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Original Research Article

Electrochemical Determination of Doxorubicin in Injection Samples Using Paste Electrode Amplified with Reduced Graphene Oxide/Fe_3O_4 Nanocomposite and 1-Hexyl-3-methylimidazolium Hexafluorophosphate

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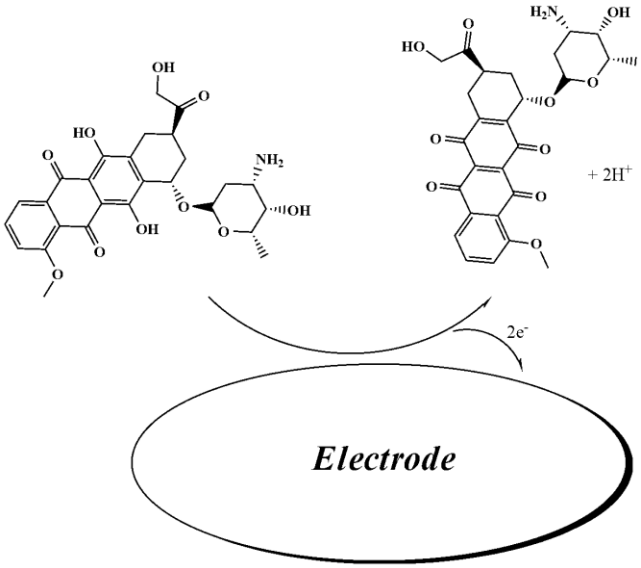
ABSTRACT

In this study, a doxorubicin electrochemical sensor was fabricated by modification of paste electrode (PE) with reduced graphene oxide/Fe_3O_4 nanocomposite (rGO-Fe_3O_4-NC) and 1-hexyl-3-methylimidazolium hexafluorophosphate (HMIZHFP). The rGO-Fe_3O_4-NC/HMIZHFP/PE was shown to have good catalytic effect for oxidation of doxorubicin in aqueous solution and oxidation current of anticancer drug was improved about 2.76 times. In addition, oxidation of doxorubicin was shown in a linear dynamic range 3.0 nM-280 µM with detection limit 1.0 nM at surface of rGO-Fe_3O_4-NC/HMIZHFP/PE. The recovery data 99.33-103.7 % was calculated for measurement of doxorubicin in injection and pharmaceutical serum using rGO-Fe_3O_4-NC/HMIZHFP/PE as sensor that is acceptable for a new analytical sensor.

GRAPHICAL ABSTRACT



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Introduction

Cancer has been known as the main cause of human mortality for many years and in recent years, due to the progress of urbanization and the presence of synthetic materials in human nutrition and environmental pollution, its diversity has increased [1-5]. Anticancer drugs are used as a primary treatment for the dangerous cancer in chemotherapy [6]. However, the side effects of using such drugs have always been a major obstacle in their use and controlling the dose of anti-cancer drugs and measuring them in biological samples has been important and necessary [7].

Doxorubicin is a phenolic-based anthracycline anticancer drug prescribed to treat various cancers such as breast cancer, bladder cancer, and blood cancers [8]. Doxorubicin helps to chemotherapy by blocking topo isomerase 2. Due to different side effects such as fast or irregular heartbeat, fever or chills, pain at the injection site, and difficult urination accompanied by fever or chills, controlling doxorubicin dosage on chemotherapy process by analytical methods is very important. Therefore, researchers suggested many different strategies for determination of doxorubicin level in biological samples [9-15].

In between, attention to electrochemical methods showed more benefits due to ability for online analysis, fast response, low cost, easy operation and more diversity [16-25]. On the other hand, modification of electrochemical sensors created high diversity and powerful ability for selective analysis of biological and pharmaceutical compounds in the recent years [26-35].

