Determination of Acetaminophen Via TiO$_2$/MWCNT Modified Electrode

Ali Asghar Pasban 1, Elham Hossein Nia 2, Masoumeh Piryaei 3*

1 Refining Technology Development Division, Research Institute of Petroleum Industry, Tehran, Iran
2 Department of Chemistry, Faculty of Science, Karaj Branch, Islamic Azad University, Karaj, Iran
3 Department of Biology, Faculty of Science, Payam Nour University, Tehran, Iran

Received: 2017-05-31              Accepted: 2017-07-17              Published: 2017-08-20

INTRODUCTION

Acetaminophen or paracetamol is a drug commonly used to relieve pains such as aches, headaches, menstrual cramps and fever. It is sold under various brand names like tylenol, panadol and aspirin-free anacin. Acetaminophen is also used in combination with narcotic analgesics, which increases its efficacy and reduces the risk of narcotics abuse. It is considered safe for human use when the recommended dose is not exceeded. But because of its wide availability, deliberate or accidental overdose is fairly common. Overdose of acetaminophen may cause nausea, vomiting, sweating and exhaustion. Very large overdose can cause liver damage and death within days. Therefore, there is a clear need to find a selective analytical technique, which has high sensitivity and can be used in the standard analysis for detecting the concentration of acetaminophen in the application.

© 2017 Published by Journal of Nanoanalysis.

How to cite this article

Keywords: Multi wall carbon nanotubes, Titanium dioxide nanoparticles, Composite, Acetaminophen, Cyclic voltammetry.
Several methods for analytical determination of acetaminophen have been reported in literature; liquid chromatography [1], spectrometry [2], spectrophotometry [3], capillary electrophoresis [4], amperometric [5] and flow injection analysis [6, 7] which are known to produce acceptable results. However, they have some limitations, disadvantages such as high cost and time constraints are known to prevail. Consequently, the development and application of electrochemical sensors and methods for the determination of acetaminophen has received considerable interest in the past few decades [8,9].

Previously, the use of carbon nanotubes modified electrode for detection of acetaminophen has been reported [10, 11], but to the best of our knowledge on the use of MWCNT/TiO_2 composite modified electrodes in the determination of acetaminophen has not been reported. In this regard, we have fabricated the MWCNT/TiO_2 composite electrode to detect acetaminophen [12, 13]. The result is a new type of modified electrode that has fast response and high sensitivity. Thus, we were able to report a successful implementation of the new sensor in the determination of acetaminophen in pharmaceutical tablets.

EXPERIMENTAL

Multi wall carbon nanotubes (MWCNTs) (purity of 95%, diameter of 20-49 nm, length of 5-15 µm) and TiO_2 nanoparticles (dispersed in water by 5% weight, <100 nm particle size) were purchased from Aldrich, USA and used without any further purification. Acetaminophen was purchased from the market. All other reagents used in the experimental were of analytical graded and solutions were prepared with deionized distilled water and deaerated with oxygen-free nitrogen gas before each measurement. Solution containing acetaminophen and 0.1 M phosphate buffer solution (PBS) at pH 7.0 were prepared just before running each experiment.

All the electrochemical experiments were performed by Bioanalytical Systems (BAS, West Lafayette, IN, USA) CV-50W voltammetric analyzer, which was connected to an external computer. A conventional three-electrode cell was used: a platinum wire as a counter electrode, an Ag/AgCl (3 M NaCl) as a reference electrode, modified and unmodified (bare) glassy carbon electrode (GCE) as working electrodes.

Preparation of MWCNT/TiO_2/GCE

First of all, the surface of the bare glassy carbon electrode (3 mm diameter) was polished carefully with alumina using a microcloth pad followed by ultrasonic grinding for 1 min in distilled water, rinsed with distilled water and dried before use. Then, 1 mg MWCNT was dispersed into 1 mL dimethyl formamide and same volume of distilled water within 0.5 h by ultrasonication. A known amount of the MWCNT/DMF suspension and TiO_2/water dispersion were deposited onto the cleaned GCE surface using a microsyringe. The two solutions diffused each other homogeneously on the surface of the GCE. The composite was then dried in an oven for 2 min (40°C) to remove the solvents. Finally, the modified electrode was cooled in room temperature for further measurement.

