Electrocatalytic Oxidation and Sensitive Determination of N-Acetyl-L-Cysteine at Cyclodextrin-Carbon Nanotubes Modified Glassy Carbon Electrode

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The electrochemical behavior and electroanalysis of N-acetyl-L-cysteine (NAC) were studied at a glassy carbon electrode modified with β-cyclodextrin (β-CD) and carbon nanotubes (β-CD/MWCNT/GCE). The β-CD/MWCNT/GCE displayed excellent electrocatalytic performance to the catalytic oxidation reactions of NAC. Because NAC is selectively enriched by β-CD, the β-CD/MWCNT/GCE can solve the problems of the signal attenuation caused by the adsorption of the NAC oxidation product. The influence of the experimental conditions on the NAC electrochemical behavior was also considered, when using a modified electrode. The mechanism and kinetics of the catalytic oxidation reactions of NAC were monitored by the cyclic voltammetry and chronoamperometry. The catalytic oxidation rate constant k $(4.21\pm0.05)\times10^3$ $M^{-1}S^{-1}$ was calculated using electrochemical approaches. The results showed that in 1.0×10^{-3} M of potassium ferricyanide solution, the current signals were proportional to the NAC concentration from 4.4×10^{-4} M to 8.0×10^{-2} M $[I_p(10^{-6}A) = 0.58412 + 5.38\times10^3\ c(M),\ R^2 = 0.9934]$, and the detection limit ($S/N = 3$) was 5.02×10^{-5} M. For 80 mM NAC, six successive measurements yielded R.S.D. of 3.4%, which shows that the sensor is reproducible. The proposed method can be applied for the determination of NAC in routine analysis.

Keywords: chemical modified electrode, carbon nanotubes, cyclodextrin, N-Acetyl-L-cysteine, electrochemical determination.

УДК 543.08

INTRODUCTION

As a glutathione precursor, N-Acety1-L-Cysteine (NAC) is an important mercapto supplying agent, which plays crucial roles in the anti-apoptotic drugs, being an antitoxic, anti-oxidating agent that eliminats free radicals and prevents radiation damage effects. Traditionally, NAC is used in the treatment of respiratory tract diseases, but recently it has been also found superior to the treatment of cancer, AIDS and some other grave diseases [1]. The determination of NAC has received considerable attention due to its pharmaceutical and clinical importance in such areas as the protein characterization, analysis of commercial tablets, and injection samples. Commonly used methods for the determination of NAC include high performance liquid chromatography [2], iodometric titration [3], chemiluminescence [4], and electrochemical method. However, many of them are insufficiently sensitive, time consuming and employed in expensive instrumentations. Compared to other options, an electro-analysis has the advantages of being highly sensitive and easy to use. Therefore, it is timely to explore and develop a simple and reliable electrochemical method for the determination of NAC.

Currently, the electrocatalytic oxidation of NAC has attracted much interest of researchers because of its high overpotential on solid electrodes, such as glassy carbon electrodes (GCEs) and metal electrodes [5, 6]. Nowadays various modified electrodes are used in the electrochemical studies on NAC oxidation including a copper ferrocyanide modified electrode [7], Fe_2O_3-CoHCF modified electrode [8], and a pyrroloquinoline quinone modified electrode [9]. Moreover, the electrolyte $K_3Fe(CN)_6$ is found to act as electron transfer medium in the electrocatalytic oxidation at a carbon paste electrode [10–12]. In our previous paper, we reported a near-infrared luminescence quenching method for the detection of phenolic compounds using the NAC-protected gold nanoparticles-tyrosinase hybrid material [13].

Recently, cyclodextrin and its derivatives have been widely used in the design and synthesis of the molecule selective chemical sensors. In addition, electrochemical sensors based on cyclodextrins and their inclusion complexes have been applied in the electrochemical synthesis, batteries and anti-corrosion chemistry. For instance, El-Hady [14] designed a hydroxypropyl-β-cyclodextrin modified carbon paste sensor applied successfully to the determination of catechins. Lee et al. [15] coated the

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surface of the sensing element with a layer of α-cyclodextrin for the tyrosine detection.

