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Application of Cu(II) Nanocomplex Modified Graphite Screen Printed Electrode to Improve the Sensitivity for Norepinephrine Detection

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Abstract- A Cu(II) nanocomplex, $[CuCl_2(salophen)].H_2O$[salophen=o-phenylenediaminebis(salicylidenaminato)], was synthesized. The electrochemical properties of the as-prepared Cu(II) nanocomplex modified graphite screen printed electrode (Cu/SPE) were investigated using cyclic voltammetry (CV) and differential pulse voltammetry (DPV). Moreover, as a nanosensor for the determination of norepinephrine the Cu/SPE exhibited excellent electrocatalytic activity for the oxidation of norepinephrine with a faster electron-transfer rate. The DPV technique was used for the trace determination of norepinephrine. The dependence of current *vs.* concentration was linear from 0.3 to 300.0 μM with a regression coefficient of 0.9992, and the detection limit of norepinephrine was 0.09 μM. Finally, the method was applied to the selective and precise analysis of norepinephrine in norepinephrine injection.

Keywords- Norepinephrine, Cu(II) nanocomplex, Graphite screen printed electrode, Voltammetry

1. INTRODUCTION

Norepinephrine as an important catecholamine plays multiple significant roles including as a hormone and a neurotransmitter. As a stress hormone, norepinephrine affects parts of the brain where attention and responding actions are controlled. When norepinephrine acts as a drug it increases blood pressure by increasing vascular tone through adrenergic receptor

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activation. The resulting increase in vascular resistance triggers a compensatory reflex that overcomes its direct stimulatory effects on the heart, called the baroreceptor reflex, which results in a drop in heart rate called reflex bradycardia [1,2]. The concentrations of norepinephrine are elevated (2.86 ng mL^{-1}) in urine and plasma in several diseases and are of clinical interest, especially in the diagnosis of pheochromocytoma, neuroblastoma and ganglioneuroma. Norepinephrine is associated with many disorders including multiple sclerosis, ganglia neuroblastoma, Parkinson's disease, DNA breakdown in cardiac myoblast cells, diabetes, and HIV replication. Consequently, determination of its content in human blood or urine can be used to diagnose some diseases [3-5].

Various methods have been used to determine the concentration of norepinephrine in human blood or urine, including chromatography (HPLC) [6,7], capillary electrophoresis (CE) [8], spectrophotometry [9], and fluorescence spectrometry [10]. However, most of these methods suffer from some disadvantages including time-consuming, complicated treating process, high costs and low sensitivity [11]. Consequently, electrochemical methods have been performed in medical, biological and environmental analysis because of their fast response, simplicity, time saving, low costs relatively high sensitivity and excellent selectivity [12-25]. However, at traditional working electrodes, norephnephrine exhibit poor electrochemical response due to sluggish electrode kinetics and formation of final oxidation products on the electrode leading problems such as electrode fouling, low sensitivity and reproducibility [26-28]. Hence, considerable attempts have been devoted to modify the electrode surfaces with selective recognition material in order to improve the analytical performance in norepinephrine sensing.

The nanostructure materials have different and important physical and chemical properties because of their nanoscale. Due to these features, nanomaterials including catalytic activity or selectivity, and the large surface area-to-volume ratios can be used as a tool to develop and improve analytical processes [29-31]. The range of nanomaterial used in electrochemistry is wide and diverse; that said, the properties of electrodes for selected tasks have been improved and optimised by means of their 'chemical modification'. That is, by immobilising nanoaprticles on the surface of conventional electrode materials, their properties can be changed notably, for example in respect to the electron transfer kinetics for various selected target species. Therefore, using electrochemical methods by electrode modified with nanoparticles in addition to improving the surface of electrode for oxidation of analytes and reducing the overvoltage increases the sensitivity, accuracy, and selectivity of electrode [32-47].

Screen-printed electrodes are frequently used in analytical applications because of their unique properties such as small size, low detection limit, fast response time, high reproducibility, etc. which makes possible mass production of electrodes and the development of practical ''in situ'' analysis [48-55].

