



Original Research Article

A Simple Electrochemical Sensor for Rapid Determination of Oxycodone

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ABSTRACT

Oxycodone is an opioid medicine that is widely prescribed for the treatment of the diseases that are accompanied with sever and chronic pains. In the recent decade, residual pharmaceutical compounds (especially antibiotics and analgesics) have begun to be considered as emerging environmental pollutants due to their continuous input and persistence to aquatic ecosystem even at trace concentrations. Besides, oxycodone is very addictive and at high dosages cause serious life-threatening side effects including bradycardia, circulatory collapse, respiratory depression and even death. In this respect, developing a rapid, simple and sensitive analytical method for the determination of oxycodone is very important. Therefore, in this study, overoxidized poly(4-aminophenol) was electrosynthesized on the surface of a glassy carbon electrode and its applicability for the measurement of oxycodone was investigated for the first time. The modified electrode was characterized by Fourier-transform infrared spectroscopy (FT-IR), cyclic voltammetry (CV) and square wave voltammetry (SWV) techniques. The obtained voltammograms showed a well-defined peak for oxycodone at +1.36 V (vs SCE). The influence of all of the effective experimental parameters on the signal intensity was investigated and optimized. Under the optimized conditions, the designed sensor exhibited two dynamic ranges (20-100 μM) and (100-1000 μM) with $y = 0.0701x + 5.8033$ ($R^2=0.9984$) and $0.0146x + 11.519$ ($R^2=0.9985$) equations respectively. The values of limit of detection (LOD) and limit of quantification (LOQ) were 5.75 and 19.17 μM respectively.

Keywords: Oxycodone, Voltammetry, Conductive Polymer, Sensor.

Introduction

The use of the electropolymerization method for modification of electrodes with conductive polymers to promote the electrocatalytic features of analytes, ameliorating the electron transfer, and lowering the overpotential has grown dramatically in the field of electrochemical sensors [1-3]. Because despite the drop-casting technique where the reproducibility of the modified electrodes is really poor, in electropolymerization, the characteristics of the created films are completely under the control of the operator, and the thickness of the polymer can be changed easily by altering the electrosynthesis conditions [4-6]. As a result, the prepared electrodes by electropolymerization procedure are more repeatable and reproducible [7, 8].

Among the conductive polymers, poly 4-aminophenol (PAP) has distinguished properties that make it more preferable for sensing purposes. Poly 4-aminophenol has two oxidizable functional groups in its chemical structure (OH and NH₂). Consequently, more reactive sites for interacting with analytes are created on the surface of the polymerized film compared to other polymers like polyaniline [9-11]. Besides, poly-4 aminophenol has high stability, superb electrocatalytic activity, and great antifouling features. Moreover, poly 4-aminophenol can be overoxidized by applying a constant positive potential. In the overoxidation process, the porosity, conductivity, and permselectivity of the polymerized film improved substantially [11]. Besides, by over-oxidization, other reactive oxygen-containing functional groups, including carbonyl and carboxyl, can be generated on the surface of the poly 4-aminophenol film, which can augment the interaction of analyte species with the electrode surface through hydrogen bonding. For the aforementioned excellent features of the overoxidized poly 4-aminophenol (Ox-PAP), this conductive film was used as a modifier for sensitive determination of various analytes, including epinephrine and uric acid, ascorbic acid, dopamine, tryptophan, and glucose [12]. On the other hand, the problem of counterfeit pharmaceutical products has become a serious concern all over the world. The appearance of forge medicines bears a lot of resemblance with the original ones but their efficacy is very poor and one of the best ways for the quality control of medications and recognition of the fake drugs from the main ones is the determination of the principal active ingredients [13]. Furthermore, due to the fact that Oxycodone (OXC, Figure 1) is a semi-synthetic addictive opioid its determination in the forensic fields is of great importance [14]. In this respect, we investigated the applicability of a modified glassy carbon electrode (Ox-PAP) as an SWV sensor for the electrochemical determination of OXC for the first time. All of the effective parameters were

optimized. The electrochemical behavior of OXC on the modified electrode surface was inspected in detail. In the end, the applicability of the designed sensor at different real samples was also checked out.

