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Full Paper

Preparation of Molecularly Imprinted Metoprolol Sensor from Poly(aniline-co-p-toluene sulfonic acid)

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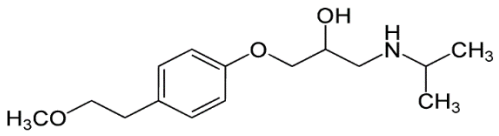
Abstract- In this study, the metoprolol (MTP), which is a beta-blocker class molecule used in hypertension treatment, was determined by modifying the glassy carbon electrode (GCE) with a molecular imprinting technique. Firstly, p-toluene sulfonic acid (PTSA) and aniline (AN) were co-electropolymerized in the presence of MTP as a template molecule on GCE and MTP contained poly(aniline-co-p-toluene sulfonic acid) (*p*(AN-co-PTSA)) film was obtained. Then, the template metoprolol molecule was desorbed from the conductive *p*(AN-co-PTSA) film structure on the GCE surface using hydrochloric acid. Obtained molecularly imprinted electrodes were used to determine MTP by the square wave voltammetry (SWV) method. The modified electrodes obtained showed a correlation coefficient (R^2) of 0.9995 in the 40-1500 µM MTP concentration range. The limit of detection (LOD) and the limit of quantification (LOQ) of the *p*(AN-co-PTSA) film modified MTP electrodes were 37.9 µM and 126.3 µM, respectively. A standard deviation of 1.33% was observed for the first three replicates with the same modified electrode. For the time reproduced electrodes, stable reproducibility was achieved between the first electrode result and the tenth electrode result. For the modified MTP electrode, the relative standard deviation (RSD%) value was calculated to be 2.53%. As result, the molecularly imprinted electrodes prepared with p(AN-co-PTSA) film have low response time, high reproducibility, good stability, and high selectivity for the determination of MTP.

Keywords- Metoprolol; Molecularly imprinted electrode; Electropolymerization; Sensor; Voltammetry

1. INTRODUCTION

"High blood pressure" which means the pressure required for blood circulation is higher than normal, must be followed under the control of an expert. High blood pressure causes considerable damage to the inner surface of the vessel due to the effect of blood on the vessel walls in the long term. For this reason, obstruction, enlargement or rupture may occur in the vessels feeding the organs. In addition to such negative effects; it can also cause organ failure by disrupting the blood flow to organs. For these reasons, high blood pressure must be controlled, the causes of hypertension must be well investigated and blood pressure must be reduced to an ideal level. Beta-blockers are generally used for this purpose. Beta blocker molecules block some effects of the sympathetic nervous system that cause rapid heartbeat and regulate heart rhythm. These drugs reduce cardiac stress by slowing the heart rate and reducing the contraction force of the heart muscles. They also reduce the spasm of blood vessels in the heart, brain, and body.

Metoprolol (MTP), whose chemical formula is shown in scheme 1, is named 1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino)propan-2-ol. It is an important beta-blocker drug used in cardiovascular system diseases treatment such as hypertension and heart rhythm disorders [1,2]. It mainly affects the β2-receptors found in the bronchi and peripheral vessels.



Scheme 1. Molecular formula of metoprolol

MTP is an important drug agent that is indicated in hypertension, chronic heart failure, stable symptomatic, angina pectoris, risk of sudden death after the acute phase of myocardial infarction and prevention of recurrence of infarction, heart rhythm disorders including tachycardia, and functional heart disorders [3,4]. Drugs containing this active ingredient are among the most prescribed drugs in the world [2]. The amount of MTP is so sensitive that even a small oral dose of the drug provides adequate blockade, and an overdose of such a-blocker can lead to increased hypotension, hypoglycemia, fatigue, bronchospasm, bradycardia and heart failure [5]. The use of MTP as a doping agent has also been seen in some cases [3,4,6]. It is very important to determine such uses and to determine MTP in body fluids in clinical determinations. The abundance of analytical methods reported in the literature for MTP determination reveals how important it is to identify this drug. Various analytical methods have been developed for the identification and detection of metoprolol alone or simultaneously with the active ingredients of other drugs. These are high technological instrumental methods such as spectroscopy [7], mass spectroscopy [8,9], chemiluminescence [10], capillary electrophoresis [11,12], fluorimetry [13,14], gas chromatography (GC) [15], liquid