It is well known that multiwalled carbon nanotubes (MWCNT) have excellent performance in promoting the electron transfer when they are used as electrodes in electrochemical reactions. However, if the carbon nanotubes are assembled with cyclodextrins, the result should be a new material simultaneously possessing unique properties of carbon nanotubes and cyclodextrins, which will provide excellent opportunities for applications as sensors [16]. It is know from literature that a β-cyclodextrin incorporated carbon nanotube modified electrode has been proposed for the determination of norepinephrine [17], of adenine, guanine, and thymine [18], of rutin [19], as well as for identification of cancer cells [20]. Karimi et al. [21–24] developed several sensors for voltammetric determination of NAC using a modified MWCNT electrode. In our previous studies, MWCNTs/Nafion modified GCE and its interaction with cyclodextrins were proved to be good for the electrochemical behavior of several dyes [25, 26]. Still, to the best of our knowledge, the electrocatalytic oxidation and electroanalytical methods of NAC at cyclodextrin-carbon nanotube modified GCEs in the potassium ferricyanide electrolyte still have not been reported so far.

In the present paper, a GCE was modified with MWCNT and a β-cyclodextrin (β-CD) composite. The modified electrode was used as the working electrode for the electro-catalytic oxidation of NAC. In addition, a novel, simple and sensitive electrochemical method with $K_3Fe(CN)_6$ as the catalyst for the determination of NAC is described and specified. This method overcomes the contamination of the electrode interface from the oxidation product of NAC and makes it possible to achieve high sensitivity and selectivity.

EXPERIMENTAL

Instruments and Reagents

All chemicals were purchased and used as received without any purification; aqueous solutions were prepared with doubly distilled water. MWCNTs (purity ≥90%) β-CD were obtained from Chinese enterprises**.** All electrochemical experiments were performed on a CHI660D electrochemical workstation (Chinese make) with a conventional three-electrode cell. A bare or modified GCE was used as working electrode. An Ag/AgCl electrode and a platinum wire were used as reference electrode and auxiliary electrode, respectively. A pH-meter (Corning, Model 140) with a double junction glass electrode was used to check the pH of the solutions.

Preparation of Electrode

A GCE was polished, in turn, with 1.0, 0.3 and 0.05 μm alumina powders on micro-cloth and then thoroughly cleaned ultrasonically with ethanol and double distilled water. MWCNT (1mg) was dispersed in 0.5 mL aqueous solution of β-CD (0.1M) with the aid of ultrasonication to give a stable black MWCNT suspension. Then 3 μL of the mixture were cast onto the surface of the GCE and then dried with an infrared lamp. Afterwards, a drop of 0.05% alcohol diluted nafion solution was spread onto the MWCNT/β-CD coated electrode to improve the permeability and stability of the film. Besides, the β-CD/GCE and MWCNT/GCE were prepared in the same way to be used for comparison purposes.

RESULTS AND DISCUSSION

Electrocatalytic oxidation of NAC with $K_3Fe(CN)_6$

In a potential range from -0.20 to 0.70V, the representative cyclic voltammograms of GCE with and without NAC or/and $K_3Fe(CN)_6$ were obtained in PBS containing 0.20M Na_2SO_4 aqueous solution. Curve *a* in Fig. 1 is the CV of the base solution, whereas at the cyclic voltammogram of the supporting electrolyte at the β-CD/MWCNT/GCE neither anodic nor cathode peaks appeared. Curve *b* in Fig. 1 shows that when NAC was added into the base solution, the oxidation peak current increased gradually with the scan progresses, and an ill-defined oxidation peak was displayed. This anodic current probably resulted from a weak interaction of carbon and sulfur atoms. Curve *c* in Fig. 1 is the cyclic voltammeter graph of 1.0×10^{-3} M $K_3Fe(CN)_6$ in the buffer solution system.

Curve *d* in Fig. 1 shows that when $K_3Fe(CN)_6$ was added to the buffer solution system containing NAC, an obvious irreversible catalytic oxidation peak appeared at about 0.2V and the oxidation peak current significantly increased with the scan progresses, indicating good electrocatalytic properties of $K_3Fe(CN)_6$ to the oxidation of NAC, when working with Na_2SO_4 as electrolyte at β-CD/MWCNT/GCE. In addition, the almost disappeared cathode peak current also indicates a strong catalytic effect.

