

Electrochemical Determination Venlafaxine at NiO/GR Nanocomposite Modified Carbon Paste Electrode

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ABSTRACT: *The electro-oxidation of venlafaxine (VEN) was investigated at a carbon paste electrode, the modified electrode by NiO/Graphene Reduce (GR) nanocomposite. The structure and morphological aspects of the nanocomposite were approved using FE-SEM, EDAX, and FT-IR. The electrode reaction process was a diffusion-controlled one and the electrochemical oxidation involved two electrons transferring and two protons participating. Under the optimized conditions, the electro-oxidation peak currents were linearly dependent on the concentration of VEN in the concentration range from 1.0- 40.0 μM with the limit of detection ($S/N=3$) as 0.05 μM . The proposed method has been successfully applied in the electrochemical quantitative determination of VEN content in real samples and the determination, results could meet the requirement of the quantitative determination.*

KEYWORDS: *Venlafaxine, Electro-oxidation; NiO/GR nanocomposite; Modified carbon paste electrode,*

INTRODUCTION

Venlafaxine (VEN) is a serotonin or epinephrine reuptake inhibitor (SNRI) class to be used clinically as an antidepressant [1, 2]. Chemically it is (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride (Scheme 1). It works by blocking the transporter "reuptake" proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitters in the synapse [3,4]. It has a simultaneous effect on noradrenaline reuptake and some weak effects on dopamine reuptake. The combination of the effects on the reuptake mechanisms appears to be

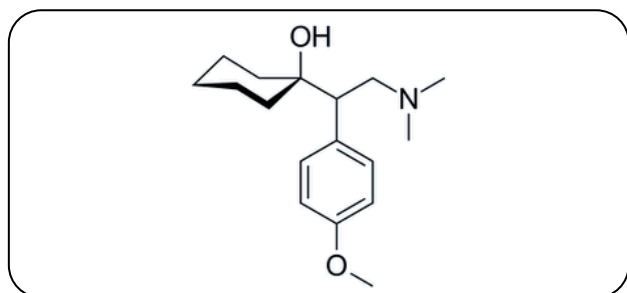
responsible for the antidepressant action of the drug. It has a broad application in the treatment of depression, generalized anxiety disorder, panic disorder, social phobia, sudden fears, and agoraphobia. On the other hand, an overdose of VEN might cause the symptoms of depression, serotonin toxicity, seizure, or cardiac conduction abnormalities. Therefore, for avoiding toxicity and adverse effects, as well as evaluating interactions and therapeutic efficiency, the drug level in body fluids such as urine and plasma of consumers is usually monitored [5-8].

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Scheme 1: Chemical structure of venlafaxine.

To the best of our knowledge, the main research methods of VEN including high-performance liquid chromatography [9-11] high-performance liquid chromatography electrospray ionization mass spectrometry (HPLC-MS/ESI) [12, 13] high-performance liquid chromatography and spectrofluorometry [14] liquid chromatography-mass spectrometry [15-20] liquid chromatography [21, 22] spectrofluorometry [23] gas chromatography-mass spectrometry [24] reversed-phase high-performance liquid chromatography [25, 26] and the electrochemical methods [27-29].

Electrochemical sensors and biosensors for pharmaceutical, food, agricultural and environmental analyses have been growing rapidly due to the electrochemical behavior of drugs and biomolecules and partly due to advances in electrochemical measuring systems [30-35]. The merger between fast, sensitive, selective, accurate, miniaturize, and low-cost electrochemistry-based sensing and fields like proteomics, biochemistry, molecular biology, nanotechnology, and pharmaceutical analysis lead to the evolution of electrochemical sensors [36]. The chemical modification of inert substrate electrodes with mediators offers significant advantages in the design and development of electrochemical sensors. In operations, the redox-active sites shuttle electrons between a solution of the analyte and the substrate electrodes often along with a significant reduction of the activation overpotential. Various properties of metal ions make them very attractive probes for selective detection of drugs in a variety of biological and chemical applications [37-44]. A further advantage of chemically modified electrodes is that they are less prone to surface at fouling and oxide formation compared to inert substrate electrodes [45-52]. To the present time, the selection and growth of an active sensing material in sensors are a challenge. Currently, it is vital to improving novel sensing materials such as graphene

