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Development of a new electrochemical sensor based on modified carbon paste electrode for simultaneous determination of norepinephrine and acetaminophen in real samples

Mohammad Reza Aflatoonian[a,b], Somayeh Tajik[a,c,*], Behnaz Aflatoonian[c], Mehri-Saddat Ekrami-Kakhki[d], Kouros Divsalar[a], Iran Sheikh Shoaie[e], Mahdieh Sheikhshoaie[f], Fariba Garkani Nejad[e]

[a]*Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran*

[b]*Leishmaniasis Research Center, Kerman University of Medical Sciences, Kerman, Iran*

[c]*Research Center for Tropical and Infectious Diseases, Kerman University of Medical Sciences, Kerman, Iran*

[d]*Esfarayen University of Technology, Esfarayen, Iran*

[e]*Department of Chemistry, Faculty of Science, Shahid Bahonar University of Kerman, Kerman 76175-133, Iran*

[f]*Department of Mining Engineering, Shahid Bahonar University of Kerman, Kerman, Iran*

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Abstract

An electrochemical method has been described for the voltammetric oxidation and determination of norepinephrine (NE) at a carbon paste electrode (CPE) modified with RuO_2 nano-roads and ionic liquid. The results indicated that the voltammetric response of norepinephrine was improved distinctly at the surface of modified electrode and the oxidation of norepinephrine at the surface of modified electrode occurs at a potential about 200 mV less positive than that of an unmodified CPE. The anodic peak was characterized and the process was diffusion-controlled. The current measured by differential pulse voltammetry (DPV) presented a good linear property as a function of the concentration of norepinephrine in the range of 0.07-400.0 µM, with a detection limit of 0.02 µM for norepinephrine. Also, this modified electrode was used for simultaneous determination of norepinephrine and acetaminophen. Finally, the proposed method was successfully applied to norepinephrine and acetaminophen determination in pharmaceutical samples and urine as real samples.

Keywords: Norepinephrine; acetaminophen; RuO_2 nano-roads; carbon paste electrode.

Introduction

Norepinephrine (NE) is one of the most important biochemical messengers in mammalian central nervous systems, existing in the nervous tissue and biological body fluid. It is released as a metabotropic neurotransmitter from nerve endings in the sympathetic

*Corresponding author: Somayeh Tajik
Tel: +98 (913) 1965532, Fax: N/A
E-mail: tajik_s1365@yahoo.com

nervous system and some areas of the cerebral cortex [1-3]. It can be used for treating myocardial infarction hypertension, bronchial asthma and organic heart disease. Extremely abnormal concentration levels of norepinephrine may lead to the occurrence of many diseases, such as ganglion neuronal, ganglia neuroblastoma, paraganglioma and Parkinson' disease. Recent reports have indicated that norepinephrine enhances adhesion of human immune deficiency virus-1 (HIV-1)-infected leukocytes to cardiac micro vascular endothelial cells and also accelerates HIV replication *via* protein kinase [4-6]. Therefore, it is imperative to develop a fast and sensitive analysis approach for norepinephrine quantitative detection. Generally, the determination of norepinephrine is carried out by various methods, including high performance liquid chromatography [7], gas chromatography [8], chemiluminiscence [9], spectrophotometry [10] and flow injection [11]. As an electrochemical device, norepinephrine can also be studied *via* electrochemical techniques.

Acetaminophen, {N-acetyl-p-aminophenol}, (ACOP) also known as paracetamol, is one of the most used analgesic and antipyretic drugs. It's utilized extensively for relieving fever, cold, cough and pain such as headache, toothache and backache. In general, acetaminophen is considered safe and does not exhibit any serious side effects when consumed in prescribed doses. However, an overdose of acetaminophen can cause fatal circumstances in kidneys and liver such as renal failure and hepatic necrosis. Acetaminophen is a suitable alternative for the patients who are sensitive to aspirin [12]. Several techniques including titrimetry, spectrophotometry, high-performance liquid chromatography and electrochemical techniques have been applied for the determination of acetaminophen in pharmaceutical formulations and biological fluids [13].

Acetaminophen administration is known to increase brain serotonin (5-HT) levels as a result of liver tryptophan-2,3-dioxygenase (TDO) inhibition [14] and 5-HT is known to play a role in norepinephrine release in the brain [15]. Therefore simultaneous determination of norepinephrineand acetaminophen is important.

Electroanalytical methods have attracted more attention in recent years for the determination of analytes due to their accuracy, sensitivity, high speed, reproducibility, lower cost and simplicity [16-18]. The voltammetric technique is an effective detection tool for determination of simultaneous multi-analyte [19-23]. However, the oxidation potentials of norepinephrine and acetaminophen at bare electrode are too close, which lead to overlapping signals and make it hard to simultaneous detection. Therefore, it still remains a critical challenge to develop a simple, sensitive and low-cost electrochemical sensor for simultaneous detection of norepinephrine and acetaminophen. In this case, the presence of a suitable coating modifying the electrode surface may induce electrocatalytic properties that on the one hand anticipates the signal of the analyte and, on the other hand, increases the sensitivity of detection [24-26].

The carbon paste electrode provides a flexible platform for the fabrication of varieties of electrochemical sensors due to simple and easy fabrication procedure, low background current, inexpensiveness, amenability to various

modifiers and modification methods and biocompatibility [27].

Nanomaterials have become the topic of intense researches in the recent years because of their unique properties and the promising applications in any aspect of nanotechnology. In particular, metal nanoparticles were found as ideal supporting materials for the electrocatalytic activities because they have their own fascinating surface structure, good electrical and mechanical properties, strong stability and limited aggregation and high performance. These properties clearly support their use as catalysts for commercially viable applications. Therefore, the nanostructures can be employed for efficient transport of electrons, in fabrication electrochemical nanosensors [28].

Among others, ruthenium metal, which has the great advantage of being a relatively cheap platinum group member, has a stable molecular form, and Ruthenium (Ru) is also a noble metal that acts as a catalyst, received much attention over, because of its high activity in oxidation and reduction reactions [29,30].