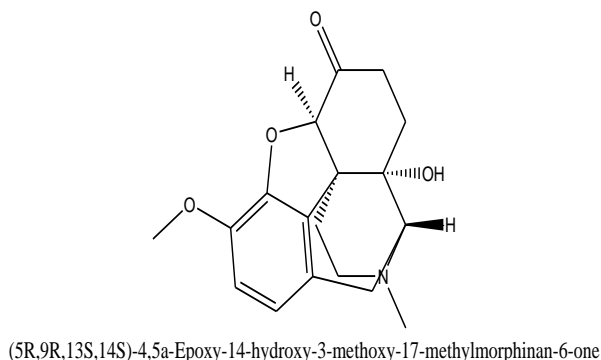


Figure 1. The chemical structure and IUPAC name of OXC

Experimental

Chemicals and Reagents

All employed reagents and components were obtained from Merck (Darmstadt, Germany) or Sigma-Aldrich and utilized without further purification. OXC was purchased from Hakim Darou Pharmaceutical Company (Tehran, Iran). The stock solution of OXC (1.0×10^{-3} mol L⁻¹) was prepared by ethanol. It was attempted to prepare a supporting electrolyte by mixing potassium nitrate (KNO₃) (1.0×10^{-1} mol L⁻¹) and hydrochloric acid (HCl) (1.0×10^{-2} mol L⁻¹) in all electrochemical measurements. Fresh human serum samples were obtained from the Tehran province blood transfusion organization (Tehran, Iran). DDW was used to prepare all solutions. Serum and pharmaceutical samples were prepared for analysis according to the procedure explained in [15, 16].

Apparatus

The Metrohm 797 VA Computrace Polarograph was used as a base to execute all electrochemical experiments, including CV and SWV. The pH was measured with a Metrohm 827 pH meter (Herisau, Switzerland) with a combined glass electrode. Ag/AgCl (saturated KCl) electrode, GCE, and Pt electrode were all purchased from Azar Electrode Company (Urmia, Iran). A three-electrode GCE-containing system 2 mm in diameter, a modified GCE used as working electrode,

platinum electrode used as the counter electrode, and a saturated calomel electrode (SCE) used as a reference electrode were employed. SEM-EDS (MIRA3 TESCAN) was used to evaluate the surface morphology of the developed electrode.

Fabrication of modified electrode

Prior to each measurement, the GCE surface was polished on a polishing cloth with 0.3 μm alumina slurry for 120 s and underwent ultrasonic cleaning, each for 5 min, with ethanol and re-distilled water. CV was utilized to conduct poly(p-aminophenol) (PAP) electrochemical deposition on GCE in a 5 mol L⁻¹ SDS + 5 mol L⁻¹ P-aminophenol + 1 mol L⁻¹ HCl solution [37]. Polymerization voltammograms were achieved through ten repetitive potential cycles from -0.645 to 1.955 V vs. SCE at a scan rate of 100 mV s⁻¹. The PAP/GCE was over-oxidized for 40 s at +1.1 V in 0.12 M NaOH solution for a stronger conductive and porous surface. Ultra-pure water was used to wash the modified electrode, referred to as Ox-PAP/GCE.

Results and Discussion

Electrosynthesis and characterization of the polymer film

Figure 2 demonstrates the cyclic voltammograms of p-aminophenol electropolymerization. The modified electrode was donated as PAP/GCE. An irreversible oxidation peak was detected during a CV scan at 1.56 V for p-aminophenol without corresponding cathodic processes during the reverse scan. Furthermore, reduction peaks and quasi-reversible oxidation were identified at \approx +0.67 and +0.31 V, respectively. During the p-aminophenol oxidation process, the peaks may be produced by the intermediate species [17]. The gradual decline of the peak currents of the two anodic peaks and the real increase of the cathodic peak current with its potential shift to more negative values with repetitive CV cycles demonstrated a high polymer content on the electrode surface [18]. The PAP/GCE over-oxidized with + 1.2 V for 300 s in 0.1 mol L⁻¹ NaOH solution to ensure a more porous surface and higher conductivity. Electrochemical sensor response is a function of its physical morphology. In this respect, the morphology of the electrode surface during the modification process was evaluated by SEM, and the obtained SEM images are presented in Figure 3. As can be seen, after electropolymerization, a thin layer film with a globular structure covered the surface of GCE homogeneously [17]. Then, by overoxidizing the PAP film at high

