



# Enhanced electrochemical biosensing of Buprenorphine opioid drug by highly stabilized magnetic nanocrystals

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## ABSTRACT

Herein, we report the synthesis of a spherically stabilized monodisperse magnetic nanocrystal for drug sensing. An optimized ratio of carbon paste material with the magnetic nanocrystal was used for electrochemical sensing of buprenorphine. The buprenorphine cathodic peak current  $I_p$  at CS-MNCs/CP electrode was 10 fold higher than that of unmodified CP electrode. CS-MNCs/CP electrode is applicable to determine buprenorphine in the linear range of 0.02–68.0  $\mu$ M with a limit of detection (LOD) of 4.3 nM. Fast response time, high sensitivity and ease of preparation method without using any specific electron transfer mediator or specific reagent are the advantages of the sensor. The modified electrode was applied to the determination of buprenorphine in human biological fluid at micromolar level without any pretreatment or separation step.

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## 1. Introduction

Buprenorphine (BUP) is a synthetic baine base opioid drug. Partial agonist activity at  $\mu$ -opioid receptors, made BUP useful to treat the opioid addiction [1]. Low dosage of BUP has been used for the treatment of acute and chronic pain [2,3]. In addition, the results of recent laboratory studies which indicate the reducing symptoms of depression and response to negative affective stimuli, made BUP interesting for medicals [4,5]. However, the potential of a significant overlap of BUP with normal physiological activity in biological fluids may cause a wide range of physiological reactions from asymptomatic to comatose. Therefore, it is a main treatment key to obtain both the route of administration of the drug and a tolerance level to opioids of the individual. The widespread use of BUP in medicine has led to an increased toward developing the new methods for monitoring the concentration of BUP in biological fluids. At this time several analytical methods have been developed for determination of BUP in biological samples. The most common methods currently reported for determination of BUP include gas chromatography–mass spectrometry (GC–MS) [6–8], atmospheric pressure chemical ionization mass spectrometry (APCI–MS) [9], liquid chromatography (LC) [10,11] and electrospray mass spectrometry (ESI–MS) [12–14]. However, in these studies, liquid–liquid

extraction combined with a solid-phase extraction was employed as sample pre-treatment processes which generally require laborious and time-consuming equilibrium, clean-up and evaporation procedures. However, the high cost and relative inaccessibility facilities, lack of sensitivity and difficulties remain major obstacles in being adapted for routine analytical methods [15–17].

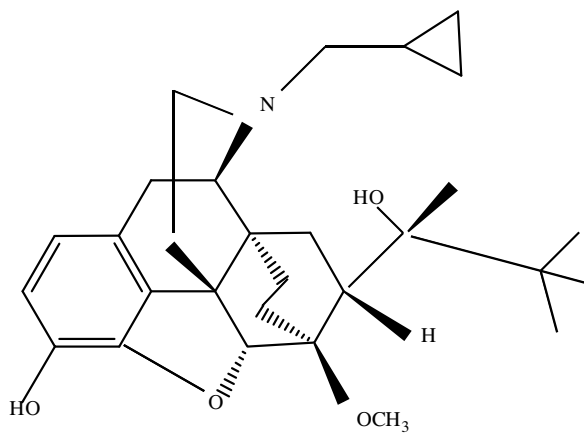
Recently, due to high sensitivity and selectivity, low cost and short time of analysis, electrochemical methods, mainly stripping voltammetry are applied to analysis of biological molecules successfully [18,19]. At this time, limited reports are available on the voltammetry determination of BUP. Costa-Garcia et al. probed the electrochemical behavior of BUP using carbon paste electrode [20]. They showed that, different pH media cause oxidation of phenolic and/or amino groups of BUP with different electrochemical processes. In other work, Costa-Garcia et al. coupled carbon paste electrode to a flow system incorporating a thin layer flow cell [21]. Behpour et al. showed that presence of an enhancer exhibit a detection limit at nanomolar level [22].

However, modification with nanomaterials can grant some advantages such as large specific surface area, high electrocatalytic behavior and more adsorption sites on the carbon paste electrode surface which improve its electrochemical behavior.

Citrate stabilized magnetic nanocrystal (CS-MNCs) is a nanocrystal that has a negative zeta potential at a wide range of pHs. CS-MNCs cause a high density of negative charges on the carbon paste electrode (CPE) surfaces that improve the electrostatic interaction between negatively charged electrode surface and positively

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Scheme 1. Molecular structure of BUP.

charged BUP (Scheme 1). This electrostatic interaction accumulates the electrochemical process on the electrode surface. In this paper, carbon paste electrode was modified with a highly monodisperse citrate stabilized magnetic nanoparticle. The method is successfully applied to the determination of BUP in human biological fluid without any pre-treatment or separation steps.

## 2. Experimental section

### 2.1. Chemicals

Borate buffer (pH 8.5) was prepared. Ferric chloride hexahydrate ( $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , >99%), sodium hydroxide ( $\geq 97\%$ ), and hydrochloric acid (37%), were purchased from Merck (Germany). BUP ( $\geq 99\%$ ) was kindly supplied by Soha Daru. (Tehran, Iran).

