can affect

the sensitivity of the measurement. Consequently, LSV was used for the investigation of the adsorption time of oxazepam on the modified electrode surface. As the pre-concentration time increases, the peak current increases rapidly (until the 60 s). After that, the peak current was constant (**Fig. 8**). According to the results, 60 s was selected as the optimal preconcentration time to achieve greater sensitivity in quantitative measurements.

The electron transfer coefficient (α) is obtained by drawing the Tafel plot in the form of the *log I* vs. *E* values at a scan rate of 10 mV s^{-1}. The slope of the Tafel plot is $n_\alpha(1-\alpha)F/2.3RT$ based on the following equation:

$$\log I = \log I_0 + \frac{(1-\alpha)n_\alpha F}{2.3RT}$$

In which n_α, R, T, and F are the number of the involved electrons in the reaction, an ideal gas constant (8.314 $J{\cdot}K^{-1}{\cdot}mol^{-1}$), temperature and a Faraday constant (96485.332 C mol^{-1}), respectively. Based on the results, by assuming $n_\alpha = 2$ [38-40], the α from the slope of the Tafel diagram was estimated to be 0.014.

Based on the below equation and the reduction reaction of oxazepam with two electrons on the surface of the modified electrode, the heterogeneous electron transfer rate constant (k_s) was 1.92 s^{-1}. This relatively high value of k_s demonstrates that the modifier can increase the electron transfer rate and improve the electrocatalytic performance of oxazepam.

$$\log k_s = \alpha \log(1-\alpha) + (1-\alpha)\log\alpha - \log\frac{RT}{nFv} - \frac{\alpha(1-\alpha)nF\Delta E_P}{2.3RT}$$

