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ORIGINAL ARTICLE / ÖZGÜN MAKALE

A TALE OF CAPTOPRIL DETECTION BASED ON AN ELECTROCHEMICAL MIP SENSOR

KAPTOPRİL TESPİTİ İÇİN ELEKTROKİMYASAL BİR MIP SENSÖRÜNÜN HİKAYESİ

Aysu YARMAN[1]*, Sevinc KURBANOGLU[2]

[1]Turkish-German University, Faculty of Science, Molecular Biotechnology, 34820, Istanbul, Türkiye
[2]Ankara University, Faculty of Pharmacy, Department of Analytical Chemistry, 06560, Ankara, Türkiye

ABSTRACT

Objective: *In this study, it was aimed to develop a voltammetric method using sensors prepared with the molecular imprinting technique for the detection of Captopril, an antihypertensive drug.*
Material and Method: *With the molecular imprinting method, molecularly imprinted polymers were formed on the surfaces of glassy carbon electrodes. The analysis of Captopril was carried out using the differential pulse voltammetry method, and the performance of the sensor was examined.*
Result and Discussion: *A linear analysis was performed up to 50 pM Captopril with a limit of detection value of 2.62 pM. Selectivity studies have shown that Captopril has a higher electrochemical response than other interfering substances, such as paracetamol, ascorbic acid, and L-proline.*
Keywords: *Biomimetic sensors, buffer effect, captopril, molecularly imprinted polymers*

ÖZ

Amaç: *Bu çalışmada antihipertansif bir ilaç olan Kaptoprilin tespitine yönelik moleküler baskılama yöntemi ile hazırlanmış sensörler kullanılarak voltametrik bir yöntem geliştirilmesi amaçlanmıştır.*
Gereç ve Yöntem: *Moleküler baskılama yöntemi ile camsı karbon elektroların yüzeylerinde moleküler baskınlanmış polimerler oluşturulmuş ve differansiyel puls voltammetri yöntemi ile Kaptoprilin analizi gerçekleştirilmiş, sensörün performansı incelenmiştir.*
Sonuç ve Tartışma: *2,62 pM teşhis sınırı değeri ile 50 pM Kaptopril seviyesine kadar doğrusal bir analiz gerçekleştirilmiştir. Seçicilik çalışmaları, Kaptoprilin, diğer girişim yapabilecek, parasetamol, askorbik asit ve L-prolin gibi maddelere göre daha yüksek elektrokimyasal cevaba sahip olduğunu göstermiştir.*
Anahtar Kelimeler: *Biyomimetik sensörler, kaptopril, moleküler baskılanmış polimerler, tampon çözelti etkisi*

INTRODUCTION

Cardiovascular diseases (CVD), a group of disorders of the heart and blood vessels, are the leading cause of death worldwide [1]. In 2019 it was estimated that 17.9 million people died due to the CVDs. 85% were due to heart attack and stroke [1].

Hypertension (elevated blood pressure), defined using specific systolic and diastolic blood pressure levels, increases the risk of heart, brain, kidney, and other diseases. Globally 1.4 billion people

* **Corresponding Author / Sorumlu Yazar:** Aysu Yarman
e-mail / e-posta: yarman@tau.edu.tr, **Phone / Tel.:** +90216333340

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have been estimated to have high blood pressure, only 14% of whom have it under control [2]. Captopril (CAP, (2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid) is an antihypertensive drug, which is an angiotensin-converting enzyme inhibitor. It is widely used to treat congestive heart failure [3-5]. However, it has possible side effects like proteinuria, neutropenia, or skin rashes. Therefore, its determination in biological fluids and pharmaceutical dosage is necessary [6-8]. In addition to spectroscopical and chromatographical methods, a spectrum of electrochemical sensors has been developed for CAP detection [9]. Electrochemical methods provide some advantages, such as simplicity, cost-effectiveness, and sensitivity.