Nanomaterials with high surface area and unique properties showed more advantages in different fields of research [36-50]. Properties such as electrical conductivity, thermal stability, good mechanical properties, and high surface area of nanomaterials have created a revolution in science [51-65]. Electrochemical sensors are one of the scientific topics that have been strongly influenced by nanotechnology [66-70]. Application of nanomaterials as modifiers has created a new view in fabrication of highly sensitive electrochemical sensors [71-75].

Therefore, in this study, a highly sensitive electrochemical sensor was fabricated for determination of doxorubicin by modification of PE by rGO-Fe_3O_4-NC and 1HMIZHFP. The rGO-Fe_3O_4-NC/HMIZHFP/PE was used for determination of doxorubicin with acceptable recovery data in injection and pharmaceutical serum samples.

Material and methods

Graphene oxide, iron (III) chloride, iron (II) sulfate, sodium hydroxide, sodium hydroxide, graphite powder, paraffin oil, HMIZHFP, doxorubicin and phosphoric acid were purchased from Sigma and Merck Company. Stock solution of doxorubicin (0.01 M) was prepared by dissolving of 0.135 g doxorubicin into 25 mL distilled water. In addition, rGO-Fe_3O_4-NC was synthesized by reported procedure by our previous reported paper [76]. All of electrochemical signals were recorded by Potentiostat/Galvanostat machine (Ivium-Vertex) using Ag/AgCl/KCl_{sat} as reference electrode.

Preparation of rGO-Fe_3O_4-NC/HMIZHFP/PE

The rGO-Fe_3O_4-NC/HMIZHFP/PE was organized using hand mixing composition containing of 80 mg rGO-Fe_3O_4+940 mg graphite powder in the presence of 2 drops of HMIZHFP +8 drop of paraffin oil as binders for 65 min using a mortar and pestle.

Real sample preparation

Doxorubicin injection and dextrose saline were purchased from local pharmacy and then diluted by PBS, and directly used for real sample analysis.

Result and Dissection

Electrochemical investigation

Oxidation/reduction behavior of doxorubicin was investigated using rGO-Fe_3O_4-NC/HMIZHFP/PE as electrochemical sensor in

pH range 4.0-9.0 (Figure 1 inset). The cyclic voltammograms showed a quasi-reversible behavior in this pH range and linear relation between oxidation signal of doxorubicin and pH value with equation E=0.061 pH=+1.0201 (R^2=0.9945) that showed suggested mechanism in scheme 1 is acceptable for doxorubicin [77].

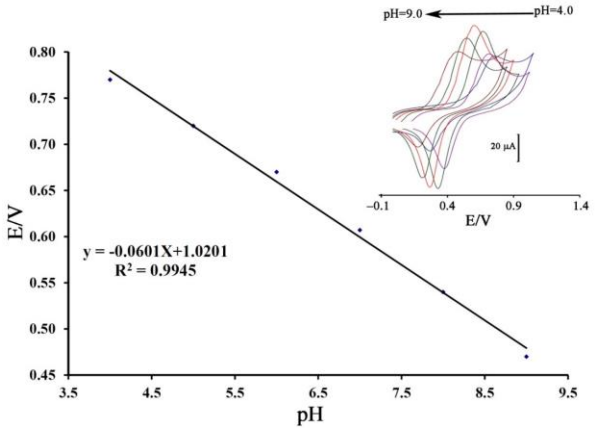
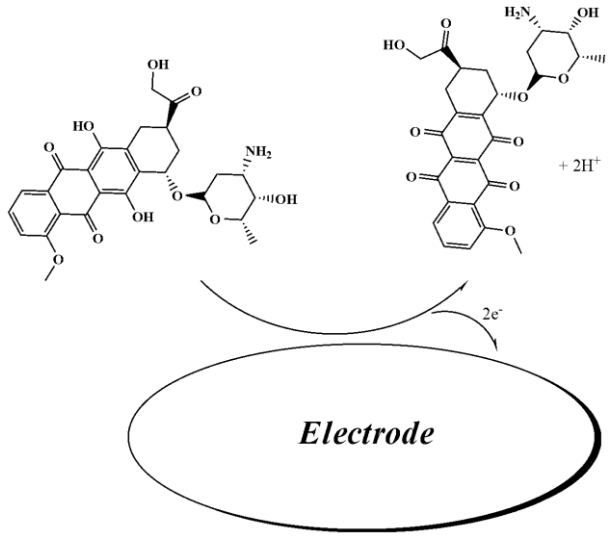


