Fe$_2$O$_3$/MWCNTs modified microdialysis electrode for dopamine detection

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Abstract

Dopamine (DA) is an essential neurotransmitter which plays important roles in human’s biological and cognitive processes, specifically learning, memory, emotions, and movements. Abnormality of dopamine level can signal the trace of neurological diseases. Dopamine detection, therefore, can be useful in detection of symptoms and diseases related to brain disorders such as Parkinson’s and depression. This study aimed at examining usage of hematite iron oxide (Fe$_2$O$_3$) as electrochemical sensors for dopamine detection. Nanoparticulate Fe$_2$O$_3$ was synthesized, microstructurally examined, and tested for its electrocatalytic activities. The synthesized powder showed a single phase with an average particle size of 93.9 nm. Electrocatalytic activities of the powder, measured in dopamine hydrochloride solutions with concentrations ranging from 0.1 to 10 $\mu$M, were evaluated by cyclic voltammetry technique. At applied voltage of 0.33 V, peak currents corresponding to oxidation reactions between dopamine and Fe$_2$O$_3$ electrode were detected. With sensitivity of Fe$_2$O$_3$ electrode in the range between 0.021 and 0.033 $\mu$A $\mu$M$^{-1}$, the Fe$_2$O$_3$ nanoparticles exhibited fair sensing ability.

1. Introduction

Dopamine (DA) is a monoamine neurotransmitter that plays a major role in motivation, learning, cognition and movement control of humans [1, 2]. Concentrations of dopamine in the range between 10 nM and 1 $\mu$M are normally detected in the extracellular fluid of the central nervous system [3, 4]. It has been extensively reported that neurological disorders such as Parkinson’s, Alzheimer’s and Huntington’s diseases, Tourette’s syndrome, schizophrenia and psychosis are associated with the abnormal levels of dopamine [5–7]. Detection of dopamine, therefore, is vital for diagnosis of diseases related to abnormal levels of dopamine.

In general, detection of chemical and neurotransmitters can be feasible through utilization of enzymatic and enzyme-less sensors. While enzymatic method has limitations in terms of enzyme deactivation, high cost, slow response time and incapability of sensing materials reuse, non-enzymatic sensors attract great interest due to their simplicity, rapidness, high sensitivity and ability of sensing in real-time analysis [8, 9].

Attributed to intrinsic redox nature of dopamine, non-enzymatic detection using electrochemical technique can be employed in examination of dopamine level. According to Hosseini et al electrochemical oxidation of dopamine in aqueous solutions occurs in three steps: (i) formation of O-dopaminoquinone via oxidation reaction, (ii) conversion of O-dopaminoquinone to leucodopaminochrome, and (iii) oxidation of leucodopaminochrome to form dopaminochrome [10].

With high availability and excellent characteristics such as biocompatibility and excellent catalytic activity, iron oxide is among promising electrochemical sensing materials. Detection of dopamine using iron oxide-based nanostructures as a sensing material has been reported. According to Fayemi et al mechanisms related to dopamine detection are described by the following reactions [11]:

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In general, the catalytic performance of Fe₂O₃ is highly dependent on its morphology and crystalline sizes. This study, therefore, aims at examining usage of nanopaticulate iron oxide (Fe₂O₃) synthesized by solution combustion technique as electrochemical sensor for dopamine detection.

2. Materials and methods

2.1. Powder synthesis
Iron oxide powders was synthesized by solution combustion techniques, using glycine (H₂NCH₂COOH, Daejung) as combustion fuel. Aqueous solution, containing iron (III) nitrate (Fe(NO₃)₃·9H₂O, Deajung) and glycine with the molar ratio of iron nitrate: glycine equal to 0.031:1.1 was used as initial reagents for combustion process. The combustion reaction was initiated by heating the prepared solution at 400 °C. As the combustion was completed, combusted powder was collected and calcined at 800 °C for 3 h.

