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The Electrochemical Sensor for Selective Solid Phase Extraction of Pseudoephedrine Hydrochloride in a Real Sample

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Abstract

In the current study, a new technique was developed for quantification and qualification of pseudoephedrine hydrochloride (PSE) in a real sample, which was based on electrochemical sensors and molecular imprinted polymer (MIP). The carbon paste electrode (CPE) was modified and optimized by a different ratio of MIP. MIP/CPE was used as the extraction and working electrode. Differential pulse voltammetry (DPV) method was utilized for measurement. The MIP (molecularly imprinted polymer) and NIP (non-imprinted polymer) were synthesized by various ratios of functional monomer (methacrylic acid) and cross-linker (ethylene glycol dimethacrylate) and template (pseudoephedrine hydrochloride). Some parameters such as pH, extraction time, MIP/CP ratio, stirring rate, and concentration of sample were optimized, and under these conditions, the oxidation peak current was proportional to the pseudoephedrine hydrochloride concentration over a range of 10-500 µM with the coefficient of determination 0.992 (R^2). The limit of detection (LOD) was found about 0.274 µM and the limit of quantification (LOQ) was located about 0.825 µM. The relative standard deviation (RSD) was about 1.17%. The results indicated that the modified electrode had a specific ability in selective extraction of pseudoephedrine hydrochloride.

Keywords: Molecular imprinted polymer, Carbon paste modified electrode, Pseudoephedrine hydrochloride, Voltammetric sensor.

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Introduction

Pseudoephedrine (PE) is an alkaloid in the clinic for the treatment of bronchitis and asthma [1] and in high doses has amphetamine-like properties that can create tachycardia, nervousness, seizures, psychosis and hypertension [2, 3]. The concentration of PSE in serum, saliva, and plasma is µg/L or even less than this amount [4, 5] in clinic pharmacokinetic studies. As a result, this compound is listed as a forbidden substance by the International Olympic Committee medical commission and in a too high concentration of this alkaloid, an athlete is suspected to be "positive." Therefore, in the last years, various methods such as GC [6], LC–mass spectrometry [7], HPLC [8], spectrophotometry [9], LC-ion trap spectrometry [10], and capillary electrophoresis (CE) [11, 12] have been adopted to sensitive determine the PSE in its pharmaceutical samples and human serum. The CE methods can be coupled with sensitive detection techniques such as fluorescence [13-15], and MS for analytical method [16]. The novel techniques show varying degrees of successes as well as limitations, such as expensive methods and harsh reaction conditions.

As a result, a simple and sensitive procedure was progressed for the detection of Pseudoephedrine hydrochloride (PSE). Since in the clinical and environmental assays, the electrochemical determination of analyte is a straightforward, sensitive, and graceful method, in the current study, the PSE detection was researched at the CPE that was modified with a molecularly imprinted polymer. The MIP sensor because of its exclusive site has advantages such as simple preparation, width in the linear range, stability, low detection limit (DL), and high selectivity. Molecularly imprinted polymer is a kind of synthesized material and is an established method for specific molecular recognition. It was first introduced by Wullf in 1972 for the covalent approach [17], and Mosbach for non-covalent synthesis [18]. MIP is also used to make selective adsorbents [19, 20]. The MIPs are useful in separation [21], drug delivery [22], sensing [23], catalysis [24], carbon paste electrode fabrication [25] and solid-phase extraction (SPE) [26]. Solid phase extraction (SPE) is a selective method that has been prepared for concentration and determination before and is coupled with different measurement methods such as FAAS [27], HPLC [28], and in this paper, it is coupled with electrochemical methods.

MIP has unique advantages such as selectivity, durability in different solvents, simplicity, and convenient preparation, high-temperature endurance, and used to molecular species determination [29, 30]. Sensors made with MIP have been successfully progressed and used for the trapping and sensing of toxins, drugs, solvents, herbicides, and biological and vital molecules such as peptides and proteins [31-33]. In this paper, we focus on prepare of carbon paste electrode that modified by MIP for the determination of PSE in a real sample. The oxidation of PSE is the basis of this process so that

the PSE is extracted selectively by a modified carbon paste electrode, and then the oxidation occurs. The proposed sensor is pure, highly selective and low cost with long term stability.

Experimental

Reagents and solutions

Pseudoephedrine hydrochloride (PSE) as hydrochloride salts ((1s-2s)-2-methylamino-1-phenylpropane-1-ol hydrochloride) is from Tehran Pharmacy Company (Tehran, Iran). Methacrylic acid (MAA), methanol, acetonitrile (ACN), chloroform, acetone, acetic acid, (all from Merck), ethylene glycol dimethacrylate (EGDMA), graphite powder and 2, 2-azobisisobutyronitrile (AIBN) (all from Fluka) were used without further purification. The rest of the other chemical reagents were prepared with analytical purity. The liquid pasting agent for the graphite is Paraffin. The stock solution of PSE (5×10^{-4}mol L^{-1}) was developed in Briton Robinson (BR) buffer solution (pH=11.0), and working standard solutions of PSE were achieved by proper dilution of stock solution with BR buffer.