chromatography [16], high performance liquid chromatography (HPLC), reverse-phase liquid chromatography [17] and some other combined methods [18-24]. Although these methods are used quite frequently, they require time-consuming and tedious steps for sample pre-treatment such as extraction. In addition, since these techniques require expensive instrumentation and operating costs are high, it is of great importance to use a simpler, faster, and lower-cost method for metoprolol determination. Electrochemical methods have been shown to be highly useful in the determination of analytes in medical, biological, and environmental samples due to their advantages such as simplicity, short-term analysis, low cost and on-site measurements [25-27]. For this reason, electrochemical methods can be shown as an alternative for MTP determination in body fluids or in the control of drug production processes. However, the number of studies on the determination of MTP by electrochemical methods is limited [28-30]. In addition to the methods mentioned above, the determination of drug active ingredients can be carried out electrochemically by using molecularly imprinted polymers. Molecular imprinting technique is a very practical and easy technique in terms of preparation steps. In this technique, the selection of monomers containing functional groups with suitable interactions for the template molecule is very important. In this way, after the template molecule has been separated, suitable and selective molecular spaces for the analyte can be easily obtained. For this reason, the MIP technique is often preferred for the production of selective membranes, electrodes, or sensors. In electrochemical analysis techniques, bare electrode structures are generally not selective and respond to any molecule that is oxidized or reduced at a certain potential. But there are gaps on the electrode surface prepared with the MIP technique, through which only the molecule to be analyzed can pass. Therefore, only the signals belonging to the molecule to be analyzed are seen. In particular, the production of MIP modified electrodes with the electropolymerization technique has attracted great interest due to its ease of preparation, easy control of film thickness, and high reproducibility [31]. Another important advantage of electrochemically produced MIP modified electrodes is that the sensor sensitivity increases due to the increase in the electrode surface area, since a conductive film layer is used .

Molecular imprinted polymers are important materials that can be used successfully in sensor designs, separation, and purification processes [32]. Molecularly imprinted polymers are highly cross-linked polymeric structures that are synthesized by different polymerization techniques in the presence of a template molecule [33]. Electropolymerization, sol-gel chemistry, or conventional polymerization techniques are generally used in MIP synthesis. Removal of the template molecule after polymerization creates a cavity for the analyte that maintains affinity and selectivity. Thanks to these selective gaps and cavities, highly sensitive and selective electrodes and sensors can be prepared easily. In particular, molecularly imprinted polymers are of great importance in the preparation of polymer-coated selective electrodes as sensor structures [34-40].

Molecular imprinting is the process of forming specific recognition sites on the polymer by binding the analyte to the template molecule [41]. By placing special recognition areas in the printed space of the MIPs, the template molecule is made more selective against interference rather than selectivity based on shape and size. In addition to hydrogen bonds, dynamic covalent bonds, hydrophobic interactions, supramolecular and some coulombic interactions, different functional monomers are used to form metal-chelate and π-π sequences. MIPs have been widely used to produce molecular cavities of desired shape and size in electrode surface coatings of different thicknesses for chemosensors fabrication. Electropolymerization technique, on the other hand, is the most suitable method for the synthesis of conductive and non-conductive MIP coatings [42]. Especially in this technique, the film thickness can be easily controlled by the applied voltage, current density, and application time [31]. Molecular imprinting is the preparation technique of artificial receptors with specific recognition sites and selectivity for a particular analyte. Cross-linked polymeric structures are prepared containing the conjugate of the analyte determined in this technique [43]. On the other hand electrochemical sensors are frequently used sensors because of their simple, cost-effective, and short-time signaling characteristics [44,45]. When these sensors are combined with the molecular suppression method, the sensitivity, and selectivity of the sensor increase even more.

