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A graphene-based electrochemical sensor for sensitive detection of paracetamol

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ABSTRACT

An electrochemical sensor based on the electrocatalytic activity of functionalized graphene for sensitive detection of paracetamol is presented. The electrochemical behaviors of paracetamol on graphene-modified glassy carbon electrodes (GCEs) were investigated by cyclic voltammetry and square-wave voltammetry. The results showed that the graphene-modified electrode exhibited excellent electrocatalytic activity to paracetamol. A quasi-reversible redox process of paracetamol at the modified electrode was obtained, and the over-potential of paracetamol decreased significantly compared with that at the bare GCE. Such electrocatalytic behavior of graphene is attributed to its unique physical and chemical properties, e.g., subtle electronic characteristics, attractive π–π interaction, and strong adsorptive capability. This electrochemical sensor shows an excellent performance for detecting paracetamol with a detection limit of 3.2×10^{-8} M, a reproducibility of 5.2% relative standard deviation, and a satisfied recovery from 96.4% to 103.3%. The sensor shows great promise for simple, sensitive, and quantitative detection and screening of paracetamol.

1. Introduction

It is very important to develop simple, sensitive, and accurate methods for detecting active ingredients since drug monitoring plays an important role in drug quality control, and this has a great impact on public health. Paracetamol (acetaminophen, N-acetyl-p-aminophenol) is widely used as an antipyretic and analgesic drug. It is an effective and safe agent that is applied to reduce fever, relieve coughing, colds, and pain including muscular aches, chronic pain, migraine headache, backache, and toothache [1–3]. Generally, limited use of paracetamol does not exhibit any harmful side effects. However, overdosing and the chronic use of paracetamol produce toxic metabolite accumulation that will cause kidney and liver damage [4]. Thus, a simple, fast, sensitive, and accurate analytical method for determining paracetamol in pharmaceutical preparations and human plasma is needed. A variety of methods have been used for determining paracetamol in pharmaceutical tablets and biological fluids, e.g., spectrophotometry [5], titrimetry [6], liquid chromatography [7], chemiluminescence [8], and electrochemical techniques [1–4,9–16]. However, spectrophotometric, titrimetric, and chemiluminescence methods involve a tedious extraction process before detection, whereas liquid chromatography is time-consuming that makes them unsuitable for a routine analysis. Since paracetamol is electroactive, and most electroanalytical techniques are selective, highly sensitive, inexpensive, less time-consuming, of a wide dynamic range and quick response, electrochemical techniques can be considered for the determination of paracetamol as a strong alternative to the above mentioned methods. They are widely applied to detect paracetamol in pharmaceutical preparations. The nanomaterial-modified electrodes have been used for electrochemical studies of paracetamol because of their unusual characteristics, for example, carbon nanotube-modified basal-plane pyrolytic graphite electrodes [2], nanogold-modified indium tin oxide electrodes [3], a polyaniline-multi-walled carbon nanotube composite [4], single-wall carbon nanotube-dicetyl phosphate films [9], glassy carbon electrodes (GCEs) modified with carbon-coated nickel magnetic nanoparticles [10], C60-modified GCE [12], and poly(acid yellow 9)-nano-TiO_2 modified GCE [15]. These methods showed good sensitivity, selectivity, stability, and a low detection limit because of the unique electronic and catalytic properties of nanomaterials. To the best of our knowledge, there is no report based on using graphene-modified electrodes for the determination of paracetamol.