Apparatus

A three-electrode system potentiostat/galvanostat Autolab (Metrohm model PGSTAT12) was used to obtain the electrochemical data. A centrifuge (Behdad Universal Centrifuge, Isfahan, Iran) was used as a phase separation in the washing process. The pH values for the pH adjustment of the sample solution were measured with the Metrohm pH-meter (model 780). UV-Vis spectrophotometer (Agilent 8453) was used to determine residual PSE in MIP during the washing procedure. FT-IR spectrometer (Perkin Elmer FT-IR spectrum two) was used for recognition MIP structure.

Procedures

Preparation of Molecularly imprinted polymer

In Figure 1, the schematic MIP preparation for PSE was shown.

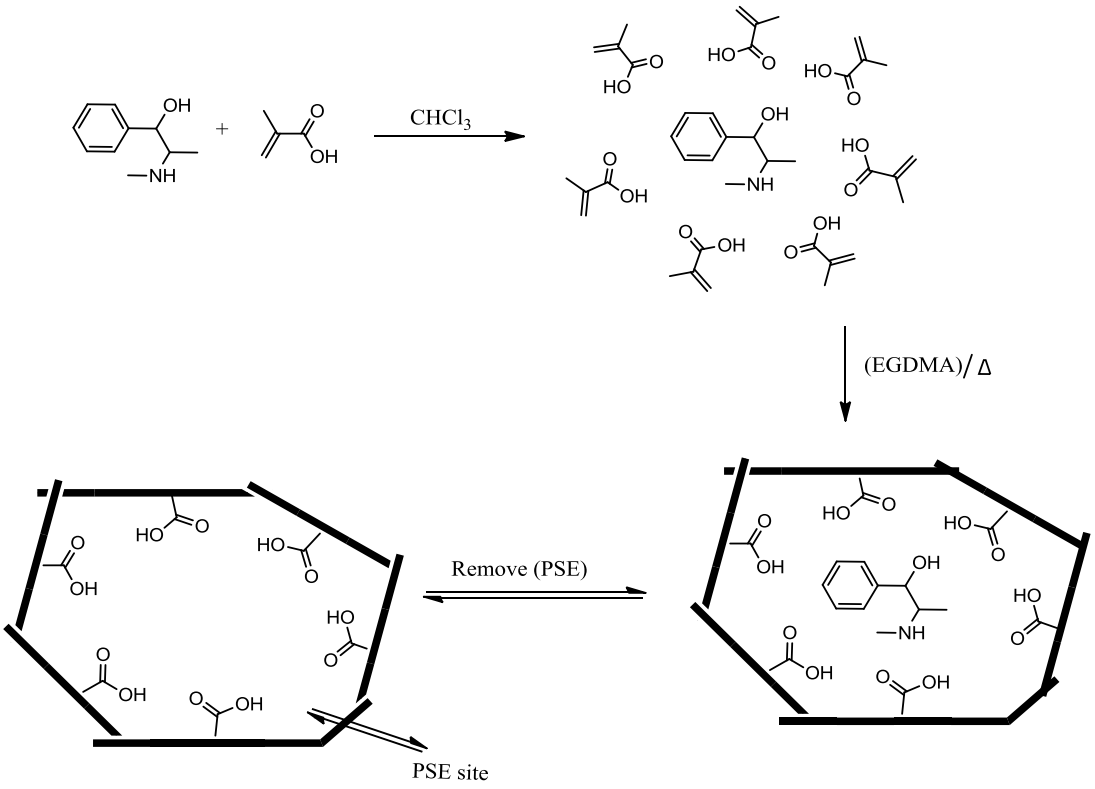

Figure 1. MIP schematic procedure.

The MIP was prepared for PSE by a non-covalent approach. Template molecule PSE (0.218 mmol), the functional monomer MAA (0.436 mmol), and 35 ml of chloroform was stirred via sonication for 10 min. Then EGDMA (13.77mmol) [34] and AIBN (0.347 mmol) were added and purged with N_2 (10 min). The mixture was stirred in a 60˚C water bath for 22 h, and the preparation polymer was filtered and dried at the room temperature (12 h). The template was removed by soxhlet extraction with a mixture of methanol/acetic acid solution (10:1, v/v, of 98% methanol and pure acetic acid) (18h). Then MIP was washed three times (at every step 50 ml of distilled water). A similar process was used in the non-imprinted polymers (NIP) synthesis, while the PSE is absent.

The MIP modified carbon paste electrode preparation

The PSE sensor was made by mixing a MIP (or NIP), graphite powder, and paraffin of varying mass ratios (Table 1). To obtain a homogeneous mortar, each mixture was mixed for at least 15 min, and the total mass of the paste was 0.1 g. The dough was placed in the bottom hole (2×3 mm) of a Teflon electrode. Then a Cu wire was mounted for the connection between the electrode and potentiometer, and to refresh the electrode surface after each experiment, and the electrode surface was polished with

a butter paper. As can be seen in Table 1, the E-4 electrode showed the best results. After determining the optimum electrode composition condition, this electrode was used for the voltammetric determination of PSE.

Table 1. Electrodes percentage composition (MIP: graphite powder: paraffin).