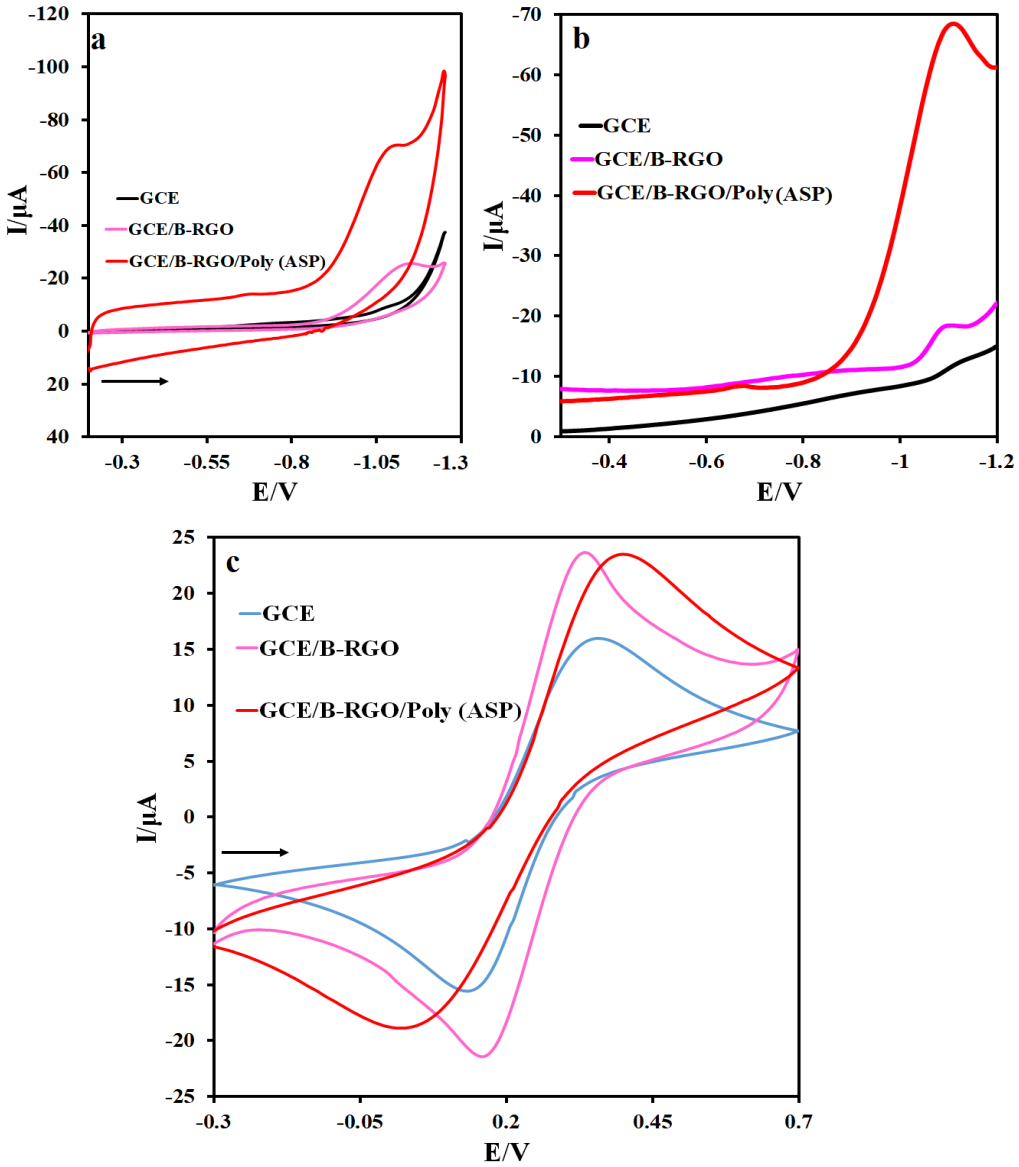

Fig. 4. (a) CV and (b) LSV of oxazepam (15 µM) solution on the surface of the different electrodes in Briton-Robinson buffer with pH= 7 at a scan rate of 50 mV/s and (c) CV of hexacyanoferrate probe redox with a concentration of 1 mM in 1 M KNO_3

