Amplified Electrochemical Sensor for Nano-molar Detection of Morphine in Drug Samples

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In this research, carbon paste electrode (CPE) was modified with MgO/SWCNTs nanocomposite and 1-methyl-3-octylimidazolium tetrafluoroborate (MOCITFB) and then used as a highly sensitive analytical approach for the determination of morphine in drug samples. In this study, the MgO/SWCNTs was synthesized using the simple precipitation method. The TEM image displayed the decoration of MgO nanoparticles with diameter ~ 40 nm at surface of SWCNTs. In addition, the electrochemical behavior of morphine was also investigated at surface of MgO/SWCNTs/MOCITFB/CPE with different pH values. The findings displayed an electro-oxidation mechanism in the presence of one electron and one proton. Moreover, the oxidation signal of morphine showed a linear calibration curve in the concentration range of 3.0 nM to 320 µM with the detection limit pf 0.8 nM at surface of MgO/SWCNTs/MOCITFB/CPE. Moreover, the MgO/SWCNTs/MOCITFB/CPE was successfully used for the determination of morphine in injection sample with recovery range of 98.41% to 102.49%.

Keywords: Morphine, MgO/SWCNTs, 1-methyl-3-octylimidazolium tetrafluoroborate, Nanocomposite, Modified sensor

1. INTRODUCTION

Morphine, as a famous opioid drug, is prescribed after many surgeries to relieve pain. Many research papers have confirmed that morphine has direct, peripheral analgesic properties [1,2]. In addition, morphine can be prescribed for both chronic and acute pain, which also is frequently used for pain during labor and myocardial infarction [3, 4]. Nevertheless, the dangers of morphine’s overuse such as feeling sick, constipation, and sleepiness, have made the control of the dose of the drug as well as its sequential analysis in biological samples important [5, 6]. Therefore, many analytical methods were suggested to determine the role of morphine in pharmaceutical and biological samples [7-11].
Furthermore, due to their many advantages, attention to electrochemical sensors has increased in the recent years [12-18].

Electrochemical sensors with a wide range of applications, easy operation, and low cost showed more advantages compared to the other analytical methods [19-25]. Additionally, with the advent of nanotechnology and the identification of many advantages of this type of materials [26-43], a new revolution was created in the design of electrochemical sensors [44-52]. In order to create sensitive and selective sensors, the targeted modification of nanomaterials has made some electrochemical tools as incredible approaches for the fabrication of decomposition sensors [53-63]. Nanomaterials such as carbon nanotubes, metal nanoparticles, and relative composites were rapidly used in the manufacture of sensitive electrochemical sensors [64-72].

Ionic liquids were suggested as green solvents with high catalytic activity and electrical conductivity [73-75]. Recently, ionic liquids showed more advantages for the modification of electrochemical sensors, especially carbon paste based sensors as binders [76, 77]. Moreover, two fold amplification of electrochemical sensors using nanomaterials and ionic liquids created a high electrical conductivity condition for the fabrication of highly sensitive electrochemical sensors [78-80]. The increased active surface area and electrical conductivity are known as two major advantages of nanomaterials and ionic liquids in the modification of electrochemical sensors [81-83].

In this study, MgO/SWCNTs and MOCITFB were introduced as two conductive mediators for the modification of CPE. Thereafter, the MgO/SWCNTs/MOCITFB/CPE showed a powerful ability for the determination of morphine with the detection limit of 0.8 nM.

2. EXPERIMENTAL

2.1. Materials and instruments

Morphine sulfate, magnesium nitrate hexahydrate, SWCNTs-COOH, sodium hydroxide, phosphoric acid, MOCITFB and paraffin oil were purchased from Sigma-Aldrich. Graphite powder was purchased from Merck. Stock solution of Morphine sulfate (0.01 M) was prepared by 0.668 g morphine sulfate into 10 mL distilled water. Electrochemical investigation was done by Vertex-Ivium potentiostat/galvanostat.