RESULT AND DISCUSSION

Current Enhancement of Acetaminophen

Voltammetric behaviour of acetaminophen in 0.1 M phosphate buffer solution (pH 7.0) were studied using cyclic voltammetry at various electrodes of the MWCNT/TiO_2/GCE; MWCNT/GCE and unmodified GCE within the potential range of 0-800 mV using a scan rate of 100 mV/s (Figure 1). During the electrochemical experiment, the small redox peaks of 0.2 mM acetaminophen at bare GCE (Figure 1c) and greatly increased redox peaks at MWCNT/GCE (Figure 1b) were observed. An electrochemical response of the MWCNT/TiO_2/GCE composite (5 µL MWCNT/5 µL TiO_2) film was characterized in the redox process of acetaminophen and remarkable peak currents were found; at +471 mV potential was observed for the oxidation peak current while at +324 mV peak potential vs. Ag/AgCl was observed for the reduction peak current as shown in Figure 1a. The MWCNT/TiO_2 composite film was composed of 5 µL of MWCNT dispersed in DMF and 5 µL TiO_2 dispersed in water were used in this experiment.
A. Pasban and E. Hossein Nia / Determination of Acetaminophen Via TiO\textsubscript{2}/MWCNT Electrode

**J. Nanoanalysis., 4(2): 142-149, Summer 2017**

The process was found to be a quasi-reversible behavior for acetaminophen (ipa/ipc $\approx$ 1.34). It can be seen when the MWCNT/TiO\textsubscript{2}/GCE composite was used, a peak current enhancements in the order of 2.3 folds for the oxidative current and 2.0 folds for the reductive current were obtained as compared to when only MWCNT/GCE was used. And when the composite electrode compared with a bare GCE, the higher currents of 8.5 folds for the oxidative current and 11.0 folds for the reductive current were obtained.

Besides current improvement, a slight shift of peak potential in the direction of positive value was observed for the MWCNT/ TiO\textsubscript{2} modified GCE as compared to bare electrode potential. The most probable reason of this remarkable peak current enhancement is that, the nano or micro grade size and larger surface area of the nanoparticles led to higher current in the electrochemical reaction.

**Effect of pH**

The effect of pH on voltammetric response of acetaminophen was investigated in the range of pH 2.0-12.0 using pH buffer solutions. The voltammetric peak currents of acetaminophen redox obtained in different pH conditions were shown as well-defined at the MWCNT/TiO\textsubscript{2} composite (10 $\mu$L MWCNT/5 $\mu$L TiO\textsubscript{2}) modified GCE.

Figure 2 shows the cyclic voltammograms recorded at various pH values (pH 6.0,10.0) for 0.2 mM acetaminophen. The height of the peaks in this region is almost same, means the pH working range is wider when the use of the MWCNT/TiO\textsubscript{2}/GCE for the detection of acetaminophen. As can be seen in the Figure 3, the redox current increase with increasing pH value (2.0 to 5.0), then between the pH value of 6.0 and 10.0, the value of the redox current is found to be optimized, after which it begins to decrease.

The peak potentials shift toward the origin and Figure 4 presents a linear dependence of peak potentials on pH at the modified electrode which is expressed by the following equations: $E_{pa}=-52.2 \text{pH}+844.1$ with $R^2=0.942$ for the oxidation and $E_{pc}=53.2 \text{pH}+699.4$, $R^2=0.944$ for the reduction process of acetaminophen. From the foregoing observations, it can be inferred that the peak potentials and peak currents of acetaminophen for both the oxidation and the reduction process are dependent on pH value.

