Iranian Journal of Analytical Chemistry
Volume 11, Issue 2, September 2024 (123-132) Original Research Article
مجله ایرانی شیمی تجزیه
دوره ۱۱، شماره ۲، مهرماه (۱۳۲-۱۲۳)

Electrochemical Determination of Carbidopa Using Molecularly Imprinted Polymer Modified Glassy Carbon Electrode

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Received: 7 July 2024 **Accepted:** 30 August 2024
DOI: 10.30473/IJAC.2024.72874.1311

Abstract
The molecularly imprinted polymer (MIP) sensor for the rapid and immediate detection of carbidopa (CD) has been investigated. Additionally, a voltammetric sensor based on MIP with a glassy carbon electrode (MIP/GCE) has been developed for CD detection. Under optimal conditions, we observed a strong linear correlation between the sensor's peak current and CD concentrations ranging from 1.0 to 1000.0 μM, with a low limit of detection (LOD) of 0.3 μM (S/N = 3). The modified electrode demonstrated satisfactory electrocatalytic properties for CD oxidation, allowing the sensor to selectively detect CD even in the presence of high concentrations of similar compounds. Furthermore, it was confirmed that MIP/GCE effectively detected CD in urine samples.

Keywords
Molecularly Imprinted Polymer Sensor; Glassy Carbon Electrode; Carbidopa; Electro Catalytic; Voltammetry Techniques.

1. INTRODUCTION

Parkinson’s disease is a neurodegenerative disorder affecting the central nervous system. It primarily occurs due to the loss of neurons in the substantia nigra, an area in the midbrain, which leads to a deficiency of the neurotransmitter dopamine. Unfortunately, dopamine itself is not effective in treating Parkinson's disease because it cannot cross the blood-brain barrier (BBB). Instead, researchers have turned to Levodopa (LD), a metabolic precursor of dopamine, which has become the standard treatment for this condition. Parkinson’s disease is characterized by a significant reduction of dopamine in the central nervous system. In contrast to dopamine, L-DOPA can cross the blood-brain barrier via a storable transporter and is converted into dopamine by the enzyme L-aromatic amino acid decarboxylase within the brain. To enhance treatment efficacy and reduce toxicity, CD is often administered alongside LD in pharmaceutical formulations containing 10% to 25% CD. Research suggests that CD functions as a peripheral L-aromatic amino acid decarboxylase inhibitor, exhibiting minimal pharmacological activity when administered alone at standard doses to patients with Parkinson's disease. Since CD does not cross the BBB, it helps increase the effective concentration of dopamine in the brain by inhibiting the peripheral conversion of LD to dopamine. This reduction in peripheral dopamine formation also helps mitigate side effects such as nausea, cardiac arrhythmia, and vomiting [1-12]. In recent years, analytical methods for drug separation and detection have gained significant attention. Various techniques have been developed for drug detection, with the most commonly used methods including HILIC-MS/MS, spectrophotometry, LC–MS/MS, and capillary zone electrophoresis with amperometric detection. [13-16].

Electroanalytical methods have recently gained considerable attention due to their advantages, including simplicity, cost-effectiveness, and quick analysis times, positioning them as a compelling alternative to colorimetric determination. Among these methods, electrochemical techniques are particularly noteworthy for their exceptional sensitivity, high accuracy, capability to detect multiple components simultaneously, potential for miniaturization, and ease of modification

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compared to other techniques. Electrochemical detection is recognized as one of the most effective approaches for trace analysis, providing high selectivity that is often linked to improved sensitivity and reduced costs.

However, trace-level analysis encounters challenges such as high redox potentials and the low sensitivity of electroactive materials on unmodified electrode surfaces. These challenges can be addressed or alleviated through the surface modification of electrodes. Furthermore, surface modification enhances electrode kinetics, leading to improved detection selectivity and sensitivity. In recent years, the development of electrochemical sensors with high sensitivity for applications in medical diagnostics, environmental monitoring, and food safety has proven to be both challenging and highly sought after [17-26].