2.2. Synthesis of MgO/SWCNTs

At this stage, 100 mL magnesium nitrate hexahydrate (0.1 M) + 1.0 g SWCNTs-COOH was stirred for 30 min at 45 °C. Afterward, the 100 mL sodium hydroxide (0.2 M) was slowly added to the previously obtained solution and then stirred for 1 h. Also, black sample was filtered and then washed for five times. Subsequently, obtaining powder was dried for 18 h at 120 °C and then calcinated for 3 h at 600 °C. Thereafter, the MgO/SWCNTs nanocomposite was characterized using TEM method and obtaining image showed the decoration of MgO nanoparticle with diameter about 40 nm at surface of SWCNTs (Figure 1).
2.3. Fabrication of MgO/SWCNTs/MOCITFB/CPE

For the fabrication of MgO/SWCNTs/MOCITFB/CPE, 0.95 g graphite powder along with 0.05 gr MgO/SWCNTs were mixed into mortar and pestle in the presence of 10 mL ethanol. After the evaporation of ethanol, the paraffin oil and MOCITFB with ratio 8:2 (v:v) were added to the mixture and the obtained paste was input at the end of glass tube and then used as working electrode.

3. RESULTS AND DISCUSSION

3.1. Electrochemical investigation

Figure 2. Current peak potentials -pH curve for electro-oxidation of 500 μM morphine. Inset) linear sweep voltammogram of 500 μM morphine at surface of MgO/SWCNTs/MOCITFB/CPE in the pH range 5.0-9.0
Redox behavior of morphine with different pH values was investigated in this part. As shown in Figure 2, oxidation current peak potentials of morphine shifted to negative value with changing pH=5.0 to pH=9.0 with slope 60.1 mV/pH, which confirmed that the number of electron and proton is equal in redox mechanism of morphine (Scheme 1) [84]. On the other hand, the maximum oxidation current was observed for morphine at pH=7.0 and this pH was then selected as optimum condition for next steps.

Figure 3. LS voltammogram of 500 µM morphine at surface of a) CPE, b) MgO/SWCNTs/CPE, c) MOCITFB/CPE and MgO/SWCNTs/MOCITFB/CPE
The linear sweep voltammogram 500 µM morphine was recorded at surface of CPE (Figure 3 curve a), MgO/SWCNTs/CPE (Figure 3 curve b), MOCITFB/CPE (Figure 3 curve c), and MgO/SWCNTs/MOCITFB/CPE (Figure 3 curve d), respectively. Along with moving CPE to MgO/SWCNTs/MOCITFB/CPE, the oxidation current of morphine has increased from 6.9 µA to 23.4 µA, respectively. This improvement in the oxidation current of morphine confirmed the good catalytic activities of MgO/SWCNTs nanocomposite and MOCITFB for the modification of CPE [85].

On the other hand, the oxidation current of morphine showed a linear relationship with $ν^{1/2}$ in the scan rate ranged from 10 to 200 mV/s. This linear relationship confirmed the diffusion control process [86-91] to the electro-oxidation of morphine at surface of MgO/SWCNTs/MOCITFB/CPE (Figure 4).

In the present study, the diffusion coefficient ($D$) of morphine at surface of MgO/SWCNTs/MOCITFB/CPE was determined by recording chronoamperograms of 10.0 µM, 300.0, and 500 µM morphine by applying potential 750 mV (Figure 5 A). Recording Cottrell’s plot was then used for the determination of diffusion coefficient ($D$). Also, the mean value of $D$ was determined to be $\sim 4.8 \times 10^{-5}$ cm$^2$/s.

The differential pulse voltammetric method was used for the investigation of linear dynamic range as well as the limit of the detection of morphine using MgO/SWCNTs/MOCITFB/CPE, as an analytical tool (Figure 6 inset). The results show a linear relationship between the oxidation current of morphine and its concentration in the range of 3.0 nM to 320 µM with equation $I = 0.0929 C_{\text{morphine}} + 1.9291$ ($R^2 = 0.9918$) using MgO/SWCNTs/MOCITFB/CPE as an analytical sensor. Notably, the detection limit was calculated to be about 0.8 nM at surface of MgO/SWCNTs/MOCITFB/CPE. These values are comparable and in some cases better than previous reports (see table 1).
Figure 5. A) Chronoamperograms of a) 100.0 μM, b) 300.0 and c) 500 μM morphine. B) Cottrell’s plot relative to chronoamperograms.