In this study, an electrochemical sensor for CAP determination based on a molecularly imprinted polymer (MIP) developed. Molecular imprinting stands out as a promising technique to replace biological recognition elements such as antibodies and enzymes in the field of bioanalysis and biosperation. Initially introduced by Wulff and Mosbach, this method involves the polymerization of functional monomers, either with or without cross-linkers, in the presence of a target analyte (template). The subsequent removal of the template results in the production of binding cavities that mirror the template's size, shape, and functionality. This process aims to generate artificial antibodies, often called plastibodies, which exhibit molecular recognition capabilities in bioanalytical applications [10–13]. Although MIPs for low-molecular-weight substances like pharmaceuticals, narcotic drugs, amino acids, toxins, sugars, and pesticides have been successfully prepared, it is still challenging for biomacromolecules like proteins or viruses due to their structural complexity and fragility under MIP preparation conditions [14-29]. However, increasing attention has been paid to the fabrication of MIPs due to their ease of preparation, cost-effectiveness, and stability under various conditions like extreme pHs, high temperatures, or organic solvents.

Herein, we describe a simple approach to fabricate an electrochemical MIP sensor to detect CAP. The MIPs were prepared in situ on a glassy carbon electrode using *o*-phenylenediamine (o-PD) as a functional monomer. All steps of MIP preparation were studied using the gate effect on the redox marker ferricyanide/ferrocyanide. Moreover, the sensor was applied in pharmaceutical dosage, and the effect of interfering substances was investigated.

MATERIAL AND METHOD

Reagents

o-Phenylenediamine dihydrochloride (*o*-PD), captopril, paracetamol (acetaminophen), and L-Proline were purchased from Sigma (Steinheim, Germany), ascorbic acid, ferricyanide and ferrocyanide from Merck (Germany). Kapril® 25 mg was obtained from GENSENTA Ilaç Sanayi ve Ticaret A.Ş. All reagents were of analytical grade and used without further purification.

Instruments

Electrochemical experiments were conducted in a homemade cell with a three-electrode system using PalmSens potentiostat (Utrecht, The Netherlands). A glassy carbon electrode (GCE, diameter: 3 mm), an Ag/AgCl electrode (in 3 M KCl), and a platinum wire served as the working electrode, the reference electrode, and the counter electrode, respectively.

Preparation of CAP-MIP/GCE and working solutions

The MIP-sensor was fabricated by electrodepositing the polymer directly on a GCE in a solution of 0.5 mM CAP and 5 mM *o*-PD (in 100 mM acetate buffer, pH 5.2) utilizing cyclic voltammetry (Figure 1). The potential was swept between 0 and 0.8 V with a scan rate of 50 mV/s with different scan numbers. For the removal of template molecules, different strategies have been applied. Rebinding and removal of CAP were followed by changes in DPV responses of 5 mM $[Fe(CN)_6]^{3-/4-}$ solution (in 100 mM KCl) by applying respective conditions: The potential range: -0.2 - 0.7 V, potential step: 5 mV, pulse amplitude: 25 mV, and pulse duration: in these measurements 0.7 s [14].

For the electrochemical analysis, an aliquot from the stock solution of CAP was prepared as 500 ppm, and then desired concentrations were obtained by diluting the stock solution, used for the rebinding studies.