In the present work, we describe the preparation of a carbon paste electrode modified with RuO_2 nano-roads and ionic liquid (RuO_2-IL/CPE) and investigate its performance for the determination of norepinephrine in aqueous solutions. We also evaluate the analytical performance of the modified electrode for quantification of norepinephrine in the presence of acetaminophen.

Experimental

Apparatus and chemicals

An Autolab potentiostat/galvanostat (PGSTAT 302N, Eco Chemie, the Netherlands) was applied for measuring electrochemicals. General Purpose Electrochemical System (GPES) software was employed to control conditions of experiments. A conventional three-electrode cell was used at 25±1ºC. An Ag/AgCl/KCl (3.0 M) electrode (Azar Electrode, Urmia, Iran), a platinum wire (Azar Electrode, Urmia, Iran), and RuO_2-IL/CPE were used as the reference, auxiliary and working electrodes, respectively. pH was measured by a Metrohm 710 pH meter.

Norepinephrine, acetaminophen, and all the remaining reagents had an analytical grade. They have been prepared *via* Merck (Darmstadt, Germany). Orthophosphoric acid and the related salts that were above the pH range of 2.0–9.0 were used for preparing the buffer solutions. RuO_2 nano-road were synthesized in our laboratory as reported previously [31]. A typical SEM can be seen in Figure 1.

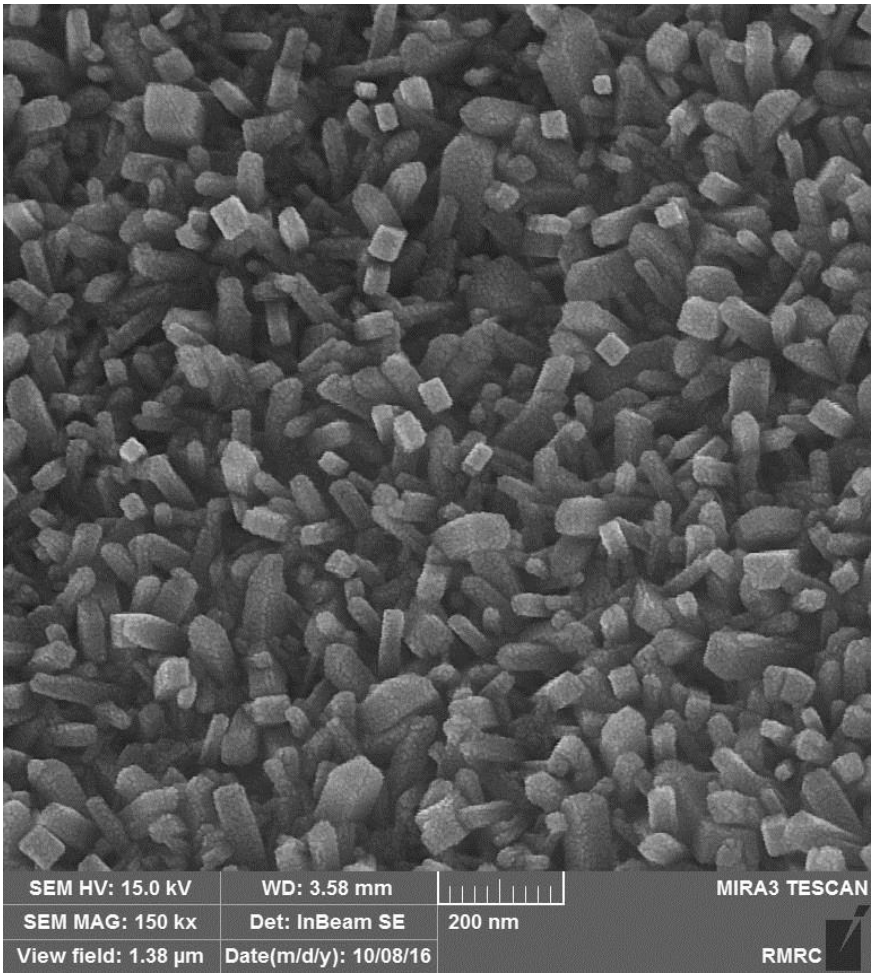

Figure 1. SEM image of RuO_2 nano-roads

Preparing electrode

The RuO_2-IL/CPE was prepared by hand mixing 0.95 g graphite powder and 0.05 g RuO_2-nano-roads with a mortar and pestle. Then, 0.3 mL IL and 0.6 mL of paraffin oil were added to the above mixture and mixed for 15 min until a uniformly wetted paste was obtained. Then, the paste has been packaged to the bottom of a glass tube (ca. 3.4 mm i.d. & 10 cm long). A copper wire placed over carbon paste led to an electrical contact. If necessary, a novel surface has been gained by pushing an excessive paste out of tube and polishing with a weighing paper.

Preparing real samples

The norepinephrine injections was diluted 10 times with water; then, different volumes of the diluted solutions were transferred into a 10 mL volumetric flask and diluted to the mark with PBS (pH 7.0). The diluted sample was spiked with different amounts of norepinephrine and acetaminophen.

Five 125 mg acetaminophen tablets were ground. Next 125 mg of the powder was taken and dissolved in 25 mL of distilled water by sonication. Various samples were prepared by taking and diluting different aliquots of this sample in a 25 mL volumetric flask using the phosphate buffer soltion (pH=7.0). The diluted sample was spiked with different amounts of norepinephrine and acetaminophen.

Samples of urine have been kept in a refrigerator directly after gathering. Ten

millilitres of samples have been centrifuged for fifteen minutes at 2,000 rpm. The supernatant has been filtered by a 0.45 µm filter. Next, various volumes of solution have been transported into a 25 millilitres volumetric flask and diluted to the mark with PBS (pH= 7.0). This diluted urine samples were anaesthetized with different amounts of norepinephrine and acetaminophen. The content of norepinephrine and acetaminophen has been analyzed by the suggested procedure by employing the standard addition method.