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According to the previous points, it is important to create suitable conditions for analysis of norepinephrine in biological fluids. In this study, we describe application of novel Cu(II) nanocomplex as a nanostructure sensor for voltammetric determination of norepinephrine. The proposed sensor showed good electrocatalytic effect on norepinephrine. The modified electrode shows advantages in terms of selectivity, reproducibility and sensitivity. Eventually, we evaluate the analytical performance of the suggestion sensor for norepinephrine determination in drug sample.

2. EXPERIMENTAL

2.1. Apparatus and chemicals

The electrochemical measurements were performed with an Autolab potentiostat/galvanostat (PGSTAT 302N, Eco Chemie, the Netherlands). The experimental conditions were controlled with General Purpose Electrochemical System (GPES) software. The screen-printed electrode (DropSens, DRP-110, Spain) consists of three main parts which are a graphite counter electrode, a silver pseudo-reference electrode and a graphite working electrode.

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

2.2. Synthesis of Cu(II) nanocomplex

Salophen ligand was synthesized similar to a previously described method [54]. Cu(II) nanocomplex is prepared by a facile low-temperature (<100 ºC) synthesis route at atmospheric pressure via reaction of salophen ligand, copper chloride under reflux. Typically, $Cu(Cl)_2.6H_2O$ (1 mmol), salophen ligand (1 mmol) and methanol (20 ml) were mixed and sonicated (2 h, 60 ºC). The obtained green solid was further purified by two-step processes using double solvent extraction with water and methanol. The solid was finally dried in a vacuum desiccator at 80 ºC for 2 h prior to a further analysis or use.

2.3. Preparation of modified electrode

The bare graphite screen printed electrode was coated with Cu(II) nanocomplex as follows. A stock solution of Cu(II) nanocomplex in 1 ml aqueous solution was prepared by dispersing 1 mg Cu(II) nanocomplex with ultrasonication for 1 h, and a 5 µl aliquot of the Cu(II) nanocomplex/H_2O suspension solution was casted on the carbon working electrodes, and waiting until the solvent was evaporated in room temperature.

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2.4. Preparation of real samples

The NE injection solutions was diluted 100 times with water; then, different volume of the diluted solution was transferred into a 10 mL volumetric flask and diluted to the mark with phosphate buffer (pH 7.0).

3. RESULTS AND DISCUSSION

3.1. Electrocatalytic oxidation of norepinephrine at a Cu/SPE

The electrochemical behavior of norepinephrine 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 norepinephrine. Thus the electrochemical behavior of norepinephrine was studied in 0.1 M PBS in different pH values (2.0<pH<9.0) at the surface of Cu/SPE by CV. It was found that the electrocatalytic oxidation of norepinephrine at the surface of Cu/SPE was more favored under neutral conditions than in acidic or basic medium. Thus, the pH 7.0 was chosen as the optimum pH for electrocatalysis of norepinephrine oxidation at the surface of Cu/SPE.

Fig. 1 depict the cyclic voltammetric responses for the electrochemical oxidation of 200.0 µM norepinephrine at Cu/SPE (curve a) and bare SPE (curve b). The anodic peak potential for the oxidation of norepinephrine at Cu/SPE (curve a) is about 185 mV compared with 65 mV for that on the bare SPE (curve b). Similarly, when the oxidation of norepinephrine at the Cu/SPE (curve a) and bare SPE (curve b) are compared, an extensive enhancement of the anodic peak current at Cu/SPE relative to the value obtained at the bare SPE (curve b) is observed. In other words, the results clearly indicate that the Cu nanocomplex improve the norepinephrine oxidation signal.

The effect of potential scan rates on the oxidation current of norepinephrine has been studied (Fig. 2). The results showed that increasing in the potential scan rate induced an increase in the peak current. In addition, the oxidation process is diffusion controlled as deduced from the linear dependence of the anodic peak current (I_p) on the square root of the potential scan rate ($\nu^{1/2}$) over a wide range from 10 to 500 mV s^{-1}.

Fig. 3 shows the LSV of a Cu/SPE obtained in 0.1 M PBS (pH 7.0) containing 100.0 µM norepinephrine, with a sweep rate of 10 mV s^{-1}. The points show the rising part of the voltammogram (known as the Tafel region), which is affected by the electron transfer kinetics between norepinephrine and Cu/SPE. If deprotonation of norepinephrine is a sufficiently fast step, the number of electrons involved in the rate determining step can be estimated from the slope of the Tafel plot. The inset of Fig. 3 shows a Tafel plot that was drawn from points of the Tafel region of the LSV. The Tafel slope of 0.1244 V obtained in this case agrees well with the involvement of one electron in the rate determining step of the electrode process, assuming a charge transfer coefficient of α=0.53 [56].

