A Sensitive SiO$_2$@Fe$_3$O$_4$/GO Nanocomposite Modified Ionic Liquid Carbon Paste Electrode for the Determination of Cabergoline

Baniasadi, Mohammad**
Bam University of Medical Sciences, Bam, I.R. IRAN

Maaref, Hamed*+
NanoBioEletrochemistry Research Center, Bam University of Medical Sciences, Bam, I.R. IRAN

Dorzadeh, Athareh
Bam University of Medical Sciences, Bam, I.R. IRAN

Mohammad Alizadeh, Parsa
Student Research Committee, School of Public Health, Bam University of Medical Sciences, Bam, I.R. IRAN

ABSTRACT: In this study, the initial report on determining cabergoline via nanostructure-adjusted ionic liquid carbon paste electrode with aqueous solutions is described. For this purpose, an original adjusted carbon paste electrode that uses SiO$_2$@Fe$_3$O$_4$/GO nanocomposite and 1-methyl-3-butylimidazolium bromide as a binder (SiO$_2$@Fe$_3$O$_4$/GO/CPILE) was designed. Cabergoline oxidation peak at SiO$_2$@Fe$_3$O$_4$/GO/CPILE surface was 500 mV that was approximately 200 mV less compared to the oxidation potential pertaining to the CPE surface subjected to a similar state. Moreover, there was an increase in the peak current of approximately 3.0 times greater at SiO$_2$@Fe$_3$O$_4$/GO/CPILE surface in comparison to that of the CPE. The relevant linear response range and detection limit were determined as 0.07–500.0 and 0.01 μM, correspondingly. The adjusted electrode was successful in determining cabergoline within real specimens entailing adequate results.

KEYWORDS: Cabergoline; Carbon paste electrode; SiO$_2$@Fe$_3$O$_4$/GO nanocomposite; Ionic liquid.

INTRODUCTION

Cabergoline, N-[3-(dimethylamino)propyl]-N-(ethylamino)carbonyl-6-(2-propenyl)-ergoline-8b-carboxamide is a derivative of ergot alkaloid that exhibits dopamine agonist behavior [1]. Evidently, it invokes long term hindrance in prolactin secretion within hyperprolactinemia patients and rats. Furthermore, it is evident that Parkinson symptoms are appeased within monkeys treated with MPTP in addition to being...
influential in treating Parkinson’s disease [2-6]. Inadequate UV fluorescence and absorbance is displayed by cabergoline in addition to insufficient volatility and stability, thus analytical techniques, namely gas chromatographic methods and high-performance liquid chromatography using fluorescence or UV detection are not suitable for sensitive determination [7]. Numerous methods are established and approved to ascertain cabergoline e.g. electrochemical techniques, liquid chromatography-tandem mass spectrometry, and high-performance liquid chromatographic spectrophotometry electrospray ionization tandem mass spectrometry [8-12]. From the aforementioned techniques, electroanalytical techniques are defined by adequate speed, accuracy, affordable cost, and instrumental simplicity [14-22]. The cabergoline structure possesses indole moiety including a pyrrole ring and a benzene ring. Redox responses may emanate from indole derivatives [2].

The carbon paste electrodes consisting of an organic liquid and carbon particles are extensively implemented for electrochemical sensing and biosensing because of its cost-efficient trait, fabrication simplicity, and revivable surface [23-25]. Moreover, the inadequate competency of unadjusted electrodes concerning the direct electrochemical behavior of various electro-active substances has resulted in an added focus on adjusted electrodes and mediators for catalyzing electrochemical oxidation and/or reduction [26-53]. RTILs i.e. room-temperature ionic liquids containing exceptional physiochemical traits e.g. high viscosity, high thermal stability, insignificant vapor pressure, vast electrochemical windows, and great ionic conductivity are the centers of focus as an alternate binder in preparing electrochemical sensors. The fabricated ionic liquid-based carbon paste electrodes facilitate electron transfer rate in addition to enhanced selectivity and sensitivity to determine various environmental and biological species [54, 55].

A 2D substance is known as Graphene Oxide (GO) has been the center of studies due to its exceptional properties e.g. extensive specific surface area, optimal electrical conductivity, and mechanical rigidity. Moreover, various traits of functional molecules may be substantially enhanced via adsorption onto graphene support. Currently, the graphene sheet and inorganic substance combination has enabled extensive graphene utilization. GO-magnetic hybrids are fabricated for numerous uses. Iron-based spinel oxides namely, cost efficient Fe₃O₄ are subjected to researches as anode materials pertaining to electro catalysts. In addition, Coating the surface of magnetite nanoparticles with inert silica nanoparticles is a strategy to prevent aggregation of magnetite nanoparticles, improving their chemical stability, and providing better protection against toxic chemicals [56-58].