Electrode	%(W/W)		
	MIP(%)	Graphite powder(%)	Paraffin(%)
E-1	0	75	25
E-2	0	70	30
E-3	5	65	30
E-4	10	60	30
E-5	20	50	30
E-6	30	40	30

The PSE determination by MIP/CP electrodes

The MIP/CP electrode was embedded in PSE working solution (BR buffer at pH =11) by a fixed stirring rate and time. The electrode was washed with distilled water for 30 seconds, and after washing, the MIP/CP electrode was placed in an electrochemical cell (10 mL BR buffer). Cyclic voltammograms were recorded from 0.0 V to +1.3 V (scan rate = 50 mVs^{-1}) in BR solution of pH=9. DPV experiments were performed between the same potential range at a pulse width 0.05 sec, pulse height of 7 mV, and pulse period 0.14 sec [35]. In the real samples analysis and all electrochemical experiments, a similar procedure was used.

The PSE determination in a real sample

The human blood sample was obtained from Fakhrieh hospital. To preparation of human serum sample, 10 mL of the blood sample was kept for 10 min and then, 5 mL acetonitrile was added to the solution, and the mixture was stirred. To separate the precipitated proteins, the mixture was centrifuged for 10 min at 2500 rpm. The human serum was diluted to 100.0 mL by BR buffer to adjust the pH to 11. For the preparation of the drug sample solution, 1 mL of drug syrup of PSE was diluted to 100.0 mL by BR buffer to adjust the pH to 11. The concentration of the sample solution should be in the linear range for each experiment. The standard addition procedure was obtained for recovery.

Results and discussion

Electrochemical behavior of PSE at the modified electrodes

The preliminary studies were carried out by cyclic voltammetry in the potential range from 0.0 to +1.3 V (Ag/AgCl) in BR solution of pH=9 at CP and MIP–CP electrodes. According to the cyclic voltammetric behavior of pseudoephedrine, an oxidation peak at around +1.16 V was observed with no cathodic peak on the reverse scan. The cyclic voltammetric behavior of pseudoephedrine hydrochloride at the MIP, NIP, and bare carbon paste electrodes is shown in Figure 2. As can be seen, the resulting peak current at the MIP/CPE was sharper and more durable than the NIP/CPE and bare carbon paste electrodes. The selective binding sites in the MIP and non-selective binding sites in the NIP has caused that most of the PSE molecules were weakly adsorbed to non-specific sites and in the washing step can be removed from the electrode surface. Thus, the MIP was used in the fabrication of the sensor as a selective recognition element. The resulting current of this well-defined oxidation peak was used to determine PSE concentrations. In the following, differential pulse voltammetry (DPV) was selected to achieve a sensitive and lower detection limit.

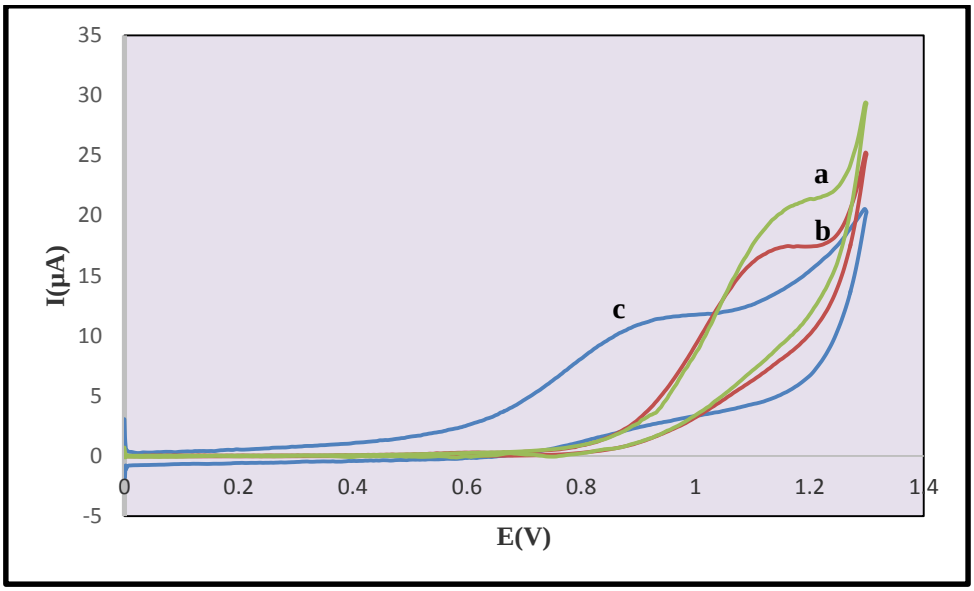

Figure 2. Cyclic voltammogram of 5.0×10^{-6}mol L^{-1} PSE on: a) MIP/CPE, b) NIP/CPE, and c) bar carbon paste electrode in PSE solution. Extraction time =10 min, electrochemical condition: BR buffer at pH= 9 and potential scan rate = 50 mVs^{-1}.

Characterization of MIP/CP and NIP/CP electrodes

The synthesized MIP polymer was verified by FR-IR (Figure 3), and scanning electron microscopy (Figure 4). In the FT-IR spectrum, the strong band was observed in the leached and un-leached MIP at 1730 cm^{-1}, which indicate a stretching band of C=O. The range of hydrogen bonding of –OH group in the MAA of leached MIP and the corresponding vibration bands at 3438 was shifted to ~3420, and 1458 cm^{-1} was shifted to ~1461 cm^{-1} in the spectrum of the un-leached MIP, respectively. Moreover, a sharp band at ~2956 cm^{-1} and a broadband at 1156 cm^{-1} (-CH aliphatic, -C-COOH),

which were found in the spectrum of leached MIP polymer, were shifted toward ~2930 and 1138 cm^{-1}, in the range of the un-leached MIP, respectively.