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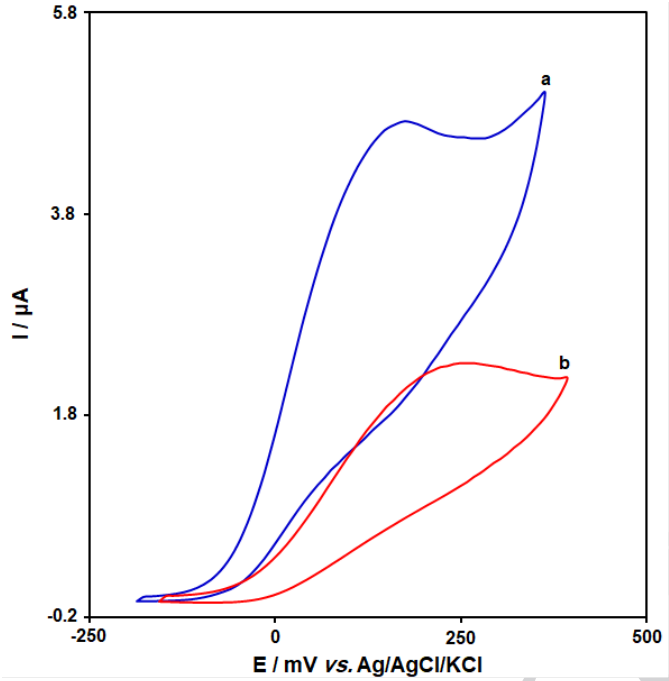

Fig. 1. Cyclic voltammograms of (a) Cu/SPE and (b) bare SPE in 0.1 M PBS (pH 7.0) in the presence of 600.0 µM norepinephrine at the scan rate 50 mVs^{-1}

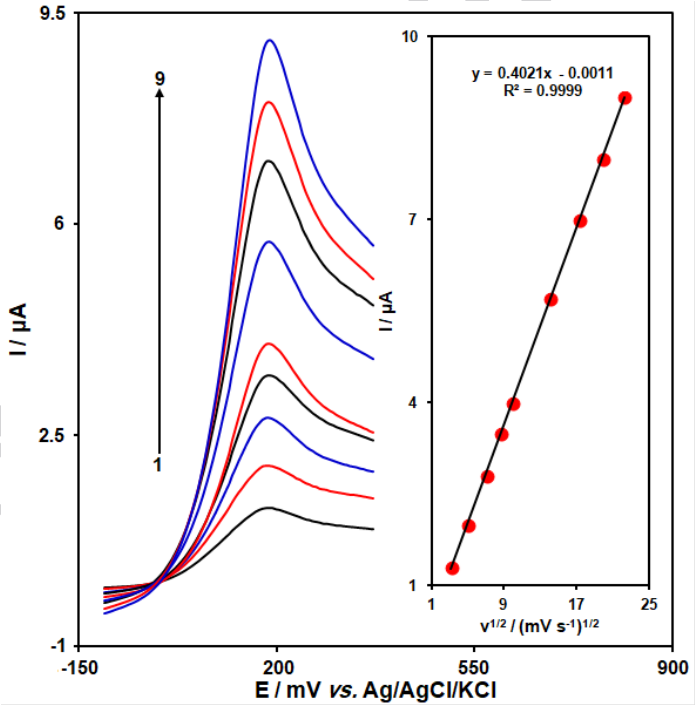

Fig. 2. LSV of Cu/SPE in 0.1 M PBS (pH 7.0) containing 200.0 µM norepinephrine at various scan rates; numbers 1-9 correspond to 10, 25, 50, 75, 100, 200, 300, 400 and 500 mV s^{-1}, respectively. Inset: variation of cathodic peak current *vs.* $v^{1/2}$