2.2. Characterization
An x-ray diffractometer (Phillips, X’Pert) was employed in phase identification of the calcined powders. The diffraction measurements were conducted over 2θ angles ranging from 20° to 80° with scanning rate and step sizes of 0.7° min⁻¹ and 0.02°, respectively. Morphology of the powders was examined by scanning electron microscope (FEI Quanta 450) and transmission electron microscope (JEM-2200FS). Particle sizes of the oxide powders were determined using the Image J Software and Scherrer’s equation (4):

\[ D = \frac{0.9\lambda}{\beta \cos \theta} \]

where D is crystallite size (nm), \( \lambda \) is the wavelength (nm), \( \beta \) is the full width at half maximum (radian) of the diffracted peak with the highest intensity, and \( \theta \) is the diffraction angle (degree) of the diffracted peak.

Electrocatalytic activities of the synthesized iron oxide were evaluated using cyclic voltammetry technique. A potentiostat (Metrohm AutoLab: PGSTAT204) with an applied voltage and scan rate ranging between −0.8 to 0.8 V and 12.5 to 100 mV s⁻¹, respectively was used in the measurements.

To prepare the working electrode for the voltammetry measurement, the synthesized iron oxide particles were impregnated into multi-walled carbon nanotubes (MWCNTs) by hydrothermal technique. The oxide powder was mixed with MWCNTs and water with the ratio of iron oxide: MWCNTs: water = 1:1:0.8 in a Teflon-lined autoclave and heated at the temperature of 120 °C for 6 h. The iron oxide/MWCNTs composite was dispersed in 0.06 M ethanol. 2μl of the suspension was injected into a microdialysis electrode with the dimension of 220 μm in diameter and 4 mm in length with Pt and Ag/AgCl used as the counter electrode and the reference electrode, as shown in figure 1, respectively.

Detection of dopamine was conducted in 1 μM dopamine hydrochloride ((HO)₂C₆H₄CH₂CH₂NH₂·HCl), Sigma Aldrich) with concentrations ranging from 0.1–10 μM. Selectivity determination of dopamine in presence of glucose (C₆H₁₂O₆, Daejung), ascorbic acid (C₆H₈O₆, Daejung), and acetylcholine (C₇H₁₇NO₃, Sigma Aldrich) were conducted by chronoamperometry technique in solution containing 10 μM of glucose, ascorbic acid, cholin acetate, and dopamine hydrochloride.
3. Results and discussion

3.1. Chemical composition
Iron oxide powder was successfully synthesized by the solution combustion technique. X-ray diffraction pattern of the synthesized powder, as shown in figure 2, indicated a single phase corresponding to hematite (Fe₂O₃, JCPDS 01-089-0599). Iron oxide is a polymorphic material, which is commonly observed in three phases; hematite (α-Fe₂O₃), maghemite (γ-Fe₂O₃), and magnetite (Fe₃O₄). Hematite is considered as the most thermodynamically stable, biocompatible, and environment-friendly among the three phases [12]. Nevertheless, exploitation of hematite in some electronic applications is hindered as a result of low conductivity. In order to improve electronic properties of hematite for sensor application, hematite can be affixed onto surfaces of highly conductive materials, specifically multi-walled carbon nanotube (MWCNTs) to attain Fe₂O₃/MWCNTs composite with superior conductivity.

3.2. Microstructure and specific surface area
Particle morphology of the synthesized iron oxide powder was examination by scanning electron microscope (SEM) and transmission electron microscope (TEM), as shown in figure 3. Results from electron micrographs revealed uniaxial particles and slightly elongated particles with an average size of 93.86 ± 19.5 nanometer (via SEM) and 94 ± 30 nanometer (via TEM), was observed. Results from SEM and TEM, as shown in table 1, were in close proximity. In addition, an average crystallite size, determined by Scherer’s equation, was in the same range with those of the image analysis.

Specific surface area of 8.69 m² g⁻¹ was observed. Assuming that the particles are spherical, nonporous and also the theoretical density of the individual materials, the relationship between particle size and specific surface area was expressed by the following equation (5) [13]:

\[ D_p = \frac{6000}{\rho \times SSA} \] (5)

where \( D_p \) is average particle size (nm), \( \rho \) is density of the powder and (g cm⁻³) and SSA is the specific surface area (m² g⁻¹). From the equation, average particle size of the powder was 130.3 nanometer. Greater values of particle size determined from specific surface area compared to those obtained from image analysis revealed presence of particle agglomeration.