Graphene, the 2D honeycomb lattice of sp^2-bonded carbon atoms, has attracted tremendous attention from both the theoretical and experimental scientific communities in recent years because of its unique nanostructure and extraordinary properties [17,18]. It has become a novel and very promising material for nanoelectronics [19]. Graphene sheets have extraordinary electronic transport properties and high electrocatalytic activities [18,20,21], and they have been investigated as electrode materials in opto-

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electronic devices [22,23], electrochemical super-capacitors [24], fabricated field-effect transistors [25], and constructed ultrasensitive chemical sensors [26,27], such as pH sensors [28], gas sensors [29–31], and biosensors [32]. For instance, nafion–graphene nanocomposite film was used as enhanced sensing platform for ultrasensitive determination of cadmium [26]. Graphene–chitosan modified electrode was applied in selective determination of dopamine, and showed a better performance than multi-walled carbon nanotubes-modified electrode [27]. In general, graphene has a large surface area, excellent conductivity, and strong mechanical strength. Furthermore, the oxidized rings of functionalized and defective graphene sheets contain abundant C–O–C (epoxide) and C–OH groups, while the sheets are terminated with C–OH and –COOH groups [33,34]. Defects of graphene may change its electronic and chemical properties [19]. The functionalized and defective graphene sheets are more hydrophilic and can be easily dispersed in solvents with long-term stability [35]. Moreover, they are more easily produced in mass quantities as compared with the carbon nanotubes. They may be used to prepare some novel graphene-based nanocomposite films, which could facilitate the further manipulation and processing of these materials for developing novel electronic devices, such as chemical sensors and biosensors.

This paper describes a novel electrochemical sensor that was fabricated with graphene-modified glassy carbon electrodes (GCEs), and the electrochemical properties of the sensor were investigated. It can be used for ultrasensitive determination of paracetamol in pharmaceutical products with square-wave voltammetric (SWV) techniques. The results show that a graphene-modified electrode exhibits excellent performance for detecting paracetamol.

2. Experiments

2.1. Reagents and apparatus

Paracetamol, ascorbic acid (AA), dopamine (DA), $NH_3{\cdot}H_2O$, and NH_4Cl were purchased from Sigma. The stock solution of paracetamol (0.01 M) was prepared by dissolving paracetamol into ethanol and stored in a refrigerator at 4 °C. All other chemicals are of analytical grade. All the solutions were prepared using deionized or ultrapure water (18 MΩ cm).

The electrochemical experiments were performed with a CHI620c Electrochemical Analyzer (CHI, Austin TX) with a three-electrode system. A GCE (Ø = 3 mm) serves as the working electrode, a platinum wire as the auxiliary electrode, and an Ag/AgCl/3.0 M KCl as the reference electrode, respectively. Cyclic voltammetric (CV) experiments were carried out in a quiescent solution at 50 mV s^{-1} in an electrochemical cell filled with 5.0 mL of buffer solution. Paracetamol was determined with SWV with the following parameters: step potential, 10 mV; amplitude, 20 mV; frequency, 10 Hz. Before the experiment, graphene/GCE was transferred to a buffer solution for refreshing by CV until the peak of paracetamol disappeared completely. Scanning electron microscopic (SEM) experiments were carried out with the LEO-982 SEM (German). Transmission electron microscopic (TEM) experiments were performed with a JEOL-TEM-2010 microscope with a point-to-point resolution of 0.194 nm and an operating voltage of 200 keV.

2.2. Preparation of the graphene

The graphene was prepared according to the method reported in the literature [35,36]. Briefly, natural-flake graphite was reacted with concentrated sulfuric acid and nitric acid with potassium chlorate for 96 h. After the graphite was oxidized, the mixture was added to excess water, washed with a 5% solution of HCl, and repeatedly washed with water until the pH of the solution was 7.0 (neutral solution). Then through extremely rapid heating and successful splitting of graphite oxide, wrinkled graphene sheets functionalized with hydroxyl and carboxylic groups were obtained.

2.3. Preparation of the graphene-modified electrode

The bare GCE was polished with 0.05 μm gamma alumina powder before it was used, rinsed ultrasonically with 1:1 HNO_3, ethanol, and deionized water, respectively, and dried at room temperature. Graphene was dispersed in ethanol (1 mg/mL) with ultrasonication for 30 min. Five microliters of the graphene suspension was cast on the surface of GCE and dried in air. Prior to use, the modified electrode was carefully rinsed with water to remove the loosely attached graphene at the electrode, and dried in an air stream.