The differential pulse voltammetry (DPV) was used to study the electrochemical behavior of NAC at the β-CD/MWCNT/GCE. As shown in Fig. 2, when the concentration of NAC increased, the oxidation peak current was found to gradually increase, suggesting a good electrochemical response of the modified electrode to NAC. However, the oxidation potential was found to shift negatively, which may be due to the accumulation of an oxidized product of NAC on the electrode surface.

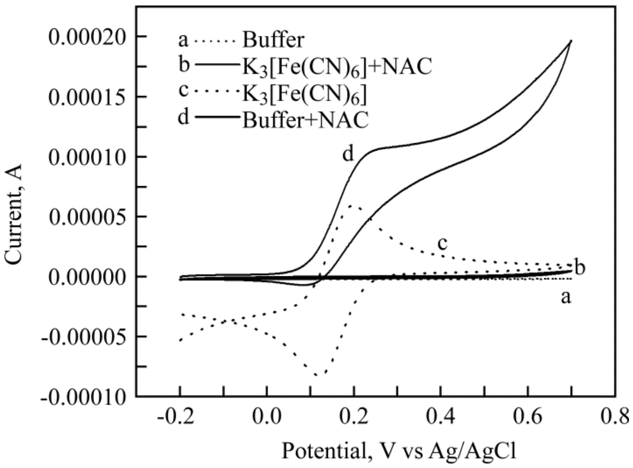

Fig. 1. CVs of (a) PBS; (b) PBS+8×10^{-2} NAC; (c) PBS+1.0×10^{-3} M $K_3Fe(CN)_6$; (d) PBS+8×10^{-2} NAC+1.0×10^{-3} M $K_3Fe(CN)_6$ at β-CD/MWCNT/GCE. Scan rate: 50 mV/s.

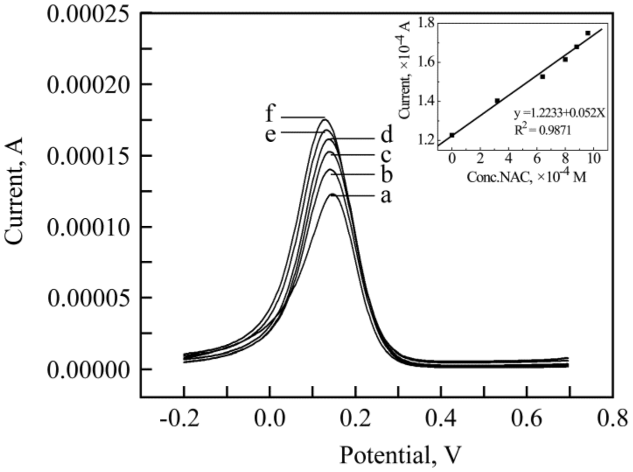

Fig. 2. DPVs of β-CD/MWCNT/GCE in buffer, for different concentration of NAC($\times10^{-4}$ M) (a) 0; (b) 3.2; (c) 6.4; (d) 8.0; (e) 8.8; (f) 9.6. Scan rate: 100 mV/s. Inset: Plot of electrocatalytic peak currents vs. NAC concentration.

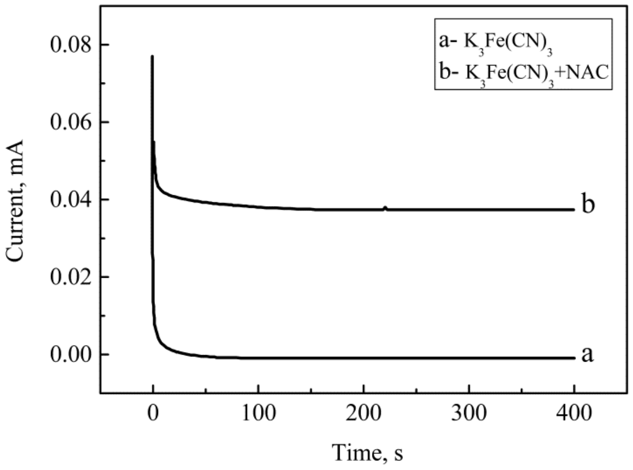

Fig. 3. Chronoamperograms of 1×10^{-3} M $K_3Fe(CN)_6$ in the absence (b) and presence (a) of 8×10^{-2} M NAC.