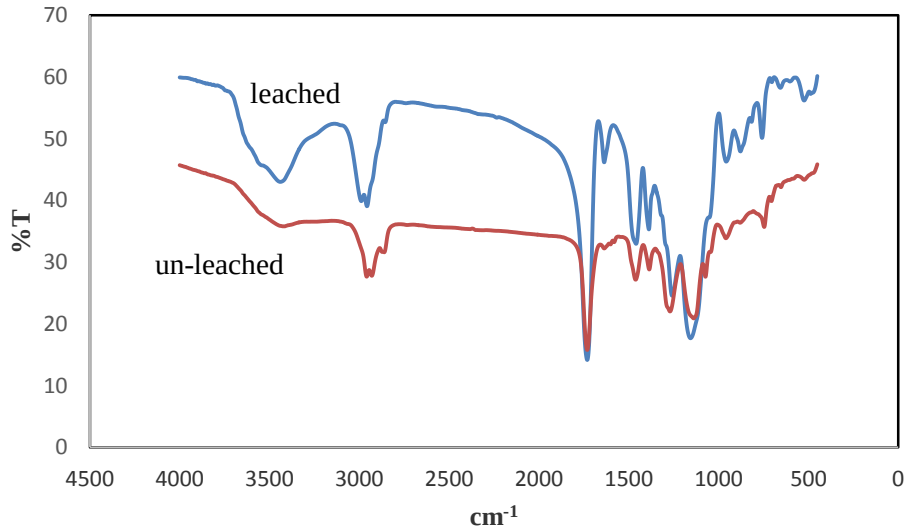

Figure 3. Fourier transforms infrared spectroscopy spectrums of MIP (leached and un-leached).

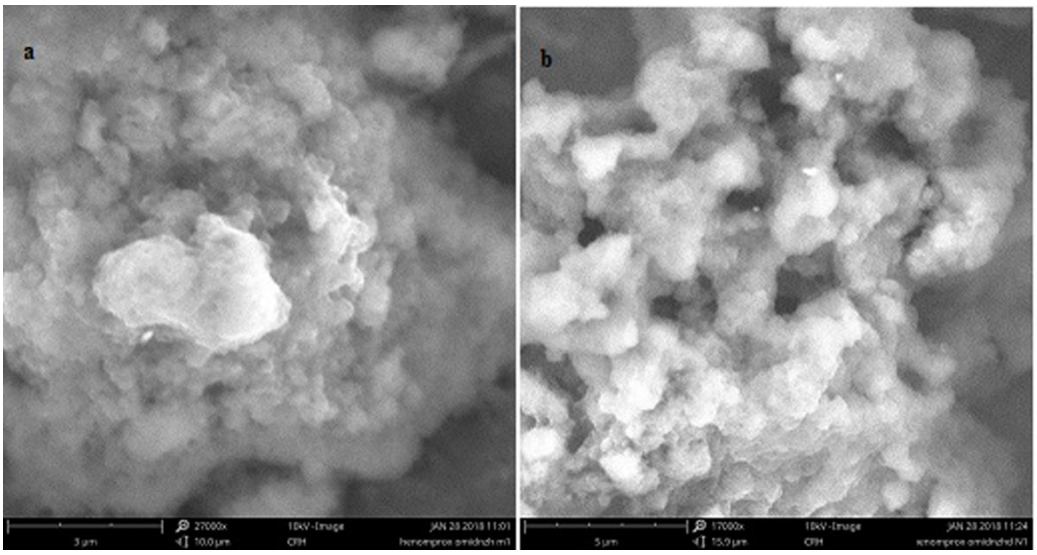

Figure 4. SEM **(**Scanning electron microscopy); a) MIP, b) NIP.

The selectivity of the MIP/CPE

For this purpose, first, bare carbon paste electrode, MIP/CPE, and NIP/CPE were incubated (10 min) into a solution of PSE (1×10^{-5}M), and cyclic voltammetry was applied for its electrochemical activity. As can be seen in fig.2, the cyclic voltammograms of MIP-CP and NIP-CP of PSE was different. The

MIP/CPE and NIP/CPE were immersed in solutions of PSE (10 min), and then, the cyclic voltammograms were recorded into BR buffer at pH of 9.0. The selective site of the PSE molecule was improved peak current at the MIP/CP electrode. The voltammogram of the MIP/CP electrode was sharper than that for its NIPs, which indicates that the MIP control sites are suitable for the printing molecule. The hydroxyl and amino group of PSE can interact with the–COOH group of the monomer (MAA). So, the functional groups play an important role in its selective binding site, and in comparison to NIP/CP and carbon paste electrodes, the MIP/CPE can uptake PSE intensively from the sample solution (pH=11). However, the electrode was washed just after its extraction by distilled water for a short time (30s) to evaluate the PSE keeping power by MIP. The result indicated that the response of the CP electrode disappears after washing the electrode (Figure 5).

The weakly absorbed and non-specifically adsorbed PSE molecules can be removed from the CP electrode surface and cannot be removed from MIP/CP electrode surface by the washing process because the selective binding sites of MIP can absorb PSE, since the binding site in CPE is non-selective. Therefore, washing time is another parameter on the response of the electrode that was also investigated (30 s) in this study.