### 2.2. Instruments and measurements

TEM measurements were taken on a Philip CM 120 (120 kV). SEM measurements were made using a Scanning TESCAN (Vega). IR studies were run on Spectrum 65 – PERKIN-ELMER FTIR spectrophotometer. All electrochemical measurements were performed with an Autolab potentiostat/galvanostat (PGSTAT 302N, Eco Chemie, Netherland). GPES software was used to control the experimental conditions. A conventional three electrode system and a personal computer for data storage were used. All potentials are referred to Ag/AgCl/KCl electrode. All experiments were performed at room temperature. pH measurements were made with a pH meter model Metrohm-780 (Switzerland).

### 2.3. Synthesis of MNCs nanocrystals

High quality monodisperse spherical  $\text{Fe}_3\text{O}_4$  MNCs with tunable size was synthesized according to literature method with minor modifications [23]. Typically,  $\text{FeCl}_3$  (0.32 g, 4.0 mmol) and trisodium citrate (0.10 g, 0.68 mmol) were first dissolved in ethylene glycol (20 mL), afterward, NaAc (0.60 g) was added with stirring. The mixture was stirred vigorously for 30 min and then sealed in a Teflon-lined stainless-steel autoclave. The autoclave was heated at  $200^\circ\text{C}$  and maintained for 10 h, and then allowed to cool at room temperature. Synthesized MNCs were washed with ethanol and purified by precipitation with acetone.

### 2.4. Preparation of sensor

The citrate stabilized magnetic nanocrystal modified carbon paste electrode (CS-MNCs/CP) was prepared according to literature

with little modification [24]. Briefly, the bare carbon paste electrode was prepared by mixing the graphite powder with paraffin oil at composition 70:30 (w/w) to get a homogenous paste. The modified carbon paste electrode was prepared by mixing graphite powder, MNCs and paraffin oil with various weight ratios. Paste was then packed into one end of a Teflon holder and electrical contact was established with a copper wire. The electrode surface was polished and used. The electrode surface regeneration was made by using an excess of paste out of tip and polishing till the electrode surface had a shiny appearance. The activation of CS-MNCs/CP was achieved by applying a high anodic potential (+0.9 V) in 0.1 M HCl solution.

### 2.5. Procedure

$40\ \mu\text{M}$  BUP and 5 mL borate buffer (pH 8.5) were transferred into an electrochemical voltammetric cell. After deoxygenation for 4 min with pure  $\text{N}_2$ , the differential pulse voltammograms were recorded by applying a cathode potential scan from  $-0.35$  to  $-0.55$  V at scan rate of  $100\ \text{mVs}^{-1}$ . The differential pulse reduction peak current ( $I_p$ ) of BUP was recorded at  $-0.47$  (Ag/AgCl). The increment  $I_p$  of peak currents were obtained by deducting the peak currents of BUP and the calibration curves were obtained by plotting the increment  $I_p$  of the peak currents versus BUP concentration.

### 2.6. Sample preparation

Human blood plasma and urine samples were prepared according to literature [29]. Briefly, human serum and urine samples of three healthy volunteers were mixed and then stored at  $-20^\circ\text{C}$  until analysis. To eliminate the complex matrix of biological fluids, the standard addition method was used. For this propose  $100\ \mu\text{L}$  human serums or urine was transferred into 3 polypropylene centrifugation tubes containing a certain concentration of BUP, and mixed well with 1 mL of methanol to denature and precipitate of proteins. The solutions were centrifuged using an Eppendorf centrifuge (Hamburg, Germany) for 4 min at 12,000 rpm. The clear supernatant layers of these solutions were filtered through  $0.45\ \mu\text{m}$  Whatman filters to produce protein-free samples spiked with appropriate amount of BUP.

To determine the BUP content of a commercial tablet using the method, 5 tablets were accurately weighted and average weight of each tablet was calculated. The tablets were powdered and after mixing, a portion (2.0 mg) of powder was dissolved in 50 mL ethanol. After centrifuging at 8000 r.p.m., the supernatant was collected. The solution was diluted to 50 mL and an appropriate amount of the solution was used for electrochemical analysis.

## 3. Results and discussion

### 3.1. Characterization of MNCs nanocrystals

The FTIR spectrum of MNCs is presented in Fig. 1a. The absorption peak at  $581\ \text{cm}^{-1}$  is corresponding to the Fe–O vibration of the magnetite phase of nanocrystal. The observed bands at  $1536$ – $1375\ \text{cm}^{-1}$  are related to symmetric and asymmetric stretches of carbonyl group [25]. A surface area of MNCs was measured according to BET procedure [25]. The results show that a Surface area of MNCs is  $408.0\ \text{m}^2/\text{g}$ . The zero charge pH ( $\text{pH}_{\text{zpc}}$ ) is defined as the zero pH in the net surface. The  $\text{pH}_{\text{zpc}}$  of MNCs was determined experimentally. The  $\text{pH}_{\text{zpc}}$  was measured in pH range of 2–12. pH values were adjusted with aqueous solutions HCl and NaOH (0.1 M). 0.02 g of the nanocrystal was added to each solution (10 mL). The supernatant was decanted and its pH was measured ( $\text{pH}_{\text{Final}}$ ). The  $\text{pH}_{\text{zpc}}$  value was determined as a point at which the curve of  $\text{pH}_{\text{Final}}$  vs  $\text{pH}_{\text{Initial}}$  intersects the line  $\text{pH}_{\text{Initial}} = \text{pH}_{\text{Final}}$  [26]. The results are presented in Fig. 1c which indicates that the  $\text{pH}_{\text{zpc}}$

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