2.4. Sample preparation and measurement procedures

Under optimal conditions, a series of $NH_3{\cdot}H_2O$–NH_4Cl buffer solutions (0.1 M) containing different concentrations of paracetamol were analyzed using above prepared electrodes and calibration curve, therefore, was obtained.

Five tablets (equivalent to 500 mg of APAP in each tablet) of paracetamol pharmaceutical formulation were accurately weighed and finely powdered in a mortar. An adequate amount of the powders was weighed and transferred to a 100 mL calibrated flask and dissolved with ethanol. The standard addition method was used for analyzing the pharmaceutical samples and paracetamol-spiked human plasma samples for the validation of the sensor.

3. Results and discussion

3.1. Characterization of graphene dispersed in ethanol

Graphene dispersed in ethanol was characterized with TEM. Fig. 1A shows the image of the wrinkled graphene sheet with no aggregation, indicating that the functionalized graphene sheets were well dispersed in ethanol solvent, and the suspensions were stable at room temperature for about 3 weeks. The inset of Fig. 1A is the selected-area electron diffraction (SAED) of nanocomposite material yielding a double six-spot-ring pattern, which confirms the benzene-ring pattern of the graphene sheet [18]. Fig. 1B shows the SEM image of graphene film on the surface of the GCE, revealing the typical crumpled and wrinkled graphene sheet structure on the rough surface of the film.

3.2. Electrochemical behaviors of paracetamol on graphene/GCE

A CV was used to investigate the electrochemical behavior of paracetamol on a graphene/GCE and a bare GCE in the buffer solution containing $NH_3{\cdot}H_2O$–NH_4Cl (0.1 M, pH 9.3) at a scan rate of 50 mV s^{-1}. At the bare GCE (Fig. 2a), paracetamol shows an irreversible behavior with relatively weak redox current peaks at E_{pa} (anodic peak potential) = 0.368 V and E_{pc} (cathodic peak potential) = 0.101 V. However, as can be seen from Fig. 2b, paracetamol exhibits a pair of well-defined redox waves on the graphene-modified GCE with E_{pa} = 0.273 V and E_{pc} = 0.231 V, and the over-potential of paracetamol becomes lower than that on the bare GCE with a shifting of 95 mV. The redox peak currents are higher than that at the bare GCE with $I_{pa}/I_{pc} \approx 1$. The redox performs a quasi-reversible process because the nanocomposite film of graphene can accelerate the electrochemical reaction. It can be seen from Fig. 2c that there is a large background current at the graphene-modified GCE, which is caused by a larger surface area of the nanocomposite film on the GCE [10]. The effect of scan rates on