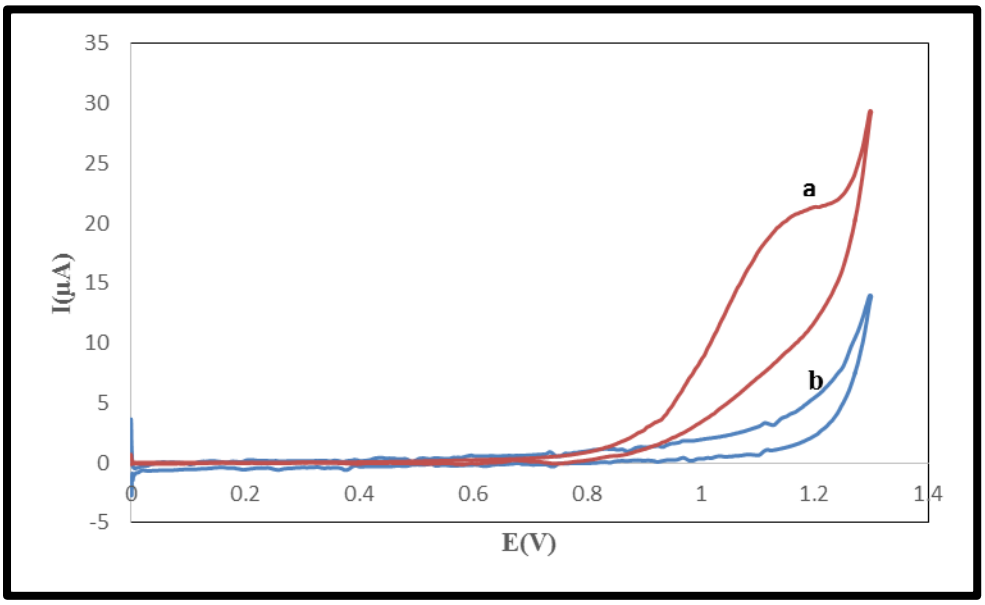

Figure 5. Cyclic voltammograms of 5.0×10^{-6} molL^{-1} PSE solution; a)MIP-CPE and b) the bare carbon paste electrode (extraction time=10 min ; pH=9 and potential scan rate = 50 mVs^{-1}) after washing.

Parameters optimization for PSE detection

The voltammetric response of the sensor depends: carbon paste composition, electrochemical determination conditions, and extraction parameters.

Optimization of MIP/CP composition

In the current study, the electrodes were made by different percent of MIP, graphite, and paraffin mixture. The MIP in the mix serves to increase the sensitivity and selectivity of the electrodes because MIP has a specific site for PSE and graphite is a conductive material that transmits from the Cu wire and the potentiometer, paraffin is a binder that serves as an adhesive between MIP and graphite that can form a paste to the mixture and makes the electrode material less soluble when used in an aqueous solution. For finding the best percentage combination, the amount of MIP, graphite, and paraffin was changed, and the peak current was recorded (Table 1). As seen in Table 1, the best results are at 10:30:60 (w/w %) ratio of MIP (or NIP), paraffin, and graphite. It is true that an increase in carbon maybe take the conduction to higher and increase electron transferring capability, but the response will be less in excessive of graphite.

This may be because the selectivity of the electrode decreases in the absence of a MIP. The higher weight ratios of MIP to graphite, the recognition sites were increased on the surface of the electrode and the more enhancements in electrode response, but, at higher weight ratios than 10%, the electron transfer capability and the conductivity decrease at the surface of the electrode. The electrode response decreased in the amount of paraffin (binder) by more than 30% that may be due to paraffin insulation and consequently reduced conductivity of the electrode surface. Thus, the best composition of the MIP: graphite: binder was chosen as the weight ratio of 10:30:60 (w/w %), respectively (Figure 6).

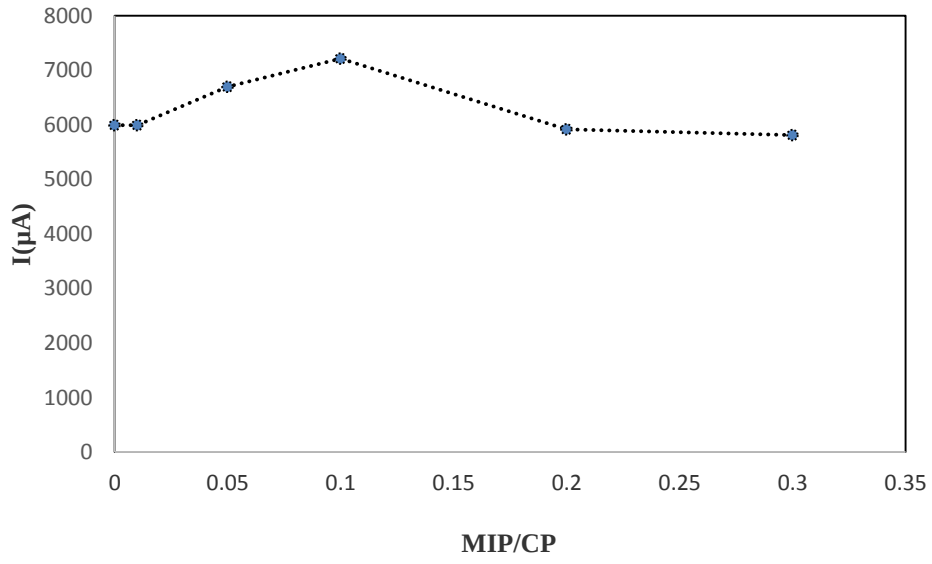

Figure 6. Optimization of MIP/CP composition for pseudoephedrine hydrochloride (1×10^{-5}M), electrode retention time=10 min, time of washing electrode =30 s, solution stirring rate=250 rpm. Potential scan rate=50 mVs^{-1} in BR buffer (pH=9).