Result and discussion

Electrochemical properties of norepinephrine on RuO_2-IL/CPE surface

The electrochemical behaviour of norepinephrine is dependent on the pH value of the aqueous solution (Figure 2). Therefore, pH optimization of the solution seems to be necessary in order to obtain the electrocatalytic oxidation of norepinephrine. Thus, the electrochemical behaviour of norepinephrine was studied in 0.1 M PBS in different pH values (2.0< pH<9.0) at the surface of RuO_2-IL/CPE by CV. It was found that the oxidation of norepinephrine at the surface of RuO_2-IL/CPE was more favoured under neutral conditions than in acidic or basic medium, because the obtained current was more than other pHs.

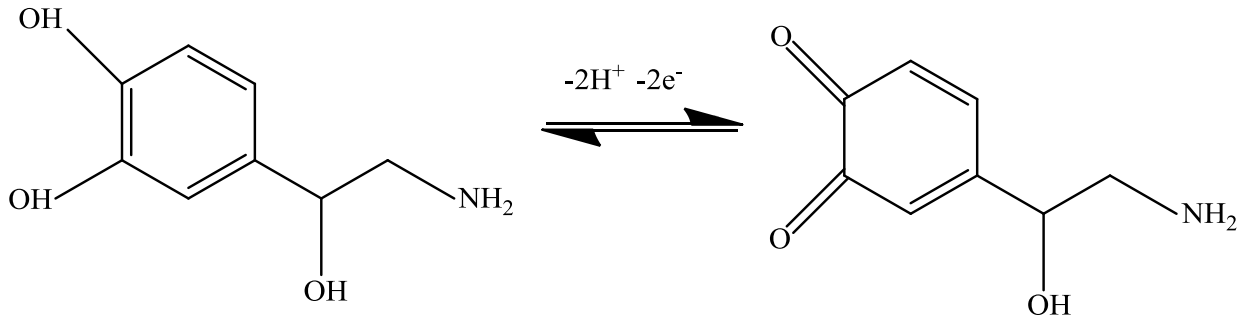

Figure 2. Electrochemical mechanism for oxidation of norepinephrine

Figure 3 depicts the CV responses for the electrochemical oxidation of 200.0 µM norepinephrine at unmodified CPE (curve a), RuO_2/CPE (curve b), IL/CPE (curve c), and RuO_2-IL/CPE (curve d).

Figure 3 shows that the anodic peak potential is about 440 mV for norepinephrine oxidation on the bare CPE surface (curve a) and 240 mV on the RuO_2-IL/CPE surface (curve d). According to these curves, the peak potential obtained for the oxidation of norepinephrine on the modified electrode surface switches 200 mV to negative values compared to that on the bare electrode surface. Based on the norepinephrine oxidation on the IL/CPE (curve c) and RuO_2-IL/CPE (curve d) surfaces, the anodic peak current has been increased on the RuO_2-IL/CPE compared to the IL/CPE, suggesting the enhancement of the peak currents by RuO_2-nano-roads presence in the CPE. There are some merits for IL/CPE, including rapid electron transfer, proper antifouling characteristics, higher conductivity, and catalytic nature of ILs. The IL mass was placed inside the paraffin oil and carbon that link the granules. A significant improvement was seen in the IL/CPE conductivity, in line with our electrochemistry findings.

