Electrochemical Investigation of Acetaminophen with a Carbon Nano-tube Composite Film Electrode

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Electrochemical behaviors of acetaminophen at a multi-wall carbon nano-tube composite film modified glassy carbon electrode were investigated by cyclic voltammetry, linear sweep voltammetry and chronocoulometry. Compared with that obtained at the unmodified electrode, the peak currents were enhanced significantly, and the oxidation peak shifted towards more negative potential with the reduction peak shifted positively. The peak-to-peak separation turned narrow, and suggested that the reversibility was improved greatly. Experimental parameters, such as scan rate, pH and accumulation conditions were optimized. It was found that a maximum current response can be obtained at pH ~ 5.0 after accumulation at −0.50 V for 80 s. The oxidation peak current was found to be linearly related to acetaminophen concentration over the range of 5.0 × 10⁻⁷ ~ 1.0 × 10⁻⁴ mol L⁻¹ with a detection limit of 5.0 × 10⁻⁸ mol L⁻¹. A convenient and sensitive electrochemical method was developed for the determination of acetaminophen in a commercial paracetamol oral solution. Its practical application demonstrated that it has good selectivity and high sensitivity.

Key Words: Acetaminophen, Multi-wall carbon nano-tube, Electroanalysis

Introduction

Acetaminophen, N-acetyl-p-aminophenol, is important and extensively used as an alternative to aspirin without the secondary effects of the salicylates on the gastric mucosa.¹ In proper therapeutic dose, < 1 g/time (or < 2 g/day), acetaminophen is readily metabolized and is safe to patients with sensitivity to aspirin, therefore, is often self-prescribed without medical control, to alleviate moderate pain, to calm fever, lumbar pain, migraine or nonspecific indications. Most references state that the maximum daily dose of acetaminophen is 4 g. Patients taking more than this amount, especially those with certain risk factors, are more likely to develop toxicity. Recent studies have shown that overdose of acetaminophen is associated to hepatic toxicity and renal failure despite of its apparent innocuous character.²⁻⁶ It is therefore important to develop an analytical technique to determine acetaminophen accurately.

To date, numerous methods have been proposed for analysis of acetaminophen in pharmaceutical preparations, such as titrimetric analysis,⁴ spectrophotometry,⁵⁻¹⁰ spectrophotometry,¹¹ high performance liquid chromatography,¹²⁻¹⁵ capillary electrophoresis,¹⁴,¹⁵ flow injection analysis,¹⁶⁻¹⁷ and electroanalysis.¹⁸⁻²² Spectrophotometric methods usually require sample pre-treatments (e.g. extraction, complex formation, etc.) which can be laborious and time consuming. Compared with other techniques, voltammetric techniques are more selective, less time-consuming and widely used for the determination of acetaminophen. A relatively simple and rapid electrochemical method for the detection of acetaminophen in 1.0 mol L⁻¹ HCl solution was developed with glassy carbon electrode.¹⁸ Chemically modified electrodes have also attracted attentions, C-60-modified glassy carbon electrode,¹⁹ boron-doped diamond thin film electrode,²⁰ nanogold modified indium tin oxide electrode²¹ and a Cu(II)-conducting polymer complex modified electrode²² have been constructed for the determination of acetaminophen in pharmaceutical and medical applications.

The present work reports the electrochemical behaviors of acetaminophen at a multi-wall carbon nano-tube/dihexa-decyl hydrogen phosphate/polyethylene glycol composite film modified glassy carbon electrode. The negative shift of the oxidation peak potential and the great enhancement of the oxidation peak current reveal that the film has a strong catalytic function towards the oxidation of acetaminophen, due to the unusual properties of carbon nano-tube such as strong adsorptive ability, huge specific area, subtle electronic properties as well as excellent electrocatalytic activity. Based on the sensitive current response, a simple and convenient method is developed for the determination of acetaminophen in pharmaceutical preparations.