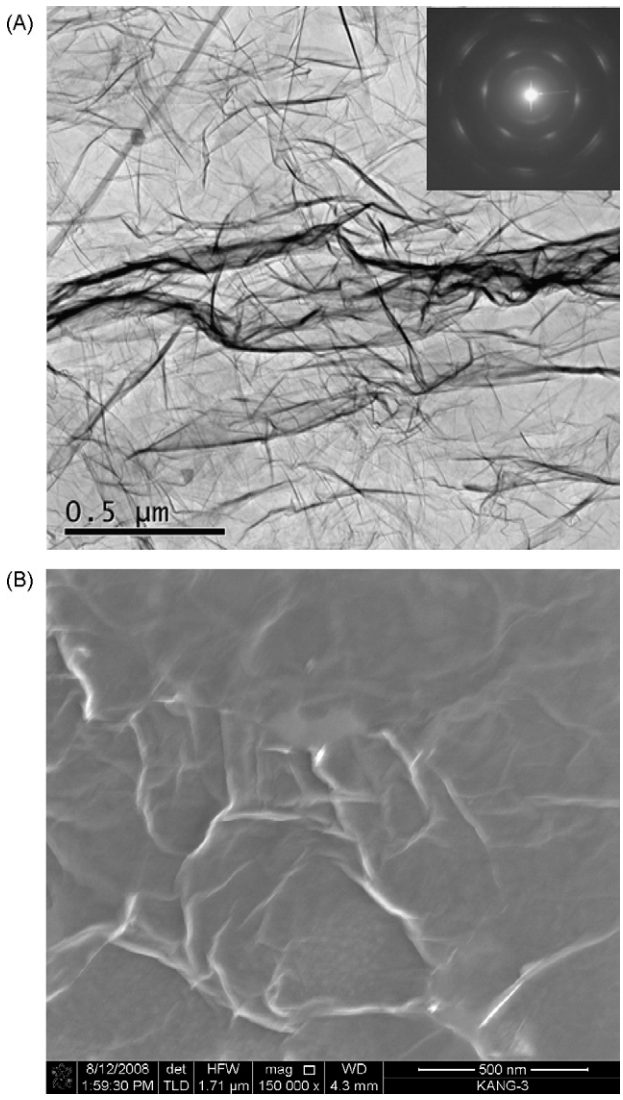


Fig. 1. TEM (A) of graphene in ethanol solvent and SEM (B) image of graphene-film modified GCE.

the redox of paracetamol at the graphene-modified GCE was investigated by cyclic voltammetry (Fig. 3). The redox peak currents at the graphene-modified GCE in the paracetamol solution increased linearly with the scan rate in the range from 20 to 300 mV s^{-1}

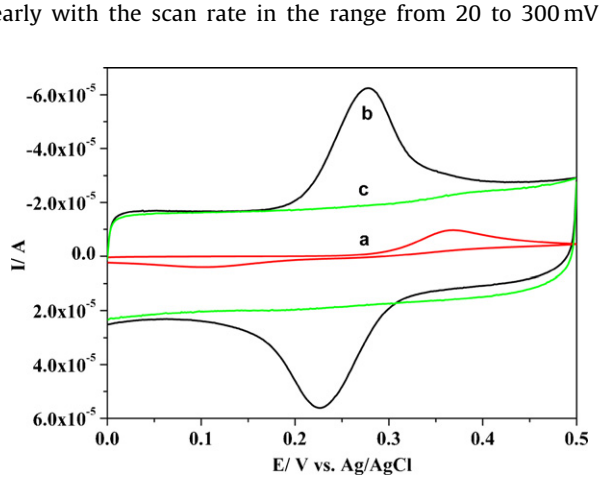


Fig. 2. CVs recorded at a bare GCE (a) with 100 μM paracetamol; graphene/GCE with (b) 20 μM paracetamol and without paracetamol (c) in the buffer of 0.1 M $NH_3{\cdot}H_2O$–NH_4Cl, pH 9.3, scan rate: 50 mV s^{-1}.

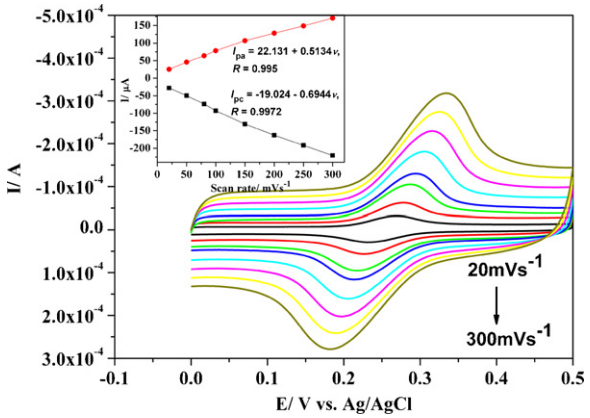


Fig. 3. CVs acquired on graphene/GCE with 20 μM paracetamol in the buffer of $NH_3{\cdot}H_2O$–NH_4Cl (0.1 M pH 9.3) at different scan rates from 20 to 300 mV s^{-1}. Inset is the plot of the peak current of paracetamol versus scan rate.