Optimization of PSE extraction conditions

The main parameters which were useful in the PSE extraction and had to be optimized were the pH of the solution, extraction time, and the stirring rate. To optimize the pH of the PSE solution, the MIP sensor was incubated into a 1×10^{-5}molL^{-1} PSE solution for 10 min in BR over the pH range of 8-13, while in all cases, the solution was stirring, and pH of the analysis solution was constant at 9. The results are shown in Figure 7. As can be seen in Figure 7, in the pH range of 8–11, the amount of extracted PSE increases, and at pH values higher than 11, the voltammetric response decreases; thus, the pH of 11 was selected and fixed by BR for the extraction step. The other main parameter is the extraction time that must be examined. For this purpose, the prepared MIP/CP electrode was incubated at various extraction time, and the voltammetric response was recorded. The results were shown in Figure 8. According to these results, increasing incubation period up to 15 min did not affect voltammetric responses. Also, the stirring rate in the extraction period must be examined. The stirring rate on the PSE extraction was evaluated and found that with increasing stirring rate up to 500 rpm, the voltammetric response was increased, as seen in Figure 9.

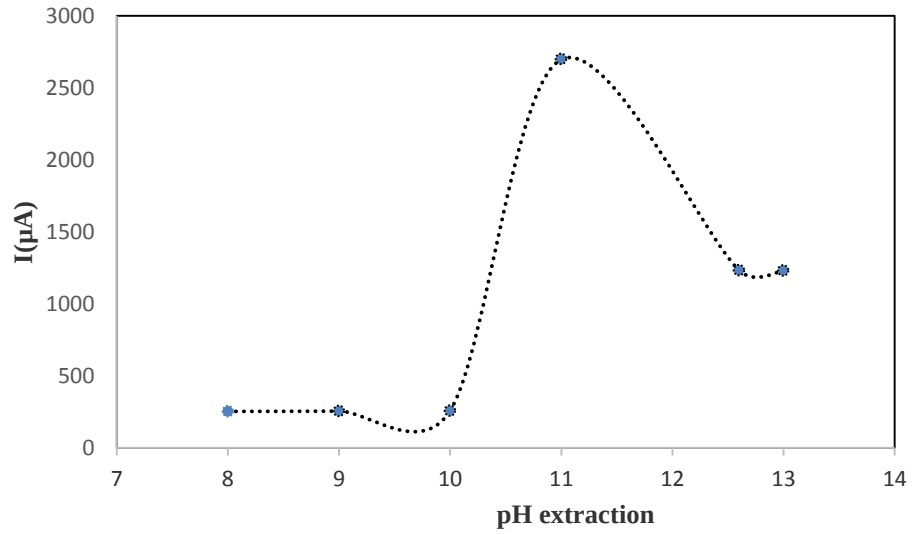

Figure 7. The pH optimization for pseudoephedrine hydrochloride (1×10^{-5}M) extraction; electrode retention time=10 min, time of washing electrode =30 s, solution stirring rate=250 rpm. Potential scan rate=50 mVs^{-1} in BR buffer (pH=9).

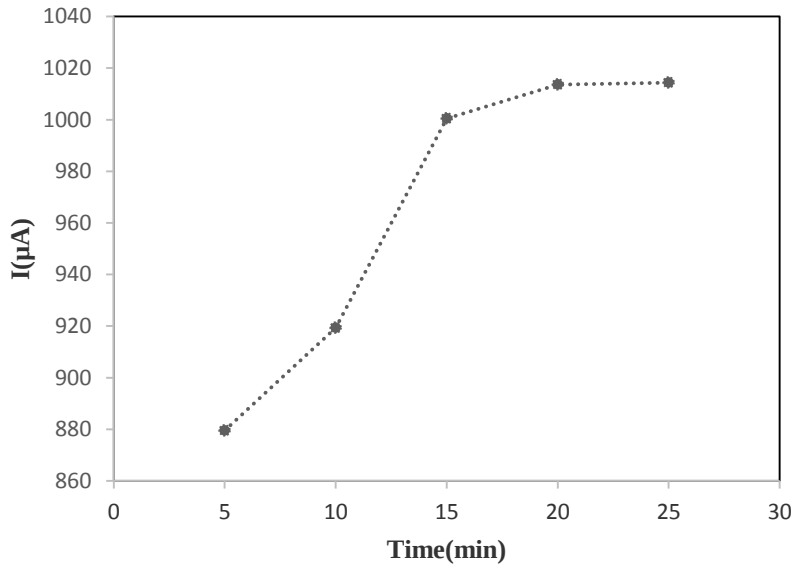

Figure 8. The required time optimization for pseudoephedrine hydrochloride (1×10^{-5} M) extraction: time of washing electrode =30 s, solution stirring rate=250 rpm. Potential scan rate=50 mVs^{-1} in BR buffer (pH=9).