potentials, the coated polymeric substrate changes significantly. As it is obvious from Figure 5B, the surface of the Ox-PAP/GCE electrode is covered by a swollen like a heterogeneous film with randomly distributed large spherical particles and the layer porosity enhanced remarkably in comparison to the PAP/GCE [18].

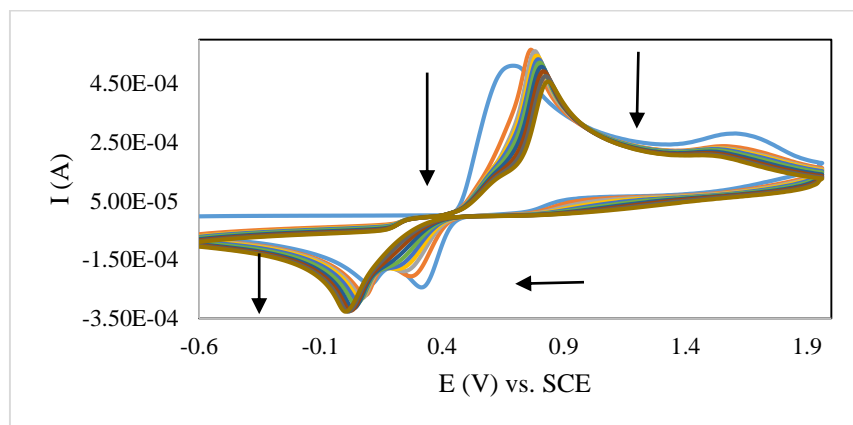


Figure 2. Cyclic voltammogram of p-aminophenol electropolymerization in a 5 mM p-aminophenol monomer + 1 M HCl solution on GCE in the presence of 5 mM SDS at a scan rate of 100 mV s^{-1} . The arrows indicate the trends of current during CVs.

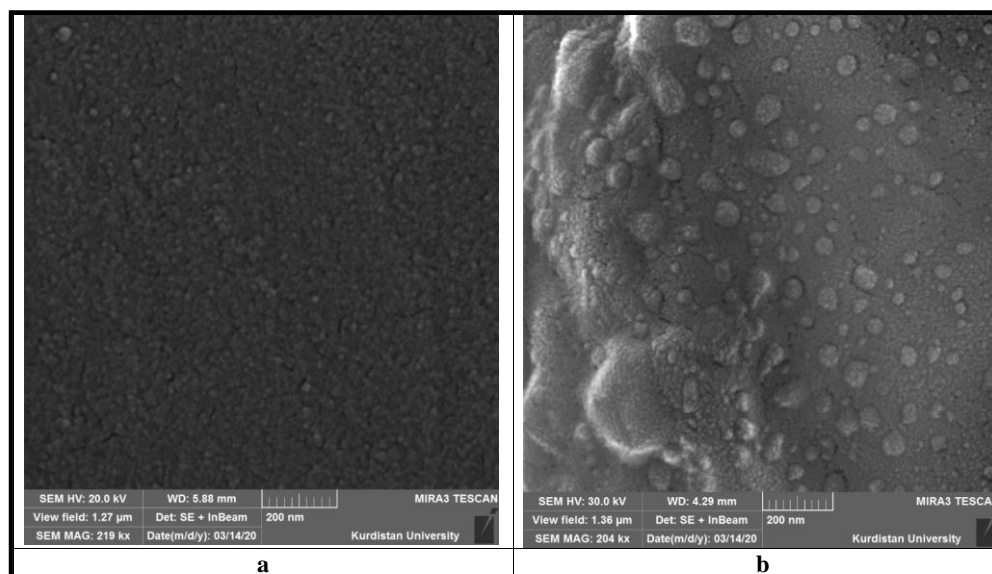


Figure 3. The SEM images of PAP/GCE (a) and Ox-PAP/GCE (b)