and nanoparticles capable of enhancing the analytical properties of the electrode surface. Among them, nanosized metal oxide particle modified electrodes have emerged as a promising alternative for the quantification of organic and inorganic compounds. Metal oxide nanoparticles have some distinct benefits such as the low influence of the solution resistance, high-mass transport rate, low detection limits, and better signal-to-noise ratio compared to the conventional macro electrodes [53-58]. They also have an extensive range of technological applications including catalysis, microelectronics, and chemical/biological sensors. Metal oxides in the nanometer range deliver three important functions for electroanalysis: roughening of the conductive sensing interface, catalytic properties, and conductivity properties [59-72]. Various nanomaterials for the modification of the electrode surfaces and improvement of their electrochemical characteristics have been reported in recent years.

However, the electro-oxidation and electrochemical determination of VEN at NiO/GR nanocomposite modified carbon paste electrode have not been reported in the literature to the best of our knowledge.

In this work, we successfully synthesized NiO/graphene reduces (GR) nanocomposite and found its remarkable performance in venlafaxine detection. This work would provide new thinking and a new method for the detection of venlafaxine. It developed an original electrochemical sensor on the basis of NiO/graphene reduce (GR) nanocomposite for differential pulse voltammetric to determine venlafaxine within serum specimens.

EXPERIMENTAL SECTION

Apparatus and chemicals

All solutions were freshly prepared with double distilled water. VEN and all the other reagents were of analytical grade and were obtained from Merck (Darmstadt, Germany). The Universal buffer solutions were prepared from phosphoric acid, acetic acid, boric acid, and its salts in the pH range of 2.0- 9.0.

Electroanalysis was performed using Metrohm Autolab PGSTAT101 equipped with NOVA software (Ecochemie, Utrecht, the Netherlands), and the three-electrode system contained a platinum counter electrode, an Ag/AgCl reference electrode, and the NiO/GR/CPE

as the working electrode. The FE-SEM and EDAX (Mira 3-XMU) were applied for morphological and structural investigation. FT-IR analysis was recorded using a JASCO FTIR-4100 spectrometer (JASCO, Japan).

Preparation of NiO/GR nano-composites

Graphene Oxide (GO) synthesized by using modified hummers approached [73]. NiO/GR nano-composites were prepared by the following pathway: solutions of $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.59 g) and ascorbic acid (0.06 g) in distilled water (20.0 mL and 10.0, respectively) was added to a stirred water solution (30 mL) of GO (0.06 g), and the resultant mixture was stirred for 1 h. Then, a solution of KOH (0.07 g in 20.0 mL distilled water) was dropwise added to it while stirred and heated at 180 °C for 12 h. Then it washed with distilled water and ethanol as well as eventually dried.

Preparation in spiked serum

Human serums of two healthy volunteers were collected and frozen until assay. The samples were centrifuged (2500 rpm) for 5 min and then filtered through the Millipore membrane filter (0.45 μm pore size and each serum (1.0 mL) were spiked with VEN. For electrochemical determination of VEN, the serum was diluted 5.0 times with a 0.05 M buffer Universal solution in pH=8.0 and was transferred into the electrochemical cell. The contents of the VEN in the plasma samples were determined using the standard addition method.

Preparation of the modified electrode

NiO/GR/CPE was made by mixing 800 mg of graphite powder and 50 mg of NiO/GR nano-composite. Then, 5 mL diethyl ether was added and the slurry was hand-mixed in a mortar. After vaporization of diethyl ether, 200 mg paraffin oil was added and mixed in a mortar and pestle to get a uniformly wetted paste. The resulting pastes were pressed into the hole at the end of the electrode.