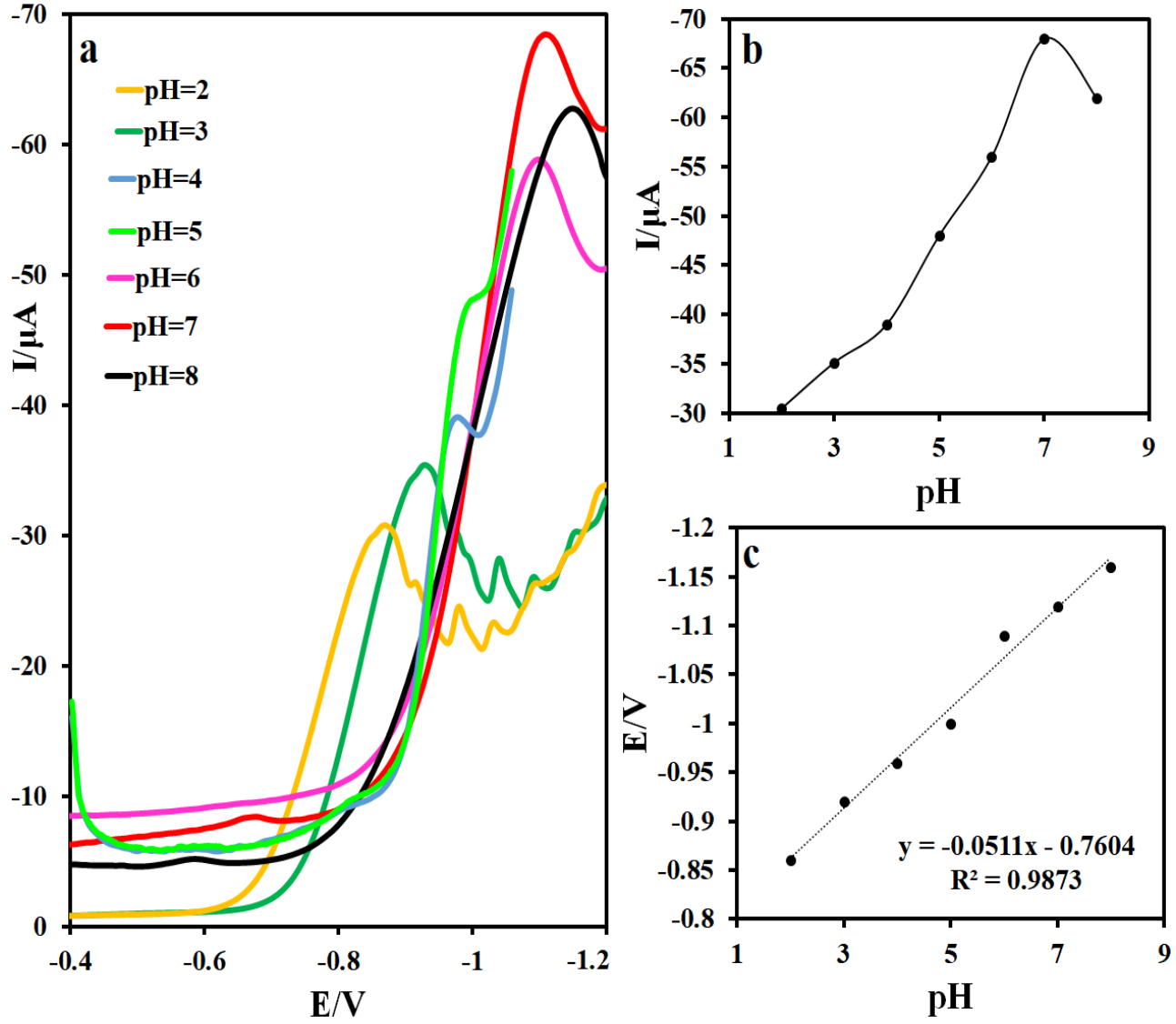

Fig. 5. (a) LSV of oxazepam (15 µM) on the B-RGO/Poly(ASP)|GCE in Briton-Robinson buffer with different pHs at a scan rate of 50 mV/s, (b) I-pH diagram and (c) E-pH diagram