It has been demonstrated that intentional chemical modification of the electrode surface with an appropriate modifier can effectively control the rates and selectivity of electrochemical reactions [27-44]. Among the different types of electrodes utilized in electrochemical determinations, GCEs have demonstrated significant stability and resistance. In electroanalytical methods, the redox reactions of analytes frequently necessitate a high overpotential because of the slow rate of electron transfer at conventional electrodes. Additionally, conventional electrodes typically exhibit poor performance in analyte detection, which has led to a growing interest in their modification. Previous studies have indicated that surface modification of electrodes not only significantly reduces overpotentials but also enhances the rate of electron transfer. One common approach for chemical modification involves the application of MIPs on the electrode surface. MIPs are created by polymerizing functional monomers and cross-linkers around a template, which can be the target analyte or a closely related molecule. This process results in the formation of cross-linked three-dimensional cavities that are selective for the target. These cavities are tailored to match the size, shape, and chemical functionality of the template. Once the template is removed, the cavities become available for the selective binding of the analyte from various samples, including biological fluids. In addition to their high selectivity, MIPs also exhibit excellent thermal, mechanical, and physicochemical stability. Numerous studies across different fields, including food, environmental, and pharmaceutical analyses, have demonstrated the versatility of MIPs for sample preparation. [45-49].

The current study investigated the response characteristics of an electrochemical sensor array coated with a MIP. The MIP was synthesized through precipitation polymerization in the presence of template molecules. This approach is a form of heterogeneous polymerization, where the monomers and initiators are dissolved in a solvent, leading to the formation of a polymer that is insoluble and precipitates from the solution.

2. EXPERIMENTAL

2.1. Chemicals and Apparatus

All chemicals and reagents including methacrylic acid (MAA) as monomer, ethylene glycol dimethacrylate (EGDMA) as cross linker, azodiisobutyronitrile (AIBN) as initiator, citric acid, and CD were purchased from Sigma-Aldrich and Merck with high purity.

For the electrochemical experiments, an Autolab potentiostat/galvanostat (PGSTAT 302N; Eco Chemie, The Netherlands) was employed, and the system was monitored using general-purpose electrochemical software. A traditional three-electrode cell was utilized at a temperature of 25±1 °C. The electrodes included a platinum wire as the auxiliary electrode, a MIP/GCE as the working electrode, and an Ag/AgCl/KCl (3.0 M) as the reference electrode. Additionally, a Metrohm 710 pH meter was used to measure pH levels.

For each differential pulse voltammetry (DPV) measurement, the working electrode was first immersed in 5 mL of a specified concentration of CD and 0.1 M PBS (prepared from 0.1 M H_3PO_4 and 0.1 M NaOH, pH 7.4) at room temperature. After washing the working electrode with PBS, it was placed into the three-electrode cell. DPV measurements were then conducted in 25 mL of 0.1 M PBS at pH 7.0, also at room temperature.

2.2. Synthesis and Procurement of MIPs

The synthesis and characterization of MIP and NIP were described in our previous work, except that CD was used instead of levodopa. [50].

2.3. Preparing the Modified GCE

The GCE was polished prior to all experiments using 0.01 g of alumina powder. After each polishing phase, it was thoroughly rinsed with doubly distilled water. Subsequently, the electrode underwent sonication in a 1:1 mixture of nitric acid and acetone, followed by rinsing with doubly distilled water. Finally, the electrode was set aside to dry at room temperature.

To coat the bare GCE with MIP, a stock solution was prepared by dispersing 20 mg of MIP in 5 mL of a 1:1 solution of nitric acid and acetone, using ultrasonic agitation for one hour. A 6 µL of this MIP suspension was then applied to the working

DOI: 10.30473/IJAC.2024.72874.1311

electrode of the GCE, allowing the solvent to evaporate at room temperature.

2.4. General Analytical Procedure

A 25 mL solution of PBS (0.1 M, pH 7.0) was combined with an appropriate volume of a 10 µM CD standard solution in an electrochemical cell. Next, a three-electrode system was assembled. An accumulation potential of 200 mV was then applied to the electrode for 30 s, followed by rinsing with 0.1 mL of PBS (0.1 M, pH 7.0). After washing, the modified electrode was electrochemically evaluated in 25 mL of PBS (0.1 M, pH 7.0) using DPV. It is important to note that after all measurements are completed, the electrode will need to be refreshed.