The comprehensive study of relevant literature did not highlight any investigations on simultaneously determining cabergoline electrocatalytic behavior by applying an adjusted carbon paste electrode with SiO₂@Fe₃O₄/GO nanocomposite and 1-methyl-3-butylimidazolium bromide as a binder (SiO₂@Fe₃O₄/GO/CPLE). Therefore, an adjusted electrode was fabricated whilst investigating its performance in cabergoline quantification. The final adjusted electrode was applied to determine cabergoline concentration within real specimens.

**EXPERIMENTAL SECTION**

**Apparatus and chemicals**

The electrochemical measurements were conducted using an Autolab PGSTAT 302 N (Eco Chemie, the Netherlands) potentiostat/galvanostat. The functioning state was supervised on a General Purpose Electrochemical System (GPES) software. An electrochemical system of three electrodes consisting of an optimal SiO₂@Fe₃O₄/GO/CPLE, a platinum wire in the role of a counter electrode and an Ag/AgCl/KCl (3.0 M) reference electrode was employed to conduct measurements. The pH values were derived via a Metrohm 710 pH meter. The required cabergoline and relevant analytical grade reagents were acquired from Merck Co. and double distilled water was used to prepare the test solutions. Orthophosphoric acid buffers and relevant salts were then assembled (pH= 2.0 to 9.0).

**Preparation of SiO₂@Fe₃O₄/GO nanocomposite**

In order to carboxylate GO, a GO aqueous suspension of 50 mL was subjected to dilution by a factor of 2 in order to achieve 2 mg mL⁻¹ concentration before being bath sonicated for a period of one hour to achieve a translucent solution. chloroacetic acid (Cl–CH₂–COOH) (10 g) and NaOH (12 g) were also added to GO suspension and hence bath sonicated for a period of two
hours in order to transform –OH ZnSups to –COOH by conjugating acetic acid moieties resulting in G-COOH. The produced G-OOH solution was subjected to neutralization and purification through repetitive filtering and rinsing.

Approximately 0.06 grams of GO-COOH was diluted within 42 mL of water using ultrasonic irradiation (Sono swiss SW3-H, 38 kHz, Switzerland) for a period of 20 minutes. The concoction was then stirred further intensely for a period of 30 minutes under a temperature of 60 °C. In the next stage, 106.2 mg of FeCl$_3$·6H$_2$O was included whilst stirring. Upon vigorous stirring for 30 minutes at N$_2$ atmosphere, 57 mg of FeSO$_4$·7H$_2$O was included and stirring commenced for another 30 minutes under N$_2$ atmosphere. Finally, 18 mL of 6% NH$_4$OH aqueous solution was included in the concoction in a drop-wise manner under a temperature of 60 °C for an hour and then reacted for a further 2 hours. The N$_2$ atmosphere was utilized amidst reaction to avert critical oxidation. The response concoction was subjected to centrifugation using double distilled water prior to being dried. The acquired black precipitate was Fe$_3$O$_4$/GO nanocomposite which was ready to use. Fe$_3$O$_4$/GO nanocomposites were assembled using developing layers of silica onto Fe$_3$O$_4$/GO surface. 15 mL of ethanol, 90 mL of tetraethoxysilane (TEOS), 0.6 mL ammonium hydroxide, and 0.6 mL of water was included in a 250 mL three-neck flask under a 40 °C temperature water bath. Fe$_3$O$_4$/GO was included in the solution amidst mechanical stirring. Extraction of solution aliquots took place upon the passing of 12 hours via centrifugation and then washed using water. It was finally vacuum dried under 60 °C temperature overnight (see Fig. 1) (59).

**Electrode preparation**

SiO$_2$@Fe$_3$O$_4$/GO/CPILEs are normally assembled via blending 0.96 grams graphite powder and 0.04 g of SiO$_2$@Fe$_3$O$_4$/GO nanocomposite within a mortar, about 0.03 mL ionic liquids with the addition of 0.4 mL paraffin oil to the concoction. In the next stage, the suspension was subjected to mixing for 20 minutes and the produced uniform paste was placed in a glass tube of ca. 3.4 mm i.d. × 15 cm. A copper wire is placed within the carbon paste from the opposing side to enable electrical contact. The electrode external surface was then polished using abrasive paper prior to being used.