(inset, Fig. 3; linear regression equations: $I_{pa} = 22.131 + 0.5134\nu$, $R = 0.995$; $I_{pc} = -19.024 - 0.6944\nu$, $R = 0.9972$). This indicates that the modified-electrode reaction of paracetamol is a surface-confined process. In the scan rates ranging from 80 to 300 mV s^{-1}, the liner regression equations of the E_{pa} and E_{pc} vs. the logarithm of the scan rates are expressed as $E_{pa} = 0.1436 + 0.0308 \ln \nu$ and $E_{pc} = 0.3296 - 0.0245 \ln \nu$ with $R = 0.9984$ and 0.9946, respectively. Based on the slopes of the lines $RT/(1-\alpha)nF$ and $-(RT/\alpha nF)$, the value of the electron-transfer coefficient (α) and the electron-transfer number (n) were calculated as 0.56 and 2.

3.3. Optimization of the experimental conditions

The electrochemical redox behavior of paracetamol at graphene-modified electrode in different media (such as 0.1 M pH 4.50 HAc-NaAc, pH 7.02 PBS, pH 9.3 $NH_3{\cdot}H_2O$–NH_4Cl) was investigated by cyclic voltammetry (Fig. 4A). In the buffer system of $NH_3{\cdot}H_2O$–NH_4Cl, the redox of paracetamol shows a pair of well-defined redox waves, a quasi-reversible process and the lowest anodic peak potential. Therefore, $NH_3{\cdot}H_2O$–NH_4Cl (0.1 M) buffer solution was applied to determine paracetamol. Fig. 4B shows the influence of pH on the redox reaction of paracetamol at the graphene-modified electrode. As can be seen, with pH value of the solution increasing, the redox peak shifted negatively, which indicates that the redox reactions involve the protons [37]. The formal potential ($E^{o\prime}$) changed linearly, depending on a pH from 8.6 to 10.3, and the equation was $E^{o\prime} = 0.5748 - 0.0458$ pH. Based on the $dE_p/dpH = 0.059X/\alpha n$, the proton number ($X$) was estimated about 1. In this work, the buffer solution of $NH_3{\cdot}H_2O$–NH_4Cl (0.1 M, pH 9.3) was chosen as the supporting electrolyte.

The relationships between the peak current (I_p) of paracetamol and the amount of graphene on a GCE was investigated by CV (Fig. 5A). The I_p clearly increased as the amount of graphene at a GCE from 1 to 5 μL increased, and then the I_p increased slightly from 5 to 8 μL. However, the I_p decreased while the amount of graphene exceeded 10 μL, which may be ascribed to the thicker film of graphene hampering the electrical conductivity. The volume of graphene suspension on the surface of the GCE was kept at 5 μL in this work.

The influence of accumulation potential on the I_p of paracetamol at graphene/GCE was also investigated by SWV (data not shown). The I_p slightly increased as the potentials shifted negatively from 0.2 to −0.3 V. To improve the signal-to-noise ratio, a potential of 0.0 V was applied as the accumulation potential to verify high sensitivity. However, the accumulation time had a remarkable effect on peak current. The I_p increased greatly with time and reached