3. RESULTS AND DISCUSSION

3.1. Electro-chemical Behaviors of CD on the NIP/GCE and MIP/GCE sensors

Fig. 1 displays the cyclic voltammetry (CV) behavior of CD on the NIP/GCE sensor (Curve b) and MIP/GCE sensor (Curve a) in a 0.1 M PBS solution (pH 7) containing 50.0 µM CD. The Fig. 1 indicates that the electrochemical response of CD on the NIP/GCE sensor is negligible, which can be attributed to the non-conductive properties of the NIPs that hinder electron transfer. In contrast, a significantly higher oxidation current for CD is observed on the MIP/GCE sensor, indicating a greater binding affinity between MIP and CD, which leads to an enrichment of CD on the surface of the MIP/GCE sensor.

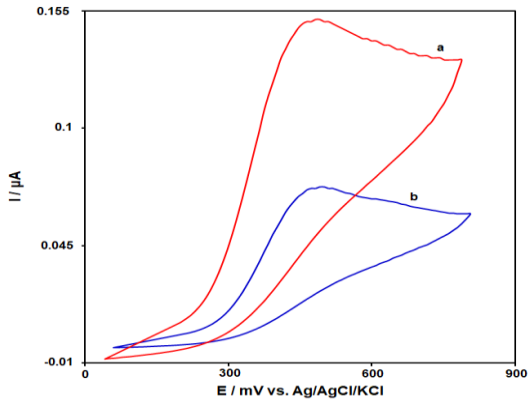

Fig. 1. CVs of a) MIP/GCE sensor and b) NIP/GCE sensor, with an accumulation potential of 200 mV applied for 30 s at a concentration of 100.0 µM CD in PBS (0.1 M, pH 7.0). In both cases, the scan rate was set to 50 mV s^{-1}.

The mechanism can be as follows:

When the analyte is added to the polymer, interactions occur between the analyte and the cavities created in the polymer. These interactions can include hydrogen bonds, van der Waals forces, and electrostatic interactions. These interactions allow the analyte to bind specifically and with high selectivity to the polymer. Therefore, considering the presence of oxygen and nitrogen groups in the structure of the CD molecule and the presence of oxygen groups in the template, the interaction between the CD molecule and the template can be of the hydrogen bonding type. Additionally, depending on the environmental conditions, electrostatic interactions may also play a role.

3.2. Optimizing the Experimental Conditions

To enhance the performance of the MIP/GCE sensor, several parameters were investigated and optimized, including the concentration of MIP, accumulation potential, accumulation time, type of buffer, buffer concentration, and buffer pH, all in a solution containing 50.0 µM CD.

3.3. Optimization of Type of Buffer on the MIP/GCE sensor

The impact of buffer type on the determination process of CD was investigated using solutions containing 100.0 µM CD, with the results presented in Fig. 2. As shown in the inset (Fig. 2), the electrode response significantly increases in PBS, which can be attributed to the ionic strength of the PBS.

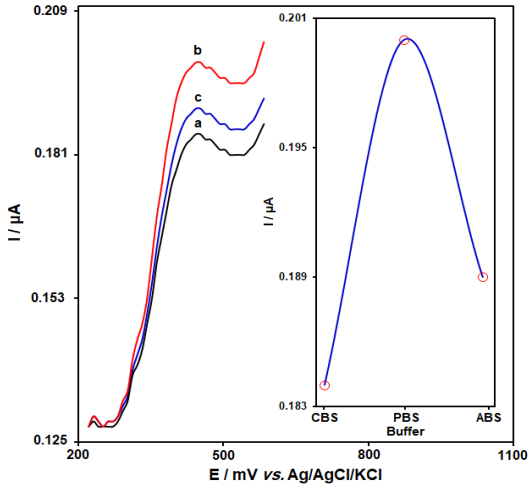

Fig. 2. DPVs of MIP/GCE sensor with an accumulation potential of 200 mV applied for 30 s at a concentration of 100.0 µM CD in various buffers. Panels a–c correspond to acetate (a), phosphate (b), and citrate (c) buffers, respectively. Inset: A plot of peak current (I_p) as a function of the different (acetate, phosphate, and citrate) buffers.