Within the scope of this research, taking advantage of the molecular imprinting technique; for the modification of electrodes, a voltammetric MTP sensor with high stability and selectivity has been developed by electropolymerization method. For this purpose; first of all, it was checked whether GCE modified by electropolymerization is sensitive to MTP and the response was obtained to MTP with MIP modified electrodes. In order to determine the sensitive biosensor property of MTP electrodes modified with AN and PTSA; parameters such as polymerization pH, scan rate, film layer thickness and deposition potential were optimized using the SWV method and then linear MTP response was obtained in the large analyte concentration. Subsequently, the *p*(AN-co-PTSA) modified electrode's selectivity, sensitivity, reproducibility, and linearity results for the MTP beta-blocker were shown. We believe that the developed MIP-based voltammetric MTP sensor can be an alternative for the direct determination of metoprolol without any interference effect.

2. EXPERIMENTAL

2.1. Materials

Reagents were purchased in analytical grade and used. AN, PTSA, hydrochloric acid (HCl), nitric acid (HNO_3), phosphoric acid (H_3PO_4) and sulfuric acid (H_2SO_4) were obtained from Sigma-Aldrich Chemical Company. Sodium monohydrogen phosphate (Na_2HPO_4), potassium dihydrogen phosphate (KH_2PO_4), potassium chloride (KCl) and sodium chloride (NaCl) were supplied from Merck Chemical Company. Metoprolol is the active ingredient of the drug

named "Beloc®", so this drug was obtained from the pharmacy and used in experimental studies after purification.

2.2. Instrumentation

In this study, all experiments for voltammetric MTP determination were performed using Ivium Vertex One brand potentiostat. This Potentiostat device is controlled by Ivium Soft™ software, which includes data acquisition, data analysis and a wide variety of electrochemical techniques**.**

Faraday cage was used to protect the measurement unit from magnetic and electrical effects caused by the environment in voltammetric determinations. A BAS brand C3 (cell stand) cage was used as a Faraday cage and in the control of electrochemical test cells. Voltammetric measurements and modification of electrode structures with *p*(AN-co-PTSA) film were performed in 10 mL electrochemical cells.

Ag/AgCl in 3 M NaCl as reference electrode and platinum wire electrode as auxiliary electrode were used for the determination of MTP.

Thermo Scientific STAR A-111 pH-meter was used for the preparation of buffer solutions and pH measurements. Before each experiment using the pH meter, the instrument was calibrated with buffer solutions of pH 7.00 (Merck 4939) and pH 4.00 (Merck 9475), respectively.

Cleaning the glass cells; It is first washed with detergent, then Millipore brand Elix 20 is rinsed with distilled water. Then immersed in 6 M HNO_3 solution for at least one hour, preferably overnight. Finally, it is rinsing with ultrapure water and drying in the oven.

2.3. Cleaning of Electrodes

For the working electrode, mechanical cleaning procedure; firstly, after dropping a few drops of aqueous alumina slurry paste with particle sizes of 0.3 and 0.05 µm onto a velvet disc, the electrode was moved for 1-2 minutes without pressing too much to draw the figure "8". After the electrode was rotated 90 degrees, the same process was repeated and the glassy carbon electrode was mechanically cleaned. Then the electrode was rotated 90 degrees and the same process was repeated and the glassy carbon electrode was mechanically cleaned. Then, it was washed with ultrapure water and cleaned by ultrasonic bath for about 1 minute in ethyl alcohol: water (1:1) solution to completely remove alumina residues. Finally, GCE was electrochemically cleaned with 5 cycles in 0.5 M H_2SO_4 solution in the potential range of (-700) - (1700) mV by the CV method. It is also very important to clean the reference and auxiliary electrodes after use in order to make sensitive and repeatable measurements in voltammetric sensor studies. Therefore, the Reference electrode was cleaned with ultrapure water after each use and stored in a 3 M NaCl solution. Auxiliary electrodes were burned after use and cleaned by washing with ultrapure water.