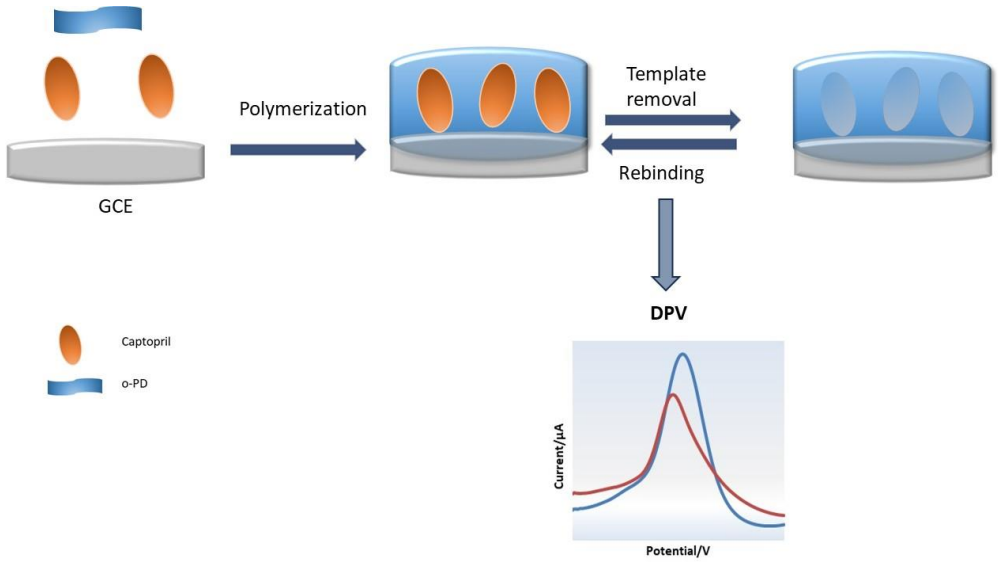

Figure 1. Workflow of the CAP-MIP/GCE

CAP stock solution from pharmaceutical dosage forms Kapril® was prepared by crushing ten tablets of Captopril film-coated tablets containing 25 mg CAP and, after homogenized, weighing an amount that is equal to one tablet, was dissolved in the working buffer solution, sonicated for 10 min and filtered. Following than, desired concentrations were obtained by diluting the stock solution.

RESULT AND DISCUSSION

Polymerization Step

Electropolymerization is one of the elegant ways to prepare MIPs with controlled thickness in situ on the surface of transducers. Moreover, it provides faster preparation time and eliminates the use of a cross-linker. Based on former experiences *o*-phenylenediamine was chosen as an electroactive monomer, and captopril was the target analyte (Figure 1) [24,26].

As seen from the CVs, an irreversible peak observed at around 450 mV during the first cycle decreased in successive cycles, indicating the formation of a non-conducting polymer film (Figure 2). Non-imprinted polymer (NIP) was also prepared like MIP but without the template captopril, had a similar behavior during electropolymerization (data not shown).

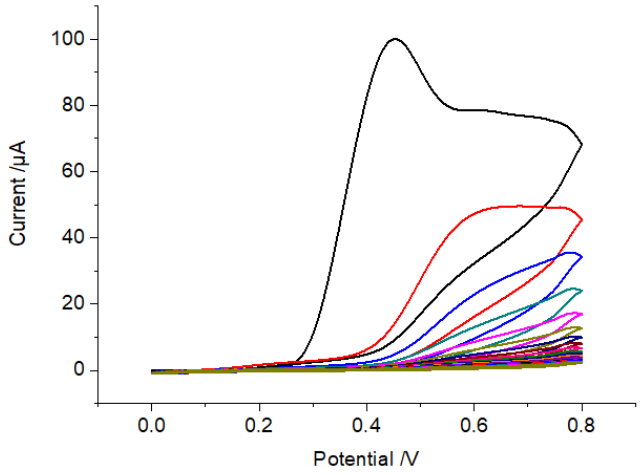

Figure 2. Cyclic voltammograms during electropolymerization of 5 mM *o*-PD in the presence of 0.5 mM Captopril in 50 mM acetate buffer, pH 5.2 (Scan rate: 50 mV/s, 20 cycles)

We followed the steps of MIP sensor fabrication and application by the most common technique assessing the diffusional permeability of the polymer layer to a redox marker, ferricyanide/ferrocyanide (Figure 3). This method is known for its simplicity, cost-effectiveness, and high sensitivity. It allows for the characterization of each step of MIP synthesis and the measurement of target-rebinding to the MIP, applicable to low-molecular-weight targets, (bio)macromolecules, and (nano)particles [11,30]. In the case of low-molecular-weight molecules, like CAP, the cavities formed after template removal exhibit diameters comparable to that of the redox marker (Figure 3) [11]. Various mechanisms have been proposed to explain the impact of target binding on the current signal of the redox marker. These include alterations in the MIP film's porosity or the marker's diffusion rate, doping-dedoping effects, and changes in the electric double layer [31]. This concept is known as the "gate effect," initially introduced by Yoshimi et al. for a theophylline-imprinted polymer [31]. However, the complex mechanism behind the "gate effect" is not yet fully understood.