Catalytic Oxidation Rate Constant k

Chronoamperometry was used to study the mass transfer kinetics and to obtain heterogeneous catalytic rate constant. Under the selected experimental conditions, the potential of β-CD/MWCNT/GCE as sensors for the NAC measurement was evaluated by chronoamperometry, and the developed sensor was applied to an aqueous solution of $K_3Fe(CN)_6$ with or without NAC. The current–time curves of β-CD/MWCNT/GCE in the absence and presence of NAC are shown in Fig. 3, indicating a more significant electrocatalytic effect of $K_3Fe(CN)_6$ on the NAC oxidation at this electrode.

Because $K_3Fe(CN)_6$ can act as homogeneous mediator for the electro-oxidation of NAC, it should follow a chronoamperometric equation as below:

$$I_C/I_L = \lambda^{1/2}[\pi^{1/2}\mathrm{erf}\,(\lambda^{1/2}) + \exp\,(-\lambda)/\lambda^{1/2}] \qquad (1)$$

where I_C is the catalytic current in the presence of NAC, I_L is the diffusion-limited current in the absence of NAC, and $\lambda = kc^0t$ (k is the catalytic rate constant, c^0 – the bulk initial concentration of NAC) is the argument of the error function. When λ exceeds 1.5, the error function is almost equal to, the reaction zone is in the pure kinetic region, and the above equation can be reduced to

$$I_C/I_L = \pi^{1/2}\lambda^{1/2} = \pi^{1/2}\,(kc^0t)^{1/2}. \qquad (2)$$

The plot of λ vs. t can be given by combining Eq. (2) with the experimental data, and then one can simply calculate the value of the catalytic rate constant k from the slope ($c^0 = 8\times10^{-2}$ M). The advantage of this method is that it is not necessary to know the diffusion coefficient or the electrode area. In this study, I_C and I_L were measured at $t > 55$ ms, where $I_C/I_L > 1.5$, and the catalytic oxidation rate constant k $(4.21\pm0.05)\times10^3$ $M^{-1}S^{-1}$ was calculated. This value of the catalytic rate constant is near the value that was reported for the electrooxidation of NAC on a palladized aluminum electrode covered by the Prussian blue film [5]. The value of k explains well the sharp shape of the peak observed for the electrochemical oxidation of NAC in the presence of $K_3Fe(CN)_6$ on the surface of a GCE.

The pH of a solution can have more pronounced effects on the catalytic activity of $K_3Fe(CN)_6$. Therefore, the electrochemical behavior of $K_3Fe(CN)_6$ at the β-CD/MWCNT/GCE was investigated in the pH range from 1 to 10. The results show that the peak current decreases with the increase of the pH of the aqueous solution. It is an indicator of the participation of protons in the electrode reaction of $K_3Fe(CN)_6$ under these reaction conditions. The findings of the current study are consistent with those of Jahan [11]. However, in order to eliminate the interference to NAC and improve the usefulness and feasibility of the proposed method, it is necessary to maintain the pH at normal physiological conditions (when pH is around 7). Therefore, the pH of 7.4 was chosen as optimum for the electrooxidation of NAC on the CD/MWCNT/GCE surface.

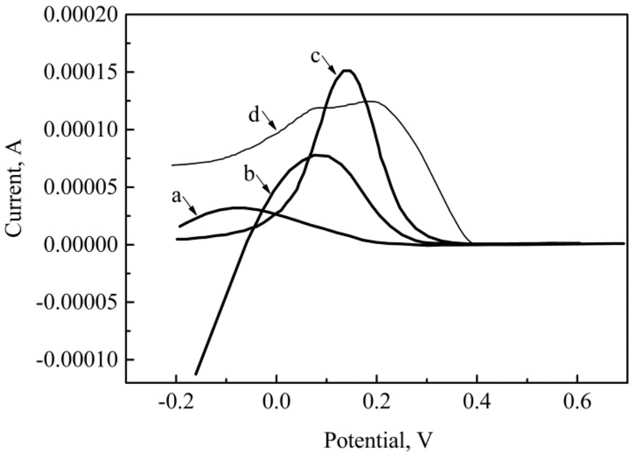

Fig. 4. DPVs of 3.2×10^{-4} M of NAC at bare GCE (a); β-CD/GCE (b); β-CD/MWCNT/GCE (c); MWCNT/GCE (d).