2.4. Procedure

2.4.1. Preparation of molecular imprinting solution

Molecular imprinting solution was prepared in 0.1 M phosphate buffered saline solution, PBS, (0.01 M Na_2HPO_4, 0.0018 M KH_2PO_4, 0.137 M NaCl and 0.0027 M KCl) (adjusted to pH 1.20 with the appropriate amount of H_3PO_4) to contain final concentrations of 6 mM AN, 4 mM PTSA and 1 mM MTP.

2.4.2. Preparation of Standard MTP solution

After the metoprolol stock solution was dissolved in ultrapure water, electrochemical performance of the *p*(AN-co-PTSA) film modified electrodes were investigated by adding appropriate amounts to 0.1 M PBS adjusted to pH 7.00.

2.4.3. Modification of GCE

Modifying the electrode surface by coating it with a polymer is required in order to increase the selectivity, sensitivity, and repeatability of a voltammetric measurement. For this purpose, modification of bare GCE was carried out in a solution containing 1 mM MTP, 6 mM AN, and 4 mM PTSA by the CV method.

2.4.4. Preparation of Metoprolol Imprinted Electrochemical Sensor

The PBS (pH 1.20) solution containing 1 mM MTP, 4 mM PTSA and 6 mM AN was mixed with a magnetic stirrer for 5 minutes to ensure the interaction of the template molecule with the functional monomer. Bare GCE was immersed in a cell containing 5 mL of monomer solution and electrochemically polymerized at a film thickness of 5 cycles in the potential range of (0)-(+1500) mV by CV method. In this way, the analyte (MTP) was arrested by being trapped in the polymer.

2.4.5. Desorption of the Template Molecule

In order to remove the template molecule from the MTP doped *p*(AN-co-PTSA) film modified electrodes structure, a desorption agent that can break the physical interactions between the template molecule and the conductive polymeric film should be used. In the study, 0.1 M HCl solution was used as the desorption agent that could break these physical interactions. MTP imprinted GCEs were kept in 200 mL 0.1 M HCl solution for different periods of time and then it was checked whether the desorption process took place efficiently or not by the SWV method. It has been determined that the optimum holding time is 24 hours. In all subsequent studies, the desorption process was performed using a 24-hour holding time.

3. RESULTS AND DISCUSSION

3.1. Determination of MTP Peak Potential

The SW voltammograms of background solution and of 2 mM MTP were taken on bare GCE, and on molecularly imprinted GCE in PBS (pH 1.20). As a result, as seen in Figure 1, a sharp and clear MTP oxidation peak was obtained on the molecular imprinted GCE electrode at approximately +1380 mV, while no peak of 2 mM MTP was seen on the bare GCE. These results showed that the obtained MIP modified electrode was sensitive and responsive to MTP molecule.

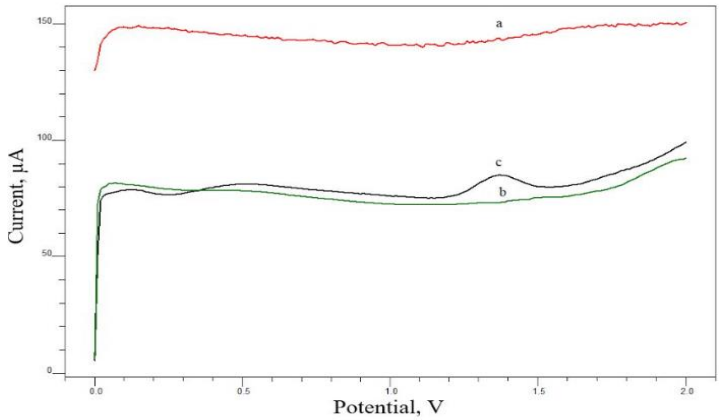


Figure 1. SW voltammograms of 2 mM MTP solution on bare (a), background solution on molecularly imprinted GCE (b) and 2 mM MTP on molecularly imprinted GCE (c) in PBS (pH=1.20)

3.2. The Effect of pH on the Polymerization of the Metoprolol Template Molecule and the Functional Monomer

The effect of polymerization solution pH on the electrochemical response of MTP was investigated using the SWV method with a modified electrode in 0.1 M PBS between pH 1.00 and 2.00. The optimum pH was found to be 1.60 (Figure 2).