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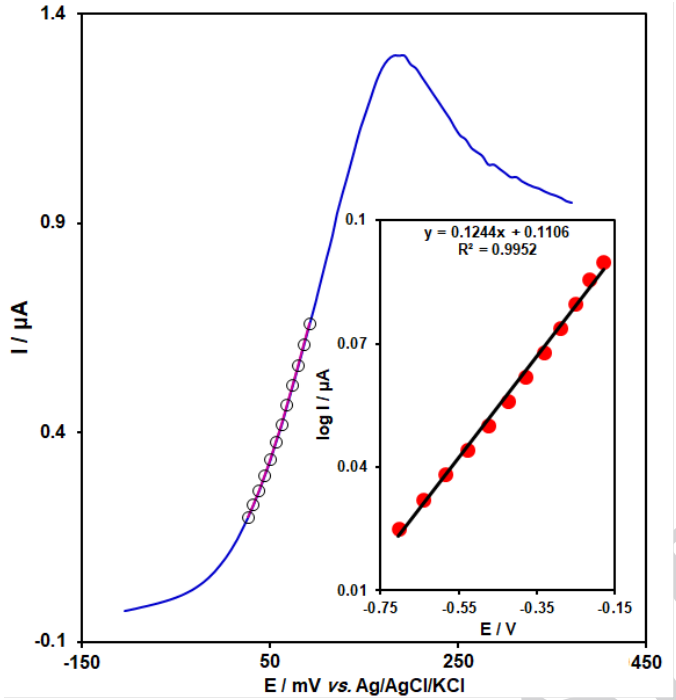

Fig. 3. LSV (at 10 mV s^{-1}) of a Cu/SPE in 0.1 M PBS (pH 7.0) containing 100.0 µM norepinephrine. The points are the data used in the Tafel plot. The inset shows the Tafel plot derived from the LSV

3.2. Chronoamperometric measurements

Chronoamperometric measurements of amitriptyline at Cu/SPE were carried out by setting the working electrode potential at 0.35 V for the various concentrations of norepinephrine in PBS (pH 7.0) (Fig. 4). For an electroactive material (norepinephrine in this case) with a diffusion coefficient of D, the current observed for the electrochemical reaction at the mass transport limited condition is described by the Cottrell equation [56].

$$I = nFAD^{1/2}C_b\pi^{-1/2}t^{-1/2}$$

Where D and C_b are the diffusion coefficient (cm^2 s^{-1}) and the bulk concentration (mol cm^{-3}), respectively. Experimental plots of I *vs.* $t^{-1/2}$ were employed, with the best fits for different concentrations of norepinephrine (Fig. 4A). The slopes of the resulting straight lines were then plotted *vs.* amitriptyline concentration (Fig. 4B). From the resulting slope and Cottrell equation the mean value of the D was found to be 6.38×10^{-6} cm^2/s.

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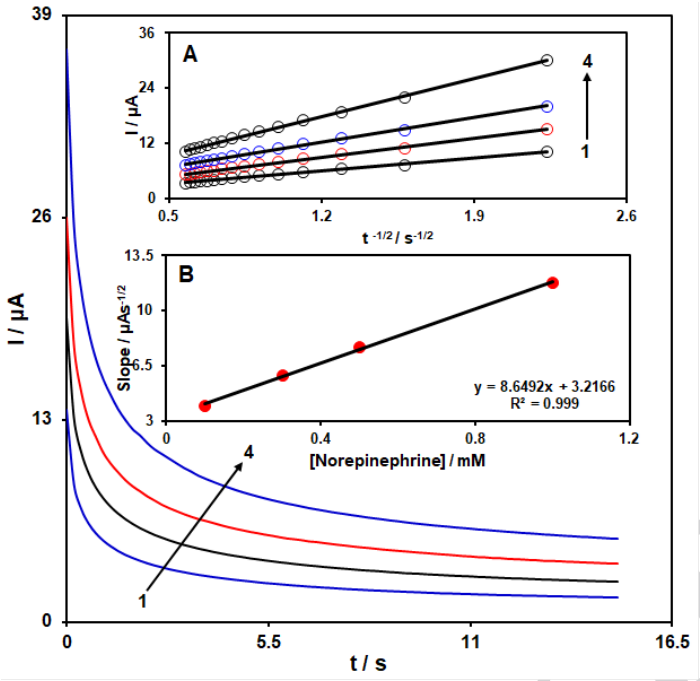

Fig. 4. Chronoamperograms obtained at Cu/SPE in 0.1 M PBS (pH 7.0) for different concentration of norepinephrine. The numbers 1–4 correspond to 0.1, 0.3, 0.5 and 1.0 mM of norepinephrine. Insets: (A) Plots of I *vs.* $t^{-1/2}$ obtained from chronoamperograms 1–4. (B) Plot of the slope of the straight lines against norepinephrine concentration.