For comparison reasons, a series of SiO$_2$@Fe$_3$O$_4$/GO nanocomposite carbon paste electrodes lacking IL (SiO$_2$@Fe$_3$O$_4$/GO/CPE), IL-modified CPEs lacking SiO$_2$@Fe$_3$O$_4$/GO nanocomposite (CPILE), and unadjusted CPEs without IL and SiO$_2$@Fe$_3$O$_4$/GO nanocomposite were assembled using an identical method to the original electrode method and then tested.

**The real specimens**

Upon gathering, the urine specimens were preserved in a refrigerator. Before use, 10mL of every specimen was subjected to centrifugation at 2000 rpm for a quarter. Then, filtering was conducted on the supernatant using a 0.45 μm filter and various solution volumes were placed into a 25 mL flask prior to dilution to the mark via PBS of pH=7.0. The specimens were spiked using different cabergoline quantities.

The serum samples were then centrifuged prior to being filtered and diluted using PBS pH=7.0 and spiked using various quantities of the same composite.

**RESULTS AND DISCUSSION**

**Electrochemical characterization of electrodes**

[Fe(CN)$_6$]$^{3-}$/4$^+$ pairs are typically used as an electrochemical probe to investigate the traits of the sensors. The SiO$_2$@Fe$_3$O$_4$/GO/CPILE electrochemical performance was conducted within 5.0 mM [Fe(CN)$_6$]$^{3-}$/4$^+$ redox probe. According to Fig. 2, the SiO$_2$@Fe$_3$O$_4$/GO/CPILE redox peaks are substantially improved compared to that of the unadjusted CPE and SiO$_2$@Fe$_3$O$_4$/GO/CPILE. The reason can be accredited to the exceptional electron mediator property of the ILs
and the vast surface areas of the SiO$_2$@Fe$_3$O$_4$/GO nanocomposite whilst accelerating the transfer of electrons thus leading to the greater current reaction. The SiO$_2$@Fe$_3$O$_4$/GO/CPILE peak potential ($\Delta$E$_p$) among the cathodic and anodic peak potential is approximately 68 mV. This value for the unadjusted CPE is 128 mV. Thus, an insignificant $\Delta$E$_p$ value pertaining to SiO$_2$@Fe$_3$O$_4$/GO/CPILE shows an expeditious and quasi reversible electron transfer scheme, proving the ability of the electrode in providing an optimal microenvironment to undertake effortless electron transfer response.

Real surface areas of the SiO$_2$@Fe$_3$O$_4$/GO/CPILE and CPE were acquired via CV by employing 5.0 mM K$_3$Fe(CN)$_6$ which acted as a probe under various scan rates. The Randles-Sevcik formulation was used for the reversible procedure:

$$I_p = \pm \left(2.69 \times 10^5\right)n^{3/2}AD^{1/2}Cv^{1/2}$$  \hspace{1cm} (1)

Such that $I_{pa}$ (A) denotes anodic peak current and $n$ represents electron transfer number. A denotes electrode $D$ surface area, $D$ denotes diffusion coefficient, $C$ is the K$_3$Fe(CN)$_6$ concentration in (mol cm$^{-3}$), $v$ represents scan rate. In the case that 5.0 mM K$_3$Fe(CN)$_6$ within 0.1 M KCl electrolyte where $n = 1$ and $D = 7.6 \times 10^{-6}$ cm$^2$s$^{-1}$, thus from the $I_{pa} - v^{1/2}$ relation slope, real surface areas are derived. The findings indicate that for the CPE, the electron surface area is 0.1719 cm$^2$ and for the SiO$_2$@Fe$_3$O$_4$/GO/CPILE, the surface area is 0.2647 cm$^2$. Hence, the surface areas for SiO$_2$@Fe$_3$O$_4$/GO/CPILE were 1.54 times greater compared to that of the CPE. Although, the analyte peak current increase at SiO$_2$@Fe$_3$O$_4$/GO/CPILE surface does not only result from the surface area the IL and SiO$_2$@Fe$_3$O$_4$/GO nanocomposite synergic impact on cabergoline oxidation is also influential.

