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An electrochemical glutathione biosensor: Ubiquinone as a transducer

Jing Ru [1], Jie Du [1], Dong-Dong Qin, Bao-Mei Huang, Zhong-Hua Xue, Xi-Bin Zhou, Xiao-Quan Lu *

Key Laboratory of Bioelectrochemistry & Environmental Analysis of Gansu Province, College of Chemistry & Chemical Engineering, Northwest Normal University, Lanzhou 730070, China

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ABSTRACT

In this paper, coenzyme Q_{10} (Ubiquinone, CoQ_{10}) was used for the first time as a transducer to construct electrochemical biosensor for effectively detecting γ-L-glutamyl-L-cysteinyl-glycine (glutathione, GSH). CoQ_{10} modified electrode was fabricated by attaching its gel mixed with multi-walled carbon nanotubes (MWNTs)/ionic liquid (IL). In the optimum conditions, based on the increasing of reduction peak current of CoQ_{10} caused by GSH through voltammetric technology, it was found that the peak current of CoQ_{10} was linear with the concentration of GSH in the range from 4.0×10^{-9} to 2.0×10^{-7} mol L^{-1} at the pH 7.00, and the limit of detection was 3.2×10^{-10} mol L^{-1} ($S/N=3$). The results revealed that this method could be used to determine GSH in actual blood samples with the superiority of excellent selectivity, high stability and sensitivity. The strategy explored here might provide a new pathway to design novel multi-function transducers for detecting GSH, which has unique characteristic and potential application in the fields of sensor and medical diagnosis.

1. Introduction

Coenzyme Q_{10} (2,3-dimethoxy-5-methyl-6-decaprenyl-1, 4-benzoquinone, CoQ_{10}) is a fat soluble, vitamin-like quinine commonly known as ubiquinone or ubidecarenone [1,2], which is found to play an important role in biological systems and respiratory chains of mitochondria [3,4], existing in humans, most mammals and other edible vegetables oil [5–7]. CoQ_{10} is also a kind of electronic receptor [8], which can take part in electron and proton transfers [9–11], photosynthetic reaction [12–14], undergoing oxidation and reduction through a free-radical intermediate [15], etc. Because of the critical role of CoQ_{10} in biochemistry [16], Ma and co-workers reported that the functionalization of CoQ_n was embedded in a biomimetic membrane to mimic the initial stages of respiration [6], Murai revealed that the interactions of nicotinamide adenine dinucleotide (NADH)/CoQ_n oxidoreductase in mitochondrial were explored by photoaffinity labeling [17]. However, due to the strong hydrophobility of CoQ_{10}, its electrochemical investigations can only be performed in non-aqueous solutions. Therefore, only few methods had been reported for the immobilization of unfunctionalized CoQ_{10} on the electrode surface directly so far. Hence it still remains a great challenge to immobilize the unfunctionalized CoQ_{10} on the electrode surface and explore its electrochemical behaviors.

γ-L-Glutamyl-L-cysteinyl-glycine (glutathione, GSH) is a tripeptide, which contains an unusual peptide link between the amine group of cysteine and the carboxyl group of the glutamyl side chain [18–21]. GSH can be used as an indicator of some human diseases [22–27], including Alzheimer's, Parkinson's diseases, diabetes, macular degeneration and HIV disease. In addition, GSH shows other crucial functions [28,29], for example, Kalgutkar et al. revealed that GSH was a kind of nucleophilic reagent compound, which was prone to nucleophilic displacement reaction under some conditions [30–33], a few reports showed that nanomaterial modified electrodes had superior electrocatalytic properties for detecting GSH [34,35]. Till now, many kinds of methods have already been reported to research GSH, such as high performance liquid chromatography [36], spectrofluorimetry [37], spectrophotometry [38] and potentiometry [29,39]. However, most of these methods were intricate and time costing, so it remains a challenge to develop a simple, rapid and sensitive method for detecting GSH in biological samples.