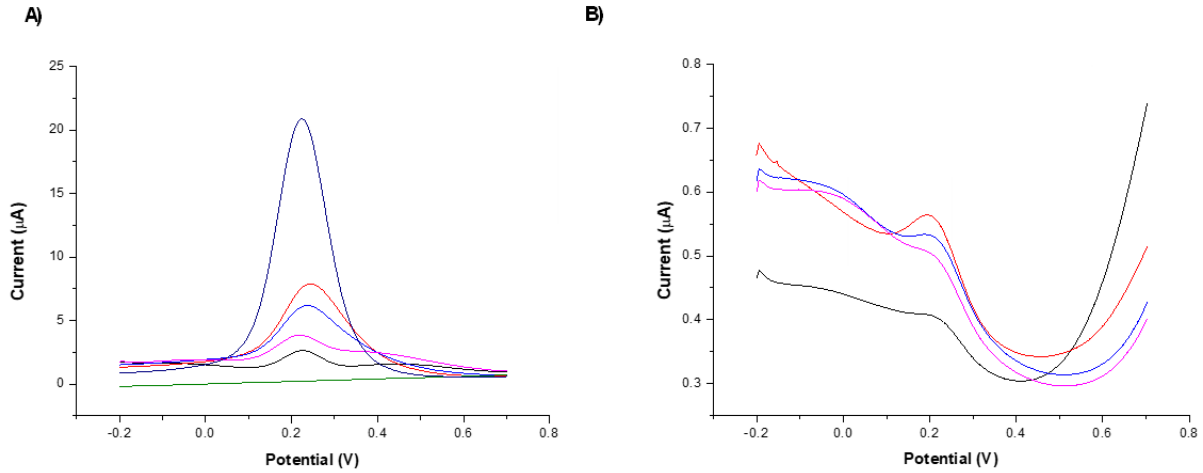

Figure 3. Differential pulse voltammograms A) Bare GCE: Dark purple. CAP-MIP/GCE after electropolymerization (black), template removal (red), 1 h incubating in buffer (blue), 40 pM CAP binding (pink) and B) NIP/GCE after electropolymerization (black), template removal (red), 1 h incubating in buffer (blue), 10 pM CAP binding (pink)

Template Removal

Template removal is one of the most crucial steps in fabricating MIP sensors [32]. Harsh conditions may cause deformation of the structure of the polymeric film, whereas milder conditions might not be strong enough for the complete removal of the template molecules. As a result, the binding capacity of the MIP is low. In this study, several procedures were applied to remove the captopril molecules from the polymer.

Milder acidic conditions, e.g., 50 mM glycine-HCl buffer, pH 2.2 (overnight incubation), cannot remove the template molecules from the polymeric film. By contrast, incubation in 0.1 M H_2SO_4 caused the observation of 75% of the ferricyanide signal at the bare electrode. Moreover, the combination of acidic (0.3 M H_2SO_4) and electrochemical procedure (CV, scanning between -1.0 V and 1.0 V) caused a complete loss of the polymeric film. On the other hand, template molecules were successfully removed in 0.1 M NaOH solution by applying the cyclic voltammetric technique between -1.0 V and 1.0 V (10 scans).