The specific features of this method are shown in Table 1 and compared with other electrochemical methods. Its successful application to quantify the content of acetaminophen in commercial pharmaceutical preparations demonstrates that the film electrode has potential in practical use.

Experimental Section

Apparatus. All electrochemical experiments were carried out on a CHI-660A electrochemical workstation (CH Instrument Inc., USA) with a conventional three-electrode system including the multi-wall carbon nano-tube composite film modified glassy carbon electrode as working electrode,
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**Table 1. Comparison of electroanalytical data for acetaminophen determination**

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Analytical range</th>
<th>Limits of detection</th>
<th>Accumulation time</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>This method</td>
<td>$5.0 \times 10^{-7} \sim 1.0 \times 10^{-6}$ mol L$^{-1}$</td>
<td>$5.0 \times 10^{-8}$ mol L$^{-1}$</td>
<td>80 s</td>
<td>[18]</td>
</tr>
<tr>
<td>Glassy carbon electrode</td>
<td>$6.6 \times 10^{-6} \sim 1.3 \times 10^{-5}$ mol L$^{-1}$</td>
<td>0.05 mmol L$^{-1}$</td>
<td>60 s</td>
<td>[19]</td>
</tr>
<tr>
<td>C-60-modified electrode</td>
<td>0.05 ~ 1.5 mmol L$^{-1}$</td>
<td>0.05 mmol L$^{-1}$</td>
<td>10 s</td>
<td>[20]</td>
</tr>
<tr>
<td>Boron-doped diamond electrode</td>
<td>0.1 ~ 8.0 mmol L$^{-1}$</td>
<td>1.8 $\times 10^{-7}$ mol L$^{-1}$</td>
<td>20 s</td>
<td>[21]</td>
</tr>
<tr>
<td>Gold nanogold modified indium tin oxide electrode</td>
<td>$2.0 \times 10^{-7} \sim 1.5 \times 10^{-6}$ mol L$^{-1}$</td>
<td>$2.0 \times 10^{-7}$ mol L$^{-1}$</td>
<td>50 s</td>
<td>[22]</td>
</tr>
<tr>
<td>Cu(II)-conducting polymer complex modified electrode</td>
<td>0.09 ~ 0.93 mg L$^{-1}$</td>
<td>0.09 mg L$^{-1}$</td>
<td>160 s</td>
<td>[26]</td>
</tr>
<tr>
<td>Glassy carbon electrode</td>
<td>0.09 ~ 0.93 mg L$^{-1}$</td>
<td>0.09 mg L$^{-1}$</td>
<td>160 s</td>
<td>[26]</td>
</tr>
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</table>

Reagents. Acetaminophen was obtained from Study Center of National Standard Substance (Beijing, China). Stock standard solution of acetaminophen was prepared from ethanol and stored in a refrigerator until use. An aqueous solution was prepared daily by simple dilution of the stock solution with phosphate buffer. Dihexadecyl hydrogen phosphate (DHP) was bought from Fluka (Switzerland). Polyethylene glycol 10000 (PEG) were the stock solution with phosphate buffer. Dihexadecyl aqueous solution was prepared daily by simple dilution of ethanol and stored in a refrigerator until used. An electrode. The samples were prepared by successive cyclic voltammetry was applied for the electrochemical investigation of 1.0 $\times 10^{-5}$ mol L$^{-1}$ acetaminophen at the film electrodes in phosphate buffer (pH = 5.0). As shown in Figure 1, the surface morphology of the composite film electrode was shown in Figure 1. It can be seen obviously that many carbon nano-tubes are fixed on the glassy carbon electrode surface. The freshly prepared composite film electrodes were activated in PB solution by successive cyclic voltammetry was applied for the electrochemical investigation of 1.0 $\times 10^{-5}$ mol L$^{-1}$ acetaminophen at the film electrodes in phosphate buffer (pH = 5.0). As shown in Figure 1, the surface morphology of the composite film electrode was shown in Figure 1. It can be seen obviously that many carbon nano-tubes are fixed on the glassy carbon electrode surface. The freshly prepared composite film electrodes were activated in PB solution by successive cyclic scans from $-0.20$ V to $1.00$ V until the stable voltammograms were obtained. A similar procedure was applied for the dihexadecyl hydrogen phosphate film electrode preparation without multi-wall carbon nano-tube and Polyethylene glycol 10000.