RESULTS AND DISCUSSION

Nanocomposite characterization

Fig. 1 shows the FT-IR spectra of (A) GR and (B) NiO/GR. The band at 1100 cm^{-1} corresponds to the C–O (alkoxy) stretching peak. The peaks at 2917 and 2857 cm^{-1} are attributed to the –CH vibration mode of –CH₂ and a band at 1624 cm^{-1} is attributed to the bending vibration of

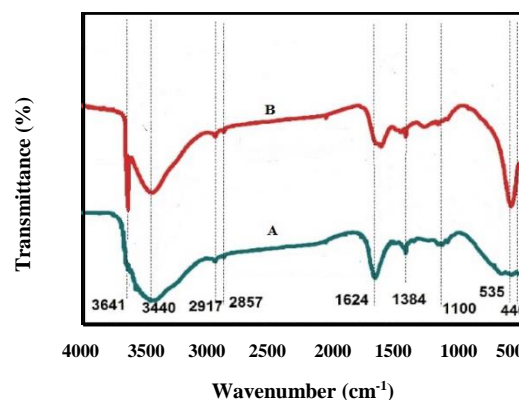


Fig. 1: FT-IR of A) GR, B) NiO/GR nano-particles.

adsorbed water molecules and O–H of the hydroxyl group. The broadband at 3440 cm^{-1} can be assigned to hydrogen-bonded O–H groups stretching vibration that in the figure 1B, with the incomplete removal of the hydroxyl group, the intensity of this peak has decreased. In Fig. 1B the peaks at 535 and 446 cm^{-1} can be assigned to Ni–O vibrations ascribed to Ni–OH. The sharp peak at 3641 cm^{-1} corresponds to the stretching vibration mode of nonhydrogen-bonded hydroxyl groups, which indicates the connection of oxygen to the nickel-metal in the nanocomposite.

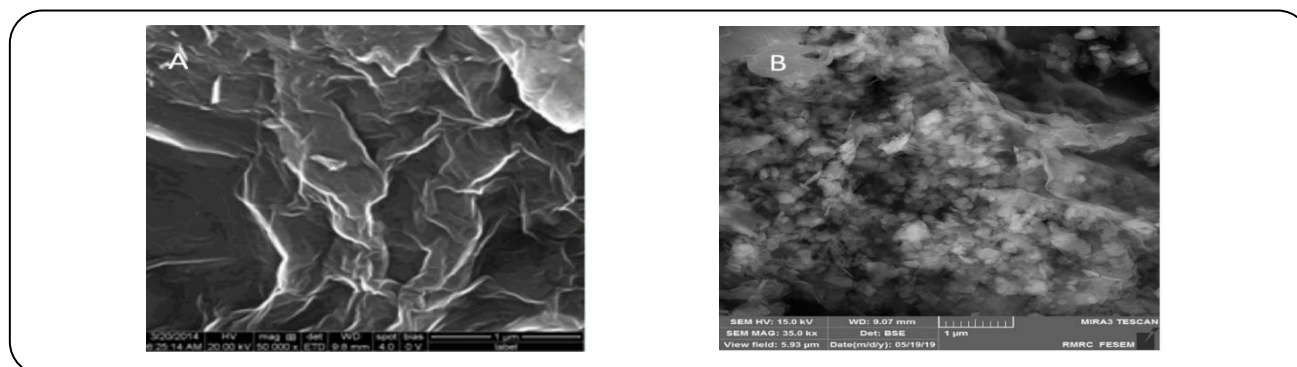
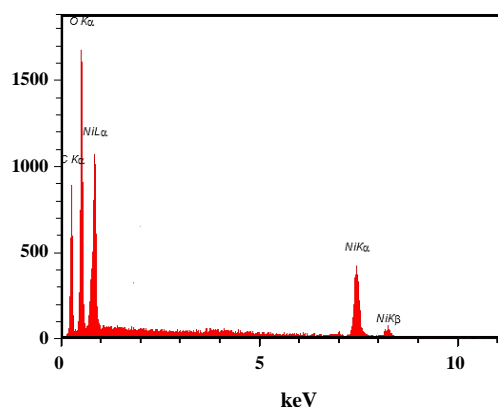
The FE-SEM images (Fig. 2A) showed the structure with wrinkled layers of GR. Fig. 2B show the illustration of NiO/GR nano-particles which have dimensions below 50 nm. Fig. 3 shows the EDAX analysis of NiO/GR nano-particles. The analysis confirmed that carbon, oxygen, and nickel were in the composite material.