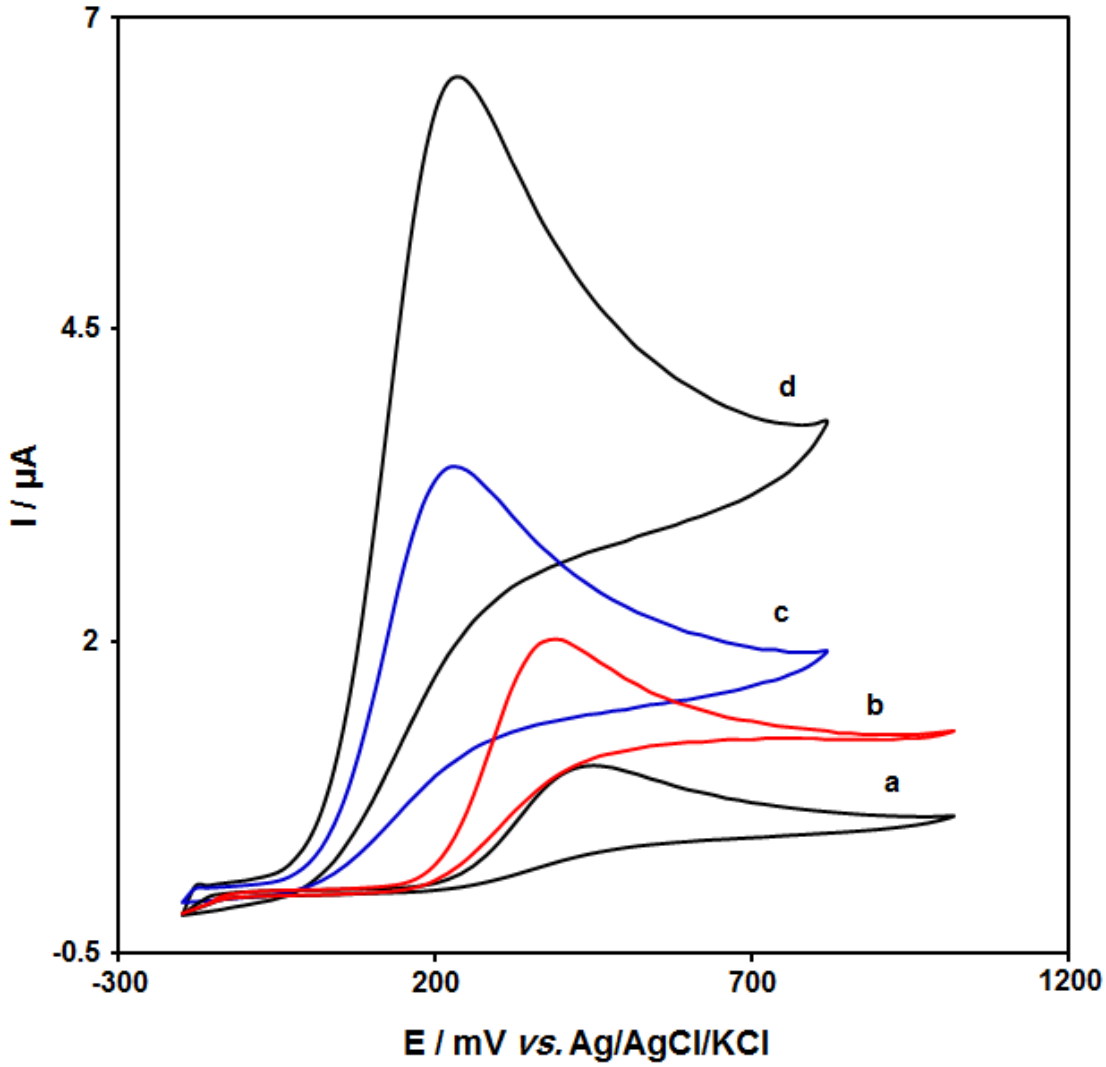

Figure 3. CVs of (a) unmodified CPE; (b) RuO_2/CPE; (c) IL/CPE and (d) RuO_2-IL/CPE in 0.1 M PBS (pH 7.0) containing 200.0 µM norepinephrine. In all cases the scan rate was 50 mV s^{-1}.

Effect of scan rate on the results

Researchers investigated the impact of the rates of potential scan on norepinephrine oxidation current (Figure 4). Findings indicated induction of enhancement in the current of the peak by the increased potential scan rate. Additionally, diffusion in oxidation processes are monitored, as inferred by the linear dependence of the anodic peak current (Ip) on the square root of the potential scan rate ($v^{1/2}$) [32].

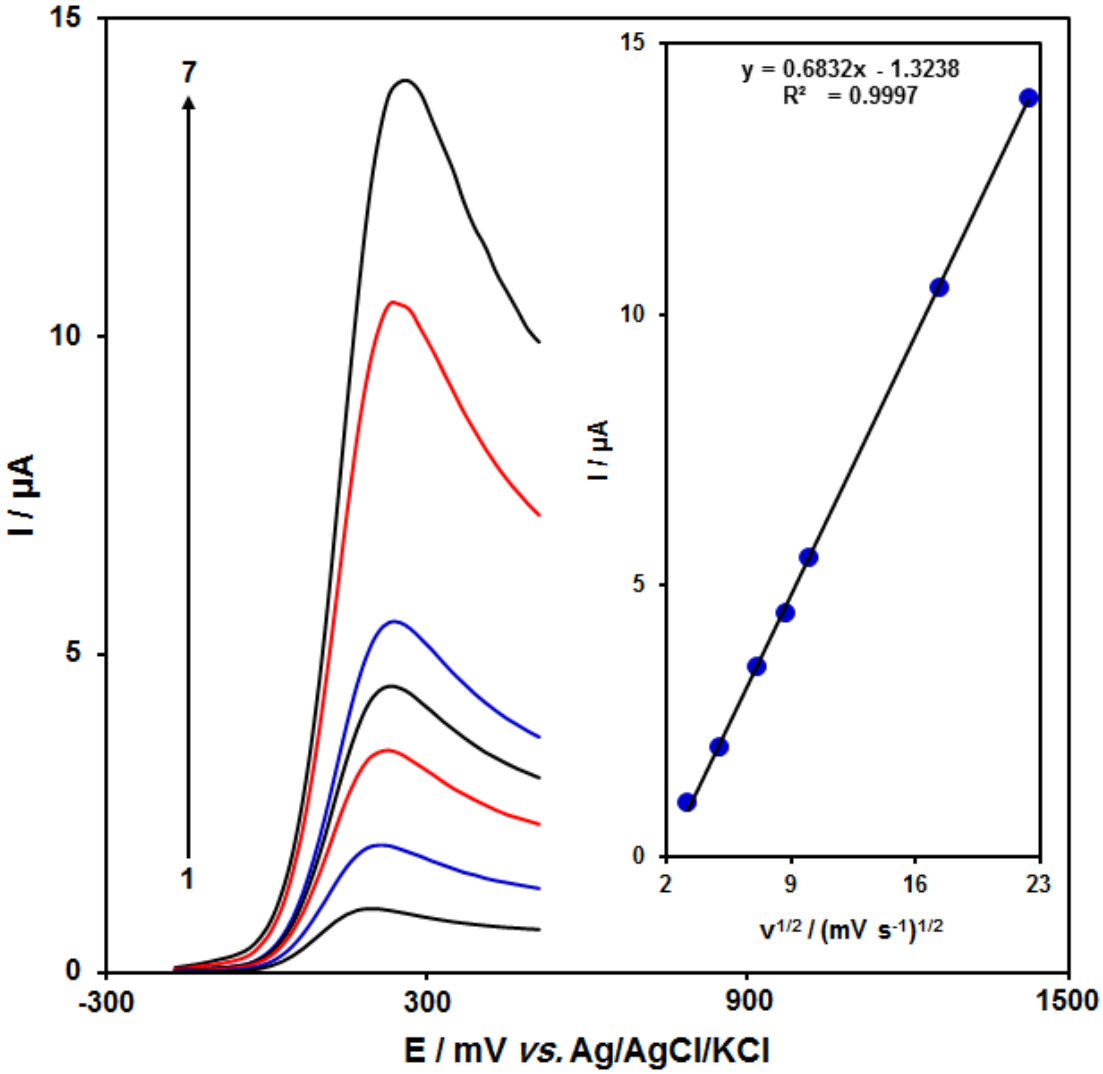

Figure 4. LSVs of RuO_2-IL/CPE.1in 0.1 M PBS (pH 7.0) containing 100.0 µM of norepinephrine at various scan rates; numbers 1-7 correspond to 10, 25, 50, 75, 100, 300 and 500 mV s^{-1}, respectively. Inset: variation of anodic peak current with square root of scan rate.