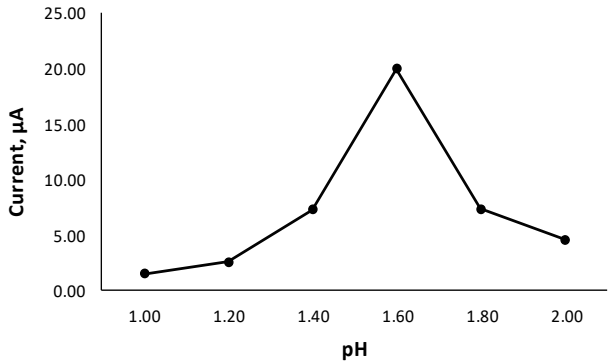


Figure 2. The effect of polymerization solution pH on MTP peak current

3.3. The Effect of Film Thickness on MTP Peak Current

As stated above; modifying the electrode surface by coating it with a polymer significantly affects the selectivity, sensitivity, and stability of a voltammetric measurement. Film thickness is also the most important parameter that affects these properties in a good or bad way. For this purpose, with the determined monomer solution ratio, different cycle numbers (3, 4, 5, 6 and 7) were applied in 0.1 M PBS solution at pH 1.60 and modified electrodes with different film thicknesses were obtained on the GCE. MTP analyses were carried out with the SWV method using electrodes with different film thicknesses. In this way, the effect of *p*(AN-co-PTSA) film thickness on MTP oxidation peak current was investigated. Obtained SWV results are given in Figure 3. According to these voltammograms, it was decided to electropolymerize at 5 cycles of film thickness.

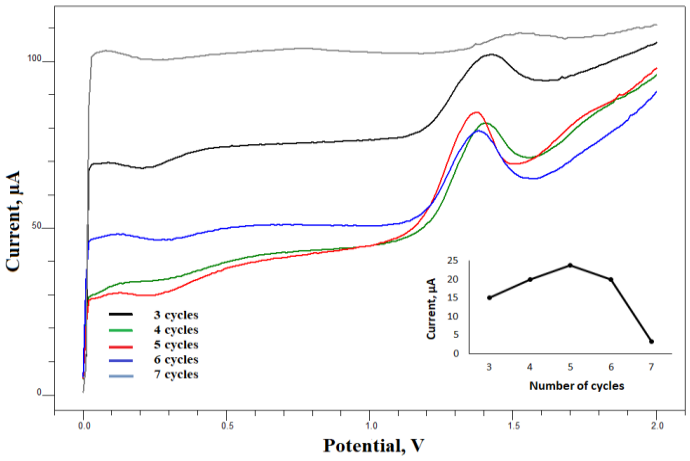


Figure 3. The effect of polymer film thickness (number of cycles) on MTP SWV peak current in 0.1 M PBS pH 7.0

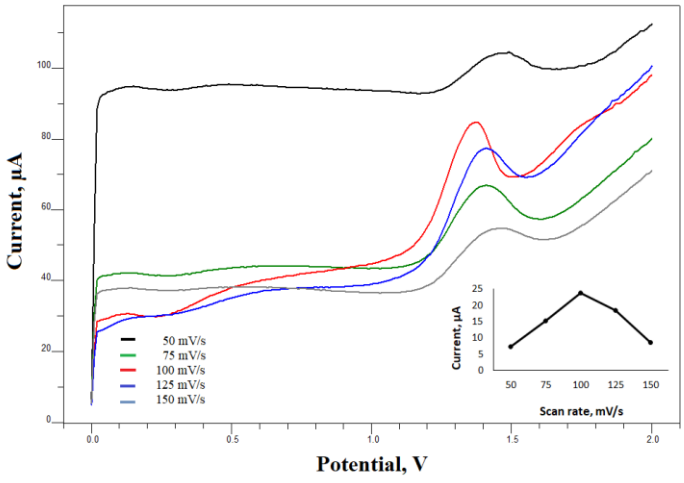


Figure 4. The effect of scan rate on MTP peak current

3.4. The Effect of scan rate on MTP Peak Current

Electropolymerization was performed with the determined monomer solution using the CV method in the (0.0) - (+2.0) V potential range, a film thickness of 5 cycles at 50, 100, 125 150 mV/s scan rates. As a result of the measurements made with the SWV method after the desorption process, it was decided that electropolymerization was appropriate with a scan rate of 100 mV/s (Figure 4).