Comparison of the Coating on Modified Electrode

In a phosphate buffer solution with the pH of 7.4, differential pulse scans were registered from -0.2V to 0.7V for bare GCE, β-CD/GCE, MWCNT/GCE, and β-CD/MWCNT/GCE, respectively, and the results are shown in Fig. 4. Curve *a* in Fig. 4 shows the DPV of NAC at bare GCE, which exhibits the lowest oxidation current; for β-CD/GCE, a larger oxidation current and a slightly better peak shape are observed (curve *b* in Fig. 4). Curve *d* in Fig. 4 shows that an electrochemical response of MWCNT/GCE is really strong, but the peak shape is not well-defined and the signal decreases gradually in a continuous scan. The reasons for this phenomenon may be that the MWCNT interface layer plays an obvious role in the catalytic oxidation of NAC, but NAC and its oxidation products were irreversibly adsorbed on the carbonaceous material, by which the active sites of the electrode surface were plugged [27]. Obviously, a clear and distinct anodic peak with a relatively good peak shape in the DPV is displayed for β-CD/MWCNT/GCE (curve *c* in Fig. 4). This performance is relative to the combination of carbon nanotubes, and β-CD definitely improves the characteristics of the NAC oxidation.

Fig. 4 used in conjunctions with Fig. 2, where the oxidation potential shifted negatively, illustrates that the β-CD/MWCNT/GCE showed an excellent electrocatalytic effect on the oxidation of NAC. A high electrocatalytic efficiency of the β-CD/MWCNT/GCE can be related to both the size and specific structure of the material. When β-CD is mixed with MWCNT in the case of ultrasonic agitation, they would be adsorbed and attached to the wall of MWCNT due to the steric hindrance and the binding force. Moreover, MWCNTs can be highly dispersed by β-CD, allowing a very uniform coating film to be formed on the electrode surface. The β-CD/MWCNT film has been evenly distributed on the surface of GCE. Therefore, MWCNTs are fully and easily accessible for NAC and, consequently, can be readily and completely used as electrochemical sensing units. The SEM and TEM images of the cyclodextrin-carbon nanotube composites show the structure of stereo-porous interspaces [20, 28, 29].

It is well known that MWCNTs have excellent catalytic effects owing to their high surface activity and electron conductivity. The roles of MWCNTs are: (i) to transfer electrons between the an electrode surface and NAC based on the intrinsic property of MWCNT; (ii) to increase the conductive area based on the high specific surface of MWCNT; (iii) to dope β-CD into the modified layer since β-CD cannot be easily modified at a bare GCE [28]. Furthermore, β-CD has a special cavity structure. When MWCNTs were modified on the surface of GCE, the rate of the electron transfer between NAC and electrode surfaces rose significantly and the electrocatalysis of NAC went up dramatically. In addition, there was a synergistic electrocatalysis between the β-CD and MWCNTs, which increases the oxidation current as a response of NAC. That is, the electron transfer rate between NAC and the electrode surface raises, and the electrocatalytic activity of NAC is improved by the β-CD-MWCNTs modified on the GCE surface.

Furthermore, curve *c* in Fig. 4 demonstrates that the signal intensity remains almost unchanged at continuous scanning. As is well known, the matching of the size and energy between β-CD and guest molecules is essential to the formation of an inclusion complex. The NAC molecule is well compatible with β-CD attributing it to a less steric hindrance and higher hydrophobicity of the mercapto group on the alkyl chain portion of the NAC molecule. That is to say, a NAC molecule penetrates deeply into the hydrophobic cavity of β-CD and a stable β-CD inclusion complex is formed. On the contrary, the molecular size of the oxidation product RS-SR is relatively large, and the hydrophilic groups -COOH and $-NH_2$ are at the both ends of the molecule. Namely, the RS-SR molecule is a poor match for the β-CD in size and energy, so the inclusion complex cannot be formed.

In brief, NAC is selectively enriched by the β-CD attached at the surface of a carbon nanotube, which plays an important role of selective filtration membranes. As a consequence, it can be affirmatively concluded that β-CD/MWCNT/GCE with excellent performance including high electrocatalytic activity is a promising anode for the determination of NAC. Moreover, it is of particular significance that the β-CD/MWCNT/GCE could be applied to solve the problems of the signal attenuation caused by the adsorption of the NAC oxidation product on electrodes, in most cases.