3.3. Electrocatalytic activities
The electrocatalytic activities of the Fe₂O₃/MWCNTs composites were examined by the cyclic voltammetry technique over the scan rates ranging from 12.5 to 100 mV s⁻¹. Cyclic voltammograms, as shown in figure 4(a), showed peak current corresponding to oxidation reactions of MWCNTs and Fe₂O₃ at applied voltage of 0.22 V and 0.33 V, respectively. As the scan rate is increased, the oxidation current peaks slightly shifted to positive potentials. Alteration of oxidation peak potentials on the scan rate denoted irreversibility of electrochemical reactions of Fe₂O₃/MWCNTs in dopamine. A similar observation was reported by Rastogi et al [14].

Electrocatalytic reactions of sensing materials in analyte solution are generally categorized into diffusion-controlled and adsorption-controlled reactions. While diffusion-controlled reactions mainly involve in rapid charge transfer of the electroactive species near the surface, adsorption-controlled reactions are mostly related to
concentrations of active sites on the surface and their ability to transfer charge. Peak currents are proportional to the square root of scan rate in diffusion-controlled reactions, whereas the peak current directly proportional to scan rate is evident in absorption-controlled reactions.

The relationship between current and scan rate in diffusion-controlled irreversible reaction can be represented by the following Randles-Sevcik equation:

\[
I_p = 2.99 \times 10^{-5} \alpha^{1/2} n^{3/2} A D^{1/2} v^{1/2}
\]

where \(I_p\) is peak current (A), \(\alpha\) is transfer coefficient, \(n\) is number of electrons, \(A\) is the working electrode area (cm\(^2\)), \(C\) is concentration (mol cm\(^{-3}\)), \(D\) is diffusion coefficient (cm\(^2\) s\(^{-1}\)) and \(v\) is scan rate (V s\(^{-1}\)).

Results from the current experiment, as shown in figure 4(b), indicated good correlation between peak current and square root of scan rate. The results suggested that the reaction between Fe\(_2\)O\(_3\)/MWCNTs electrode and dopamine is mainly controlled by diffusion mechanisms. The observation was similar to numerous studies reported by Kamyabi et al [16–18].

The relationship between current density and concentration (calibration curve) of Fe\(_2\)O\(_3\)/MWCNTs electrode measured in dopamine hydrochloride solution with concentration ranging from 0.1 to 10 \(\mu\)M was shown in figure 5. Sensitivity is generally determined from slope of the calibration curve. Sensitivity values of 0.021 to 0.033 \(\mu\)A \(\mu\)M\(^{-1}\) were evident in the current experiment. The \(R^2\) values ranging between 0.87 and 0.97 were greater than the generally accepted value of 0.75. Results from the current studies were comparable to the

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**Table 1.** Average particle sizes and crystallite size of Fe\(_2\)O\(_3\) determined from image analysis techniques and Scherrer’s equation.

|                  | Average particle size (nm) | Average crystallite size (nm) |
|------------------|----------------------------|-------------------------------|
| **SEM**          | 93.86 ± 19.5               | 94 ± 30                       |
| **TEM**          |                            | 81.86 ± 20.4                  |
| **Scherrer’s equation** |                  |                               |

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**Figure 3.** Scanning electron micrograph (a) and transmission electron micrograph (b) showing particle morphology of iron oxide powder synthesized by solution combustion technique.

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Table 1. Average particle sizes and crystallite size of Fe\(_2\)O\(_3\) determined from image analysis techniques and Scherrer’s equation.
range reported by Kamali et al. According to Kamali, oxidation peaks of iron oxide hematite with graphene oxide measured in dopamine was observed at applied potential close to 0.3 V. Sensitivity of 0.048 μA μM⁻¹ was observed in dopamine hydrochloride concentrations ranging from 0 to 90 μM [19].

Selectivity of the Fe₂O₃/MWCNTs electrode, which indicates capability of dopamine detection over the presence of interfering chemicals and neurochemicals such as glucose, ascorbic acid and acetylcholine, were evaluated using a chronoamperometry technique. The measurements were conducted at the applied voltage of 0.33 V. The chronoamperometric i-t profile, as shown in figure 6, revealed that only low-intensity peaks corresponding to glucose (Glu), ascorbic acid (AA) and acetylcholine (Ach) were present, whereas prominent high-intensity dopamine (DA) peaks were clearly evident. The results suggested relatively good selectivity of Fe₂O₃/MWCNTs electrode for dopamine detection.