3.5. Investigation of MTP Electrochemical Behavior on Modified Electrode

Modification process, by immersing the GCE electrode in 0.1 M PBS (pH: 1.20) solution containing 1 mM MTP, 4 mM PTSA and 6 mM AN, with the CV method in the (0.0) - (+1500) mV potential range, at a scan rate of 100 mV/s, it was carried out by electropolymerization with a conductive polymeric film thickness of 5 cycles. In this way, the MTP molecule from the template containing MTP was desorbed by keeping it in HCl solution for 24 hours, and further optimization studies were carried out.

3.6. The Effect of Accumulation Potential on MTP Peak Current

The effect of the deposition potential on the SWV peak current of MTP in 0.1 M pH 7.0 PBS was studied by SW stripping voltammetry in the range of -500 to 1500 mV (Figure 5). The results showed that the optimum deposition potential increased to 1.0 V and then decreased. In subsequent studies, the accumulation potential was used as 1.0 V.

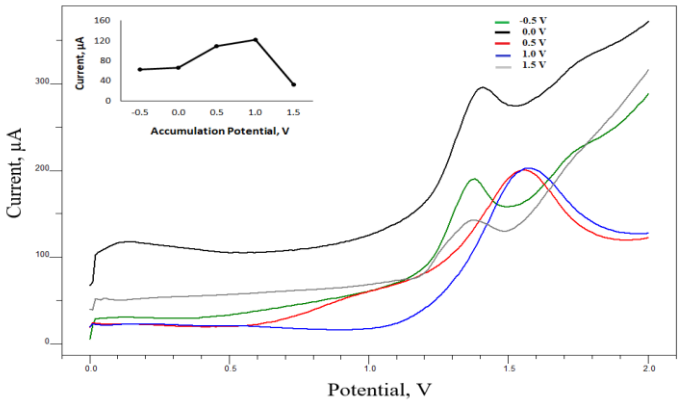


Figure 5. The effect of accumulation potential on MTP SWSV peak current in 0.1 M PBS pH 7.0

3.7. Calibration Graph

Under optimal experimental conditions shown in Figure 5, SWSV curves at different MTP concentrations were obtained with the *p*(AN-co-PTSA) film modified electrode. Linearly increasing peak currents were seen with increasing MTP concentration. As a result, the

selectivity and sensor performance of the *p*(AN-co-PTSA) film modified electrode were determined selectively over a wide linear range of 40-1500 µM (40, 50, 100, 300, 500, 700, 1000 and 1500 µM) of MTP with a detection limit of 37.9. From these results, a calibration curve with an R2 value of 0.9995 was obtained for the concentration range of 40-1500 µM metoprolol. The limit of detection was calculated from the coefficients of the calibration curve (Figure 6) with the equation LOD = 3S/m (S standard deviation; m is the slope of the calibration curve).