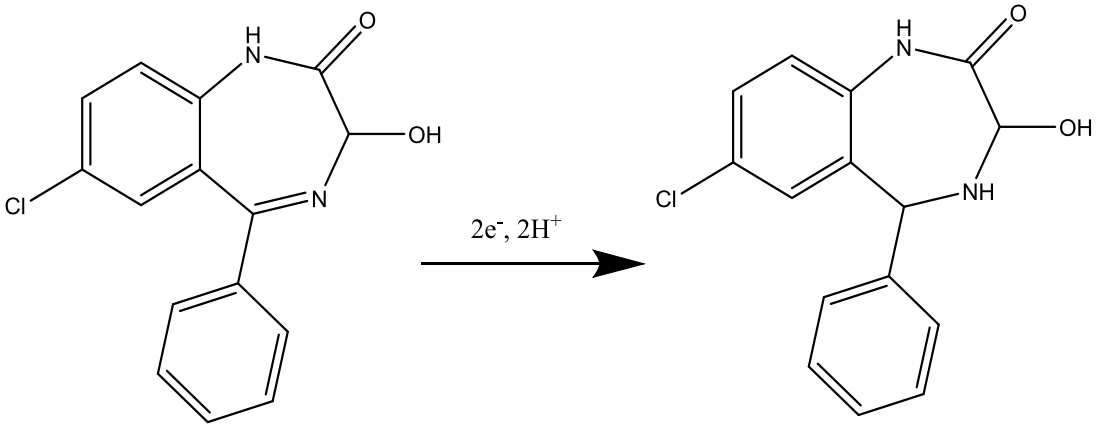

Fig. 6. Probably reduction mechanism of oxazepam on the modified electrode

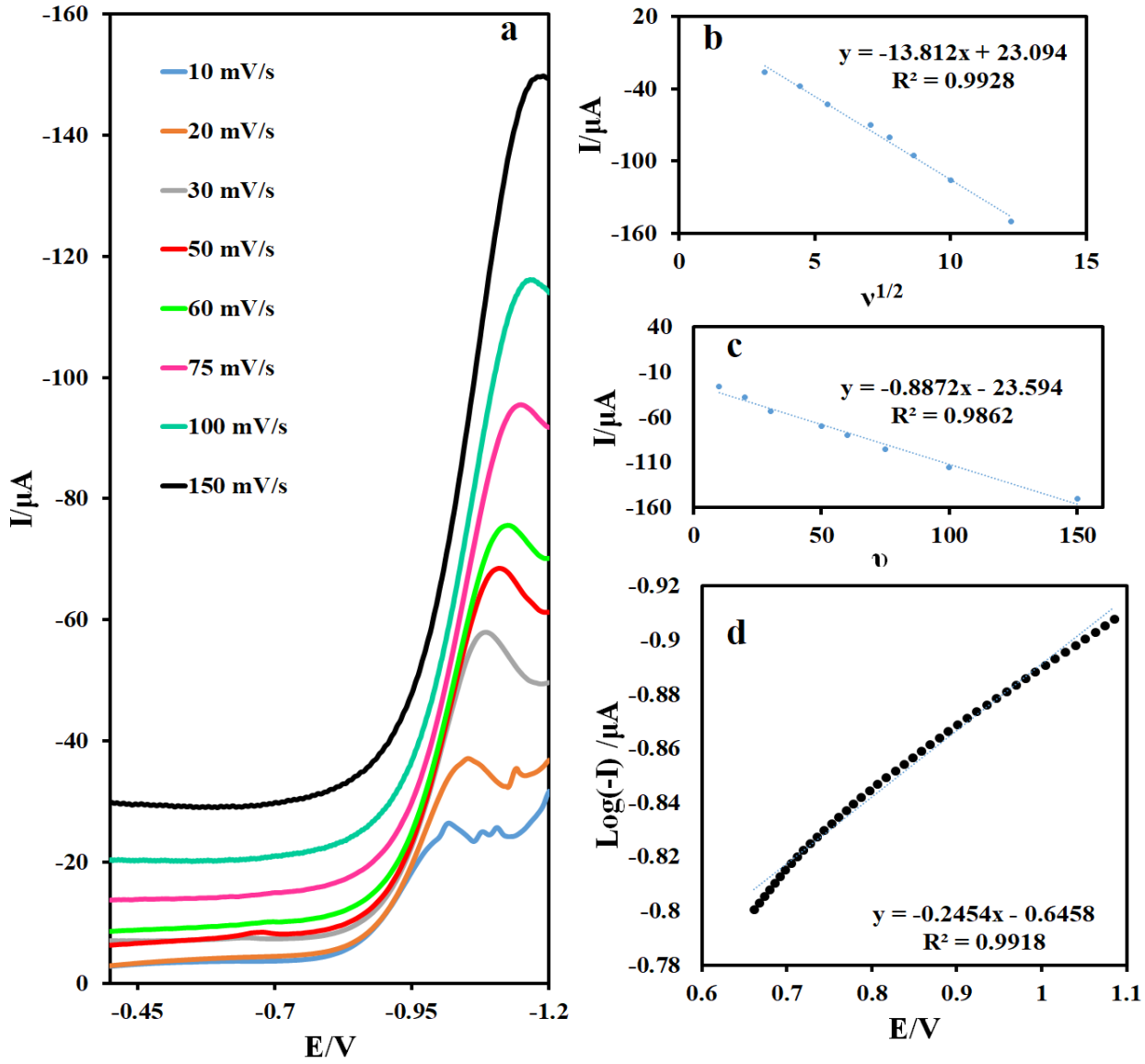

Fig. 7. (a) LSV of oxazepam (15 µM) in Briton-Robinson buffer with pH= 7 at B-RGO/Poly (ASP)|GCE surface at diverse scan rate, (b) *I* vs. $v^{1/2}$, *(c) I* vs. *v* and (d) Log *I vs. E*

3.5. Method validation and stability

Fig. 9 presents oxazepam DPVs in diverse concentrations in which peak currents are linearly proportional with concentration. The plotted calibration curve shows two linear ranges, from 0.001 to 1 µM (R^2 = 0.9953) and from 1 to 800 µM (R^2 = 0.9835), with a result repeated three times. These two linear ranges with different slopes could be attributed to the occurring monolayer adsorption in very low concentrations following the multilayer adsorption in the higher concentration. Also, the detection limit (S/N = 3) and the limit of quantification were calculated to be 0.3 and 1 nM, respectively.