It is interesting to further investigate the properties of CoQ_{10} with facile and sensitive electrochemistry method. However, there are very few examples of studies on CoQ_{10} for transducer element and biological applications [5,40–42], in this paper, CoQ_{10} was used as an attractive sensing element and a transducer. Initially, CoQ_{10} was dissolved in a mixed solution of benzene derivative and multi-walled carbon nanotubes (MWNTs)/ionic liquid (IL) to form a homogeneous gel, which was then successfully immobilized on the electrode surface. GSH determination in actual blood was evaluated at the modified electrode by simple and rapid voltammetric method. It was shown that the biosensor developed here exhibited advantages of facile set-up, high sensitivity, fast

* Corresponding author. Tel.: +86 931 7971276; fax: +86 931 7971323.
E-mail addresses: luxq@nwnu.edu.cn, taaluxq@126.com (X.-Q. Lu).
[1] These authors contributed equally.

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response and good stability, resulting from the combination of strong hydrophobility, high viscosity of ionic liquid, extremely high surface area and high conductivity of carbon nanotubes. The CoQ_{10}-based biosensor is expected to be applied for medical diagnosis, where GSH is involved.

2. Experimental

2.1. Chemicals and reagents

Coenzyme Q_{10} (CoQ_{10}) was purchased from Aladdin (Shanghai, China), nitrobenzene (NB) (Shanghai chemical Reagent Co. Ltd.) was the highest purity and was used as received. Multi-walled carbon nanotubes (MWNTs, 95% purity, diameter 20–40 nm, length 1–2 μm) were purchased from Shenzhen Nanotech port Co. Ltd. (Shenzhen, China) and purified by refluxing and as-received MWNTs in sulfuric acid and nitric acid (the volume ratio is 3:1) mixture solution for 8 h before use. Room-temperature ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate, $[BMIm]PF_6$, IL, 99% purity) was purchased from Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences (Lanzhou, China), glutathione (GSH, 98% purity) was purchased from Shanghai source leaves biological technology Co. Ltd. (Shanghai, China). 0.1 mol L^{-1} phosphate (KH_2PO_4/K_2HPO_4) buffer solution (PBS, pH = 7.0, containing 0.1 mol L^{-1} KCl) was used as supporting electrolyte. Blood samples were obtained from a local hospital and prior to use, samples were centrifuged for 5 min at 5000 rpm in order to separate serum from plasma, and then, the obtained blood serum and plasma samples were diluted 10-fold and spiked with known amount of standard GSH solution. The anticoagulant was not added in blood samples. All other reagents were used as analytical grade. Aqueous solutions were prepared with doubly distilled water, and solutions were deoxygenated by bubbling with nitrogen for 10 min. All experiments were performed at room temperature (22 ± 2 °C).

2.2. Characterization

All electrochemical experiments were performed by using CHI 832 and CHI 660 electrochemical workstation (CH Instrument Company, Shanghai, China). A three-electrode system, including a working CoQ_{10}/MWNTs/IL composite film electrode (2.0 mm diameter), a saturated calomel reference electrode (SCE) and a platinum wire counter electrode, was employed. All potentials were measured and reported according to this reference electrode. Solution pH was measured with a Sartorius basic pH meter PB-10 (RenHe Instrument Co. Ltd., Shanghai, China). SEM images were taken using a field-emission scanning electron microscope (SEM, JEOL JSM-6701F) operated at an accelerating voltage of 5 kV.

2.3. Preparation and characterization of CoQ_{10}/MWNTs/IL gel

Ionic liquids (IL) are a new type of the non-aqueous media [43], which have perfect ion conductivity [44,45]. Multi-walled carbon nanotubes (MWNTs) have highly unique electronic, mechanical, and optical properties [46,47]. The acid-treated MWNTs were dispersed into Ionic liquids (IL) to form very stable and homogeneous black gel [48] with concentration of 1 mg mL^{-1} under the assistance of ultrasonication. Then, 100 μL of 6 mmol L^{-1} nitrobenzene solution of CoQ_{10} was mixed with 200 μL MWNTs/IL gel under 10 min sonication at room temperature to give a mixture of a black gel (CoQ_{10}/MWNTs/IL gel). The resulting CoQ_{10}/MWNTs/IL gel was placed on a glass slide, which was then dried in the vacuum to remove nitrobenzene.