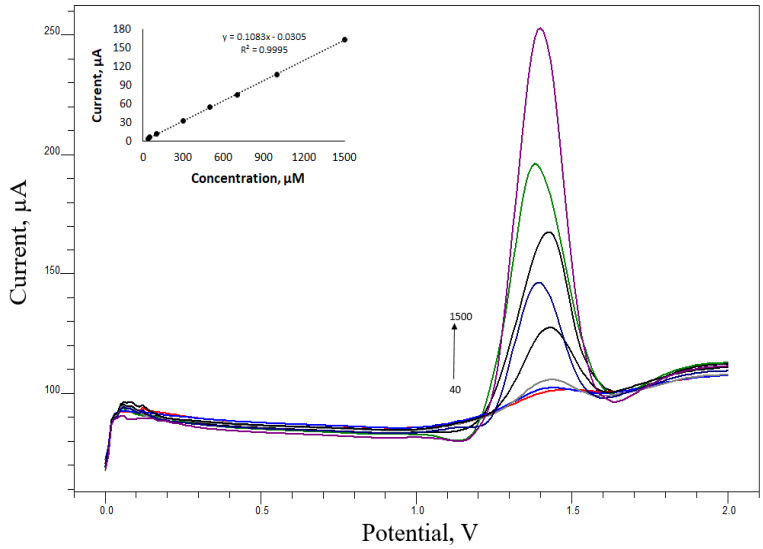


Figure 6. Square wave stripping voltammograms and calibration curve for decrease concentration of MTP in 0.1 M PBS pH 7.0

3.8. Reproducibility

One of the advantages of the electrodes prepared by the MIP method is that they give high reproducibility responses. Within the scope of the study, the reproducibility of the *p*(AN-co-PTSA) film modified electrodes prepared using the MIP technique was tested with 500 µM MTP in PBS (pH=1.60). Ten MTP measurements were made with the same *p*(AN-co-PTSA) film modified electrode. Reproducibility of the voltammetric responses this modified electrode was obtained for PBS for 500 µM MTP. These measurement results and obtained voltammograms are given in Figure 7. It can be seen from Fig. 7 that the reproducibility of the MTP selective electrode for ten measurements is very high.

From the bar graph in Fig. 7, the standard deviation and the relative standard deviation, RSD% were calculated as 1.33 and 2.53%, respectively. This electrode modification method developed for MTP determination has been proven to be reproducibility, highly stable and extremely sensitive (97.47%).

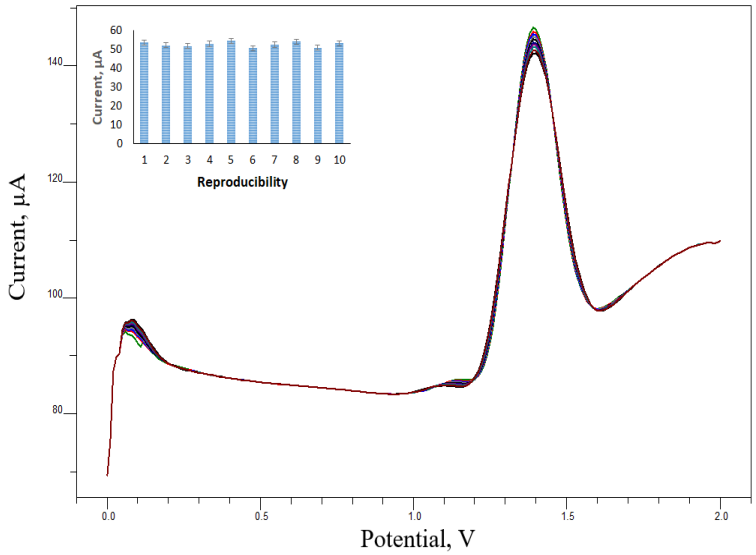


Figure 7. Reproducibility of MIP-based modified electrode for 500 µM MTP in 0.1 M PBS pH=1.60, (n=10)

4. CONCLUSION

In this study, a voltammetric sensor was prepared for the selective determination of metoprolol using a MIP technique for the first time. This metoprolol sensor was prepared by the SWSV method and showed wide linear detection range of 40-1500 µM, a detection limit of 37.90 µM, a short response time with a quantitation limit of 126.32 µM, and high stability. When compared to modified electrode, unmodified electrodes; the modified electrodes were showed better stability and reproducibility. When the calculated 1.33 standard deviation, 2.53% relative standard deviation and 97.47% stability values were taken into account, it was understood that the method was reproducible and stable.

As a result of the study, a sensitive voltammetric sensor was developed for the determination of metoprolol using a new modified electrode type with low cost, fast response, high selectivity and reproducibility. Results show that modified electrodes using MIP technique are good alternative for metoprolol determination in clinical and biomedical applications.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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