Analytical Performance of the MIP-Sensor

Rebinding studies have been conducted in acetate buffer containing different amounts of captopril. DPV was used to indicate the change in the signal of the redox marker. Under optimum conditions, a calibration plot for the determination of was obtained. (Figure 4). The sensor responded linearly up to 50 pM (R^2= 0.977) with a limit of detection of 2.62 pM and limit of quantification of 7.94 pM. The comparison of the binding affinities of CAP on MIP- and NIP-modified electrodes indicated

specific binding to the cavities formed after template removal in the polymer. As seen from Figure 3, the ferricyanide signal was completely suppressed at the NIP-modified electrode upon 10 pM CAP binding, whereas 40 pM CAP led not a complete suppression. Therefore, further calibration studies were not performed with NIP-modified electrodes. As seen in Table 1, the sensitivity of the developed sensor is higher than that of the sensors described in the literature. In contrast, the linear dynamic range is narrow, which might be improved by incorporating nanomaterials into the electrode [33].

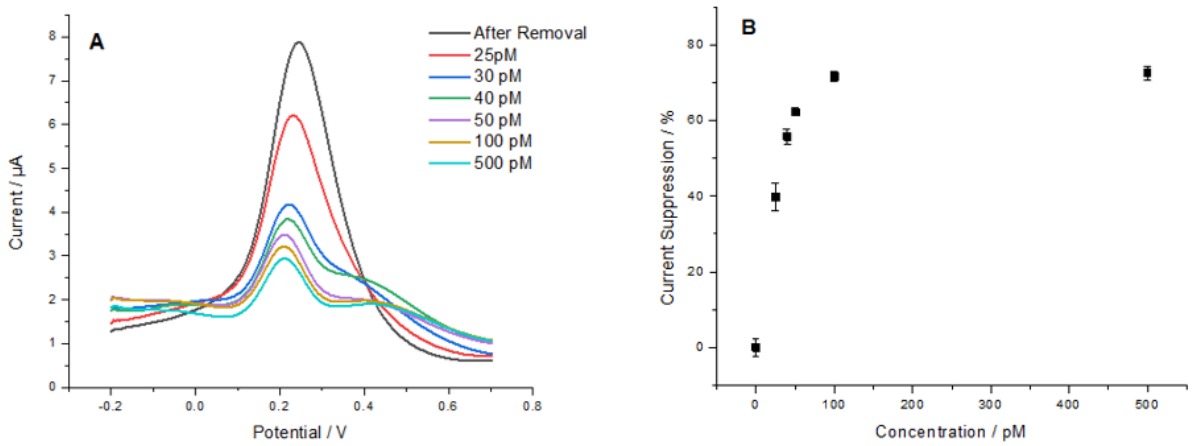

Figure 4. A) Concentration dependence of the DPV peak on the concentration of Captopril on CAP-MIP/GCE and B) Calibration graph

Table 1. Examples of Electrochemical Sensors for the Detection of Captopril

Electrode	Detection Method	Linear Dynamic Range	LOD	Reference
GSPE	CV	up to 0.8 mM	4.27 µM	[34]
CuBTC/GCE	DPV	0.5-7 µM	0.20 µM	[35]
CuO/ITO electrode	DPV	0.01 to 3.43 µM	2 nM	[36]
Au@Cu/BTC	CV	0.5-7 µM; 10-2500 µM	0.047 µM	[37]
SnO_2/rGO/Pt electrode	DPV	1-700 nM; 10-100 µM	0.061 nM; 0.0018 µM	[38]
CAP-MIP/Modified CPE	Potentiometry	3 nM-0.1 M	1 nM	[39]
CAP-MIP/GCE	DPV	up to 50 pM	2.62 pM	This work

GSPE: Graphite Screen-Printed Electrode; Cu-BTC: $C_{18}H_6Cu_3O_{12}$ (copper metal-organic framework); rGO: Reduced graphene oxide; CPE: Carbon Paste Electrode; GCE: Glassy Carbon Electrode

One notable drawback of this MIP-approach arises when dealing with low concentrations of the target substance. Detection of minute amounts causes only small decreases of a large baseline current. This difficulty is exacerbated by the fluctuation of the background current, leading to high uncertainties in determinations, which might be caused by variations in the polymer film's volume due to changes in the ionic strength and/or pH of the sample solution [40]. Just incubating in a buffer solution can also provoke a suppression of the ferricyanide signal, as seen in Figure 3. It was observed that at least one hour of pre-incubation in the buffer solution was needed to prevent false lower-concentration measurements.