3.4. Optimization of Concentration of PBS on the MIP/GCE sensor

The effect of PBS concentration on the determination process of CD was investigated using solutions containing 100.0 µM CD in PBS concentrations ranging from 0.05 to 0.3 M. The results are presented in Fig. 3. As shown in the figure, the electrode response increases

DOI: 10.30473/IJAC.2024.72874.1311

significantly at 0.1 M PBS, which can be attributed to the ionic strength of the PBS.

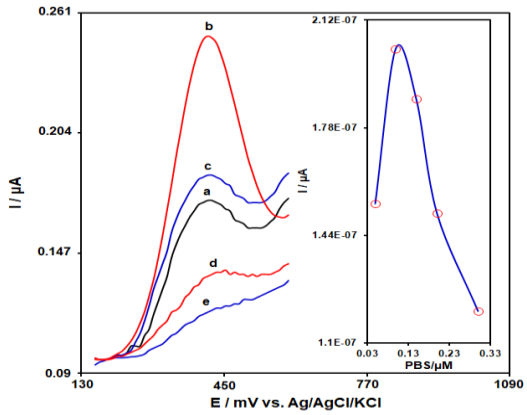

Fig. 3. DPVs of MIP/GCE sensor with an accumulation potential of 200 mV applied for 30 s at a concentration of 100.0 µM CD in various concentrations of PBS. Panels a–d correspond to concentrations of 0.05 (a), 0.1 (b), 0.15 (c), 0.2 (d), and 0.3 (e) M. Inset: A plot of I_p as a function of the different concentrations of PBS.

3.5. Optimizing pH-value on the MIP/GCE sensor

It has been observed that pH affects both the redox transfer process and the interactions between the analyte and the electrode surface modifier, significantly influencing the electrochemical behavior of the analyte. Consequently, the effects of pH on the oxidation of CD on the MIP/GCE sensor were investigated across a range of 4.0 to 10.0 using 0.1 M PBS (Fig. 4). The intensity of the oxidation peak was found to be highest at a pH of 7, decreasing as the pH increased beyond this point. Therefore, PBS with a pH of 7.0 was used as the supporting electrolyte for all subsequent detections.

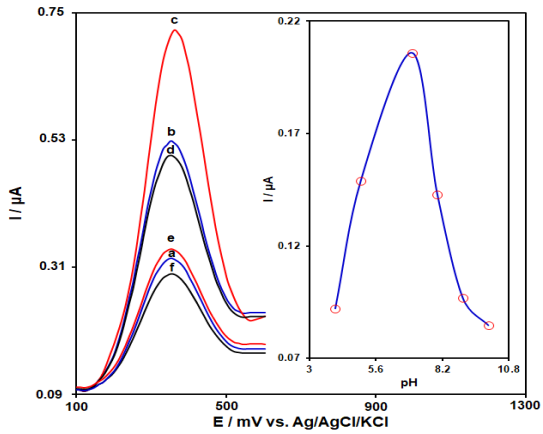

Fig. 4. DPVs of MIP/GCE sensor with an accumulation potential of 200 mV applied for 30 s at a concentration of 100.0 µM CD in PBS (0.1 M, pH 7.0) at various pH values of PBS. Panels a–d correspond to pH values of 4.0 (a), 5.0 (b), 7.0 (c), 8.0 (d), 9.0 (e), and 10.0 (f) µM. Inset: A plot of I_p as a function of the different pH values of PBS.

3.6. Concentration MIP Optimization on the MIP/GCE sensor

The impact of MIP concentration on the determination process of CD was investigated using solutions containing 100.0 µM CD in PBS (0.1 M, pH=7.0). The results are presented in Fig. 5. According to the data in Fig. 5, the electrode response increases significantly at an MIP concentration of 4.0 mg/mL.