EIS is considered an influential probe in determining the adjusted electrode’s electron transfer traits. Fig. 3 shows the CPE, CPILE and SiO$_2$@Fe$_3$O$_4$/GO/CPILE Nyquist plots within 5.0 mM [Fe(CN)$_6$]$^{3-/4-}$ possessing 0.1 M KCl. The electrode surface electron transfer resistance i.e. $R_C$ is equal to EIS semicircle diameter which may be useful in describing the electrode’s interface characteristics. A large semicircle of about 1036 $\Omega$ ($R_C$) diameter was evident at the bare CPE (curve a) which shows a significantly low electron transfer rate among the CPE and electrochemical probe [Fe(CN)$_6$]$^{3-/4-}$. Moreover, in regard to the Nyquist plots, there were significantly smaller semicircle diameters that were approximately 706 $\Omega$ (curve b) which shows the CPE electrode conductivity promoted by the IL. Upon the addition of the SiO$_2$@Fe$_3$O$_4$/GO nanocomposite to the CPILE electrode, there was a reduction of the $R_C$ down to 82 $\Omega$. The figure shows the impedance variances at the adjusted electrodes which validates the exceptional conductivity of the SiO$_2$@Fe$_3$O$_4$/GO nanocomposite which expedites electron transfer. The evident impedance variances stemmed from the IL and SiO$_2$@Fe$_3$O$_4$/GO nanocomposite synergic impact in [Fe(CN)$_6$]$^{3-/4-}$ electrochemical response as well as the surface area traits.
Fig. 4: CVs of a) SiO\textsubscript{2}@Fe\textsubscript{3}O\textsubscript{4}/GO/CPILE and b) unmodified CPE in the presence of 100.0 µM cabergoline at a pH 7.0, respectively. In all cases the scan rate was 50 mV/s.

Oxidation of cabergoline at the surface of the SiO\textsubscript{2}@Fe\textsubscript{3}O\textsubscript{4}/GO/CPILE

Cabergoline activities depend mostly on the pH solution whilst this is not the case concerning Fe/Fe\textsuperscript{3+}. Thus, pH optimization is a vital stage. Hence, CV investigations took place utilizing 0.1 PBS solutions of different pH values within the 2.0 to 9.0 range. The tests showed cabergoline electrocatalytic oxidation was more optimal with neutral pH values as exhibited via moderate increments and decrements of the cathodic and anodic peak currents. According to the data, optimal pH was 7.0 thus it was employed for all tests.

Fig. 4 shows the cyclic voltammetric reactions emanating from 100.0 µM cabergoline electrochemical oxidation at SiO\textsubscript{2}@Fe\textsubscript{3}O\textsubscript{4}/GO/CPILE (curve a) and bare CPE (curve b) surface. The relevant anodic peak potential for cabergoline oxidation at SiO\textsubscript{2}@Fe\textsubscript{3}O\textsubscript{4}/GO/CPILE was approximately 550 mV whereas it was 750 mV for the unadjusted CPE. Likewise, when comparing cabergoline oxidation at SiO\textsubscript{2}@Fe\textsubscript{3}O\textsubscript{4}/GO/CPILE and unadjusted CPE, it is evident that there is a substantial enhancement in terms of anodic peak current at SiO\textsubscript{2}@Fe\textsubscript{3}O\textsubscript{4}/GO/CPILE in relation to the acquired value for the unadjusted CPE. Essentially, the findings clarify the cabergoline oxidation signal is improved by ionic liquids and the SiO\textsubscript{2}@Fe\textsubscript{3}O\textsubscript{4}/GO nanocomposite.

pH effect

The pH effect of the existing electrolyte on the potentials and anodic peak currents was studied to obtain the optimal shape and peak current. Herein, differential pulse voltammetric evaluation was performed on several buffered solutions within the 3.0 to 9.0 pH range pertaining to the cabergoline solutions. Fig. 5 shows that in the case that the pH is enhanced to 5.0 from 3.0, there was a reduction in current and then an enhancement in peak current up to 0.7 before another reduction.

Thus, the optimal pH was 7.0. Hence, pH=7.0 and 0.1 M phosphate buffer solution was chosen as the supplementary electrolyte for the voltammetric analysis. Cabergoline $E_{p,a}$ exhibits a linear relationship with buffer solution pH (as shown in Fig. 5) for the equation (2):

$$E_{p,a} (V) = -0.0493pH + 0.9457 \quad \left( R^2 = 0.9915 \right) \quad (2)$$

Regarding the cabergoline slope of -50.0 mV/pH, equal electron and proton quantities are contributing to the electrodes’ reactions. Scheme 1 presents the assumed cabergoline oxidation technique.

Scan rate effect

The potential scan rate impact on cabergoline oxidation current is investigated (Fig. 6). The findings indicate that when the potential scan rate is enhanced, there is an enhancement in peak current. Additionally, the oxidation procedure is diffusion-controlled which is derived from linear reliance of anodic peak current ($I_p$) on potential scan rate square root ($\nu^{1/2}$) across an extensive 10 -600 mV/s range.

Chronoamperometric studies

Cabergoline chronoamperometric measurements were conducted at SiO\textsubscript{2}@Fe\textsubscript{3}O\textsubscript{4}/GO/CPILE via selecting
Scheme 1. Electro-oxidation mechanism of cabergoline at SiO$_2$@Fe$_3$O$_4$/GO/CPILE.