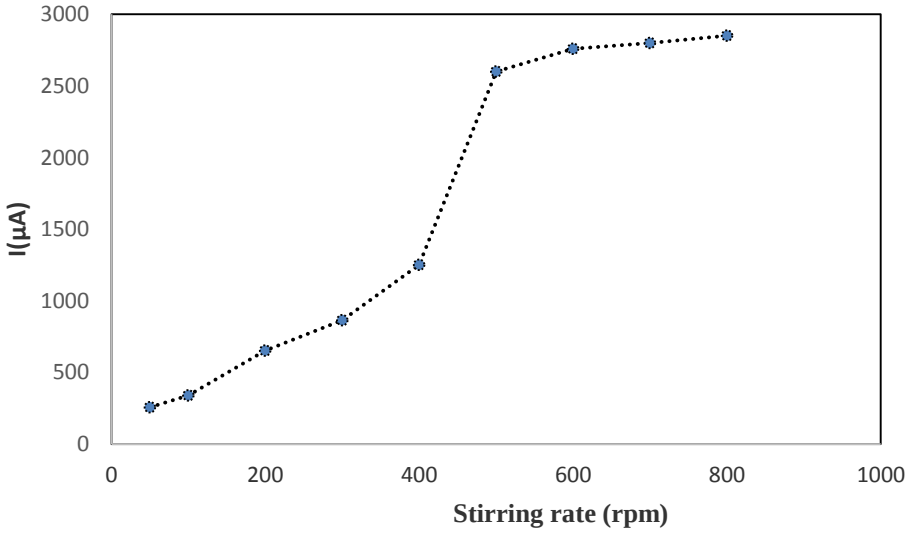

Figure 9. The stirring rate optimization for pseudoephedrine hydrochloride (1×10^{-5} M) extraction: electrode retention time=15 min, time of washing electrode =30 s. Potential scan rate=50 mVs^{-1} in BR buffer (pH=9).

Electrochemical conditions optimization

For electrochemical determination, pH, pulse amplitude, pulse width, potential step, and scan rate are the main parameters that must be optimized. The buffer plays an essential role in mass transfer and peaks current. For this reason, the buffer solution of PSE was used in the pH range of 2-12. As seen in Figure 10, the maximum oxidation peak current was seen at pH=9. Three buffers, such as acetate, phosphate, and Briton Robinson (BR) buffer at pH=9, were examined. In BR buffer, the oxidation

peak current was higher; therefore, BR at pH=9 was chosen (Figure 10). Other electrochemical parameters such as the pulse amplitude, pulse width, potential step, and scan rate were impressive in the DPV response of PSE oxidation. Thus, the DPV response of PSE was measured in the potential range of 0.9 to 1.3 V, the pulse amplitude in the range of 10–100 mV, the pulse width in the range of 0.1 to 1 s, potential in the range of 5 to10 mV and potential scan rate in the range of 10 to 100 mVs^{-1}. Consequently, the well-shaped and best sensitivity wave and sensitivity were obtained when the values of the pulse amplitude, pulse width, potential step, and potential scan rate were 50 mV, 0.14 s, 7 mV and 50 mVs^{-1}, respectively.

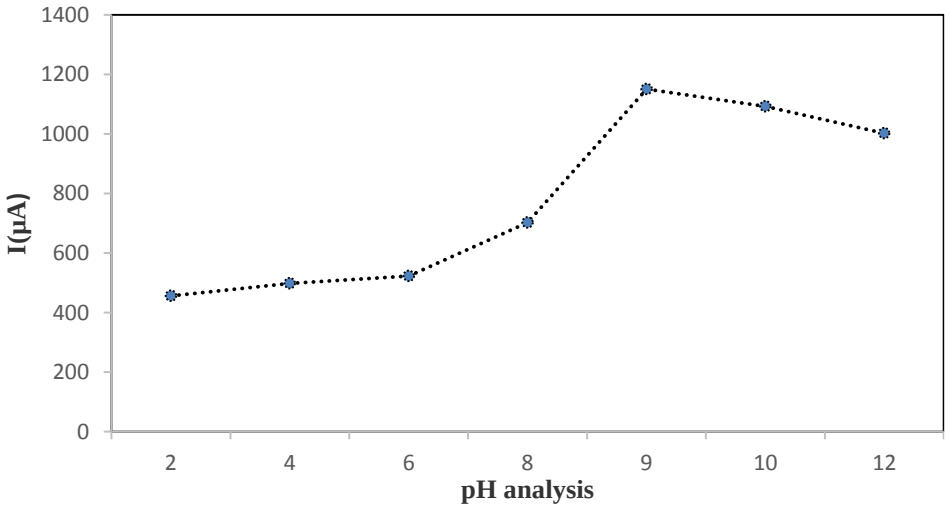

Figure 10. The pH analysis optimization for pseudoephedrine hydrochloride (1×10^{-5} M, pH=11) extraction: electrode retention time=15 min, time of washing electrode =30 s, solution stirring rate=500 rpm. Potential scan rate=50 mVs^{-1}.