A calibration curve of NAC

In order to develop a more simple and sensitive sensing procedure for the analysis of NAC, amperometry technique was employed. As we know in chronoamperometry, a higher working potential tends to mean a larger anode current and a higher sensitivity. But at higher potentials, the interference from the oxidation of the coexisting substance is inevitable in real samples. Therefore, 0.214V was chosen as the potential of the working electrode for the determination of NAC. Fig. 5 shows the current response of β-CD/MWCNT/GCE to successive additions of 1×10^{-4} M NAC into a stirred PBS containing 0.20 M Na_2SO_4 and 1×10^{-3} M $K_3Fe(CN)_6$ in a chronoamperometric experiment. It was found that after the concentration of NAC changes, the current attains the dynamic equilibrium 3 min later. The electrode response was quite rapid and proportional to the NAC concentration (Fig. 5, Inset).

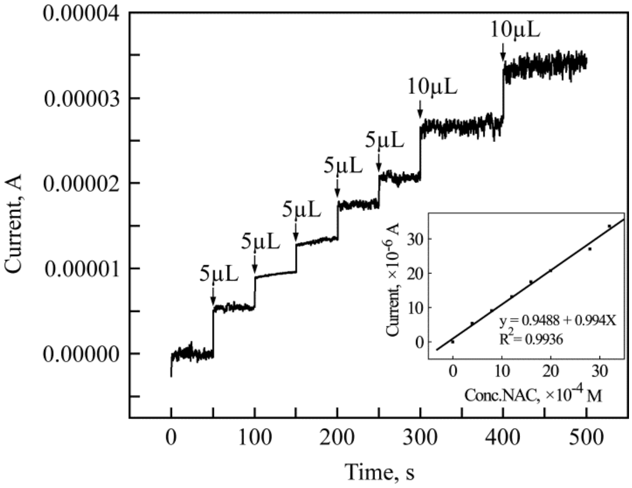

Fig. 5. Performance of β-CD/MWCNT/GCE in amperometric detection of NAC (1×10^{-4} M) at 0.214V vs. Ag/AgCl. Inset: calibration curve for NAC concentrations between 0.5 mM and 3 mM.

Under the above-described optimum conditions, the determination of NAC at varying concentrations was performed at β-CD/MWCNT/GCE. The results show that the anodic peak current is linear to the concentration of NAC from 4.4×10^{-4} M to 8.0×10^{-2} M. The linear regression equation is expressed as: $i_p = 0.58412 + 5.38\times10^3 c$, ($i_p$ (μA), c(M), $R^2 = 0.9934$), and the detection limit for NAC is 5.02×10^{-5} M. Table 1 depicts a comparison between the present results with other electrochemical studies for the NAC oxidation. It is evident that β-CD/MWCNT/GCE is stable, with a wide linear range and low detection limit.

Table 1. Comparison of the present results with other electrochemical studies for NAC oxidation

Electrode	Linearity Range (μM)	Detection Limit (μM)	Reference
Nanoparticles of iron (III) oxide core–cobalt hexacyanoferrate shell-modified carbon paste electrode	20–432	0.0209	[8]
Palladized aluminum electrode modified by Prussian blue film	2–40	0.54	[5]
Mercury Film Electrode	0.012–5.0	5000	[30]
GCE	200–4000	–	[31]
10-Methylphenothiazine Modified Carbon Paste Electrode	1.1–1300	0.8	[32]
Multi-wall carbon nanotubes modified GCE	100–10000	20	[33]
Carbon paste electrode	80–1000	60	[34]
Iron nitroprusside modified graphite paste electrode	60–14000	1050	[35]
β-CD/MWCNT/GCE	440–80000	50.2	This work

Recovery studies can show possible interferences from common excipients used in the pharmaceutical forms. To study the reproducibility and accuracy of the proposed analysis method, recovery experiments were carried out using the standard addition method. In order to find out whether the excipients show any interference with the analysis, the known amounts of pure NAC were added to the pre-analyzed pharmaceutical formulations and the mixtures were analyzed by the proposed method. The recoveries of NAC were calculated using the corresponding regression equations of the respective previously plotted calibration plots.