2.4. Preparation of CoQ_{10}/MWNTs/IL gel modified electrode

Before experiment, glass carbon electrodes (GCE) were firstly polished with 0.3 and 0.05 μm α-Al_2O_3 powder on a polishing cloth, followed by sonication with acetone, ethanol and distilled water, respectively. The prepared mixture gel was confined onto clean glass carbon electrodes by rubbing the electrode on the gel placed on a smooth glass slide [48]. Then, MWNTs/CoQ_{10}/IL nanocomposite film was immobilized on the electrode surfaces. Finally, the CoQ_{10}/MWNTs/IL gel modified electrodes were immersed into a certain concentration of GSH solution to explore electrochemical characteristics.

3. Results and discussion

3.1. Characteristics of the MWNTs/CoQ_{10}/IL nanocomposite film

The synthesis of the multifunctional nanocomposite film is started from the multi-walled carbon nanotubes (MWNTs) and coenzyme Q_{10} (CoQ_{10}) in ionic liquid (IL). The morphologies of MWNTs/IL, MWNTs/CoQ_{10}/IL and CoQ_{10}/IL film were investigated by SEM, as shown in Fig. 1A–C. The spaghetti-like tangled MWNT nanotubes can be clearly distinguished from Fig. 1A. After adding CoQ_{10} into MWNTs/IL, well-shaped MWNT nanotubes can still be seen, but it is noteworthy that apparent aggregation or crystallization of CoQ_{10} is not observed as shown in Fig. 1B, implying homogeneous dispersion of CoQ_{10} in the gel prepared. From Fig. 1C, in the absence of MWNTs, the obvious wrinkles are the cause of the IL high viscosity. The procedure of MWNTs/CoQ_{10}/IL nanocomposite film gel was repeated to obtain a dense triple-component (MWNTs, CoQ_{10}, IL) film, as shown in Scheme 1.

3.2. Electrochemical behaviour of MWNTs/CoQ_{10}/IL nanocomposite film

Fig. 2 showed the electrochemical behaviors of different samples (MWNTs/CoQ_{10}/IL, CoQ_{10}/IL, MWNTs/IL and IL) studied by cyclic voltammetric in 0.1 mol L^{-1} PBS with potential ranging from −0.4 to −0.8 V. It was found that the reduction peak of CoQ_{10} occurred at about 0.681 V on the positive scan, while on the reversed scan, no peak was observed (solid curve *a* and *b*). Compared with solid curve *b*, in the presence of MWNTs, the peak potential of CoQ_{10} did not change but the peak current (solid curve *a*) increased significantly, with difference of peak current ($i_{pa}-i_{pb}$) up to 17.69 μA. Compared with solid curve *a* and *b*, the reduction peaks of solid curve *c* and *d* were not found in the absence of CoQ_{10}. It is known that carbon nanotubes are composed of cylindrical graphite sheets having superhydrophobicity and very large van der Waals index, leading to remarkably strong hydrophobic effect in adsorption of hydrophobic organic chemicals [49]. Thus, it is possible that MWNTs may have very good adsorption to CoQ_{10} [50,51] by physical interaction. So the increased peak current may be caused by high electroconductivity and high surface area of MWNTs, leading to high amount loading of CoQ_{10}.

3.3. The effect of GSH on MWNTs/CoQ_{10}/IL nanocomposite film

The electrochemical response of GSH towards MWNTs/CoQ_{10}/IL modified electrodes was studied by CVs shown in Fig. 3. It can be seen from Fig. 3b that signal of CoQ_{10} was only observed in the absence of GSH. However, along with the addition of quantitative GSH, the reduction peak current of CoQ_{10} increased gradually (Fig. 3a), and the maximum difference of peak current ($i_{pa}-i_{pb}$) was 29.55 μA. Because CoQ_{10} is a kind of electron-defect compound, it