Electrochemical oxidation of VEN at NiO/GR/CPE

The electrochemical behavior of VEN is dependent on the pH value of the aqueous solution. Therefore, pH optimization of the solution seems to be necessary in order to obtain the electrocatalytic oxidation of VEN. Thus the electrochemical behavior of VEN was studied in 0.05 M PBS in different pH values (2.0-9.0) at the surface of NiO/GR/CPE by cyclic voltammetry. It was found that the electrocatalytic oxidation of VEN at the surface of NiO/GR/CPE was more favored under neutral conditions than in the acidic or basic medium. Thereby, the pH=8.0 was chosen as the optimum pH for VEN oxidation at the surface of NiO/GR/CPE. This value is comparable with values reported by other research groups for electro-

Table 1: Comparison of the efficiency of some modified electrodes used in the electro-oxidation of VEN.

Modified electrode	Detection limit (mol/L)	Linear range (mol/L)	Reference
Nanotube carbon modified glass carbon	2.4×10^{-8}	$3.81 \times 10^{-8} - 6.22 \times 10^{-5}$	[74]
Drops of mercury	3×10^{-6}	3×10^{-7}	[75]
Carbon modified glass with multilayer carbon nanotubes	1.69×10^{-6}	$0.2 \times 10^{-6} - 0.2 \times 10^{-3}$	[76]
Selective ion electrode containing phosphomulbide acid	-	$0.1 \times 10^{-5} - 0.1 \times 10^{-2}$	[77]
NiO/GR/CPE	5×10^{-8}	$1 \times 10^{-6} - 40 \times 10^{-6}$	This work

**Fig. 1: FT-IR of A) GR, B) NiO/GR nano-particles.****Fig. 3: EDAX of NiO/GR nano-particles.**

oxidation of VEN at the surface of chemically modified electrodes by other modifiers (see Table 1).

Study of VEN electrochemical behavior

Fig. 4 depicts the CV responses for the electro-oxidation of $10.0 \mu\text{M}$ VEN at an unmodified CPE (curve a), GR/CPE (curve b), and NiO/GR/CPE (curve c). The GR/CPE caused about 3 fold gain in the redox current of VEN compared to CPE, while the signal was significantly amplified (5 fold) at NiO/GR/CPE modified CPE, which

represented fast electron-transfer kinetically. However, NiO/GR/CPE shows a much higher anodic peak current for the oxidation of VEN compared to GR/CPE, indicating that the combination of GR and NiO nanoparticles has significantly improved the performance of the electrode toward VEN oxidation.

In Fig. 5, it is clearly evident that with increasing pH to the alkaline medium, the flow is increased, and thus the sensitivity increases. As the optimization curves show, the highest sensitivity was obtained at pH=8.0 (Universal buffer 0.05 mol/L). Evaporation of VEN in 0.75 volts relative to the Ag/AgCl reference electrode is related to oxidizing the methoxybenzene group [78]. The gradient of the potential gradient in pH (Fig. 6) was found to be 0.058, which indicates the number of electrons and protons in the oxidation mechanism of VEN. In figure 6, the oxidation mechanism of VEN is given [74].

The effect of scan rate on the electrocatalytic oxidation of VEN at the NiO/GR/CPE was investigated by cyclic voltammetry (CV) (Fig. 7). The charge of VEN at pH below 9.4 is positive, which leads to an attraction by the negative charge of graphene nano-particles surface. The relation of the oxidation peak current of VEN and scan rate in the range 10–110 mV/s is linear with the regression equation