Electrochemical measurements. Voltammetric determination of acetaminophen was carried out in a voltammetric cell with 10 mL of supporting electrolyte solution. The accumulation step was performed at $-0.50$ V for 80 s with stirring, and voltammograms were recorded from $-0.20$ V to 1.00 V after 10 s quiescence. The oxidation peak current measured at 0.40 V was applied for the quantiﬁcation of acetaminophen. After each measurement, in order to remove the previous deposits completely, the modified electrode surface was refreshed by successive cyclic voltammetric sweeps in a blank electrolyte solution to produce a reproducible electrode surface. The same procedure was applied in the samples analysis. All electrochemical experiments were carried out at room temperature (25 ± 2 °C). Removal of oxygen was achieved by using high purity N2.

Results and Discussion

Voltammetric behaviors of acetaminophen. Cyclic voltammetry was applied for the electrophotographic investigation of 1.0 $\times 10^{-5}$ mol L$^{-1}$ acetaminophen at the film electrodes.
Figure 2. Cyclic voltammograms of $1.0 \times 10^{-5}$ mol L$^{-1}$ acetaminophen at the MWNT/DHP/PEG composite film electrode in phosphate buffer (pH = 5.0). Scan rate: 100 mVs$^{-1}$.

Figure 3. Voltammograms of $1.0 \times 10^{-5}$ mol L$^{-1}$ acetaminophen at (a) the MWNT/DHP/PEG composite film electrode; (b) the DHP/PEG film electrode; (c) the unmodified electrode and (d) the DHP film electrode in phosphate buffer (pH = 5.0). Scan rate: 100 mVs$^{-1}$.

Figure 4. Linear sweep voltammograms for $1.0 \times 10^{-5}$ mol L$^{-1}$ acetaminophen at different scan rate (from a to m): 10, 30, 50, 70, 90, 100, 120, 140, 160, 180, 200, 250, 300 mVs$^{-1}$. Supporting electrolyte: 1/15 mol L$^{-1}$ phosphate buffer (pH = 5.0).

Figure 5. Linear curve indicated that the electrochemical reaction is predominantly diffusion controlled in a confined thin film.

Figure 6. Chronocoulometric curves of acetaminophen on the MWNT/DHP/PEG composite film electrode (a), the unmodified electrode (b) and the dihexadecyl hydrogen phosphate film electrode (c) were presented. The diffusion coefficient $D$ and $Q_{ads}$ of acetaminophen on the MWNT/DHP/PEG composite film electrode can be calculated according to the formula given by Anson$^{23}$.

Effects of scan rate. Effects of scan rate on the oxidation of acetaminophen were investigated by linear sweep voltammetry in the range from 10 mVs$^{-1}$ to 300 mVs$^{-1}$, and voltammograms were shown in Figure 4. The peak current increased with a positive shift in the peak potential when the scan rate increased. The detail description of the relationship between the peak current and the square root of the scan rate was given in Figure 5. The linear curve indicated that the electrochemical reaction is predominantly diffusion controlled in a confined thin film.

Chronocoulometry. Chronocoulometry, an electrochemical measuring technique used for electrochemical analysis or for the determination of the kinetics and mechanism, was applied to investigate the oxidation of acetaminophen. The chronocoulometric curves of acetaminophen at the MWNT/DHP/PEG composite film electrode (a), the unmodified electrode (b) and the dihexadecyl hydrogen phosphate film electrode (c) were presented. The diffusion coefficient $D$ and $Q_{ads}$ of acetaminophen on the MWNT/DHP/PEG composite film electrode can be calculated according to the formula given by Anson$^{23}$.

