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A sensitive electrochemical sensor for rapid and selective determination of codeine in biological samples using carbon paste electrode modified with carbon nanotube and nickel oxide nanoparticles

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Abstract. This work reports on the analytical performance of carbon paste electrodes (CPE) modified with multi wall carbon nanotubes (MWCNT) and NiO nanoparticles for the determination of codeine. The morphology of Ni nanoparticles was investigated by scanning electron microscopy (SEM). Cyclic voltammetry and differential pulse voltammetry used for qualitative and quantitative electrochemical evaluation of codeine. Under the suitable conditions, the peak current increased linearly with the concentration of codeine in the range of 0.03 to 12.00 μM, with limits of detection (LOD) and the limits of quantitation (LOQ) 0.015 and 0.05 μM respectively. The proposed electrochemical sensor was successfully applied for quantifying codeine in various real samples includes Urine, Human serum, Codeine tablet.

Keywords: Sensitive electrochemical sensor, biological, carbon, nickel oxide nanoparticles, codeine

1. INTRODUCTION

One of the roles of analytical chemistry is analysis and measurement of drug in biological and pharmaceutical industry products samples. Electrochemistry as a branch of chemistry with using nanoparticles has been much progress in measuring trace amounts of drugs. Nanoscale particles of transition metals are gaining continuous importance for various applications such as catalysts, passive electronic components and ceramic materials and electrochemical sensor for determination of drugs and ions [1-6].

Methyl morphine or Codeine (Fig. 1) is a natural opiates alkaloid from poppy or prepared from morphine by methylation, has long been used as an effective analgesic and antitussive agent [7-9].

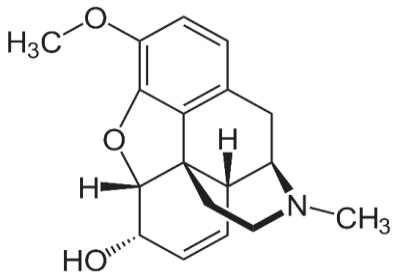

Figure 1. Structure of Codeine.

Codeine has been used for over 200 years and is available in many over-the-counter remedies for cough and for acute and chronic mild to moderate pain. It was recommended for the treatment

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of breakthrough pain when nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen were ineffective [10]. The pharmacological properties of codeine are weaker than morphine. For example, analgesic action of codeine is 1/20 of morphine activity [9-11].

Fast and sensitive method for selective determination of this biomolecule is necessary in biological fluids such as plasma and urine, because of their effect on the human body. For this purpose, several methods have been reported for the detection of codeine. High performance liquid chromatography (HPLC) with ultraviolet (UV) detection [12-14], Gas chromatography [15-18], thin-layer chromatography [19], capillary electrophoresis [20- 22], are examples of these determination methods. On the other hand, electrochemical methods offer the practical advantages involving operation simplicity, low expense of instrument, suitability for real-time detection and less sensitivity to matrix effects in comparison with above mentioned analytical methods [23, 24]. In Last year to now, several paper have been devoted to the determination of codeine by electrochemical methods. Ensafi and his research group have described the sensitive determination of codeine using the sensor based on porous silicon/palladium nanostructure for simultaneous determination of acetaminophen and codeine with detection limit of 0.3 μM for codeine [25]. As well, Pereira and coworkers were applied an electrochemical methods for simultaneous determination of promethazine and codeine. Detection limit for determination of codeine in this research was obtained 28 mg/L [26].

In this work, a new electrochemical sensor, based on nickel nanoparticles, carbon nanotube and carbon past, was fabricated and used in the determination of codeine. The electrochemical behaviors of codeine on the NiO/CNT/CPE were investigated and discussed. A new electroanalytical method of codeine was proposed with a wide linear range from 0.03 to 12.00 μM and a lower detection limit of 0.015 μM. the modified electrode exhibited good electrochemical performance with good stability, high selectivity and reproducibility. The modified electrode is very appropriate for determination of codeine in biological and pharmaceutical samples.