Optimization of effective experimental parameters

Measurement of the current dependency has been examined to assess the effect of all chemical instrumental parameters, such as pH, accumulation time and potential, pulse amplitude, voltage

step, and frequency, on the SWV response [19]. These parameters were optimized to achieve a peak signal-to-noise ratio (PSNR), whose results obtained are shown in Table 1. The impact of the pH and accumulation potential on anodic stripping peak current was investigated within the pH and potential ranges of 1-10 and -0.500 to 0.200 V versus SCE under the optimal conditions above. As illustrated in Table 1, the maximum peak current was reached at an accumulation potential of 0.065 V versus SCE and pH solution of 2.0. Thus, 0.065 V versus SCE and pH=2.0 were chosen as an accumulation potential and working solution in the process. Also tested in the range of 0-300 s was the dependency of the maximum stripping peak current on accumulation time. The stripping peak current rose in proportion from 0 to 125 s under the other optimal conditions. Thus, the peak current was constant, and 125 s was chosen for accumulation time. Other beneficial parameters such as pulse amplitude, phase voltage, and frequency on SWV response were also tested. The optimal values of 70 mV, 7 mV, and 110 Hz were selected for the parameters above, respectively.

Table 1. The optimum values of the studied instrumental parameters

Parameter	Range studied	Optimum value
pH	1-10	2
Accumulation potential (V)	-0.5 to +0.2	+0.065
Accumulation time (S)	0-300	125
Pulse amplitude (mV)	10-100	70
Voltage step (mV)	1-15	7
Frequency (Hz)	25-140	110

Analytical parameters of the sensor

Under the optimized conditions, the designed sensor exhibited two dynamic ranges (20-100 μM) and (100-1000 μM) with $y = 0.0701x + 5.8033$ ($R^2=0.9984$) and $0.0146x + 11.519$ ($R^2=0.9985$) equations respectively. The values of limit of detection (LOD) and limit of quantification (LOQ) were 5.75 and 19.17 μM respectively according to IUPAC ($3S_b/m$).

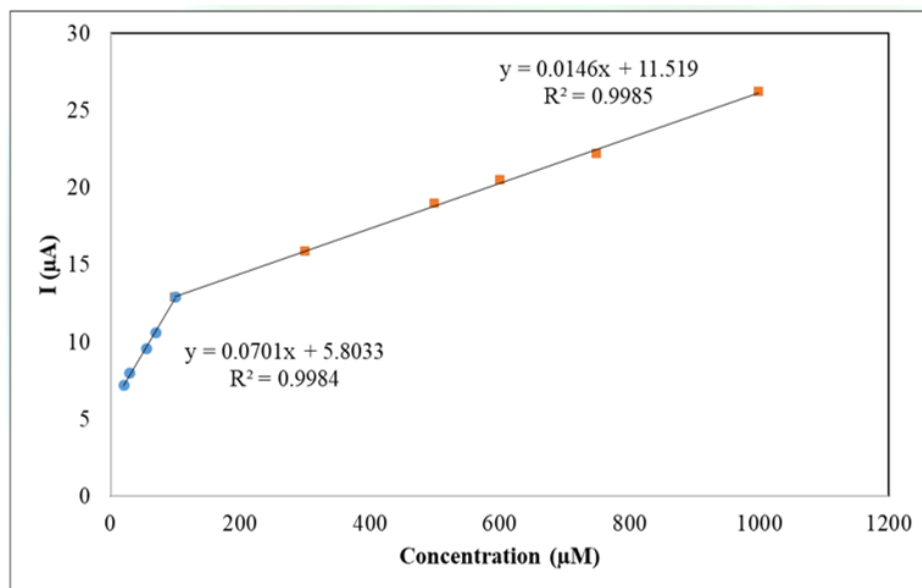


Figure 4. Plot of SWV oxidation peak current as a function of OXC concentrations

The selectivity of the proposed sensor

The selectivity of an analytical technique has an important effect on the accuracy of the obtained results. In this respect, the effects of 30 various species on the analytical response of the designed sensor were examined. Thus, a $100 \mu\text{mol L}^{-1}$ solution of OXC in the supporting electrolyte was prepared. Different amounts of the interfering species were added to the solution. The voltammogram of the sample was measured in the presence of other interfering species. The tolerance limit, defined as the maximum volume of the interfering species causing an error not higher than $\pm 5\%$ in the peak current of OXC, was calculated for the studied interfering species. The obtained results are presented in Table 2. The results indicate that the designed electrode showed an admissible selectivity towards OXC over a wide range of compounds that coexist with OXC in pharmaceutical samples, biological specimens, and some medicines prescribed simultaneously with OXC.