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The surface charge transfer resistance of the electrode surface decreased in the presence of MWNT/DHP film. It was obvious that the presence of multi-wall carbon nano-tube can improve the adsorption of acetaminophen at the electrode surface so as to enhance the determination sensitivity significantly.

**Electrochemical impedance spectroscopy.** Electrochemical impedance spectroscopy is considered to be an effective tool for investigating the property of electrode interface. Figure 7 shows the complex plane diagram (Nyquist plot, Z' vs. Z'') for the MWNT/DHP/PEG film electrode (a), the MWNT/DHP film electrode (b) and the unmodified electrode (c) in the presence of 10 mmol L$^{-1}$ K$_3$[Fe(CN)$_6$] K$_4$[Fe(CN)$_6$] (1:1)-mixture. 0.2 mol L$^{-1}$ KCl was used as supporting electrolyte.

**Influences of pH value.** The influence of pH on the oxidation of acetaminophen at the composite film electrode was investigated in the pH range from 4.5 to 8.8. The effect of pH on the oxidation peak current was shown in Figure 8, a maximum current response is observed at pH = 5.0, and a decrease is observed with pH further increase. Therefore, the concentration, $\Gamma_n$, can be obtained by the following Equation: $\Gamma_n = Q_{ab}/nF$. At the composite film electrode, $\Gamma_n$ is calculated as $1.77 \times 10^{10}$ mol cm$^{-2}$; however, it decrease to $3.33 \times 10^{10}$ mol cm$^{-2}$ at the dihexadecyl hydrogen phosphate film electrode and $1.82 \times 10^{10}$ mol cm$^{-2}$ at the unmodified electrode. It was undoubtedly that the presence of multi-wall carbon nano-tube can improve the adsorption of acetaminophen at the electrode surface so as to enhance the determination sensitivity significantly.
pH value (5.0) was adopted in the following experiment. Figure 9 displayed the dependence of the oxidation peak potential \((E_{pa})\) on the pH value. It was found that \(E_{pa}\) shifted less positively with the increase of pH from 4.5 to 8.8. A linear relationship can be obtained with following equation: \(E_p = -0.0557pH + 0.776, r = 0.996\). A slope of 0.0557 V per pH unit, from which \(m/n\) value of 1 is estimated, suggested that the proton-transfer number \((m)\) is equal to the electron-transfer number \((n)\).

**Accumulation conditions.** Accumulation conditions including accumulation potential and accumulation time can affect the amount of acetaminophen adsorbed on the composite film electrode surface so as to improve the determination sensitivity. The influence of accumulation potential on the oxidation peak current of \(1.0 \times 10^{-5}\) mol L\(^{-1}\) acetaminophen was examined after 80 s accumulation under potential range from \(-0.70\) V to 0.80 V. As shown in Figure 10, in the potential range from \(-0.80\) V to \(-0.5\) V, the oxidation peak current increased slightly. Then, it decreased when further increase in the accumulation potential and a maximum value was obtained at \(-0.50\) V. Thus the accumulation potential, \(-0.50\) V, was employed in the subsequent measurements.

From the plot of the oxidation peak current and the accumulation time, Figure 11, we can see that accumulation time also has great effects on the current response of acetaminophen at the MWNT/DHP/PEG composite film electrode. The peak current increased greatly in the first 80 s due to the more adsorption. When the accumulation was longer than 80 s, it remained almost unchanged because of the saturate adsorption.

**Calibration and interferences.** Under optimized experimental conditions, the calibration curve for the determination of acetaminophen was examined by linear sweep voltammetry. The plot of the peak current and acetaminophen concentration was shown in Figure 12. An excellent linearity was observed over a wide concentration range from \(5.0 \times 10^{-7}\) mol L\(^{-1}\) to \(1.0 \times 10^{-4}\) mol L\(^{-1}\) with a correlation coefficient of 0.996. The linear regression equation can be expressed as following:

\[\text{Ip (\mu A)} = 0.393C + 1.592, \text{ where C is in } \mu \text{mol L}^{-1}.\]

Experimental results showed that the detection limit was...
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Figure 12. Calibration curve for the determination of acetaminophen at the composite film electrode.