Figure 6. Current-concentration plot for electro-oxidation of morphine. Inset) DP voltammograms of morphine in the concentration range 3.0 nM-320 μM.

The stability of MgO/SWCNTs/MOCITFB/CPE, as an analytical sensor for the determination of morphine, was investigated in a 45-day period. The oxidation current of morphine showed a stable response (about 93% initial signal) after 45 days that confirm it as a fabricated sensor with a good stability for the determination of morphine.
Table 1. Comparison of proposed sensors for measurement morphine

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Modifier</th>
<th>LDR (µM)</th>
<th>LOD (µM)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPE</td>
<td>Gold nanoparticle+Nafion</td>
<td>0.2-260</td>
<td>0.0013</td>
<td>[92]</td>
</tr>
<tr>
<td>CPE</td>
<td>Zn$_2$SnO$_4$–graphene nanocomposite</td>
<td>0.020–15</td>
<td>0.011</td>
<td>[93]</td>
</tr>
<tr>
<td>Pencil graphite electrode</td>
<td>---</td>
<td>1–100</td>
<td>0.26</td>
<td>[94]</td>
</tr>
<tr>
<td>Glassy carbon electrode</td>
<td>Mesoporous carbon</td>
<td>0.1-20</td>
<td>0.01</td>
<td>[95]</td>
</tr>
<tr>
<td>CPE</td>
<td>MgO/SWCNTs/MOCITFB</td>
<td>0.003-320</td>
<td>0.0008</td>
<td>This work</td>
</tr>
</tbody>
</table>

In addition, selectivity of MgO/SWCNTs/MOCITFB/CPE for the determination of 15 µM morphine was investigated with an acceptable error of 5% in current and by the use of the differential pulse voltammetric method. The results are indicated in table 1, which confirm a high selectivity of MgO/SWCNTs/MOCITFB/CP as a new electrochemical approach for the determination of morphine.

In the final step, the ability of MgO/SWCNTs/MOCITFB/CPE, as new analytical tool, was checked for the determination of morphine in the two different brand injection samples.

Table 2. The selectivity results relative to the electrooxidation of 15.0 µM morphine using MgO/SWCNTs/MOCITFB/CPE.

<table>
<thead>
<tr>
<th>Species</th>
<th>Tolerant limits (W$<em>{interference}$/W$</em>{morphine}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl$^-$, K$^+$, Mg$^{2+}$, Na$^+$</td>
<td>1000</td>
</tr>
<tr>
<td>Glucose</td>
<td>670</td>
</tr>
<tr>
<td>Alanine, Lysine, glycine</td>
<td>420</td>
</tr>
</tbody>
</table>

The standard addition results were also shown to be relative to the real sample analysis that are shown in table 2. Moreover, recovery data as 98.41-102.49 % approved the powerful ability of MgO/SWCNTs/MOCITFB/CPE as an analytical tool for the determination of morphine in real samples.

Table 3. Determination of morphine in injection samples (n=4)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Added</th>
<th>Expected</th>
<th>Founded</th>
<th>Recovery%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection (1)</td>
<td>---</td>
<td>---</td>
<td>2.03±0.12</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>10.00</td>
<td>12.03</td>
<td>12.33±0.51</td>
<td>102.49</td>
</tr>
<tr>
<td>Injection (2)</td>
<td>---</td>
<td>---</td>
<td>1.98±0.18</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>10.00</td>
<td>11.98</td>
<td>11.79±0.43</td>
<td>98.41</td>
</tr>
</tbody>
</table>
4. CONCLUSION

In this paper, a novel electrochemical tool was fabricated for the determination of morphine at nanomolar level. The MgO/SWCNTs/MOCITFB/CPE has improved the oxidation signal of morphine and helps in the determination of morphine in the concentration range of 3.0 nM to 320 µM with the detection limit of 0.8 nM. Furthermore, in this study, the MgO/SWCNTs/MOCITFB/CPE displayed a powerful ability for the determination of morphine in injection samples with acceptable recovery range of 98.41% to 102.49%.

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