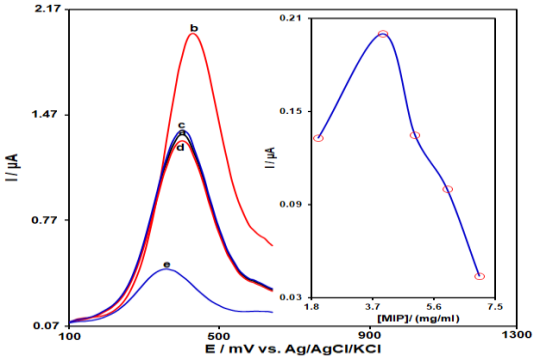

Fig. 5. DPVs of MIP/GCE sensor with an accumulation potential of 200 mV applied for 30 s at a concentration of 100.0 µM CD in PBS (0.1 M, pH=7.0) with various concentrations of MIPs. Panels a–d correspond to MIP concentrations of 2.0 (a), 4.0 (b), 5.0 (c), 6.0 (d), and 7.0 mg/mL (e). Inset: A plot of I_p as a function of MIP various concentration within the range of 2.0 to 7.0 mg/mL.

3.7. Effects of the Accumulation Potential and Accumulation Duration on the MIP/GCE sensor

It is well known that accumulation potential is a critical factor in stripping methods, greatly influencing detection sensitivity. As a result, the accumulation potential was investigated within the range of 100 to 400 mV. The graph of stripping peak current (Fig. 6) as a function of preconcentration potential indicated that the highest peak current occurred at 200 mV. Therefore, an accumulation potential of 200 mV was selected for subsequent applications.

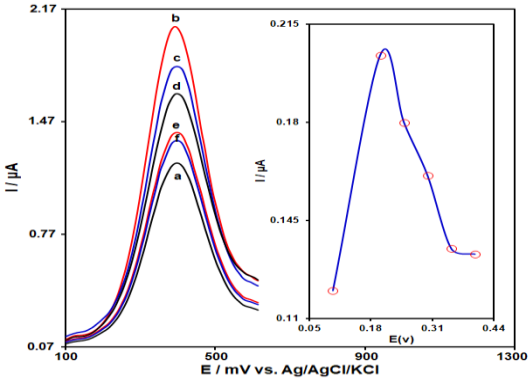

Fig. 6. DPVs of MIP/GCE sensor with varying accumulation potentials (a–d correspond to 100 (a), 200 (b), 250 (c), 300 (d), 350 (e), and 400 (d) mV) applied for 30 s at a concentration of 100.0 µM CD in 0.1 M PBS (0.1M, pH 7.0). Inset: A plot of I_p as a function of accumulation potential (100-400 mV).

DOI: 10.30473/IJAC.2024.72874.1311

Since combining the analyte with MIP requires a specific duration to achieve the highest enrichment rate, accumulation time was investigated over a range of 10 to 50 s (Fig. 7). From the results in Fig. 7, it can be concluded that the peak current reached its maximum at 30 s, after which it began to decline with longer accumulation times. This indicates that the interactions between the analyte and MIPs may involve non-specific binding. Therefore, 30 s was selected as the optimal accumulation time.

Under the optimized conditions, the following parameters were established for future research: 0.1 M PBS as the optimal buffer concentration, PBS as the preferred buffer type, 4 mg/mL of MIP as the optimal MIP concentration, 200 mV as the optimal accumulation potential, a pH of 7.0 for the PBS as the optimal pH, and 30 s as the optimal accumulation time.

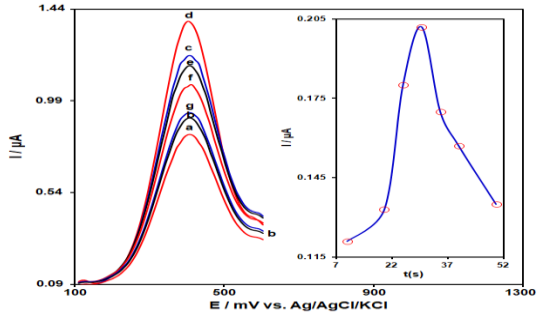

Fig. 7. DPVs of MIP/GCE sensor with an accumulation potential of 200 mV at a concentration of 100.0 µM CD in 0.1 M PBS (pH 7.0) with varying accumulation times. Panels a–f correspond to accumulation times of 10 (a), 20 (b), 25 (c), 30 (d), 35 (e), 40 (f), and 50 (g) s. Inset: A plot of I_p as a function of accumulation time (10-50 s).