To determine the repeatability of the electrode fabrication and sensor response, the 5 separated modification processes were examined and 5 repetitive DPV in 3 different concentrations (0.1, 10, 100 µM) were investigated. The relative standard deviation percentage (RSD%) of the signals associated with five different electrodes at a concentration of 10 µM was 4.3%, which shows the high repeatability of the electrode modification procedure. The repeatability or precision of the sensor response for 5 repetitive determinations at 0.1, 10, and 100 µM was used for calculating RSD% that in all cases was less than 4.9%. **Table 1** compares the results of this study and previous similar ones. The sensor reached 95% of the initial-state current in more than 25 days which shows the acceptable stability of the lab-made electrode.

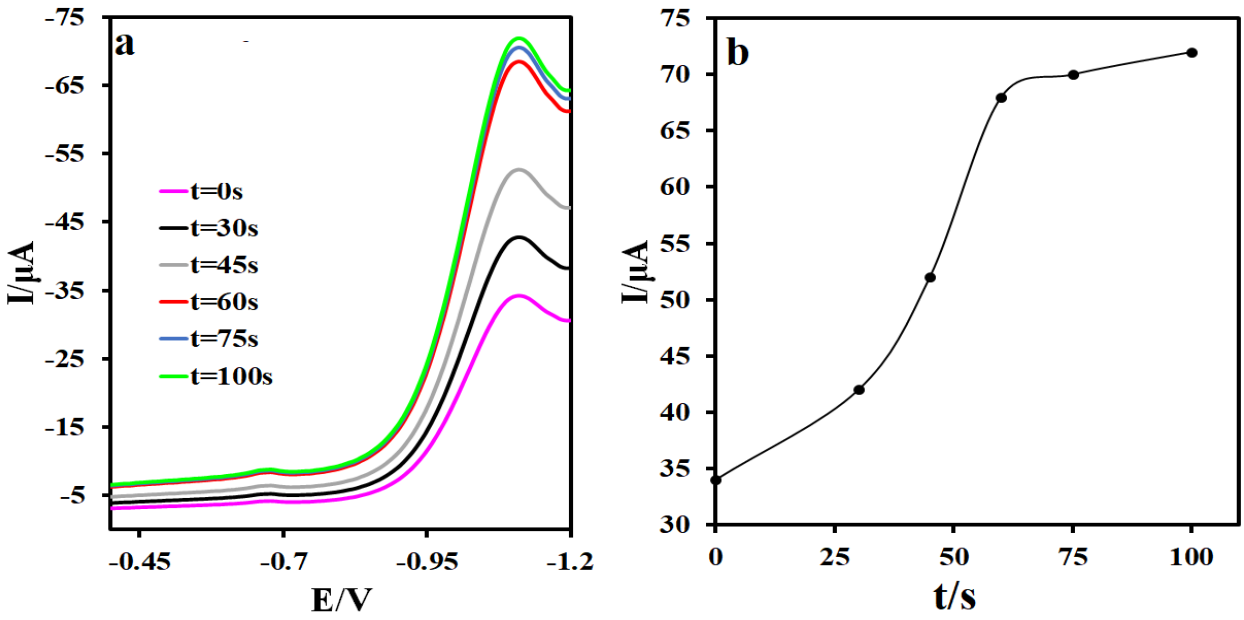

Fig. 8. (a) LSV of oxazepam (15 µM) on the B-RGO/Poly(ASP)|GCE surface in the presence of Britton-Robinson buffer electrolyte solution at different times and (b) peak current vs. pre-concentration time