Limit of detection (LOD) is key parameter that indicate performance of a sensor. LOD is generally influenced by noise level of detection signal and sensitivity of the sensor. LOD of a sensor can be calculated from the following equation (7):

\[
\text{LOD} = \frac{3\sigma}{S}
\]  

(7)

where \(\sigma\) is standard deviation of the peak current, and \(S\) is sensitivity or slope of the calibration curve.

Electrodes with low detection limit is generally desired for in-vivo detection of chemicals. Low values of LOD can be achieved by reducing standard deviation of peak current through diminution of signal interference or enhancement of sensor selectivity. Another mean to attain low LOD is through improvement of sensor sensitivity.

Figure 4. The cyclic voltammograms of iron oxide (a) and the relationship between peak current and square root of scan rate (b), measured in 1 μM dopamine hydrochloride solution at scan rates ranging from 12.5 to 100 mV s⁻¹.
The limit of detection of Fe$_2$O$_3$/MWCNTs electrode was found to be 0.3 μM, measured in the dopamine hydrochloride concentration ranging from 0.1 to 1 μM. Results from the current studies were comparable to the ranges reported by various studies, shown in table 2.

Repeatability and stability of Fe$_2$O$_3$/MWCNTs electrode were examined through recurrent measurements of oxidation peak currents in 10 μM dopamine hydrochloride solution over extensive measuring cycles. The results from repetitive cyclic voltammogram scanning revealed that at the measuring cycles lower than 200,
Degradation of oxidation peak currents was exceptionally low. As shown in Figure 7(a), the slope of the current-cycles graph was found to be $-1.82 \times 10^{-4}$, implying that peak current of Fe$_2$O$_3$/MWCNTs electrode in dopamine hydrochloride degraded by less than 1% over 100 measuring cycles. For measurements greater than 200 cycles, degradation of peak current intensified. The slope of the current-cycles graph shown in Figure 7(b) was fivefold greater than the value obtained in Figure 7(a). In the case of extensive repeated cycles, from 200 to 800 cycles, peak currents degraded by 5% over a measurement of 100 cycles.

Fair detection sensitivity at various concentration ranges, along with good selectivity and acceptable limit of detection suggested that the Fe$_2$O$_3$/MWCNTs electrode has potential usage for dopamine detection. Nevertheless, validity of dopamine detection of the electrode should be further confirmed by an in-vivo study.

### Table 2. Limit of detection of various electrodes used in dopamine detection.

| Electrode                  | Linear range ($\mu$M) | LOD ($\mu$M) | References |
|----------------------------|-----------------------|--------------|------------|
| Polypyrrrole/MCM-48/Au     | 2–120                 | 2.5          | [20]       |
| Nafion/MWCNT               | 0–10                  | 0.2          | [21]       |
| MWCNT/Fe$_2$O$_3$/2,3-Nc   | 3.27–24.3             | 1.77         | [22]       |
| EPPGE-SWCNT–Fe$_2$O$_3$    | 3.2–31.8              | 0.36         | [23]       |
| GCE/Cobalt salophen        | 1–100                 | 0.5          | [24]       |

Figure 7. Repeatability of Fe$_2$O$_3$ electrode measure in dopamine hydrochloride solution with concentration 10 $\mu$M.

4. Conclusions

Nanoparticulate of iron oxide was successfully synthesized by solution combustion technique. The synthesized powder indicated a single phase of hematite iron oxide (Fe$_2$O$_3$) with an average particle sizes of 93.9 nanometers. Electrocatalytic activities of the Fe$_2$O$_3$/MWCNTs composites in dopamine solutions with concentrations ranging from 0.1 to 10 $\mu$M were examined by the cyclic voltammetry technique. The oxidation reactions of dopamine/Fe$_2$O$_3$ occurred at the applied voltage of 0.33 V, with sensitivity in the range between 0.021 and
0.033 μA/μM. Fair detection sensitivity at various concentration ranges, along with good selectivity and acceptable limit of detection suggested that nanoparticulate iron oxide has potential usage for dopamine detection.

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