2. EXPERIMENTAL

2.1. Chemicals

All chemicals used were of analytical reagent grade purchased from Merck (Darmstadt, Germany) unless otherwise stated. Doubly distilled water was used throughout. A 1.0×10^{-2} mol L−1 codeine solution was prepared daily by dissolving 0.399 g codeine phosphate in water and the solution was diluted to 100 mL with water in a 100 mL volumetric flask. The solution was kept in the refrigerator at 4°C in the dark. Nickel chloride (NiCl2·6H2O), hydrazine hydrate (80 wt. %), sodium hydroxide (purity 99%), and dodecanethiol (purity 96%) for synthesis NiO nanoparticles were purchased from Merck company. Graphite powder with a 10 μm particle size and highly pure paraffin (both were purchased from Merck) and multiwall carbon nanotubes [>90% MWCNT basis, d×l = (110–70 nm) × (5–9 μm)] from Fluka were used as the substrate for the preparation of the working electrodes. Laboratory glassware was kept overnight in a 10% (v/v) HNO3 solution and then rinsed with DDW. Britton–Robinson (B–R) (4.0×10^{-2} mol L^{-1}) buffer solution of pH 2–11 ($CH_3COOH + H_3BO_3 + H_3PO_4$) was used as the supporting electrolyte. The pH was adjusted using 0.2 mol L^{-1} NaOH.

2.2. Instrumentation

All voltammetry experiments were performed using the Metrohm model 797 VA Computrac polarograph. A conventional three electrode cell assembly consisting of a platinum wire as an

auxiliary electrode and a saturated calomel electrode (SCE) as a reference electrode was used. Different modified CPE was used as working electrode. Scanning electron microscopy (SEM) images were conducted with a SEM-EDX, XL30; Philips scanning electron microscope (Netherland). Metrohm pH meter (Model 827) with a glass electrode (Corning) was used to adjust the solution pH.

2.3. Functionalization and purification of MWCNTs

MWCNTs were purified and functionalized, as described elsewhere [27]. A mass of 120 mg of MWCNTs was stirred in 10 mL of a 3 mol L^{-1} nitric acid solution for 20 h. The solid product was collected on a filter paper and washed several times with pure water until the filtrate solution was neutral (pH7.0). The obtained functionalized MWCNTs were then dried in an oven at 80 ^{o}C for 24 h.

2.4. Synthesis of NiO

Nickel oxide nanoparticles was synthesized according to the method proposed in Reference [28]. An appropriate amount of nickel chloride (final Ni concentration were 0.1, 0.2 and 0.3 M) and dodecanethiol was directly dissolved in 60 ml ethanol (95%) contained in a round-bottomed flask by vigorous stirring on a magnetic-stirrer equipped with a heating unit. The nickel chloride and decanethiol mixture was continuously stirred and heated to 60 ◦C, then 10 ml hydrazinium hydroxide solution (purity 80%) was added into the reaction mixture of nickel chloride and dodecanethiol and the pH value of the mixed solution was adjusted to 12 using sodium hydroxide. The mixture of the three kinds of reactants was kept at 60 ◦C and continuously vigorously stirred for 2 h. At the end of the reduction reaction, the mixed solution in the round-bottomed flask was cooled in ambient condition to room temperature. The product was collected by filtering and the residue unreacted decanethiolwas removed by fully rinsing with ethanol and acetone. Fig. 1 shows SEM image of Ni nanoparticles in different concentration.

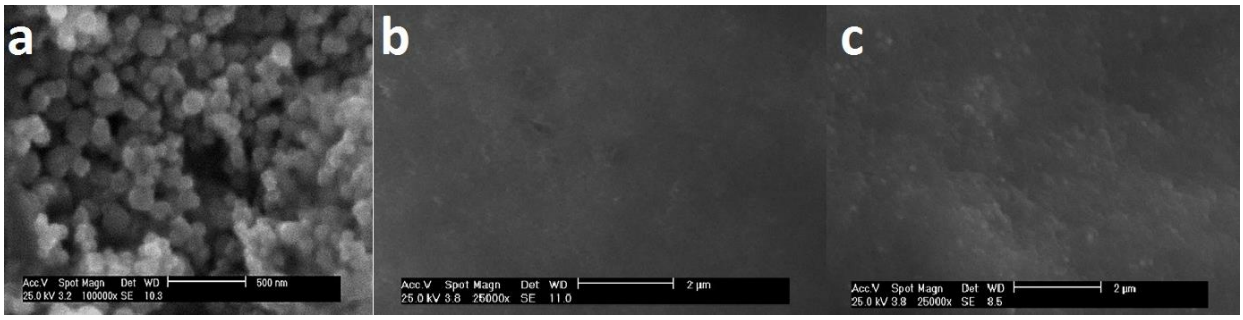

Figure 1. SEM image Ni nanoparticles formed from 0.1, 0.2 and 0.3 M of nickel chloride.