5.0 × 10⁻⁸ mol L⁻¹ (S/N = 3). A relative standard deviation of 2.8% for 1.0 × 10⁻⁵ mol L⁻¹ acetaminophen (n = 6) suggested that the composite film electrode process good reproducibility. Six composite film electrodes fabricated independently were used to determine 1.0 × 10⁻⁵ mol L⁻¹ acetaminophen, and the relative standard deviation is 3.5%, revealing an excellent repeatability of the electrode preparation. The stability of the film electrode was evaluated by measuring the peak current of 1.0 × 10⁻⁵ mol L⁻¹ acetaminophen repeatedly. After 50 times determination, the peak current deviated from its original response only 4.7%, revealing that the fabricated MWNT/DHP/PEG film electrode processes long-term stability.

In order to evaluate the specificity of the film electrode in the determination of acetaminophen, some possible interfering substances was added to 1.0 × 10⁻⁶ mol L⁻¹ acetaminophen and the oxidation peak current was measured. There was no substantial change in the current response in the presence of less than 10-fold concentration of glucose, ascorbic acid, uric acid and L-cysteine. 50-fold concentration of Zn²⁺, Fe³⁺, Ni²⁺, and Al³⁺ did not interfere with the current response of acetaminophen (signal change below 5.0%), meanwhile, 50-fold concentration of Co²⁺ cause the response of acetaminophen decrease greatly. However, 5-fold concentration of ethinyl estradiol, dopamine and hydromorphone can cause enhancement in the peak current, due to have similar structures for their hydroxyl groups and may be oxidized near the oxidation potential of acetaminophen at the film electrode.

Determination of acetaminophen in the pharmaceutical samples. The MWNT/DHP/PEG film electrode was employed to determine the content of acetaminophen in Children’s Bufferin Paracetamol Oral Solution (Shanghai Shiguibao Pharm. Co., China). The oral solution was diluted with phosphate buffer (pH 5.0) at the ratio of 1:100. After that, 10 μL of the diluted sample solution was added into an electrochemical cell containing 10 mL phosphate buffer, and the voltammograms were recorded as the mentioned procedure. The concentration of acetaminophen in the voltammetric cell calculated from the regression equation was 5.18 × 10⁻⁶ mol L⁻¹ (n = 3), therefore, the content of acetaminophen in the oral solution was 31.39 mg mL⁻¹ which was consistent well with that the certified value (32.00 mg mL⁻¹) of the analyte. UV spectroscopy was applied to evaluate the veracity of the proposed electrochemical method, and a standard curve method was developed for the determination of acetaminophen in the concentration range from 5.0 × 10⁻⁷ mol L⁻¹ to 5.0 × 10⁻⁵ mol L⁻¹. The calculated content of acetaminophen in the oral solution was 31.51 mg mL⁻¹. The results suggested that the MWNT/DHP/PEG composite film electrode was very reliable, selective and sensitive enough for the determination of acetaminophen in real pharmaceutical samples.

Conclusions

In this work, a MWNT/DHP/PEG composite film modified glassy carbon electrode was fabricated easily for the electrochemical investigation of acetaminophen by cyclic voltammetry, linear sweep voltammetry and chronocoulometry. It was found that the peak current response of acetaminophen was improved significantly and the oxidation peak shifted towards negative potential in the presence of MWNT/DHP/PEG composite film. The results indicated that the composite film provided a good platform to accumulate acetaminophen. The enhanced accumulation of acetaminophen mainly came from the unusual properties of carbon nano-tubes such as strong adsorptive ability, huge specific area. As a result, the film electrode was successfully employed for the voltammetric determination of acetaminophen. Its advantages, such as simple, sensitive, rapid and accurate, were demonstrated by the determination of acetaminophen in the pharmaceutical samples with good result.

References