Figure 1: E-pH curve for electro-oxidation of 300-µM doxorubicin at surface of rGO-Fe_3O_4-NC/HMIZHFP/PE. Inset) Relative cyclic voltammograms



Scheme 1: Electro-oxidation mechanism of doxorubicin

On the other hand, maximum oxidation signal of doxorubicin was observed at pH=7.0 and this value was selected as optimum condition. Redox behavior of doxorubicin was recorded at surface of PE (Fig. 2 curve a), rGO-Fe_3O_4-NC/PE (Fig. 2 curve b), HMIZHFP/PE (Figure 2 curve c) and rGO-Fe_3O_4-NC/HMIZHFP/PE (Figure 2 curve d), respectively. Oxidation current of doxorubicin increased from 29.49 µA at surface of PE to 81.43 µA at surface of rGO-Fe_3O_4-NC/HMIZHFP/PE. This improvement is relative to the presence of rGO-Fe_3O_4-NC and HMIZHFP at surface of PE.

Oxidation current of doxorubicin showed a linear relation with $\nu^{1/2}$ in the scan rate ranging 15-100 mV/s that confirm diffusion process [78-81] for electro-oxidation of doxorubicin at surface of rGO-Fe_3O_4-NC/HMIZHFP/PE. In addition, positive shift of doxorubicin potential at surface of rGO-Fe_3O_4-NC/HMIZHFP/PE with increasing in scan rate confirm a kinetic limitation and quasi-behavior in this study.

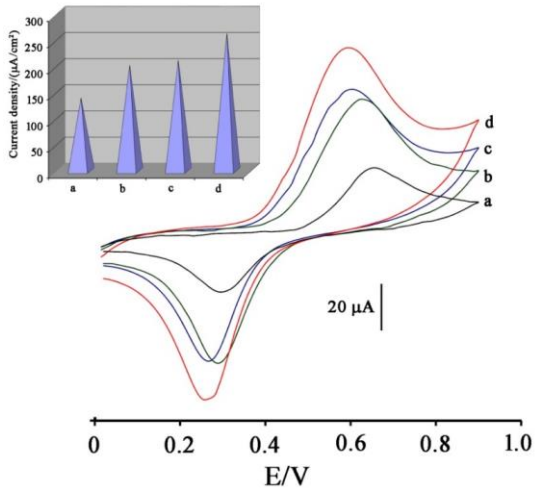


Figure 2: Cyclic voltammograms of 300 µM doxorubicin at surface of PE (curve a), rGO-Fe_3O_4-NC/PE (curve b), HMIZHFP/PE (curve c) and rGO-Fe_3O_4-NC/HMIZHFP/PE (curve d)

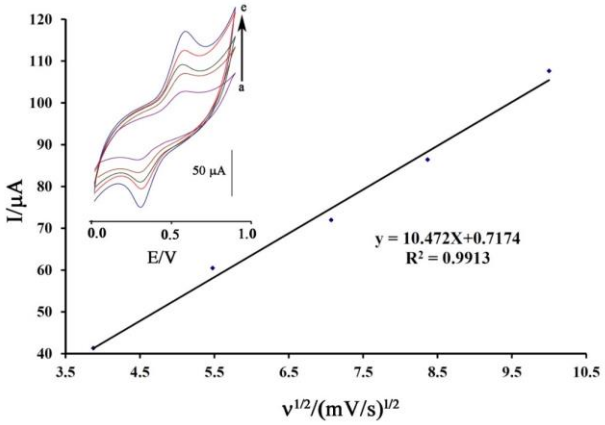


Figure 3: I-$\nu^{1/2}$ of doxorubicin at surface of rGO-Fe_3O_4-NC/HMIZHFP/PE. CV of doxorubicin at scan rate a) 15, b) 30, c) 50, d) 70 and e) 100 mV/s