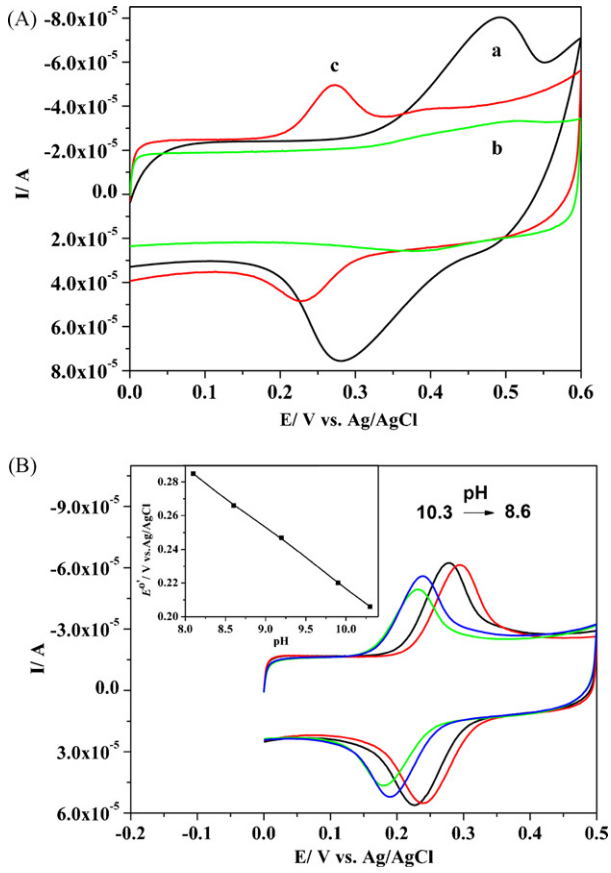


Fig. 4. (A) CVs obtained at graphene/GCE with 20 μM paracetamol in the buffer of (a) 0.1 M pH 4.50 HAc-NaAc, (b) pH 7.02 PBS, (c) pH 9.3 $NH_3{\cdot}H_2O$–NH_4Cl and (B) 0.1 M $NH_3{\cdot}H_2O$–NH_4Cl with pH values of 8.6, 9.3, 9.8, and 10.3. Inset shows the plot of equilibrate potentials versus pH values. Scan rate: 50 mV s^{-1}.

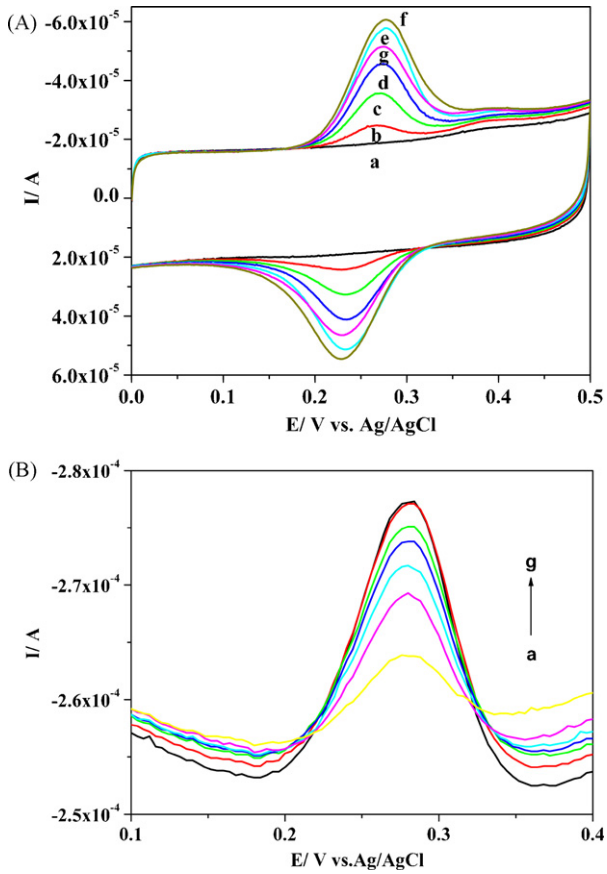


Fig. 5. (A) CVs on graphene/GCE with 20 μM paracetamol in the buffer of 0.1 M $NH_3{\cdot}H_2O$–NH_4Cl with the amount of graphene (a–g): 0, 1, 2, 3, 5, 8, 10 μL, and (B) SWV on graphene/GCE with 5 μM paracetamol for different accumulation times (a–g): 30, 60, 120, 160, 200, 240, and 300 s.