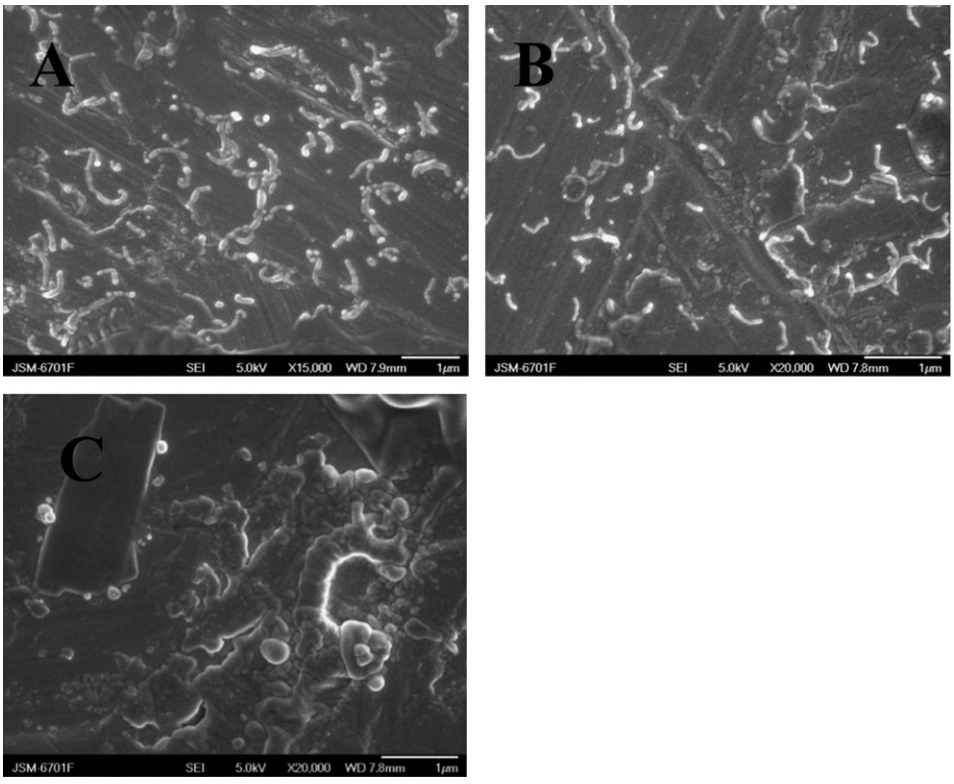
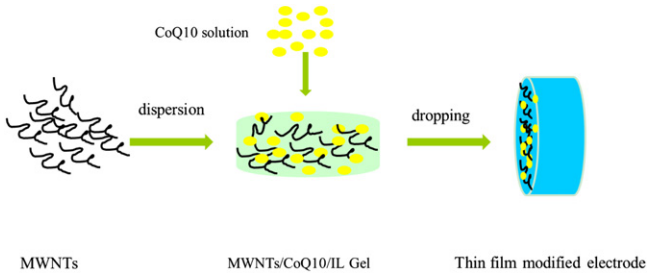


Fig. 1. Structural characterization through SEM images of nanocomposite film (the concentrations of MWNTs were 1 mg mL^{-1} in IL). (A) MWNTs/IL; (B) MWNTs/CoQ_{10}/IL; (C) CoQ_{10}/IL.



Scheme 1. The scheme is the procedures of a biosensor based on CoQ_{10} serves as a transducer for the determination of glutathione.

is used as electrophilic reagent. It is claimed that GSH is an effective electron donor reagent, hence the enhancement of peak current possibly results from the nucleophilic reaction of GSH. A possible reaction mechanism between CoQ_{10} and GSH is proposed as follows [52–54]:

$$GSH \leftrightarrow GS^- + H^+ \quad (1)$$

$$GS^- \rightarrow GS^\bullet + e^- \quad (2)$$

$$2GS^\bullet \rightarrow GSSG \quad (3)$$

$$2GSH \rightarrow GSSG + 2e^- + 2H^+ \quad (4)$$

$$CoQ_{10} + 2e^- + 2H^+ \rightarrow CoQ_{10}H_2 \quad (5)$$

3.4. The effect of pH of GSH solution

It has been reported that changes in pH may occur during the physiological experiments [55], so it is of great importance to evaluate the effect of pH on detection of GSH using MWNTs/CoQ_{10}/IL