2.5. Electrode preparation and modification

CPE was prepared by thoroughly hand mixing of graphite powder with appropriate amount of binder (paraffin oil) in a mortar using a pestle (75:25, w/w %). CNTCPE was prepared by mixing of CNTs, graphite powder and the liquid paraffin (10:65:25, w/w %). NiO/CNT/CPE was prepared by mixing of 0.01 g of NiO, 0.02 g of CNTs, 0.12 g of graphite powder and 0.05 g of the liquid paraffin. Then the mixture was mixed well for 50 min until a uniformly wetted paste was obtained. A portion of the paste was filled firmly into one glass tube. Electrical contact was made by pushing a copper wire down the glass tube into the back of the mixture. When necessary, a new surface was obtained by pushing an excess of the paste out of the tube and polishing it on a weighing paper.

2.6. Preparation of real samples

This study was conducted by the Ethics Committee and written informed consents were obtained from all volunteers. Urine samples were stored in a refrigerator at 4 °C immediately after collection. Ten milliliters of each sample was centrifuged for 15 min at 2500 rpm. The supernatant was filtered using a 0.45 μm filter and then diluted five times with B-R buffer solution (pH 7.0). The solution was transferred into the voltammetric cell to be analyzed without any further pretreatment. Standard addition method was used for the determination of codeine in the samples. In order to precipitate proteins in the plasma samples, 1.0mL of the samples was treated with20 mL perchloric acid ($HClO_4$, 20% v/v).Then, the mixture was vortexed for a further 30s and then centrifuged at 6000 rpm for 5 min. The solution was diluted five times with water and transferred in to the voltammetric cell to be analyzed without any further pretreatment. Standard addition method was used for the determination of codeine in the samples [29]. For Pharmaceutical sample preparation ten codeine tablets were powdered and mixed thoroughly. An amount of 3.0 mg of ground codeine tablet was weighed and dissolved with 10.0 mL warm water. After 30 min of sonication, the sample was filtered through a Whatman filter paper (No. 1), transferred to a 25.0 mL volumetric flask, and diluted to the mark with double-distilled water. An aliquot of 1.0 mL of this solution was transferred to a 50.0 mL volumetric flask and diluted with B-R buffer solution at pH 7.0. This solution was used for doing the electrochemical experiments.

2.7. Measurement procedures

For all measurements a known volume of codeine standard solution was pipetted into a 50 mL volumetric flask and then filled up with the supporting electrolyte. This solution was subsequently transferred quantitatively into voltammetric cell. The solutions were deoxygenated by bubbling with high-purity nitrogen for at least 10 min prior to each experiment. Cyclic voltammetry (CV) and square wave voltammetry (SWV) were employed for purposes of effect of scan rate studie and quantification of codeine, respectively. The CV and SWV were recorded between 0.7 V and 1.4 V. The calibration curve was constructed from the average of five replicate measurements for each codeine calibration solution. The peak currents (Ip) recorded using CV and SWV were evaluated from the straight lines connecting the minima before and after the peak maximum without background correction. The detection limit was calculated as three times the standard deviation for the blank solution (supporting electrolyte) divided by the slope of the calibration curve.