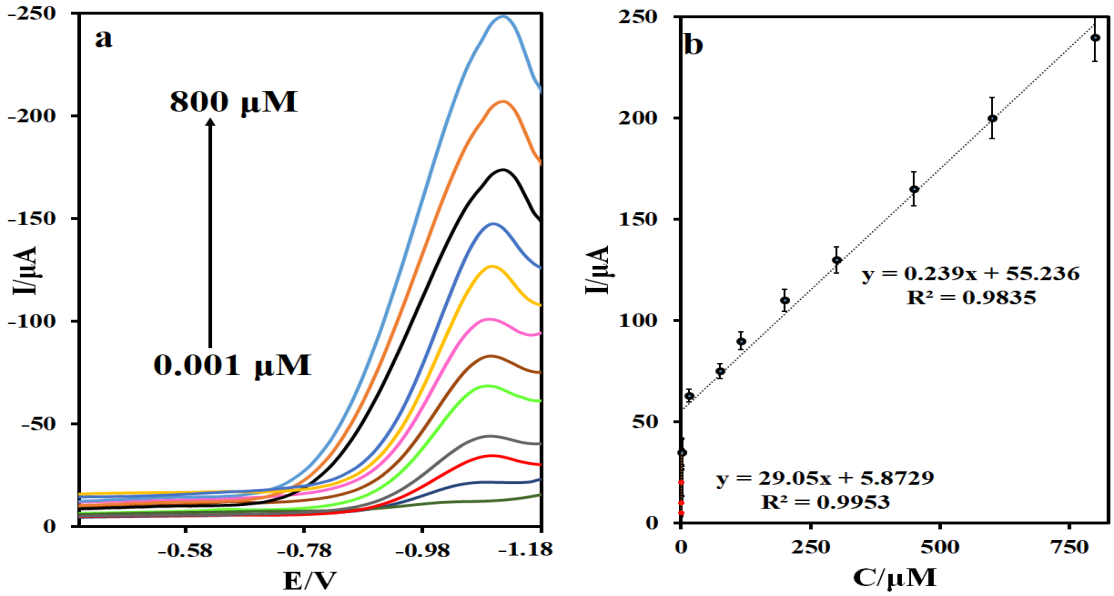

Fig. 9. (a) DPV of various concentrations of oxazepam on the B-RGO/Poly(ASP)|GCE surface under the optimal condition and (b) calibration curve

3.6. Effect of interferences

Interference study is investigated as a significant indicator of sensor selectivity. In the current study, 100 µM dopamine, 1mM citric acid, L-Cysteine, H_2O_2, 50 µM fentanyl, zolpidem, clonazepam and lorazepam were added as potential interfering electroactive species. The change of oxazepam peak current to lower than or equal to ±5% is attributed to the addition of these species indicating the reasonable selectivity of the developed sensor in complex mixtures.

3.7. Plasma analysis

Human plasma as a real sample was chosen for the investigation of the applicability of the developed sensor. The analysis of plasma was done by the standard addition method. In the case of recovery studies and matrix effect, the plasma was spiked with 3 specified concentrations of oxazepam and DPVs were recorded in optimal conditions before the calculation of recoveries. **Table 2** shows the results in which the recoveries values with RSD% for three repeated measurements were in the range of 90–101 (%RSD = 2.5 to 5.4) indicating the successful operation of B-RGO/Poly(ASP)|GCE in the real sample matrix.

Table 1. Comparison of the analytical parameters of different electrochemical sensors in oxazepam determination

Modified electrode	Method	Linear range (µM)	LOD (nM)	Ref.
Ag/N-GQD-Au electrode[a]	DPV	54-454	7700	[41]
P(DA-FA)-GCE[b]	DPV	0.025-0.047	10	[42]
Ag-Pt/GRs/GCE[c]	DPV	0.05-150	0.042	[40]
B-RGO/Poly(ASP)|GCE	DPV	0.001-800	0.3	This study

[a] Nano-ink based on silver nanoparticle‑nitrogen doped graphene quantum dots
[b] Poly dopamine-poly folic acid nanocomposite modified glassy carbon electrode
[c] Ag-Pt core-shell nanoparticles supported on graphene nanosheets

Table 2. Oxazepam determination in plasma sample by DPV using B-RGO/poly(ASP)|GCE.

Sample	Added (µM)	Found (µM)	Relative recovery(%) (n = 5)	RSD%
Plasma	0	-	-	-
	0.5	0.45	90	4.21
	1	0.93	93	4.62
	15	15.23	101.53	4.05

4. Conclusions

This study introduced a sensitive and easy-to-prepare electrochemical sensor to determine oxazepam in the plasma samples based on the modified electrode. B-RGO/poly(ASP) was used as an effective modifier for GCE modification. B-RGO/poly(ASP) was synthesized and characterized using characterization methods. The electrochemical behaviors of the modified GCE for oxazepam sensing showed better electrocatalytic activities in comparison to the unmodified GCE. Also, it exhibited very good repeatability and sensitivity for the determination of oxazepam in the presence of interference species. Finally, this developed sensing platform experienced a successful application in the determination of oxazepam in plasma as a real sample.

Conflict of interest declaration

The authors deny any financial and personal conflict of interest that could have affected the present work.

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