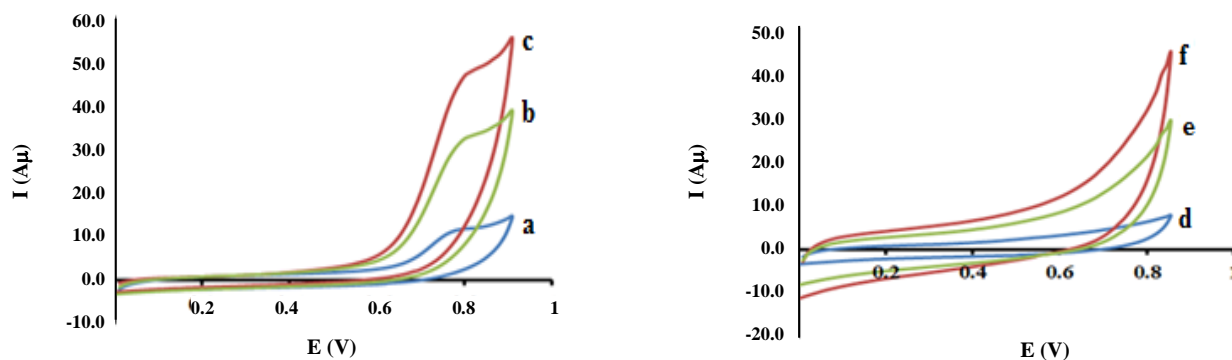


Fig. 4: CVs for oxidation current of $10.0 \mu\text{M}$ VEN at (a) CPE; (b) GR/CPEs; and (c) NiO/GR/CPE; CVs of the blank solution at: (d) CPE, (e) GR/CPEs and (f) NiO/GR/CPE. In all cases, $\text{pH}=8.0$, and the scan rate was 50 mV/s .

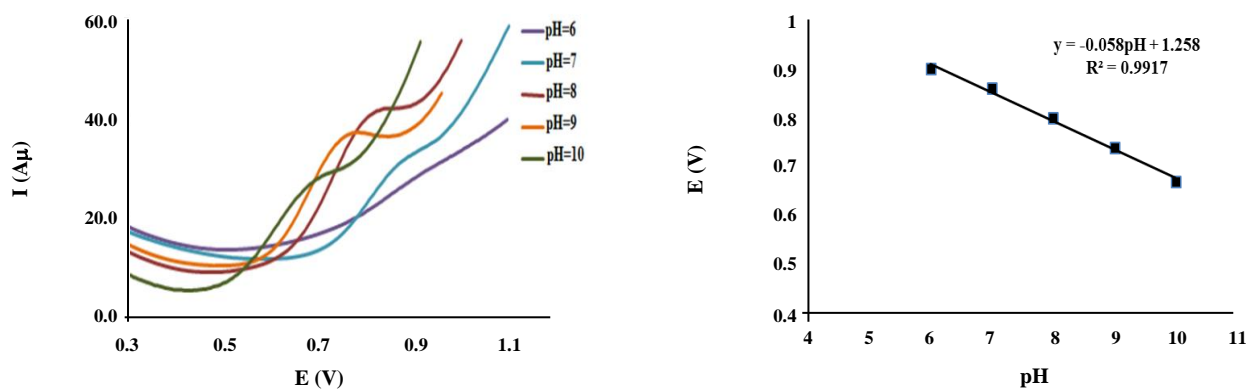


Fig. 5: CVs of $10.0 \mu\text{M}$ VEN at the NiO/GR/CPE in pH 2-11 of PBS; scan rate 50 mV/s .

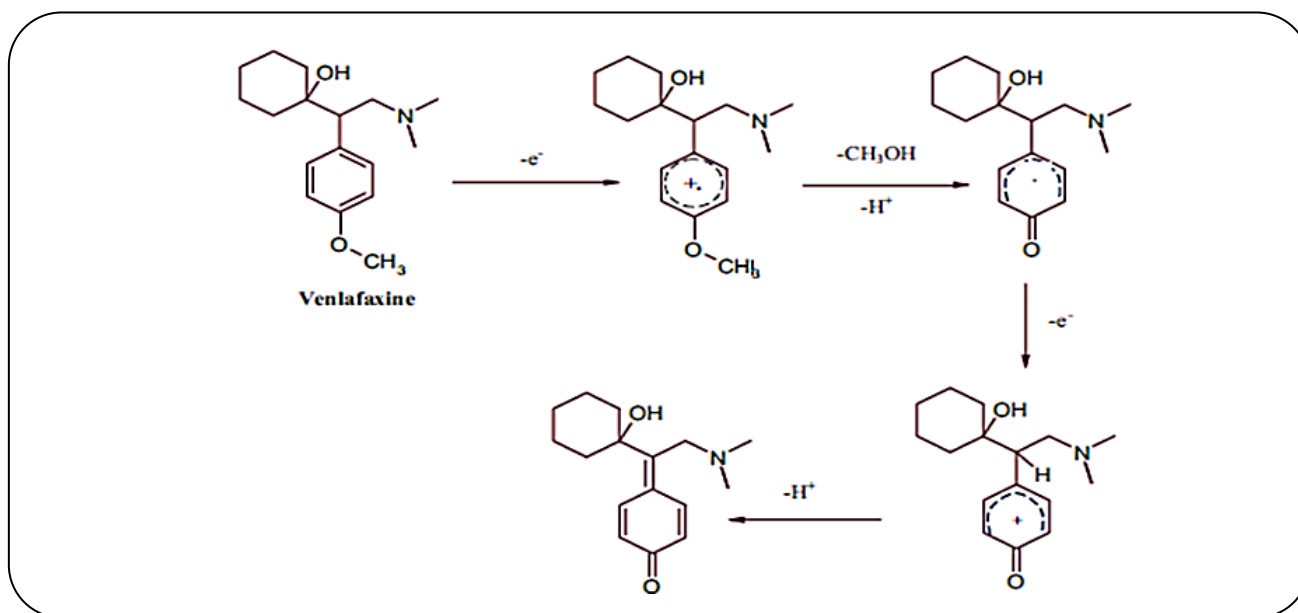


Fig.6: VEN Oxidation Mechanism [64].

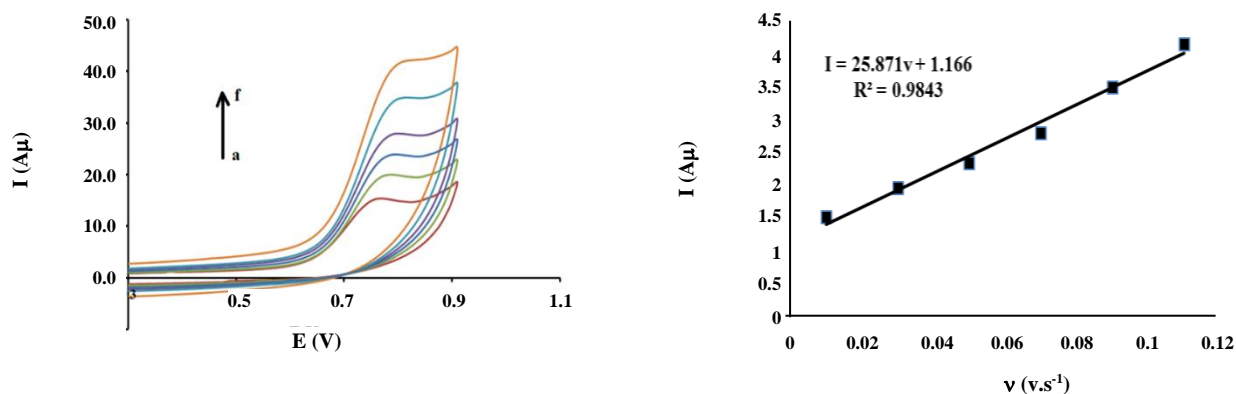


Fig. 7: Cyclic voltammograms of 10.0 μM VEN at NiO/GR/CPE with various scan rates as a) 10; b) 30; c) 50; d) 70, e) 90; and f) 110 mV/s.