Data of the ascending section of the current–voltage curves, which have been registered at a scan rate of 10 mVs^{-1} for norepinephrine, was used for drawing Tafel plot (Figure 5). Electron transfer kinetics between RuO_2-IL/CPE and substrate (norepinephrine) affect this section of voltammogram that are called Tafel region. The study achieved Tafel slope of 0.1229 V. This finding is compatible with the engagement of one electron at the rate that determines the electrode process phase, providing that charge transfer coefficients $\alpha = 0.52$ for norepinephrine [32].

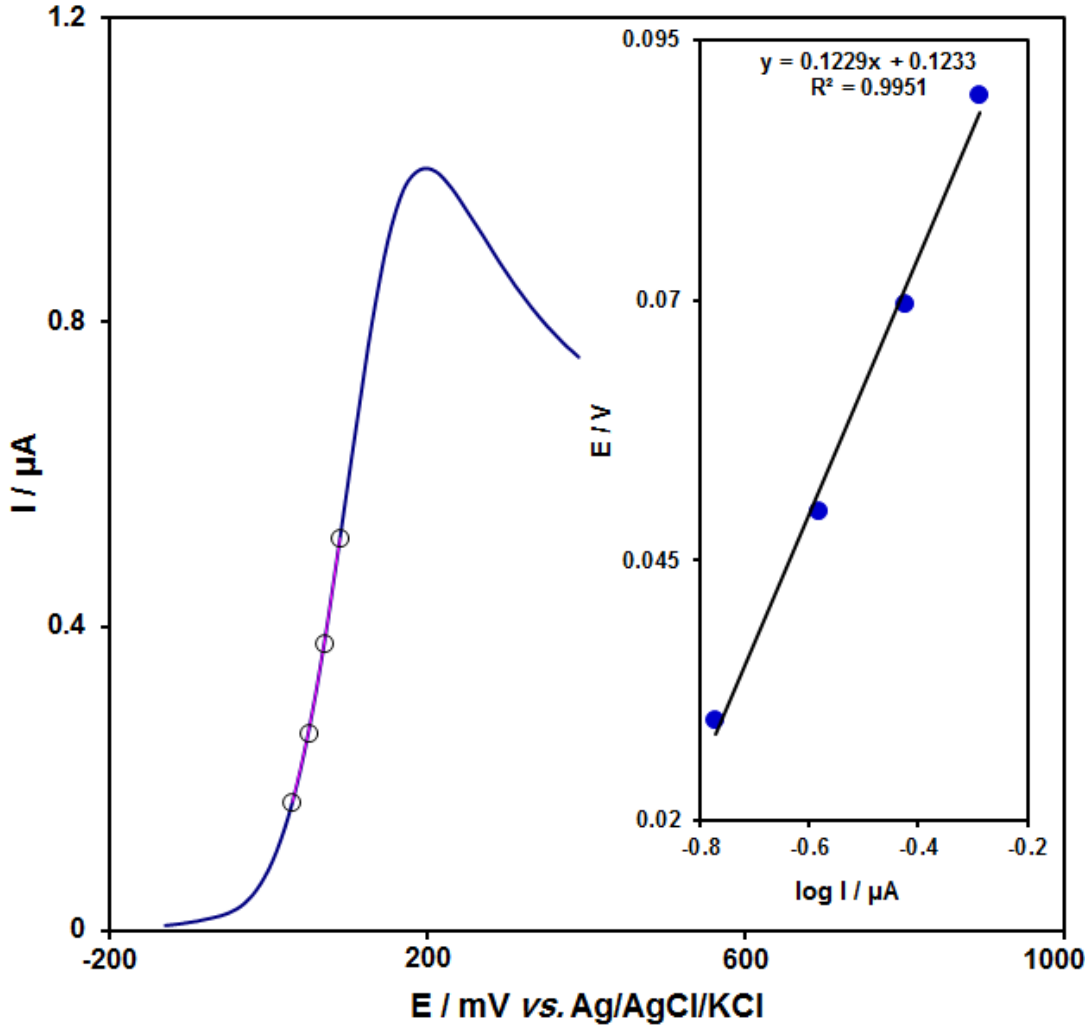

Figure 5. LSV (at 10 mV s^{-1}) of RuO_2-IL/CPE in 0.1 M PBS (pH 7.0) containing 100.0 µM norepinephrine. The points are the data used in the Tafel plot. The inset shows the Tafel plot derived from the LSV.

Chronoamperometric analyse

Chronoamperometric measurements of norepinephrine at RuO_2-IL/CPE were conducted by adjusting the working electrode potential at 0.29 V versus Ag/AgCl/KCl (3.0 M) for different concentrations of norepinephrine (Figure 6) in PBS (pH 7.0). For electroactive materials (norepinephrine in this case) with a diffusion coefficient of D, the Cottrell equation describes current seen for electrochemical reaction at the mass transport limited condition [32]:

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

where D and C_b respectively represent diffusion coefficient ($cm^2\ s^{-1}$) and bulk concentration (mol cm^{-3}). Experimental plots of I versus $t^{-1/2}$ were used with the best fits for various concentrations of norepinephrine (Figure 6A). Then, the resultant straight lines slopes were drawn against norepinephrine concentrations (Figure 6B). According to the resultant slope and the Cottrell equation, mean value of D was 4.1×10^{-6} cm^2/s for norepinephrine. This value is comparable with some previous reports (5.17×10^{-6} cm^2/s [3]).