3. RESULTS AND DISCUSSION

3.1. Electrochemical behavior of codeine

In this work, the electrochemical behavior of codeine at the CPE and modified CPEs was investigated and their determination has been performed by SWV method. Fig. 1 shows the SWV of CPE, CNT/CPE in present and NiO/CNT/CPE in present and absence of codeine in pH=7. The results showed that no electrochemical responses were obtained on the bare carbon paste electrode in present 10μM of codeine (Fig. 1a). In addition, the NiO/CNT/CPE has no oxidation peak within potential window between 0.7 V and 1.4 V in blank solution (Fig. 1b). For CNT/CPE, an electrochemical signal 10μM of codeine was obtained with the oxidation peak current of about 20 μA and the oxidation potential of 1.16V (Fig. 1c). On the other hand, at NiO/CNT/CPE, the oxidation peak current was obtained as about 50.0 μA with oxidation potential of 1.16 V (Fig. 1d). These change in the current peak indicated that presence of the NiO in CNT/CPE enhance the peak currents and decrease the capacitive current. The results confirmed that presence of NiO on CNT/CPE surface had great improvement on the electrochemical response, which was partly

due to excellent characteristics such as good electrical conductivity, high chemical stability and high surface area.

3.2. Effect of supporting electrolyte and pH

Generally in electroanalysis, detection and quantification of biomolecules depending on various factors. Type and pH of supporting electrolyte play a significant role on the peak current and peak potential of biologically electroactive compounds. The choice of the supporting electrolyte is an important stage in electrochemical studies because its composition affects the properties of the solution and the electrode–solution interface modifying the thermodynamics and kinetics of the charge transfer process [30, 31]. The effect of different supporting electrolytes on oxidation of codeine in surface of modified electrode was investigated. Various supporting electrolytes such as nitric acid, acetic acid, phosphate buffer (PBS), acetate buffer solution (ABS) and Britton-Robinson buffer solutions (BRBS) was studied. The results showed that best peak current and shapely peak was observed in BRBS. Therefore, BRBS was selected as the blank solution. Codeine is a complex molecule that can be oxidized with different groups. Anodic oxidation of codeine follows a rather complex mechanism that is pH dependent. The influence of pH on the electrochemical response of 10 µM codeine was recorded in pH range from 2 to 9 and shown in Fig. 2.

The results showed that when the pH exceeded pH 7.0, the peak currents began to decrease and even disappeared with further increasing the buffer pH. Therefore, pH 7.0, BRBS, was selected for all the experiments. Reason of this occurrence can be oxidation of the tertiary amine and 6-hydroxy group that the two peaks are completely superimposed in this pH [32].

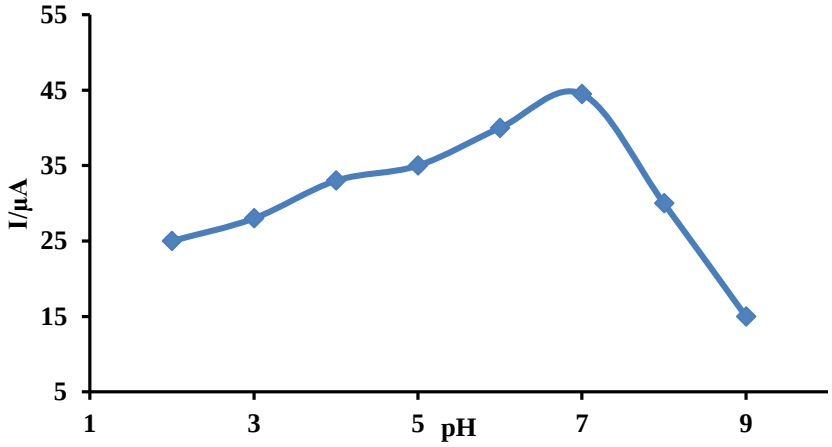

Figure 2. Effect of pH on response of sensor.

3.3. Effect of scan rate and other instrumental parameters

The effect of different scan rates in ranging from 50 to 400 mV s^{-1} on the current response of 10 µM on NiO/CNT/CPE in B–R buffer (pH 7.0) was studied. It can be seen with an increase of the scan rate, the oxidation peak current of codeine increased linearly with the square root of the scan rate, with equation $I\,(\mu A) = 1.1606v^{1/2}\,(mV\ s^{-1})^{1/2} + 2.3509$ ($R^2 = 0.997$) which demonstrates a diffusion-controlled electrochemical process. Typical CV curves of codeine at different scan rates are shown in the Fig. 3.