The rGO-Fe_3O_4-NC/HMIZHFP/PE was used as analytical tool for determination of doxorubicin by using differential pulse voltammetric method (Figure 4). Oxidation current of doxorubicin showed a linear relation with doxorubicin concentration in the range 0.003-280 µM with detection limit 1.0 nM (LOD=$3S_b$/m) (Figure 4 inset).

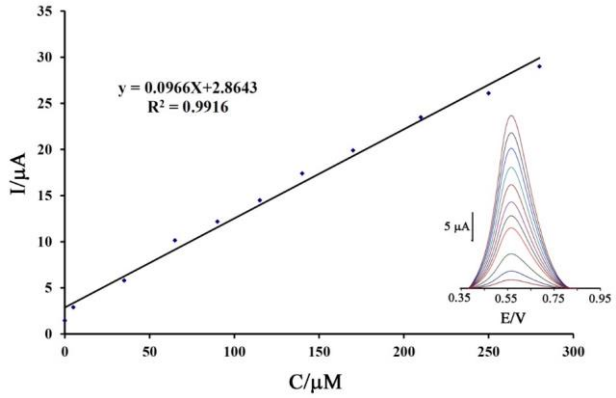


Figure 4: I-Concentration plot for electro-oxidation of doxorubicin in the concentration range 0.003-280 µM.

Inset) DP voltammograms for electro-oxidation of doxorubicin in the concentration range 0.003-280 µM

The selectivity of rGO-Fe_3O_4-NC/HMIZHFP/PE for determination of 50.0 µM doxorubicin was investigated by differential pulse voltammetric method. The results are presented in Table 1 and confirm good selectivity of rGO-Fe_3O_4-NC/HMIZHFP/PE for determination of 50.0 µM doxorubicin. In final step, the ability of rGO-Fe_3O_4-NC/HMIZHFP/PE was checked for determination of doxorubicin in injection and dextrose saline samples and the results are presented in Table 2. As can be seen, the rGO-Fe_3O_4-NC/HMIZHFP/PE showed acceptable recovery data for determination of doxorubicin.

Table 1: Selectivity data for determination of 50.0 µM doxorubicin

Species	Tolerant limits ($W_{interference}$/W $d_{oxorubicin}$)
F^- ،Li^+ ،Mg^{2+} ،Br^{-+} ،Ca^2	1000
Glucose	550
Valine and methionine	500
Urea, tryptophan and dasatinib	100

Table 2: Determination of doxorubicin in real samples (n=5)

Sample	Added (µM)	Expected (µM)	Found (µM)	Recovery %
Injection sample	---	2.00	1.98±0.08	---
	10.00	12.00	11.92±0.43	99.33
Dextrose saline	---	---	<LOD	---
	10.00	10.00	10.37±0.56	103.7
	20.00	20.00	19.78±0.76	98.9

Conclusion

In the presence study, the rGO-Fe_3O_4-NC/HMIZHFP/PE was introduced as a new and highly sensitive electrochemical tool for determination of doxorubicin. The rGO-Fe_3O_4-NC/HMIZHFP/PE was improved in oxidation signal of doxorubicin by about 2.76 times compared with PE. In addition, oxidation of doxorubicin was shown as a linear dynamic range of 3.0 nM-280 µM with detection limit 1.0 nM at surface of rGO-Fe_3O_4-NC/HMIZHFP/PE. Furthermore, the rGO-Fe_3O_4-NC/HMIZHFP/PE

was successfully used for determination of doxorubicin with recovery data 99.33 %-103.7% in injection and dextrose saline samples.

Conflict of Interest

We have no conflicts of interest to disclose.

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