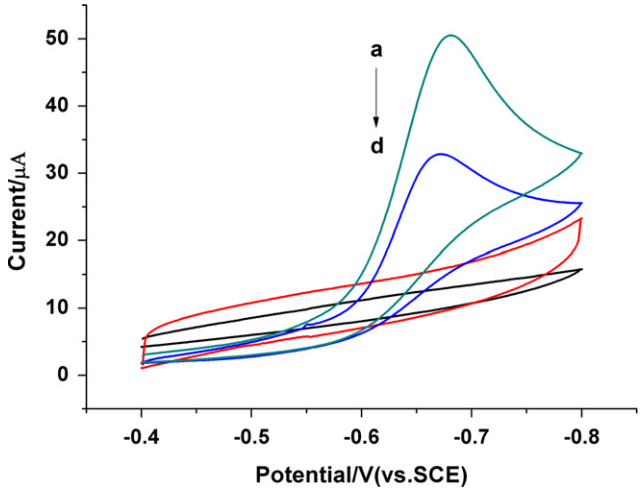


Fig. 2. The different kinds of modified electrode in 0.1 mol L^{-1} PBS by CV. (a) MWNTs/CoQ_{10}/IL; (b) CoQ_{10}/IL; (c) MWNTs/IL; (d) IL. Scan rate: 20 mV s^{-1}.

nanocomposite film. As shown in Fig. S-1 of the Supporting Information, significant changes of reduction peaks of CoQ_{10} were observed by differential pulse voltammetrys (DPVs) in 0.1 mol L^{-1} PBS containing 1×10^{-7} mol L^{-1} GSH, as pH values ranged from 4.0 to 9.0. It was found that the anodic peak potential shifted to a more negative potential with the increase of pH. This may be ascribed to the influence of the protonation of trans [56,57]. Interestingly, we found that the reduction peaks current of CoQ_{10} increased the pH range from 4.0 to 7.0, but peak current decreased subsequently when pH was higher than 7.0. This dramatic change may be due to the reduction of H^+ in the acidic condition,

associated with the pKa of different functional group of GSH, which is found to be 2.1 (COOH on glutamyl), 3.5 (COOH on glycine), 9.6 (SH) and 8.7 (NH_2), respectively [18]. Therefore, pH of 7.0 was chosen for the experiment.

3.5. The effect of scan rate

The effect of the scan rate on the cyclic voltammetric response for GSH is shown in Fig. 4. The scan was initiated from a less negative potential (E_i=−400 mV) to a lower potential (E_f=−800 mV) direction and then reversed. It was observed that the behavior of MWNTs/CoQ_{10}/IL nanocomposite film modified electrode in 0.1 M PBS (containing 1×10^{-7} mol L^{-1} GSH) at different scan rates was ranging from 10 to 200 mV s^{-1}. The reduction peak currents increased and potential shifted gradually to negative direction with increasing of scan rate. The square root scan rate ($\nu^{1/2}$) Vs. reduction peak currents are inserted (Fig. 4). It can be seen that the reduction peak currents increased linearly with square root of the scan rate. The linear regression equation was $i_{pa}=22.42+25.18\nu^{1/2}$ (R=0.9957), indicating that the reduction of CoQ_{10} was diffusion-controlled process.

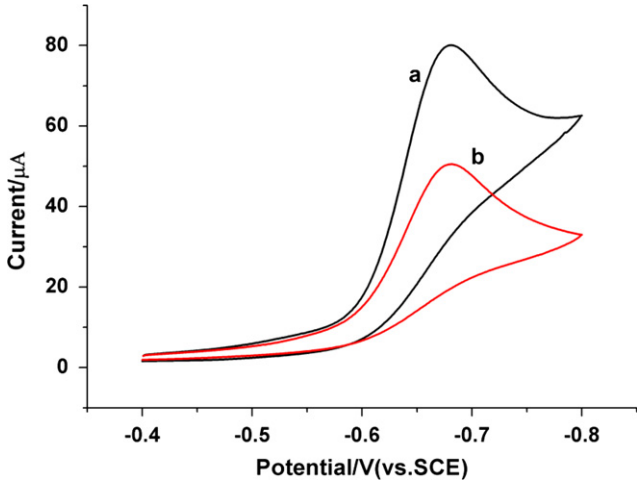


Fig. 3. (a) CVs at MWNTs/CoQ_{10}/IL modified electrode in 0.1 mol L^{-1} PBS containing 1×10^{-6} mol L^{-1} GSH. (b) CVs at MWNTs/CoQ_{10}/IL modified electrode in 0.1 mol L^{-1} PBS. Scan rate: 20 mV s^{-1}.