In an effective therapeutic process, it is essential to quantify the amount of drug used. For this purpose, the MIP-sensor was used to determine CAP in Captopril film-coated tablets. For 40 pM CAP containing sample solution, 101.95 % recovery results were obtained with Bias% of -1.95.

Cross-reactivity Studies

Since selectivity is the most essential validation parameter, cross-reactivity of potentially

interfering substances paracetamol, L-proline, and ascorbic acid was investigated. The highest suppression of the ferricyanide signal was obtained upon the rebinding of the template molecule, captopril, while paracetamol had a 4.8-fold lower while ascorbic acid had almost no effect on the ferricyanide signal of the MIP sensor. On the other hand, L-proline exhibited 1.6-fold lower suppressions than captopril, which may be caused by the fact that captopril is a derivative of L-proline (Figure 5).

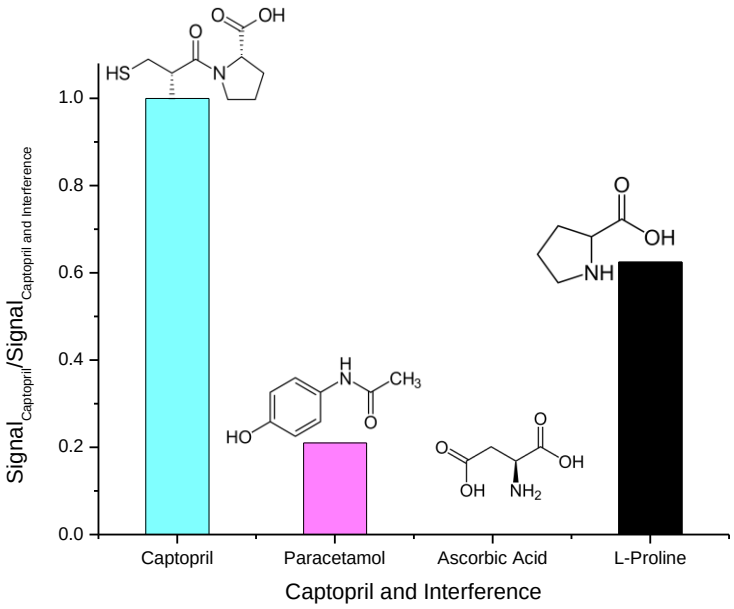

Figure 5. Cross-reactivity of interfering substances binding on the CAP-MIP/GCE

Conclusion

In this work, the first voltammetric MIP sensor was developed to detect the antihypertensive drug captopril. Evaluating the gate effect on the redox probe ferricyanide/ferrocyanide. The sensor responded linearly up to 50 pM captopril (R^2= 0.977) with a limit of detection of 2.62 pM and limit of quantification of 7.94 pM. The sensor was further successfully applied in captopril detection in pharmaceutical dosage forms. It showed high discrimination towards paracetamol, ascorbic acid, and L-Proline. One crucial issue was that one hour of pre-incubation of the MIP sensor in the buffer solution was needed to prevent false lower-concentration readout.

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AUTHOR CONTRIBUTIONS

Concept: A.Y.; Design: A.Y.; Control: A.Y., S.K.; Sources: A.Y., S.K.; Materials: A.Y., S.K.; Data Collection and/or Processing: A.Y.; Analysis and/or Interpretation: A.Y., S.K.; Literature Review: A.Y., S.K.; Manuscript Writing: A.Y., S.K.; Critical Review: A.Y., S.K.; Other: -

CONFLICT OF INTEREST

The authors declare that this article has no real, potential, or perceived conflict of interest.

ETHICS COMMITTEE APPROVAL

The authors declare that this study does not require the ethics committee's approval.

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