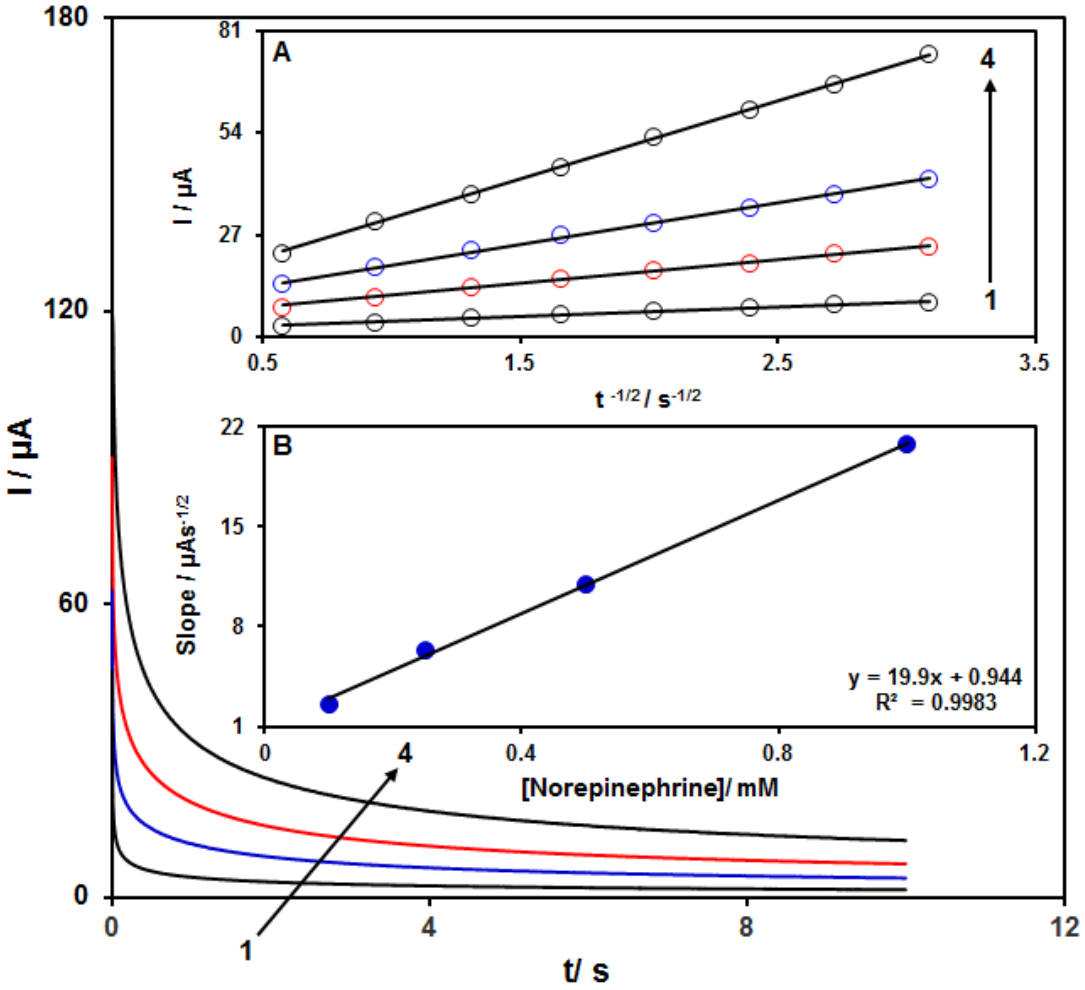

Figure 6. Chronoamperograms obtained at RuO_2-IL/CPE in 0.1 M PBS (pH 7.0) for different concentrations of norepinephrine. The numbers 1-4 correspond to 0.1, 0.25, 0.5 and 1.0 mM of norepinephrine. Insets: (a) Plots of I vs. $t^{-1/2}$ obtained from chronoamperograms 1–4. (b) Plot of the slope of the straight lines against norepinephrine concentrations.

Calibration curve and LOD

The electro-oxidation peak currents of norepinephrine at RuO_2-IL/CPE surface can be applied to define norepinephrine in the solution. Since the increased sensitivity and more suitable properties for analytical utilizations are considered as the benefits of differential pulse voltammetry (DPV), RuO_2-IL/CPE in 0.1 M PBS consisting of different distinct concentrations of norepinephrine was used to conduct DPV experiments (Figure 7) (Initial potential=25 mV, End potential=445 mV, Step potential=0.01 V and pulse amplitude=0.025 V). It was found that the electrocatalytic peak currents of norepinephrine oxidation at RuO_2-IL/CPE surface linearly depended on norepinephrine concentrations above the range of 0.07-400.0 µM (with a correlation coefficient of 0.999), while determination limit (3σ) was achieved to be 0.02 µM. These values are comparable with the values obtained by other researchers (Table 1).