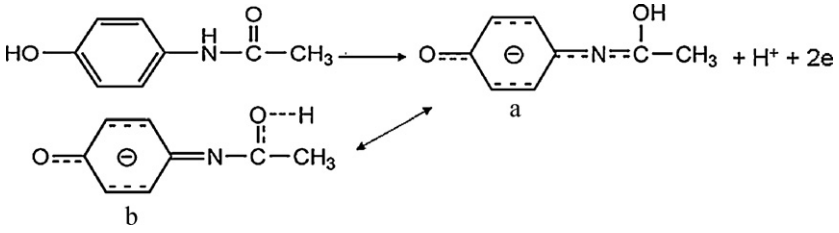
a maximum at 240 s (Fig. 5B), suggesting that graphene can effectively accumulate paracetamol. Therefore, 240 s was used as the accumulation time.

3.4. The redox mechanism of paracetamol at graphene/GCE

According to the discussion mentioned above, the redox of paracetamol belongs to a two-electron and one-proton process, and the possible redox mechanism of paracetamol on the graphene/GCE was shown in Scheme 1. During the redox process of paracetamol, the electric system was exchanged with p–π conjugation (reactant) and π–π conjugation (product). Compared with the reactant, the energy level of the product decreased, and the product was more stable, which may be because of the easily formed π–π interaction between the product molecules and the graphene sheets of sp^2-bonded carbon atoms with strengthening adsorption [36,37]. So, the reactant was easier to be oxidized, and the over-potential of paracetamol became lower than that on the bare GCE with a shifting of 95 mV. Because of the extraordinary electronic transport properties of graphene [20], it may easily provide electrons for the reduction process of the redox of paracetamol, which may result in a quasi-reversible process for the redox of paracetamol at the graphene-modified electrode. The electrocatalytic properties of graphene to paracetamol can be attributed to the defective sheets of graphene, similar to that of carbon nanotubes [38–40]. The defect sites of graphene-modified GCE can greatly improve the reactivity of the electrode surface compared with a well-polished bare glassy carbon electrode.

3.5. Analytical application

The dependence of the oxidation peak current (I_{pa}) of paracetamol on its concentration (c) was investigated in $NH_3{\cdot}H_2O$–NH_4Cl (0.1 M) buffer solution by SWV. The I_{pa} was linearly related to the paracetamol concentration in the range of 0.1–20 μM (Fig. 6A). The linear regression equation was I_{pa} (μA) = 3.798 + 4.055c



Scheme 1. The redox mechanism of paracetamol.