The accuracy of the method was checked by carrying out recovery studies. The modified β-CD/MWCNT/GCE electrode was applied to detect NAC in simulated samples of the PBS solution containing 0.20M Na_2SO_4 and 1×10^{-3} M $K_3Fe(CN)_6$. In this procedure, 10 mM of the NAC standard were added to pre-analyzed samples containing 10.0 mM of NAC before determination by the recommended method. When the relative error was ±5%, the recoveries were approximately 94.7%–104.7% for the method, as shown in Table 2.

Table 2. Determination of NAC in spiked samples ($n = 3$).

Samples	c (NAC)/mM			RSD (%)	Recovery (%)
	Initial	Added	Found		
1	10.0	10	20.94	4.2	104.7
2	10.0	15	25.77	3.9	103.1
3	10.0	20	28.41	4.6	94.7

To evaluate the selectivity of the proposed electrochemical method, the interference effects of common ions, excipients in pharmaceutical preparations and common substances present in biological fluids were checked under the optimized conditions in a standard solution of 1.0×10^{-5} M NAC. The tolerance of each foreign species was taken as the largest concentration yielding less than ±5% of the error of the adoptive concentration of NAC. No interference could be found in the presence of 250-fold glucose, sucrose, starch, Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, SO_4^{2-}, PO_4^{3-}, NO_3^-, acetic acid, propanone and ethanol. These results prove a good accuracy of the proposed method and the absence of interferences from common excipients, indicating that the proposed method can be reliably used for a routine analysis. Ease of application, sensitivity, short analysis time, low cost and reliability are its main advantages.

CONCLUSIONS

A CD/MWCNT/GC electrode has been applied to effectively catalyze the oxidation of NAC in the presence of $K_3Fe(CN)_6$ for its sensitive determination. A simple, rapid and economical electrochemical method for the determination of NAC has been successfully developed and validated with satisfactory results. The novel electrochemical sensor has been manufactured using the CD/MWCNT/GCE and the $K_3Fe(CN)_6$ medium. The results of the cyclic voltammetry implied that the CD/MWCNT/GCE is characterized by a high catalytic activity and fine stability, superior to other electrodes. The proposed electrode is reliable, simple, and rapid to prepare; it is low cost, precise, and does not require an extensive preliminary sample treatment. In conclusion, the electrochemical sensor has the advantages of good reproducibility and stability, and it is expected to be used for clinical rapid analysis of the NAC detection.

ACKNOWLEDGMENTS

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Реферат

Электрохимическое поведение и электроанализ N-ацетил-L-цистеина (NAC) были изучены на стеклянном углеродном электроде, модифицированном с использованием β-циклодекстрина (β-CD) и углеродных нанотрубок (β-CD/MWCNT/GCE). β-CD/MWCNT/GCE показывает хорошую электрокаталитическую активность при реакции каталитического окисления NAC. Поскольку NAC селективно обогащен β-CD, β-CD/MWCNT/GCE может решить проблемы затухания сигнала, вызванные адсорбцией NAC. Было также рассмотрено влияние экспериментальных условий на электрохимическое поведение NAC при использовании модифицированных электродов. Механизм и кинетика реакций каталитического окисления NAC контролировались с помощью циклической вольтамперометрии и хроноамперометрии. Константа скорости каталитического окисления $k(4{,}21\pm0{,}05)\times10^3$ М$^{-1}$С$^{-1}$ была рассчитана с использованием электрохимических методов. Результаты показали, что в $1{,}0\times10^{-3}$ М растворе гексацианоферрата калия ток был пропорционален концентрации NAC от $4{,}4\times10^{-4}$ М до $8{,}0\times10^{-2}$ М [I_p (10^{-6} А) = 0,58412 + + $5{,}38\times10^3$ c(М), R^2 = 0,9934], и пределом обнаружения (S/N = 3) было $5{,}02\times10^{-5}$ М. Для 80 мМ NAC, шесть последовательных измерений показали относительное стандартное отклонение 3,4%, что говорит о том, что сенсор имеет хорошую точность измерения. Предложенный метод может применяться для определения NAC при каждом анализе.

Ключевые слова: химически модифицированный электрод, углеродные нанотрубки, циклодекстрин, N-ацетил-L-цистеина, электрохимическое определение.