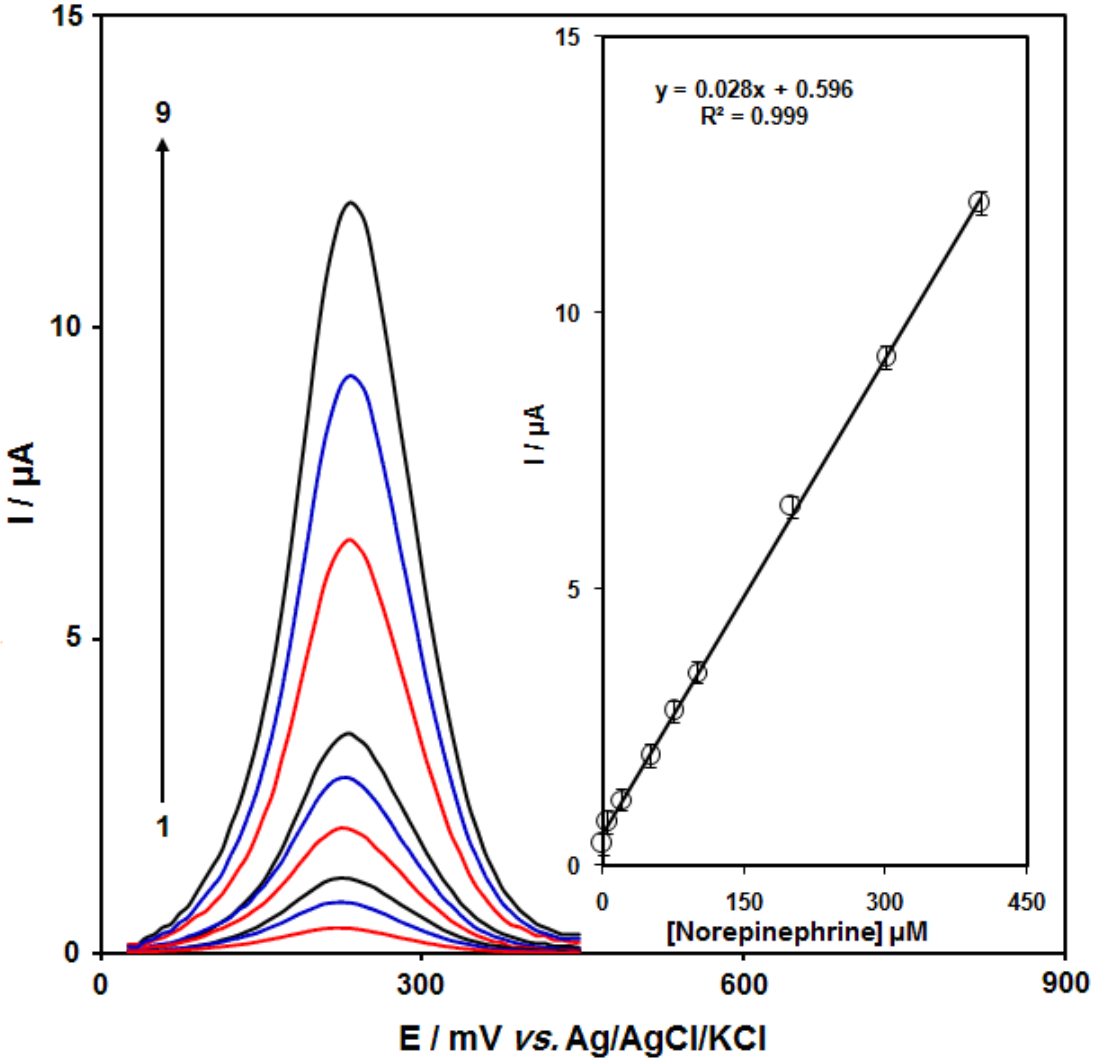

Figure 7. DPVs of RuO_2-IL/CPE in 0.1 M PBS (pH 7.0) containing different concentrations of norepinephrine. Numbers 1-9 correspond to, 0.07, 5.0, 20.0, 50.0, 75.0, 100.0, 200.0, 300.0 and 400.0 µM of norepinephrine. The inset shows the plot of the peak current as a function of the norepinephrine concentration in the range of 0.07-400.0 µM.

Table 1. Comparison of the efficiency of some modified electrodes used in detection of norepinephrine

Electrode	Modifier	LDR (µM)	LOD (µM)	Ref.
Carbon Paste	Poly (glutamic acid)	51.0–344.0	0.43	3
Screen Printed	MWNTs-ZnO/chitosan composites	0.5–30.0	0.2	5
Glassy Carbon	Molecularly imprinted polymer-coated PdNPs	0.5–80.0	0.1	61
Glassy Carbon	Graphene quantum dots/gold nanoparticles	0.5-7.5	0.15	62
Carbon Paste	RuO_2 nano-road and ionic liquid	0.07–400.0	0.02	This Work

Simultaneous determination of norepinephrine and acetaminophen

We have not seen any report about using a CPE modified with RuO_2 and IL for determining norepinephrine and acetaminophen. Moreover, due to reality that electro-chemical detection of norepinephrine in the front of acetaminophen with the help of un-modified electrodes has the caveat of interventions by acetaminophen because of relative adjacent oxidation capacities of the two specimens, it can be regarded a crucial phase. Such a phase has been conducted by simultaneous alterations of analytes concentrations and achieving DPVs (Figure 8) (Initial potential=-100 mV, End potential=500 mV, Step potential=0.01 V And pulse amplitude=0.025 V). Findings reported certain anodic at 230 and 430 mV for norepinephrine and acetaminophen oxidation, proving the use of the RuO_2-IL/CPE; these two analytes can be detected without severe interventions from each other (Figure 8).