3.8. Effects of the Scan Rate on the MIP/GCE sensor

Fig. 8 illustrates the effect of scan rate on the oxidation currents of CD. The data demonstrate that peak currents increase with higher scan rates. Additionally, it is known that the plot of peak current (Ip) against scan rate (ν) for the analyte is linear, leading to the conclusion that the oxidation processes are controlled by adsorption.

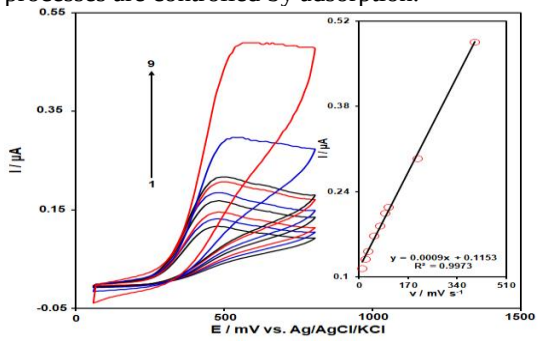

Fig. 8. CVs of MIP/GCE sensor with an accumulation potential of 200 mV applied for 30 s at a concentration of 100.0 µM CD in 0.1 M PBS (pH 7) at various scan rates. The labels 1-9 correspond to scan rates of 10 (1), 20 (2), 30 (3), 50 (4), 70 (5), 90 (6), 100 (7), 200 (8), and 400 (9) mV s^{-1}. Inset: Variation of the anodic peak current (I_{pa}) as a function of scan rate.

3.9. Calibration Carve

The calibration curve for CD detection was established using the developed MIP/GCE sensor under optimal experimental conditions. This allows for the detection of CD in solution by measuring the peak current of its oxidation at the modified electrode surface. Consequently, we conducted DPV experiments at various concentrations of CD (initial potential = 0.16 V, end potential=0.58 V, step potential=0.01 V, modulation amplitude=0.10005 V) (Fig. 9). The results indicated that the oxidation peak currents of CD at the modified electrode surface are proportional to its concentration within the range of 1.0 to 1000.0 µM. Additionally, the LOD for CD was determined to be 0.3 µM. One of the key advantages of the MIP/GCE sensor is its excellent selectivity. Additionally, the LOD (C_m) for CD was determined using the following equation:

$C_m=3S_b/m$

In the equation, m represents the slope of the calibration plot (0.0013 $\mu A \cdot \mu M^{-1}$), and S_b is the standard deviation of the blank response, which is derived from 20 replicate measurements of the blank solution. The limit of detection (LOD) was estimated to be 0.3 µM. Furthermore, Table 1 indicates that the MIP/GCE sensor is competitive with other sensors for the determination of CD.

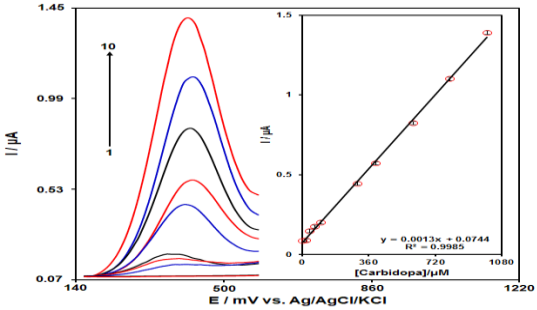

Fig. 9. DPVs of MIP/GCE sensor with an accumulation potential of 200 mV applied for 30 s in 0.1 M PBS (pH 7.0) at various concentrations of CD. The labels 1-10 correspond to concentrations of 1.0 (1), 20.0 (2), 40.0 (3), 70.0 (4), 100.0 (5), 300.0 (6), 400.0 (7), 600.0 (8), 800.0 (9), and 1000.0 (10) µM of CD. The inset shows the plots of peak current as a function of CD concentration within the range of 1.0 to 1000.0 µM.

Table 1. Comparison of some characteristics of the different methods for the determination of CD.