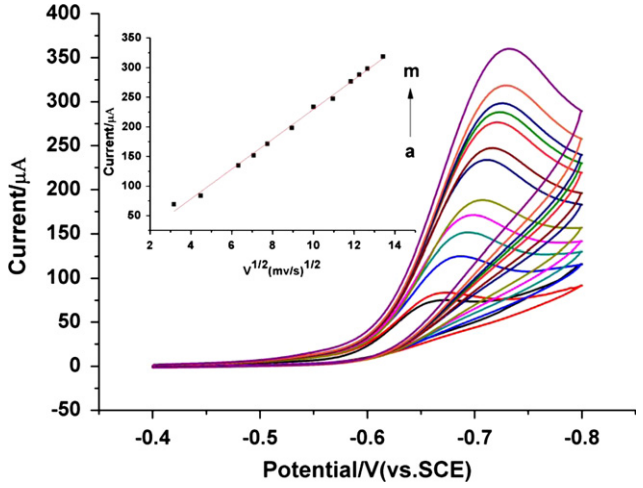


Fig. 4. CVs of MWNTs/CoQ_{10}/IL modified electrode at different scan rate: 10, 20, 40, 50, 60, 80, 100, 120, 140, 150, 160, 180 and 200 mV s^{-1}, and respectively, in 0.1 mol L^{-1} PBS containing 1×10^{-7} mol L^{-1} GSH. The inset shows the linear increasing of the reduction peak current depends on increasing the square root of the scan rate.

From Fig. 4, we also can see that the peak currents of CoQ_{10} increased rapidly, suggesting the biosensor is so sensitive that the reaction between CoQ_{10} and GSH can be completed at a certain scan rates.

3.6. The electrochemical behavior of GSH in different concentration

The electrochemical behavior of MWNTs/CoQ_{10}/IL nanocomposite film toward GSH studied by CV is shown in Fig. 5. It depicted the current response through various concentrations of GSH in the range from 4.0×10^{-9} to 2.0×10^{-7} mol L^{-1}. The increase of peak current was observed when increasing of GSH concentrations. The linear regression equation was $i_{pa}=1.6183\times10^{-4}+118.04C_{(GSH)}$, and the correlation coefficient was 0.9908 (inset Fig. 5). The limit of detection was 3.2×10^{-10} mol L^{-1} (S/N=3), an acceptable linear range from 4.0×10^{-9} to 2.0×10^{-7} mol L^{-1}. Therefore, the wide linear range and low detection limit make the MWNTs/CoQ_{10}/IL nanocomposite film appeared to be an efficient biosensor for GSH.

3.7. The determination of GSH in the presence of interfering species

To evaluate the anti-interference ability of the MWNTs/CoQ_{10}/IL-based biosensor, some possible interfering species, such as oxalic acid, uric acid, epinephrine and their mixture were also investigated at the identical experimental conditions. Differential pulse voltammetrys (DPVs) were taken in 0.1 mol L^{-1} PBS containing 1×10^{-5} mol L^{-1} of GSH and 100 μmol L^{-1} of each interfering species in Fig. S-2 of the Supporting Information. It was shown that the current-change values of MWNTs/CoQ_{10}/IL composite film modified electrode were basically unchanged in the presence of each interfering species, which was not affected by the biosensor performance in the evaluated GSH determination. As shown in Fig. S-3 of the Supporting Information, the current-change values ranged from 0.124% to 6.926% in comparison with its initial values, indicating that these substances did not produce significantly influence in the determination GSH. Hence, the interference from oxalic acid, uric acid and epinephrine is negligible, implying high anti-interference ability of the MWNTs/CoQ_{10}/IL composite for detection of GSH.