**Effect of Varying Percentages in Composite**

The effect of varying dosage/percentage of...
MWCNT (dispersed in DMF) and TiO₂ (dispersed in water) in the composite of MWCNT/ TiO₂ was studied for the redox process of 0.2 mM acetaminophen. Percentage for MWCNT (5-30 µL) and TiO₂ (5-10 µL) were coated on surface of the 3 mm diameter GCE by composite film of the MWCNT/TiO₂. Figure 5 shows the peak currents of acetaminophen increased considerably with increase in the dosage of MWCNT 5-30 µL. But an increase in the dosage of TiO₂ until 10 µL (with 5 µL MWCNT) resulted in the decrease of peak current. Obtained peak current changes of 0.2 mM acetaminophen for the both oxidation and reduction process at the MWCNT/TiO₂ composite film with different dosages of components can be seen in the result presented in Table 1.

![Graph](image1)

**Fig. 4.** Dependence of the peak potentials on the different pH of electrolyte solutions ranging from pH 2.0-12.0.

![Graph](image2)

**Fig. 5.** Cyclic Voltammogram of 0.2 mM acetaminophen on MWCNT/TiO₂/GCE with different dosages/percentages of components in the composite: (a) 30 µL MWCNT/5 µL TiO₂; (b) 25 µL MWCNT/5 µL TiO₂; (c) 20 µL MWCNT/5 µL TiO₂; (d) 15 µL MWCNT/5 µL TiO₂; (e) 10 µL MWCNT/5 µL TiO₂; (f) 5 µL MWCNT/5 µL TiO₂; (g) 5 µL MWCNT/10 µL TiO₂.
Table 1. Obtained peak currents of 0.2 mm acetaminophen on the different dosages (volume) of components (MWCNT/DMF and TiO$_2$/H$_2$O) in the composite of the MWCNT/TiO$_2$ coated onto 3 mm diameter glassy carbon electrode with a scan rate of 100 mV/s

<table>
<thead>
<tr>
<th>Volume of components in the composite (µL)</th>
<th>Peak current of 0.2 mM paracetamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiO$_2$</td>
<td>MWCNT</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
</tr>
</tbody>
</table>

The reason of dropping the peak current with increase of TiO$_2$ in the composite was TiO$_2$ nanoparticles has a poor electrochemical activity, so when the particles were increased and surrounded MWCNT, they caused to decrease the electron transfer process of acetaminophen at the modified electrode. Despite, higher dosage of MWCNT gave excellent result, it was better to use less amount of substance on limited electrode surface (only 3 mm diameter) to avoid certain errors. For rest of the studies, the MWCNT/TiO$_2$ composite film was created by the dosage of 5 µL MWCNT/DMF with 5 µL TiO$_2$/water because of some reasons described above. However, TiO$_2$ nanoparticles in the composite could enhance the electrochemical activity (or edge effect) of the MWCNT homogeneously coated onto GCE surface for the redox of acetaminophen, the dosage/percentage of components in the composite should be in the notice of the further study.

**Effect of Scan Rate**

The effect of scan rate on the oxidation and reduction of 0.2 mM acetaminophen in 0.1 M phosphate buffer solution was investigated at the MWCNT/TiO$_2$/GCE composite film by cyclic voltammetry in the range of 5-600 mV/s and voltammograms were shown in Figure 6. The oxidation and reduction peak currents increased with increase in scan rates. The relationship between the oxidation peak currents and square root of the scan rates was 0.998, expressed by the equation $y=0.73x+0.53$ were shown in Figure 7.
This linearity indicated that the electrochemical reaction was certainly and diffusion controlled mechanism. When the scan rate increased, the peak current increased significantly, following the peak current separation increased as shown in Figure 8.

Also peak potential shift was observed, while the oxidation peak potential shifts positively the reduction peak potential was negatively shifted. From a plot of the peak current against peak potential (Figure 8), the ‘zero-current’ was found for the oxidation potential at 400 mV (y=-1.77x+709.7; R²=0.990) and for the reduction potential at 417 mV (y=1.952x-813.1; R²=0.997) versus Ag/AgCl at the MWCNT/ TiO₂ composite film modified GCE in aqueous solution.