Sensors	Methods	LDR µM	LOD µM	Ref.
MCNTPE	SWV	0.6-100.0	0.4	[51]
MWCNT-PAH/GCE	DPV	2.0-23.0	0.65	[52]
CP-TNMCPE	DPV	0.1-100.0	0.069	[53]
MIP/GCE	DPV	1.0 to 1000.0 µM	0.3 µM	This work

DOI: 10.30473/IJAC.2024.72874.1311

3.10. Stability, reproducibility and repeatability

To assess the stability of the MIP/GCE sensor, the oxidation peak current of CD was monitored over 15 consecutive cycles in 0.1 M PBS at pH 7.0 with a scan rate of 10 mV/s. It was found that after 15 cycles, the electrode maintained approximately 90% of its initial current response, indicating that the developed sensor exhibits good stability with minimal performance loss after repeated use. Additionally, under the same preparation conditions, five different MIP/GCE sensors were tested, and the relative standard deviation (RSD) of the peak current (Ip) for 70.0 µM CD was measured at 3.3%, demonstrating good reproducibility. The repeatability of the MIP/GCE sensor was further evaluated by conducting four consecutive measurements with the same solution (70.0 µM CD), resulting in an RSD of 3.1% for the analyte, suggesting acceptable repeatability. The excellent stability, reproducibility, and repeatability of the MIP/GCE sensor are crucial characteristics that enhance its overall reliability and suitability for practical applications.

4. CONCLUSIONS

Our study presents an affordable and simple MIP-based GCE sensor for the sensitive detection of CD. CD -imprinted electrodes were created using a bulk polymerization method followed by drop coating onto the surface of a modified GCE. The MIP/GCE sensor demonstrated several advantageous analytical characteristics, including excellent synergistic effects, good reproducibility, high stability, excellent selectivity, and rapid response times to CD. The technique resulted in a robust and smooth on the electrode surface. Additionally, factors such as accumulation potential, accumulation time, scan rate, and CD concentration were thoroughly examined. Notably, under optimized conditions, the I_{pa} was found to be proportional to CD concentration within the range of 1.0 to 1000.0 µM, with a LOD of 0.3 µM. Therefore, it can be concluded that this sensor lays the groundwork for the development of a portable CD sensor due to its simplicity, rapid implementation, and affordability.

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DOI: 10.30473/IJAC.2024.72874.1311

Iranian Journal of Analytical Chemistry 11 (2024) 123-132

تعیین الکتروشیمیایی کاربیدوپا با استفاده از الکترود کربن شیشه‌ای اصلاح‌شده با پلیمر قالب مولکولی

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تاریخ دریافت: ۱۷ تیر ۱۴۰۳ **تاریخ پذیرش:** ۹ شهریور ۱۴۰۳

چکیده

حسگر پلیمر قالب مولکولی (MIP) برای تشخیص سریع و فوری کاربیدوپا مورد بررسی قرار گرفته است. علاوه بر این، یک حسگر ولتامتری مبتنی بر MIP با الکترود کربن شیشه‌ای (MIP/GCE) برای تشخیص کاربیدوپا توسعه داده شده است. در شرایط بهینه، ما یک همبستگی خطی قوی بین جریان پیک حسگر و غلظت کاربیدوپا از ۱/۰ تا ۱۰۰۰/۰ میکرومولار، با حد تشخیص پایین ۰/۳ میکرومولار (S/N =۳) مشاهده کردیم. الکترود اصلاح‌شده خواص الکتروکاتالیستی رضایت‌بخشی را برای اکسیداسیون کاربیدوپا نشان داد و به حسگر اجازه داد تا کاربیدوپا را حتی در حضور غلظت‌های بالای ترکیبات مشابه، به طور انتخابی تشخیص دهد. علاوه بر این، تأیید شد که MIP/GCE به طور مؤثر کاربیدوپا را در نمونه‌های ادرار تشخیص می‌دهد.

کلید واژه ها

حسگر پلیمری قالب مولکولی؛ الکترود کربن شیشه‌ای؛ کاربیدوپا؛ الکتروکاتالیستی؛ تکنیک‌های ولتامتری.

DOI: 10.30473/IJAC.2024.72874.1311