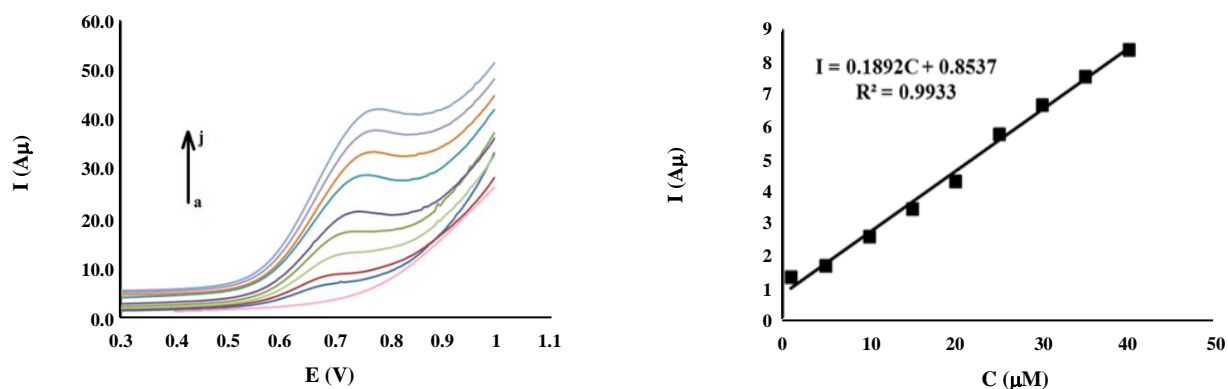


Fig. 8: DPVs for different concentrations of VEN in pH=8.0. PBS at NiO/GR/CPE. Concentrations of VEN from (a) to (j): 0, 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 35.0, 40.0 μM .

of $I_p = 7.8v + 0.0517$ ($R^2 = 0.984$) (where I_p is its oxidation response), which denotes the reaction process was a diffusion-controlled one (Fig. 7) [79-81].

Calibration plot and limit of detection

The calibration graph was obtained using differential pulse voltammetry (pulse amplitude of 90 mV, pulse time of 50 ms, and the scan rate of 50 mV s⁻¹) from the anodic current of various VEN concentrations at the NiO/GR/CPE. The calibration plot (Fig. 8) was linear in the range of 1.0–40.0 μM with the corresponding equation of $I_p(\mu\text{A}) = (0.646 \pm 0.003) C(\mu\text{M}) + (1.76 \pm 0.100)$ ($R^2 = 0.994$, $n = 5$), where C is VEN concentration. The limit of detection (at signal-to-noise the ratio of 3.0) was calculated as 0.05 μM .

Study of interference

The effects of co-existed species commonly found in biological samples were examined in VEN detection.

The largest concentration of interferences producing a variation in VEN current less than 3σ was defined as the tolerance limit, where the σ is the standard deviation of 10.0 μM VEN current in five repetitive determinations. The results of this study are shown in Table 2.

Determination of VEN in spiked serum

In order to evaluate the analytical applicability of the proposed method, also it was applied to the determination of VEN in spiked serum are given in Table 3. Satisfactory recovery of the experimental results was found for VEN. The reproducibility of the method was demonstrated by the mean relative standard deviation (R.S.D.).

The repeatability of the modified electrode

In the vicinity of venlafaxine, voltammograms were documented upon potential cycling of 20 repetitions

Table 2: Maximum tolerable concentration of interfering species for VEN concentration of 10.0 μM .

Substance	The concentration ratio of the substance to nescapine (mol/mol)
Glucose, sucrose, lactose, fructose	200
Mg^{2+} , Ca^{2+} , SO_4^{2-} , Br^- , K^+ , ClO_4^- , NO_3^-	1000
Glycine	500
Aspartic Acid	100
Urea	200
Oxalate	20
Citric acid	30
Methionine	100
Cysteine	10

Table 3: Determination of VEN in spiked serum samples. (n=5).

Real sample	Added value ($\mu\text{mol/L}$)	The value found ($\mu\text{mol/L}$)	Recovery
	3.0	3.02 (± 0.2)	106.6
Serum 1	1.0	0.93 (± 0.04)	93.0
	1.0	1.06 (± 0.06)	106.0
	4.0	3.80 (± 0.2)	95.0
	5.0	5.2 (± 0.13)	104.0
Serum 2	10.0	9.5 (± 0.3)	95.0
	10.0	10.9 (± 0.4)	109.0
	30.0	30.3 (± 0.8)	101.0

at 50 m/Vs scan rate. Based on the outcomes, there were no changes in terms of peak potentials apart from a decrease of less than 2.61%. The results validated the greater sensitivity and decreased fouling impact of NiO/GR/CPE in regard to venlafaxine and relevant oxidation byproducts.

CONCLUSIONS

In this work, the benefits of NiO/GR nanocomposite were shown for modification of a carbon paste electrode in order to study the electrochemical oxidation of VEN. The electrode exhibited a good electrocatalytic activity for the anodic oxidation of VEN compared to the conventional electrodes. The NiO/GR/CPE was used for the determination of VEN. The results showed that the proposed nanocomposite electrode has advantages such as high stability and reproducibility as well as ease of preparation, low cost, and surface renewal which might suggest promising applications in real sample analysis.

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