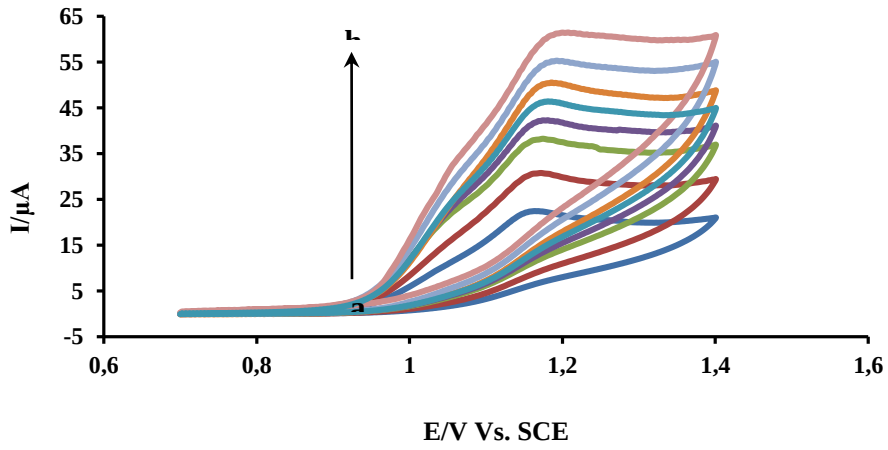

Figure 3. Effect of scan rate on response of sensor.

SWV is the pulse voltammetric method with good discrimination against the capacitive current. This effective electrochemical technique has been applied to numerous biologically and electrochemically active compounds in the analysis of their trace amounts. The optimization of SWV instrumental parameters influencing the current response is an important step in the development of electroanalytical methodology. Optimum conditions for the SWV response were recognized by measuring the current dependence on solution pH and some instrumental parameters, counting pulse amplitude, pulse duration, and potential scan rate. During optimization each parameter was changed while the others were kept constant using 10 µM codeine concentration. These parameters were optimized for obtaining maximum signal-to-noise ratio and attain best peak shape. Optimum values for the studied parameters are given in Table 1.

Table 1. Optimum of instrumental parameters

Parameter	Range studied	Optimum value
Pulse amplitude (mV)	10-150	100
Voltage step(mV)	1-10	5
Frequency (Hz)	10-100	40

3.4. Analytical characterization

Under the optimized conditions described above, in order to obtain an analytical curve for the sensor, square wave voltammograms for oxidation of different concentrations of codeine were carried out in Briton–Robinson buffer solution at pH 7.0. The SWVs clearly showed a linear dynamic range for 0.03 to 12.00 µM codeine with regression equation $I_{\mu A} = 4.795\ C_{\mu M} + 2.090$ and the correlation coefficient was 0.999. Fig. 4 shows the SWV voltammograms of codeine in linear range.

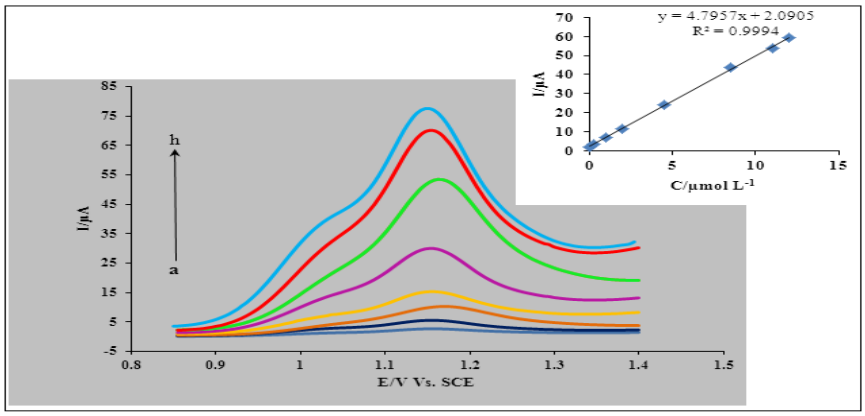

Figure 4. Calibration curve for different concentration of codeine.

The limits of detection (LOD) and the limits of quantitation (LOQ) were calculated from the oxidation peak currents of the two linear ranges using the following equations:

$LOD= 3S_b/m$

$LOD= 10S_b/m$

Where s is the standard deviation of the oxidation peak current (N=5) and m is the slope of the related calibration curve, and they were found to be 0.015 and 0.05 µM respectively. Both LOD and LOQ values confirmed the sensitivity of NiO/CNT/CPE for determination of codeine.