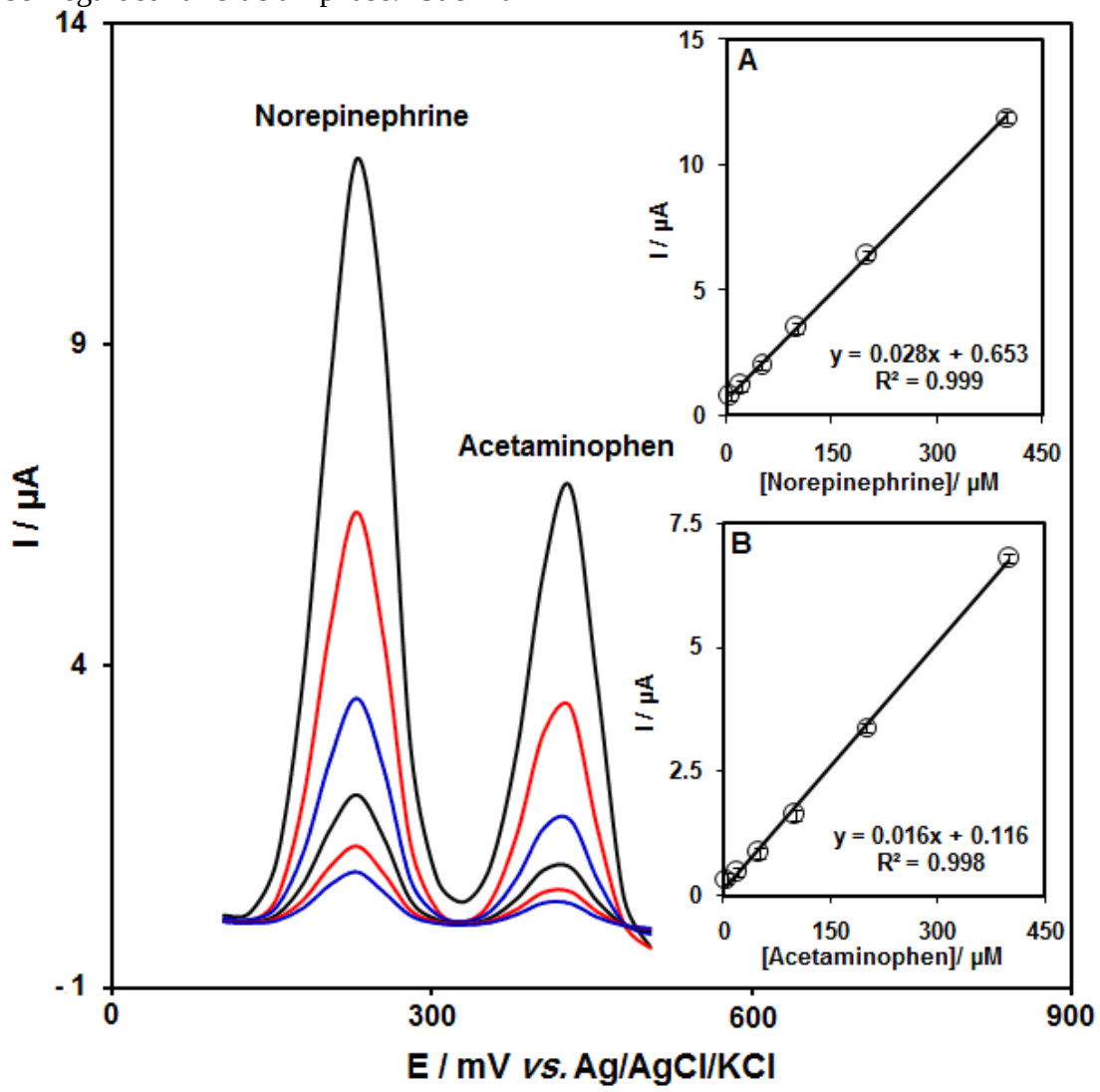

Figure 8. DPVs achieved at RuO_2-IL/CPE surface in 0.1 M PBS (pH 7.0) consisting of various concentrations of norepinephrine and acetaminophen. DPVs from internal to external respectively are corresponding to 5.0+5.0, 20.0+20.0, 50.0+50.0, 100.0+100.0, 200.0+200.0 and 400.0+400.0µM of norepinephrine and acetaminophen. Insets: (A) plot of Ip versus norepinephrine concentration and (B) plot of Ip versus acetaminophen concentration.

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The repeatability and stability of RuO_2-IL/CPE

To study the long-term stability of the RuO_2-IL/CPE, its performance was assessed over a three week period. For this purpose, the experiments were repeated after the modified electrode had been stored at room temperature for two weeks. As cyclic voltammograms demonstrated, notangible change was observed in the peak potential of norepinephrine oxidation except for a drop less than 2.7 % compared with initial response. The antifouling capacity of the modified electrode towards oxidation of norepinephrine and its corresponding oxidation products were investigated by CV analysis. Voltammograms were recorded in the presence of norepinephrine after cycling the potential 15 times at a scan rate of 50 mV s^{-1}. According to the results, the peak potentials remained unchanged except a decrement less than 2.0 %. These results confirmed that the modified RuO_2-IL/CPE offers higher sensitivity and reduced fouling effect towards norepinephrine and its oxidation products.

Analysis of real samples

To assess the applicability of the application of the modified electrode for the determination of norepinephrine and acetaminophenin real samples, the described method was applied to the determination of norepinephrine and acetaminophenin norepinephrine injection, acetaminophen tablets and urine samples. Therefore, the standard addition technique was applied. Table 2 reports the results. Acceptable recoveries of norepinephrine and acetaminophen were observed, and reproducible results were shown with regard to the mean relative standard deviation (R.S.D.).

Table 2. Determination of norepinephrine and acetaminophen in real samples. All the concentrations are expressed in µM (n = 5).

Sample	Spiked		Found		Recovery (%)		R.S.D. (%)	
	Norepinephrine	Acetaminophen	Norepinephrine	Acetaminophen	Norepinephrine	Acetaminophen	Norepinephrine	Acetaminophen
Norepinephrine injection	0	0	4.0	-	-	-	1.9	-
	2.5	5.0	6.7	4.9	103.1	98.0	3.4	1.8
	5.0	10.0	8.8	10.3	97.8	103.0	2.7	2.4
	7.5	15.0	11.6	14.8	100.9	98.7	2.1	2.9
	10.0	20.0	13.8	20.2	98.6	101.0	2.2	3.3
Acetaminophen tablet	0	0	-	7.0	-	-	-	3.2
	5.0	2.5	5.1	9.3	102.0	97.9	2.4	1.7
	10.0	5.0	9.9	12.2	99.0	101.7	3.0	2.8
	15.0	7.5	15.5	14.4	103.3	99.3	2.0	2.1
	20.0	10.0	19.5	17.3	97.5	101.8	2.9	2.3
Urine	0	0	-	-	-	-	-	-
	5.0	7.5	4.9	7.7	98.0	102.7	2.4	1.7
	10.0	12.5	10.2	12.3	102.0	98.4	3.5	2.8
	15.0	17.5	14.9	17.3	99.3	98.9	3.1	1.9
	20.0	22.5	20.6	22.4	103.0	99.6	2.1	3.4

Conclusion

Norepinephrine and acetaminophen were determined using a high sensitive, simple, and precise voltammetry technique at a modified carbon paste electrode. The modified electrode shows several advantages over the other methods such as simple preparation method, high stability, high sensitivity, long-term stability and remarkable voltammetric reproducibility. The results showed that the presence of modifier at the surface of the electrode dramatically affect the sensitivity of the electrochemical responses toward norepinephrine and acetaminophen. This new electrochemical sensor was used for determination of norepinephrine in the range of 0.07-400.0 µM, with a detection limit of 0.02 µM. Also, the proposed method was used for determination of norepinephrine and acetaminophen in some real samples.

Acknowledgements

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