3.8. Practical application in human plasma and serum

It is to further demonstrate the applicability of this proposed method for GSH determination by analyzing several real blood samples. The reduced GSH is the main nonprotein thiol in cell

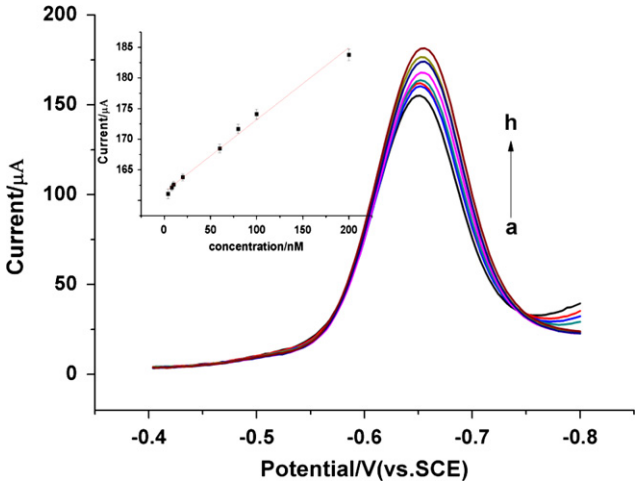


Fig. 5. DPVs at MWNTs/CoQ_{10}/IL modified electrode in 0.1 mol L^{-1} PBS containing different concentration GSH is: 4×10^{-9}, 8×10^{-9}, 10×10^{-9}, 20×10^{-9}, 60×10^{-9}, 80×10^{-9}, 100×10^{-9} and 200×10^{-9} mol L^{-1}. The inset shows the plot of peak currents vs concentration change. Scan rate: 50 mV s^{-1}.

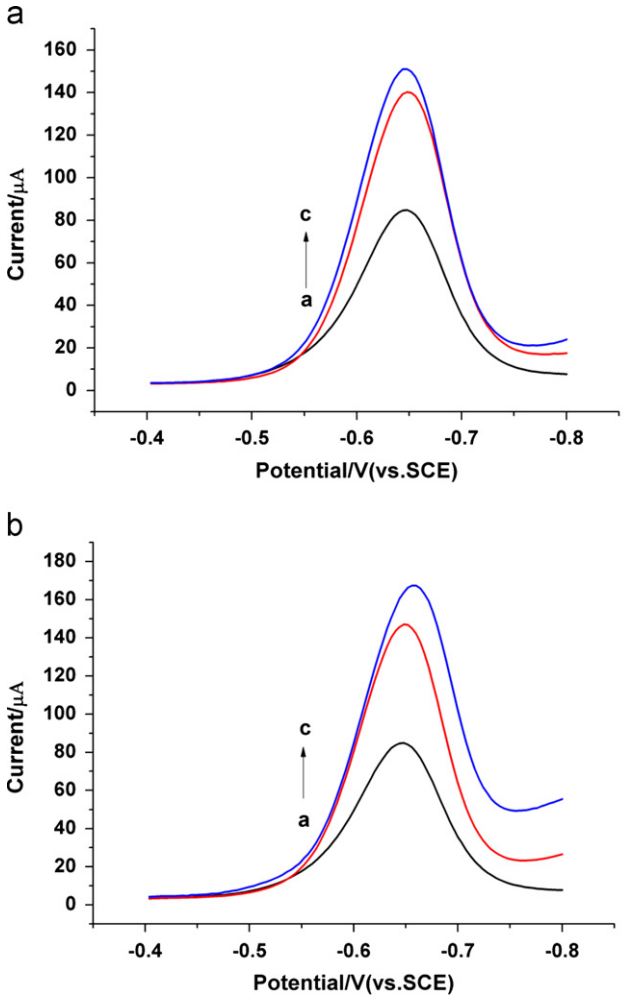


Fig. 6. (a) DPVs at MWNTs/CoQ_{10}/IL modified electrode in 0.1 mol L^{-1} PBS. (a) 0.1 mol L^{-1} PBS, (b) 0.1 mol L^{-1} PBS containing 10% blood serum, (c) 0.1 mol L^{-1} PBS containing 10% blood serum and 3.0×10^{-8} mol L^{-1} GSH. Scan rate: 50 mV s^{-1}. (b) DPVs at MWNTs/CoQ_{10}/IL modified electrode in 0.1 mol L^{-1} PBS. (a) 0.1 mol L^{-1} PBS, (b) 0.1 mol L^{-1} PBS containing 10% blood plasma, (c) 0.1 mol L^{-1} PBS containing 10% blood plasma and 3.0×10^{-8} mol L^{-1} GSH. Scan rate: 50 mV s^{-1}.