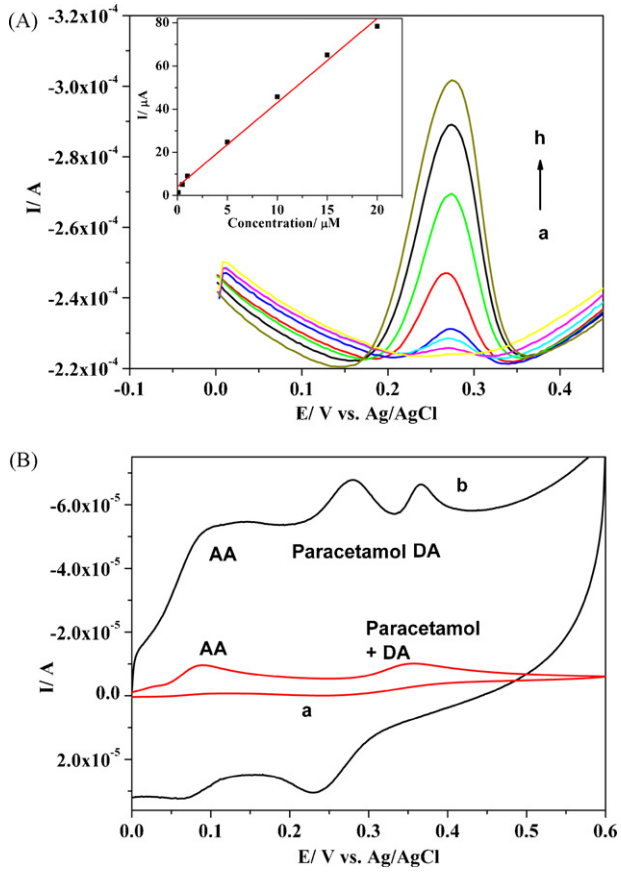


Fig. 6. SWV (A) on graphene/GCE for different paracetamol concentrations (a–h): 0.0, 0.1, 0.5, 1.0, 5.0, 10, 15, and 20 μM in 0.1 M $NH_3{\cdot}H_2O$–NH_4Cl. Inset is the relationship of current responses to paracetamol concentration. CVs (B) recorded at the bare GCE (a) and the graphene/GCE (b) with paracetamol (10 μM), AA (10 μM) and DA (10 μM) in 0.1 M $NH_3{\cdot}H_2O$–NH_4Cl, at scan rate of 50 mV s^{-1}.

(μM), with the correlation coefficient of 0.9984. The detection limit was 3.2×10^{-8} M based on the signal-to-noise ratio of 3, which is lower than those obtained on GCE modified with a (PANI-MWCNT) composite (2.5×10^{-7} M) [4], carbon-coated nickel magnetic nanoparticles (6.0×10^{-7} M) [10] and poly(acid yellow 9)-nano-TiO_2 modified GCE (2.0×10^{-6} M) [15]. It is comparable to that of the (SWNT-DCP) film (4.0×10^{-8} M) [9].

The reproducibility of the graphene-modified GCE was studied by repeating the determination of 1.0 μM paracetamol. After each determination, the used modified electrode undergoes 10 successive CV sweeps between 0.0 and 0.5 V at 50 mV s^{-1} in the buffer of $NH_3{\cdot}H_2O$–NH_4Cl (0.1 M, pH 9.3) to remove any adsorbents, and is regenerated. The six measurements achieved a good reproducibility with the relative standard deviation (RSD) of 5.2%. A refreshed electrode surface can be used for successive fifteen times without obvious performance deterioration and the RSD is 5.5%, which shows that the sensor has a good stability. The stability is ascribed to the film that is constructed with graphene–chitosan [41]. The fabrication reproducibility of six similar graphene/GCEs was investigated by detecting the response to 1.0 μM paracetamol, and the RSD is 4.6%. The results indicated that the graphene/GCE exhibited good reproducibility in the detection of paracetamol.

The interferences of DA and AA on both bare GCE and graphene-modified GCE were studied using CVs (Fig. 6B). As shown in this figure, the oxidation peaks of paracetamol and DA cannot be separated on the bare GCE (Fig. 6B, a). However, the well-defined wave of paracetamol was obtained at the graphene-modified electrode with good separations from AA and DA (Fig. 6B, b). The anodic peak potentials of AA, paracetamol, and DA were 0.144, 0.281, and 0.367 V, respectively.

The method that was developed was used to determine a kind of paracetamol (0.500 g/tablet) commercial tablets (USA, Costco wholesale corporation, NDC59606-020-30). The tablets were ground to powder and dissolved in 80% ethanol. Using the proposed method, the concentration of paracetamol of the pharmaceutical preparation was detected (0.494 g/tablet), which is in good agreement with the content of paracetamol provided by the manufacturer. The recovery tests of adding paracetamol ranging from 0.5 to 4.0 μM were performed using SWV. The recoveries of the tests were in the range from 96.4% to 103.3%. The sensor was also validated with paracetamol-spiked human plasma samples, and the recovery of the spiked sample was 104.2%. These results indicate that the sensor developed in this work has high sensitivity and selectivity for detecting paracetamol in commercial tablets and plasma samples.

4. Conclusions

A graphene-based electrochemical sensor has been demonstrated, and this sensor shows an excellent electrocatalytic activity towards the reduction and oxidation of paracetamol. Owing to the unique properties of graphene, including subtle electronic characteristics, good π–π interaction, and strong adsorptive ability, the graphene-modified GCE obviously promotes the sensitivity of the determination of paracetamol with a low detection limit. The proposed method was applied to detect paracetamol in pharmaceutical preparation tablets with detection limit (3.2×10^{-8} M) and satisfied recoveries from 96.4% to 103.3% without interference from AA and DA.

Acknowledgments

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