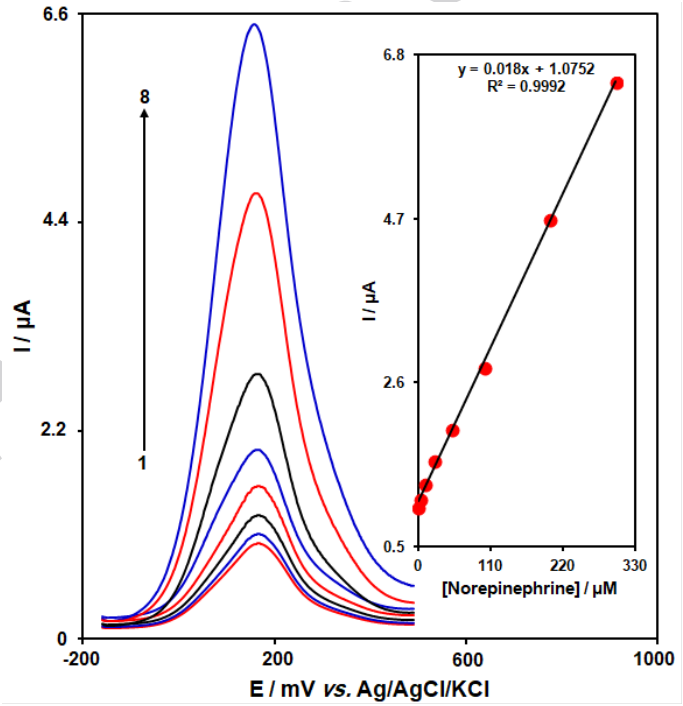

Fig. 5. DPVs of Cu/SPE in 0.1 M (pH 7.0) containing different concentrations of norepinephrine. Numbers 1–8 correspond to 0.3, 2.5, 10.0, 25.0, 50.0, 100.0, 200.0 and 300.0 µM of norepinephrine. Inset: plot of the electrocatalytic peak current as a function of norepinephrine concentration in the range of 0.3-300.0 µM

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3.3. Calibration plot and limit of detection

The peak current of norepinephrine oxidation at the surface of the modified electrode can be used for determination of norepinephrine in solution. Therefore, differential pulse voltammetry (DPV) experiments were done for different concentrations of norepinephrine (Fig. 5). The oxidation peak currents of norepinephrine at the surface of a modified electrode were proportional to the concentration of the norepinephrine within the ranges 0.3 to 300.0 μM. The detection limit (3σ) of norepinephrine was found to be 9.0×10^{-8} M.

3.4. Real sample analysis

In order to evaluate the analytical applicability of the proposed method, also it was applied to the determination of norepinephrine in norepinephrine injection. The results for determination of norepinephrine in real samples are given in Table 1. Satisfactory recovery of the experimental results was found for norepinephrine. The reproducibility of the method was demonstrated by the mean relative standard deviation (R.S.D.).

Table 1. The application of Cu/SPE for determination of norepinephrine in norepinephrine injection (n=5). All concentrations are in μM

Sample	Spiked	Found	Recovery (%)	R.S.D. (%)
Urine	0	15.0	-	1.8
	2.5	17.3	98.8	3.2
	5.0	20.4	102.0	2.6
	7.5	22.7	100.8	1.6
	10.0	24.5	98.0	2.9

4. CONCLUSION

The Cu(II) nanocomplex coated on the surface of graphite screen printed electrode, and the as-prepared modified Cu/SPE electrode was used to detect norepinephrine in aqueous solutions, thus demonstrating the electroanalytical application of the Cu(II) nanocomplex. The Cu/SPE showed a faster electron transfer rate and better electrocatalytic oxidation abilities towards norepinephrine than the bare graphite screen printed electrode. The detection limit of norepinephrine could be as low as 0.09 μM, with a linear range from 0.3 to 300.0 μM. Finally, the method was applied to the selective and precise analysis of norepinephrine in norepinephrine injection.

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