3.5. Reproducibility and repeatability

The repeatability and stability of NiO/CNT/CPE were investigated using square wave voltammetric measurements of 5.0 µM codeine. The relative standard deviation (RSD %) for six successive assays of codeine was 2.65%. From these results, one may conclude that the suggested electroanalytical methods present adequate repeatability. When using four different electrodes, the RSD % for six measurements was 3.01%. These values indicate good reproducibility of the prepared electrode for the determination of this drugs. When the electrode was stored in our laboratory at room temperature, the modified electrode retained 97% its initial response after a week and 95% after 9 weeks. These results indicate that NiO/CNT/CPE has good stability and reproducibility, and can be used for codeine determination.

3.6. Interference studies

Under optimized experimental conditions described above, in order to evaluate the selectivity of proposed method, effect of the possible interfering agents influencing the determination of codeine with fixed concentration of 1 and 8.5 µM codeine was investigated. Some of the ions such as $Na^{+,}$ K^+, Ca^{2+}, Mg^{2+}, NH_4^+, NO_3^-, Clo_4^-, SCN^- and some of the organic compounds such as dopamine, ascorbic acid, glycine, valine, glucose, sucrose and lactose were tested to check their levels of interference in the determination of codeine. The interfering agent was considered to interfere seriously when it gave a codeine signal change more than 5%. The results given in Table 2 show that the peak current of codeine is not affected by all conventional cations, anions, and organic substances.

Table 2.

Species	Tolerance limits ($W_{Substance}/W_{codeine}$)
Na^+, K^+, Ca^{2+}, Mg^{2+}, NH_4^+, NO_3^-, Clo_4^-, SCN^-	300
Dopamine	200
Ascorbic acid	400
Glycine, valine	250
Glucose, Sucrose, lactose	300

3.7. Determination of codeine in real samples

In order to demonstrate the ability of the modified electrode to the determination of codeine in real samples, determinations of codeine in pharmaceutical, urine and human serum samples that preparation methods are described in Section 2.6 were examined. The results are given in Table 3 and were comparison with reference HPLC method. The recovery values was calculated as found concentration values after spiking of codeine standard solution divided by expected codeine concentration values multiply by hundred that for this determinations were between 98.0 and 101.6%. This recovery value is satisfactory for determination of codeine in real samples and by evaluation of these results; one can conclude that the values obtained by the proposed method agree well with those acquired by reference HPLC method. These results demonstrated the ability of NiO/CNT/CPE for SWV determination of codeine with high sensitivity, accuracy and precision in real samples.

Table 3. Real sample.

Samples	Added (μM)	Found (μM)	Recovery (%)	HPLC method
Urine	0.00	0.00	-	-
	3.00	2.99 ± 0.08	99.6	3.02 ± 0.05
	6.00	6.12 ± 0.07	101.6	5.91 ± 0.06
Human serum	0.00	0.00	-	-
	3.00	3.12 ± 0.07	103.3	3.24 ± 0.08
	6.00	5.88 ± 0.09	98	5.93 ± 0.06
Codeine tablet	0.00	0.41 ± 0.06	-	0.41 ± 0.07
	0.10	0.50 ± 0.08	98.7	0.50 ± 0.07
	0.20	0.62 ± 0.05	101.5	0.62 ± 0.05

4. CONCLUSION

In the present work, we combine the advantages of NiO nanoparticles and carbon nanotube to fabricate a modified carbon paste electrode for determination of codeine in biological and pharmaceutical samples. This improved the sensitivity, stability, reproducibility, and linearity obtained for codeine determination at the NiO/CNT/CPE surface as compared to CNT/carbon paste electrodes. The selective determination of codeine in the presence of various component in B–R buffer (pH 7.0) using NiO/CNT/CPE was achieved with an excellent sensitivity. The results showed that the method was simple and sensitive enough for determination of codeine in human urine/serum and in commercial tablets with good precision, accuracy, selectivity and wide linear range (0.03 to 12.00 μM) and low detection limit.

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