**Fig. 6**: LSVs of SiO$_2$@Fe$_3$O$_4$/GO/CPILE in 0.1 M PBS (pH 7.0) containing 200.0 μM cabergoline at various scan rates; numbers 1-7 correspond to 10, 30, 50, 100, 200, 400 and 600 mV/s, respectively. Inset: Variation of anodic peak current vs. square root of scan rate.

**Fig. 7**: Chronoamperograms obtained at SiO$_2$@Fe$_3$O$_4$/GO/CPILE in 0.1 M PBS (pH 7.0) for different concentrations of cabergoline. The numbers 1–4 correspond to 0.1, 0.6, 1.0, and 1.5 mM of cabergoline. Inset: (A) Plots of I vs. $t^{-1/2}$ obtained from chronoamperograms 1–4. (B) Plot of the slope of the straight lines against cabergoline concentration.

The mean value of D derived from the Cottrell equation and the resulting slope was $1.9 \times 10^{-6}$ cm$^2$/s.

**The calibration curve and limit of detection**

Cabergoline oxidation peak current at the adjusted electrode surface may be utilized to ascertain cabergoline within a solution. Thus, DPV tests were conducted for various cabergoline concentrations as shown in Fig. 8. Cabergoline oxidation peak currents at unadjusted electrode surface corresponded to cabergoline concentrations within the 0.07 to 500.0 μM range. The Cabergoline detection limit was 0.01 μM.

A comparison is presented between SiO$_2$@Fe$_3$O$_4$/GO/CPILE analytical performances resulting from this study with the sensors contributing to...
is investigated at optimal circumstances with 20.0 μM cabergoline at pH= 7.0. The possibly contributing materials were selected among a set of materials typically observed with cabergoline within biological and/or pharmaceutical liquids. The limit of tolerance was determined as the maximal concentrations of contributing materials which led to an error that was less than ±6% in determining cabergoline. Based on the findings, urea, saturated starch solution, folic acid (vitamin B₉), glycine, phenylalanine, methionine, alanine, Cl⁻ or F⁻, Fe²⁺,CO₃²⁻, NH₄⁺, Fe²⁺, Al³⁺, SO₄²⁻, Mg²⁺, ethanol, methanol, citric acid, fructose, lactose, sucrose, and glucose were not involved in determining cabergoline.

In the vicinity of cabergoline, voltammograms were documented upon potential cycling of 20 repetitions at 50 mV/s scan rate. Based on the outcomes, there were no changes in terms of peak potentials apart from a decrease of less than 2.43%. The results validated the greater sensitivity and decreased fouling impact of SiO₂@Fe₃O₄/GO/CPILE in regard to cabergoline and relevant oxidation byproducts.

**Real samples analysis**

In order to validate the competency of the adjusted electrode to implement in real analytical cases, it was utilized to determine cabergoline within urine specimens and human blood serum. The findings for cabergoline concentration within real samples are shown in Table 2. Based on this table, there were adequate recovery results achieved for cabergoline. Cabergoline reproducibility is denoted in terms of the relative standard deviation i.e. RSD.

**CONCLUSIONS**

The adjusted paste electrode was developed via blending graphite, SiO₂@Fe₃O₄/GO nanocomposite,
Table 2: The application of SiO$_2$@Fe$_3$O$_4$/GO/CPILE for concurrent determination of cabergoline in human blood serum and urine samples (n=5). All concentrations are in µM.

<table>
<thead>
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<th>Sample</th>
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<th>Found</th>
<th>Recovery (%)</th>
<th>R.S.D. (%)</th>
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<td>-</td>
<td>-</td>
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<td>5.0</td>
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<tr>
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paraffin (SiO$_2$@Fe$_3$O$_4$/GO/CPILE) and ionic liquids. By making the most of the structural benefits of SiO$_2$@Fe$_3$O$_4$/GO nanocomposite as well as the favorable IL conductivity, the recommended sensor displayed exceptional electrochemical behavior in regard to cabergoline. The electrochemical activity of cabergoline in regard to the adjusted electrode was subjected to meticulous examination including the calculation of electrochemical parameters. This electrochemical procedure exhibits the trait of a diffusion control system and is quasi reversible. This recommended sensor exhibited favorable properties, namely long-term stability, low detection limit, extensive linear calibration range, high sensitivity, affordable cost, and simplicity. Lastly, the fabricated sensor was implemented to determine cabergoline within real specimens and sufficient recoveries were acquired.

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