Table 1
Analysis of GSH in biological samples using the proposed method ($n=5$).

Analyte	GSH				
	Background (mol L^{-1})	Added (mol L^{-1})	Found (mol L^{-1})	Recovery (%)	R.S.D. (%)
10% Human plasma	1.26×10^{-7}	3.0×10^{-8}	1.56×10^{-7}	95.8	3.98
10% Human serum	1.78×10^{-7}	3.0×10^{-8}	2.08×10^{-7}	94.9	5.06

involved in the antioxidant cellular defence with celluar concentration ranging from 0.5 to 10 mmol L^{-1} [58], and the concentrations of GSH are typically at least 1–2 μM in human blood [38]. Therefore, we chose the human serum and plasma as real samples to evaluate the performance of the biosensor through determination of GSH. After spiking 3.0×10^{-8} mol L^{-1} standard GSH solution in 10-fold diluted samples, the DPV signals of the samples were monitored and results were shown in Fig. 6a and b, respectively. As illustrated in Table 1, the detection of GSH in human plasma and serum was assessed with the standard addition method. Good relative standard deviations (R.S.D) of 3.98–5.06% were obtained, and the recoveries of these samples ranged from 95.8% to 94.9%, implying the high accuracy of biosensor for application in detecting blood samples.

3.9. Stability and reproducibility of the MWNTs/CoQ_{10}/IL composite film

The reproducibility of the biosensor was estimated by determining the peak current response in 0.1 mol L^{-1} of PBS containing 1×10^{-5} mol L^{-1} of GSH at room temperature. Three identical electrodes prepared independently in different days were evaluated under the same experimental condition. The result revealed the satisfied reproducibility of the biosensor, with a relative standard deviation (R.S.D.) of 2.44% ($n=5$). The stability of the biosensor was also determined (Fig. S-4 of the Supporting Information), after the biosensor was stored at 4 °C for 10 days, no apparent decrease of peak current of CoQ_{10} was observed. Even after 30 days, the response still maintained up to 95.1%, compared with its initial values.

The results of detecting GSH with different methods and materials reported previously by literature were shown in Table 2. It showed that the biosensor designed in this paper had comparable linear range to reported values and superior performance of lower detection limit.

4. Conclusions

In this work, we successfully constructed a glutathione (GSH) biosensor, and coenzyme Q_{10} (CoQ_{10}) was served as a transducer based on using MWNTs/CoQ_{10}/IL nanocomposite materials firstly. The results indicated that the constructed biosensor had simple, rapid response, good repeatability and lower detection limit. Moreover, it demonstrated outstanding anti-interference in the presence of epinephrine, oxalic acid and uric acid, providing supplied potential application of the biosensor in real blood samples. The method we explored here provides a new pathway to design a novel transducer for detecting GSH, which is expected to be applied to detecting GSH in clinical diagnosis.

Acknowledgements

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Table 2
Comparing performance of literature reported and our sample for the detection of GSH.

Electrode	Detection limit of GSH (mol L^{-1})	Line range of GSH (mol L^{-1})	Reference
Prussian blue modified screen printed electrode	2×10^{-6}	2×10^{-6}–5×10^{-4}	[59]
AgNPs/C-MWCNT/PANI/Au	3×10^{-7}	3×10^{-7}–3.5×10^{-3}	[60]
GSH-Px/EDAC/PG		1.9×10^{-5}–1.4×10^{-4}	[61]
CNFs-PDDA/PB/ITO		6×10^{-6}–1.74×10^{-5}	[62]
MWNTs/CoQ10/IL	3.2×10^{-10}	4.0×10^{-9}–2.0×10^{-7}	This paper

Science and Technology Support Projects of Gansu Province (No.1011GKCA025, 090GKCA036), China. The author also would like to gratefully acknowledge all the Prof. Lu's group members for the assistance of this work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.talanta.2013.03.038.

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