Repeatability, reproducibility, and stability of the modified electrode

SWV measurements for the $100 \mu\text{mol L}^{-1}$ OXC solution were used to test the repeatability, reproducibility, and stability of Ox-PAP/GCE. For investigating the repeatability of the proposed sensor, five different solutions of OXC with the same concentration were prepared, and their peak current was measured. Then the relative standard deviation (RSD%) was calculated, which was

4.05%. While the modified electrode reproducibility was explored by measuring the peak current of one OXC solution with five different electrodes, the RSD% was 5.11% for five measurement assays. To test the electrode stability, the electrode was stored for 45 days at room temperature in the lab. SWVs were recorded and compared to SWVs achieved before storage [17]. The findings revealed only minor changes in the peak current and the excellent repeatability, reproducibility, and stability of the modified electrode.

Table 2. The influence of some interfering species on the measurement of OXC ($0.1 \mu\text{mol L}^{-1}$) by the proposed method

Interfering species	Tolerance limit
Cl^-	1500
Mg^{2+} , Fe^{3+} , Fe^{2+} , Na^+ , Ca^{2+}	1000
F^- , Mn^{2+} , Cu^{2+} , Co^{2+}	800
Glucose, Lactose, Fructose, Maltose, Sucrose	600
Ibuprofen, Urea	500
L-Cysteine, L-Arginine	300
Ascorbic acid, Diclofenac	100
Levodopa, Dopamine, Mefenamic acid, Naproxen	80
Codeine, Meloxicam, Caffeine	50
Acetaminophen, Rizatriptan	15

Applicability of the proposed sensor for determination of OXC in human serum samples and pharmaceutical preparation

OXC was determined in serum and urine samples to show the capabilities of the modified electrode to assess OXC in real samples. As previously mentioned, the SWV techniques were utilized upon sample preparation and the necessary dilution measures for determining OXC in human serum and urine samples. Table 3 displays the results. A recovery test was carried out to verify the accuracy and applicability of the technique examined in real samples for OXC

determination in the human serum sample. The findings of a recovery test in Tables 3 show that OXC can be determined in both human serum and urine samples using the modified electrode.

Table 3. Determination results of OXC in biologic specimens (n=3)

Sample	Added (μM)	Found (μM)	Recovery%
Serum	---	ND	---
	50	49 ± 0.2	97.74
	80	83.4 ± 0.5	104.28
Urine	---	ND	---
	50	53 ± 0.1	106.98
	80	77 ± 0.3	96.25

Conclusion

In this study, a novel, rapid, and simple voltammetric sensor was developed for determining OXC in human serum and urine samples. For this purpose, p-aminophenol was electropolymerized on a GCE surface and then overoxidized by applying a constant potential in a basic solution to increase the porosity and conductivity of the polymer film. The influence of various parameters such as pH, accumulation potential, accumulation time, frequency, voltage step, and pulse amplitude was optimized to obtain the highest sensitivity towards OXC. Under the optimized conditions, the designed sensor exhibited two dynamic ranges (20-100 μM) and (100-1000 μM) with $y = 0.0701x + 5.8033$ ($R^2=0.9984$) and $0.0146x + 11.519$ ($R^2=0.9985$) equations respectively. The values of limit of detection (LOD) and limit of quantification (LOQ) were 5.75 and 19.17 μM respectively according to IUPAC ($3S_b/m$). The proposed electrode showed an eminent selectivity towards OXC. It was successfully applied for determining OXC in the human serum and urine specimens with acceptable recovery values.

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