Method validation

Finally, for evaluation of proposed electrode capability, the influence of PSE concentration on the voltammetric peak current at the optimal conditions was studied. The calibration curves of the differential pulse voltammogram signals versus concentrations of PSE are shown in Figure 11. As seen in Figure 11 it was observed that the signal increases with increasing concentration of PSE. The linear relationships are obtained in the range of 10 to 500 µM pseudoephedrine concentrations, respectively. The calibration curve equation is:

$$I\ (\mu A) = 0.0551\ C_{PSE} + 59.097$$

Where the correlation coefficient of a regression equation (R^2) is 0.99, according to the kS_b/m criterion, LOD (limit of detection) and LOQ (limit of quantitation) of the method were calculated,

where S_b is the standard deviation and m is the slope of the calibration curve and k=10 for LOQ and 3 for LOD. The calculated LOD and LOQ were found 2.47×10^{-7}M and 8.25×10^{-7}M, respectively. The relative standard deviation (RSD %) for eight repeated measurements of 7.5×10^{-5}molL^{-1} PSE was lower than 1.17%. The analytical characteristics of MIP/CPE for PSE determination were shown in Table 2. This level of precision indicated that the present method could be successfully applied for the determination of PSE in biological samples and pharmaceutical dosage form. The electrode can be worked for more than 16 weeks without a major change in the responses.

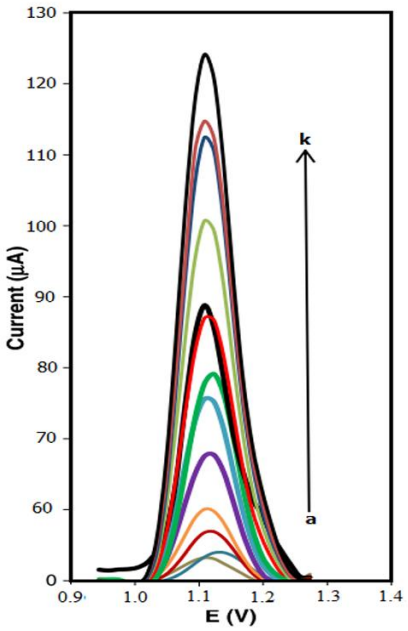

Figure 11.DP voltammograms of various concentrations of PSE at the MIP/CPE.

Table2. The Characteristics DPV electrochemical determination of PSE by MIP/CPE.

parameter	**range**
Linear rage (molL^{-1})	10×10^{-6} to5×10^{-4}M
Equation of calibration curve	I (µA) = 0.0551 C_{PSE} +59.097
R^2	0.99
LOD, molL^{-1}	2.47×10^{-7}
LOQ, molL^{-1}	8.25×10^{-7}
RSD %	1.17
Stability	16 week

The real samples analysis

MIP/CP sensor was successfully assessed to detect PSE in syrup and human serum via DP voltammetry. The measured experimental values of PSE are summarized in Table 3. The results demonstrated that the recommended method is an advance in sensor preparation of PSE.

Table 3. The PSE determination by using of the developed MIP/CPE in real samples.

Sample	Certified ($\mu mol\ L^{-1}$)	PSE added ($\mu mol\ L^{-1}$)	PSE founded ($\mu mol\ L^{-1}$)	Recovery %
PSE syrup	29.73	0	29.45±1.44	-
	29.73	20	49.41± 1.11	99.81± 5.54
	29.73	30	59.03± 1.88	99.60±6.29
Human serum		0	N.D**	-
		20	19.29±0.63	96.46±3.18
		30	29.09± 1.38	96.97± 4.62

* Three replicate determination ± standard deviation (n = 3)
** No Detection

Comparison

As can be seen in Table 4, the MIP/CPE is compared with other electrodes used for the determination of PSE [36-38]. In comparison, the MIP based electrode has lower LOD and wider linear range; thus, the results indicated that MIP/CP is a simple and sensitive method that can be applied for the determination of trace amounts of PSE from biological samples.

Table 4. The current and previously reported sensors for determination of PSE.

Electrode	Technique	Calibration data	LOD	Ref.
PVC membrane	Potentiometry	1.0×10^{-1}–1×10^{-5} M	7.9 µ M	36
PE-PT-PVC[a]	Potentiometry	5.0×10^{-5}–1.0×10^{-2} M	5.01 µ M	37
PE-SiT–PVC[b]	Potentiometry	6.31×10^{-6}–1.0×10^{-2} M	6.31 µ M	37
MWCNT–GCE[c]	Cyclic voltammetry	1–100 µ M	0.82 µ M	38
MIP-CPE[d]	DPV	10-500 µ M	0.24 µ M	this work

[a] Pseudoephedrine–phosphotungstate/ polyvinyl chloride
[b] Pseudoephedrine–silicotungstate/ polyvinyl chloride
[c] Multi- walled carbon nanotube-modified glassy carbon electrode
[d] molecular imprinted polymer-modified carbon paste electrode

Conclusions

In this study, very high sensitive and the selective sensor were developed for PSE determination at low concentrations. The proposed electrode, compared with previously reported research, has a lower detection limit, more extended stability, better reproducibility with the fast response time, easy preparation, and restructuring of the electrode surface; therefore it was used successfully for PSE determination in real samples.

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