**Calibration Curve**

Figure 9 shows the cyclic voltammograms of different concentrations of acetaminophen at the MWCNT/TiO₂ composite film modified GCE in 0.1 M phosphate buffer solution. A curve was observed from the dependence of the peak current on the concentration ranging between 0.01 and 2.00 mM of acetaminophen. Cyclic voltammograms of acetaminophen with different concentrations are shown in Figure 10.

The linear relationship was found from the dependence of peak current on concentration of acetaminophen for both the oxidation and reduction within the range of 0.01 and 1.2 mM concentration as shown in Figure 11.

![Fig. 8. A plot of the peak current against peak potential of acetaminophen at the MWCNT/TiO₂/GC composite film electrode in phosphate buffer solution using different scan rates of 5-600 mV/s.](image1)

![Fig. 9. Cyclic voltammograms were recorded at the MWCNT/TiO₂/GC composite film electrode of different acetaminophen concentration ranging from 0.01 to 2.00 mM in PBS (pH 7.0) with a scan rate of 100 mV/s.](image2)

![Fig. 10. Calibration curve for the determination of acetaminophen with various concentration ranging from 0.01 mM to 2 mM at the MWCNT/ TiO₂/GCE.](image3)

The linear equations were found with correlation coefficient as i_{pc}=89.94c-4.22; R²=0.991 and i_{pa}=113.3c-2.27; R²=0.990. From the Figure 12, the relationship between peak potential and concentration can be seen clearly. A good linearity described by the equation: y=40.09x+386.1; R²=0.942 for the oxidation and y=-35.42x+356; R²=0.909 reduction process of acetaminophen. Detection limit was calculated as 11.77 µM based on three times the standard deviation for the blank solution divided by the slope of the analytical curve.
Acetaminophen Determination
The applicability of the MWCNT/TiO$_2$/GCE in detection of acetaminophen was confirmed by its ability to detect in the presence of acetaminophen in commercially available acetaminophen tablets. Cyclic voltammetric technique was used for the determination of the extracted acetaminophen since it is a very sensitive and rapid method with low detection limit to detect the trace amounts of acetaminophen.

0.2 mM concentration of acetaminophen extracted from commercial tablets such as acetaminophen and Panadol, which contain 125 and 500 mg acetaminophen per tablet. The recoveries were obtained for the acetaminophen determination in commercial tablets using the MWCNT/TiO$_2$/GCE in 0.1 M phosphate buffer solution (pH 7.0). The voltammetric detection for acetaminophen extracted from commercial tablet sample using composite electrode was successfully applied and the recovery rates were 95±2% for the acetaminophen tablet and 96±2% for the Panadol tablet for five replicates (Table-2).
Table 2. Recovery rates of paracetamol (0.2 mm) extracted from commercially paracetamol tablet samples in 0.1 m phosphate buffer solution using MWCNT/TiO₂ composite modified glassy carbon electrode

<table>
<thead>
<tr>
<th>Chemical formulation</th>
<th>Mentioned concentration of acetaminophene (mg/tablet)</th>
<th>Obtained concentration of acetaminophene (mg/tablet)</th>
<th>Recovery (%)</th>
<th>Mean recovery (%)</th>
<th>Relative standard deviation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>125</td>
<td>120</td>
<td>96</td>
<td>95</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>119</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>115</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>122</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>118</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panadol</td>
<td>500</td>
<td>494</td>
<td>99</td>
<td>96</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>477</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>485</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>475</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>470</td>
<td>94</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

The MWCNT/TiO₂ composite film modified glassy carbon electrode has been fabricated and successfully applied in the determination of synthetic and real pharmaceutical sample by cyclic voltammetric technique. In both oxidation and reduction, the peak currents of acetaminophen were remarkably enhanced at the MWCNT/TiO₂ composite film modified glassy carbon electrode as compared to those at MWCNT modified and unmodified electrodes. Linear relationship of 0.998 and a good detection limit of 1 µM were obtained. Furthermore, some common analytical interfering substances such as ascorbic acid and methionine introduced did not affect the peak current of acetaminophen in pharmaceutical sample.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES