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# Fabrication of an Electrochemical Sensor Based on Molecularly Imprinted Polymer for the Selective Determination of Clonazepam in Various Samples: Study of the Modifier Effect

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In this research, a modified carbon paste electrode (CPE) has been constructed for the electrochemical determination of clonazepam (CLZP) in different real samples. Different modifiers including multi-wall carbon nanotube (MWCNT) molecularly imprinted polymer (MIP) as magnetic and non-magnetic modifiers are used for the surface modification. The characterization of the as-synthesized MIP was carried out using Fourier transform infrared spectroscopy (FT-IR), Field emission scanning electron microscopy (FE-SEM), simultaneous thermal analysis (STA), and Brunauer-Emmett-Teller (BET). It was found that the MIP was found to be a selective modifier to design a CLZP sensor, in an electrocatalytic process. To investigate the electrochemical behavior of the sensor and determination of CLZP, the cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques were applied, respectively. The effect of some parameters on sensor response such as pH, MIP percentage, and scan rate was studied and optimized. Under optimum conditions (pH = 7, scan rate of 50 mV $s^{-1}$), a linear range from 1.64 to 72.3 µM, a detection limit of 0.26 µM (3Sb/m; N = 5), and quantification limit (LOQ) of 0.87 µM was obtained. Besides, compared to the non-imprinted polymer sample (NIP), MIP modified-CPE (MIP/CPE) showed good sensitivity toward the CLZP drug. The prepared sensor was used to determine the CLZP drug in different real samples such as drinking water, urine, blood, and tablets.

**Keywords:** Imprinted polymers, Characterization, Electrocatalysis, Chemical modification, Drug analysis

## INTRODUCTION

The use of drugs to treat various diseases is unavoidable in today's advanced world with different types of health problems [1]. However, due to the varied effects of drugs on the body, several types of drugs are available even for a specific disease [2-4]. Medical science has helped a lot in identifying drugs in real samples which has helped cure all kinds of diseases [5,6]. The consumption of some types of drugs, including anti-stress, depression, and seizures, has increased worldwide due to the diseases related to them and has become a global challenge [7,8]. Therefore, it is crucial to identify, diagnose, and determine this group of drugs like clonazepam (5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one; CLZP), as it reduces side effects compared to similar drugs [9]. CLZP is an anti-anxiety, anti-seizure, and anti-epileptic drug that calms the human brain and nerves [10]. As a result, a fast, affordable, and accurate method is required to determine the amount of CLZP in blood and biological samples [11].

Various techniques such as gas chromatography (GC) [12], high-performance liquid chromatography (HPLC) [13], and spectrophotometry [14] have been used to analyze this drug. Among analytical methods, high-performance liquid chromatography, spectroscopy, and electrochemical techniques are more important than other methods [15]. However electrochemical methods have received more attention in recent years due to their quick response,

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affordability, high accuracy, biocompatibility, and the ability to be converted into portable kits [16].

The use of electrochemical methods for pharmaceutical compounds has been hindered by their weak signal and high overvoltage at the surface of the unmodified electrode [17]. However, modified electrochemical sensors have solved these problems to a great extent and provided a new perspective for pharmaceutical electrochemical sensors. The electrode modification process can increase the selectivity and sensitivity of the electrochemical sensors and has enabled the quantitative analysis of the target compounds at the micromolar level [18,19].

Molecular imprinted polymer (MIP) is a new trend to improve the selectivity and sensitivity of chemical sensors as an efficient modifier in surface modification [20]. MIPs are synthetic polymers with specific holes designed for the binding of target molecules [21]. They are prepared by copolymerization of the functional monomers and the target molecule in the presence of a cross-linking agent through covalent or noncovalent bonds [22,23]. Subsequent removal of the imprinted template leaves some selective holes with a shape, size, and affinity that complement the imprinted target molecule [24]. Due to its predetermined selectivity, MIP can be used as an ideal modifier for the selective determination of some drugs using modified electrochemical sensors.

In this research, a simple, economical, selective, and fast method is presented for determining the CLZP drug by electrochemical method. The study aims to improve the detection of CLZP by modifying the working electrode surface with various modifiers, including multi-wall carbon nanotube (MWCNT) and magnetic and non-magnetic MIP modifiers. After optimization, the modified sensor was applied for selective determination of CLZP in various real samples including the drug tablets water, urine, and human blood sampled.

## EXPERIMENTAL

### Material and Apparatus

All chemicals and solvents were obtained from Merck Company (Darmstadt, Germany). The CLZP drug used in the research also belongs to Darou Pakhsh Company, (Tehran, Iran). To prepare the buffer solution over the pH range of 2-10, the phosphate buffer saline (PBS), phosphoric acid, and phosphate salts were used. All solutions were prepared in double-distillated water.

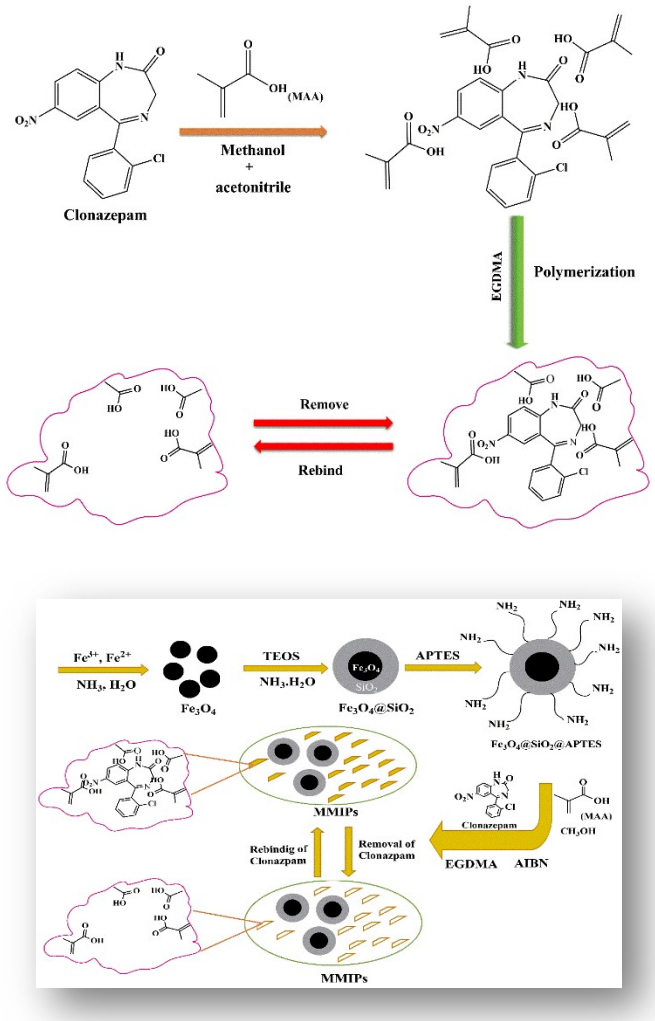
The apparatus used includes for Fourier transform infrared spectrometer (FT-IR/JASCO-680, Japan), field emission scanning electron microscopy (FE-SEM, Sigma VP, ZEISS Co, Germany), Simultaneous thermal analysis (STA, PerkinElmer STA6000, USA), and Brunauer-Emmett-Teller (BET, BELSORP miniII, Japan) the modifier characterization. The electrochemical behavior study of the drug on the constructed sensors was carried out using a Autolab PGSTAT302N Potentiostat-Galvanostat (Metrohm, Herisau, Switzerland), in cyclic voltammetry (CV) and differential pulse voltammetry (DPV) modes. The results were recorded using a three-electrode system including a carbon paste electrode (CPE) modified with the various modifiers as the working electrode, an Ag/AgCl electrode as the reference electrode, and a platinum electrode as the counter electrode.

### MIP and MMIP Synthesis

First, 1.20 mg of CLZP was dissolved in 25 ml of methanol and 15 ml of acetonitrile. Then, 51 µl of methacrylic acid (MAA) functional monomer was added to the solution and stirred for 5 min by placing it on the stirrer. Next, 562 µl of ethylene glycol dimethacrylate (EGDMA) cross-linker was added to the solution and stirred for 30 min to homogenize the solution. Then, 30 mg of azobisisobutyronitrile (AIBN) radical initiator was added to the reaction solution and stirred for 15 min. Then, the argon gas was purged for 15 min to release the dissolved oxygen from the solution. To form the polymer, the final solution was placed on a heater stirrer for 24 h at 75 °C. After drying the synthetic polymer in the oven, it was powdered and put in the Soxhlet system, using a mixture of acetic acid and methanol (1:9; v/v). After that, the polymer was washed with distilled water to reach a neutral pH. The resulting polymer was dried at room temperature. Also, it was used the same method for the synthesis of non-imprinted polymer (NIP), but without the CLZP template [25].

The preparation of magnetic MIP (MMIP) was carried out according to the literature [26] by chemical co-precipitation method, using $FeCl_2.4H_2O$, $FeCl_3.6H_2O$, and $NH_3$ at 80 °C. To stabilize the magnetic nanoparticles (MNPs) and prevent oxidation, the surface of the nanoparticles was modified using tetraethylorthosilicate (TEOS) and then aminated with 3-

aminopropyltriethoxysilane (APTES). In the next step, the MMIP modifier was polymerized in the presence of $Fe_3O_4$@ $SiO_2$@$NH_2$ as the same method.




*Scheme 1.* The schematic representation of the synthesis of MIP and MMIP samples

## Construction of MIP-modified Working Electrode

To prepare the CPE modified with MIP, NIP, MWCNT, and MMIP, 60 mg graphite powder, 30 mg paraffin oil, and 10 mg the modifier were mixed. Also, the modified CPE with different weight percentages of modifier was constructed similarly, however, by varying the ratio of the paste components. The resulting homogeneous paste from each electrode was then pressed into the tubular part of the electrode, and a copper wire was placed at the end of the electrode to establish an electrical connection. To ensure a suitable and renewable surface, the electrode was polished with special paper each time. The constructed modified CPE was then used to determine CLZP, using CV and DPV methods.

## Preparation of the Real Samples

The human urine sample was collected from a 30-year-old man and centrifuged (2000 rpm for 3 min). The supernatant was filtered using a filter, and the pH was then adjusted to 7 using PBS [27]. The blood sample was collected from the laboratory at Namazi Hospital in Shiraz, Iran. The sample was centrifuged at 4000 rpm for 15 min to separate the serum from other components and then filtered. Finally, 1 ml of serum was diluted to 5 ml by the addition of PBS and used for future analysis [2]. To examine the possible recovery of CLZP in the water sample, 10 ml of drinking water was filtered and diluted 10 times with PBS. Then, 6 mL of this sample was transferred to the electrochemical cell, and different amounts of a standard solution of CLZP were added to the cell for electrochemical analysis [26].

For CLZP analysis in a typical pharmaceutical product, 5 CLZP tablets labeled 1 mg per tablet (Tehran Darou, Tehran, Iran) were completely powdered and homogenized. Then, 80 mg of the resulting powder was carefully weighed and dissolved in 10 ml of methanol and water with ultrasound. After that, 200 µl of the solution was transferred to a flask volume (10 ml) and diluted with PBS (pH = 7). The resulting solution was used as the analytical sample and placed in the electrochemical cell to determine the CLZP content, using the DPV method [27].

# RESULTS AND DISCUSSION

## Characterization of the As-synthesized Modifier

The surface characteristics of the MIP were analyzed using the FE-SEM technique. This included the morphology and average particle size of the as-prepared MIP. The SEM image of the MIP in Fig. 1 confirmed the micro/nano-scaled structure, with some agglomerations in MIP beads. The image also showed spherical particles, with the average diameter of the MIP beads being estimated to be over 600 nm.

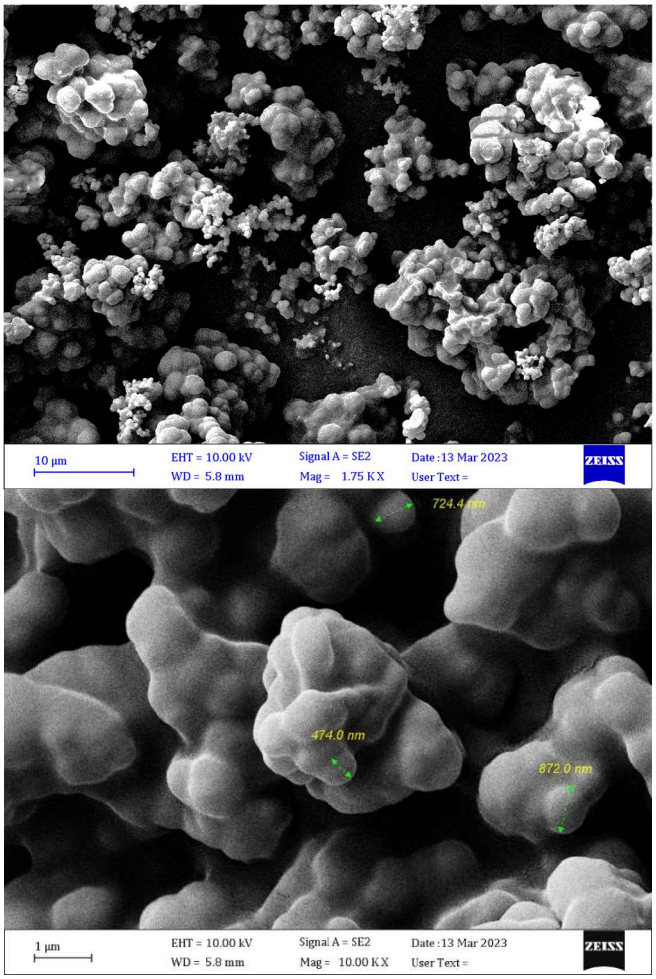



**Fig. 1.** FE-SEM image of CLZP MIP.

The FT-IR spectra of the prepared polymers, including unleached, leached MIP, and NIP samples, were recorded. The results are presented in Fig. 2. The FT-IR spectra showed a similar pattern for all samples, which may be due to the similarity of the polymeric backbones, as well as the chemical stability of the polymeric network after the leaching process [23]. The FT-IR results show a broad OH stretching vibration peak around 3500 $cm^{-1}$ for the samples. These peaks can be associated with the presence of MAA in the polymeric matrix. The stretching peak of the carbonyl group was observed at 1721 $cm^{-1}$ for both MIP and NIP, and this may have originated from MAA and EGDMA, respectively. Meanwhile, the other peaks were observed for different functional groups such as 3374 $cm^{-1}$ (N–H), 2993 $cm^{-1}$ (C=O), 1724 $cm^{-1}$ (C=O), and 1010 $cm^{-1}$ (CHO) and 2994 $cm^{-1}$ (aromatic C–H). According to the literature, the small shifts in FT-IR spectra of the samples may be related to the leaching of the imprinted molecule from the unleached MIP matrix [24,25].

The surface properties of the final MIP sample were analyzed using the $N_2$ adsorption and desorption analysis. The Brunauer-Emmett-Teller (BET) and the Barrett-Joyner-Halenda (BJH) analyses were conducted to determine the surface area, pore volume, and average pore size. According to the BJH diagram, the small pore size ($r_p$ = 1.66 nm) was obtained, thus the results revealed a mesoporous structure with a high specific surface and symmetrical cylindrical particles for the as-synthesized MIP (Fig. 2B).

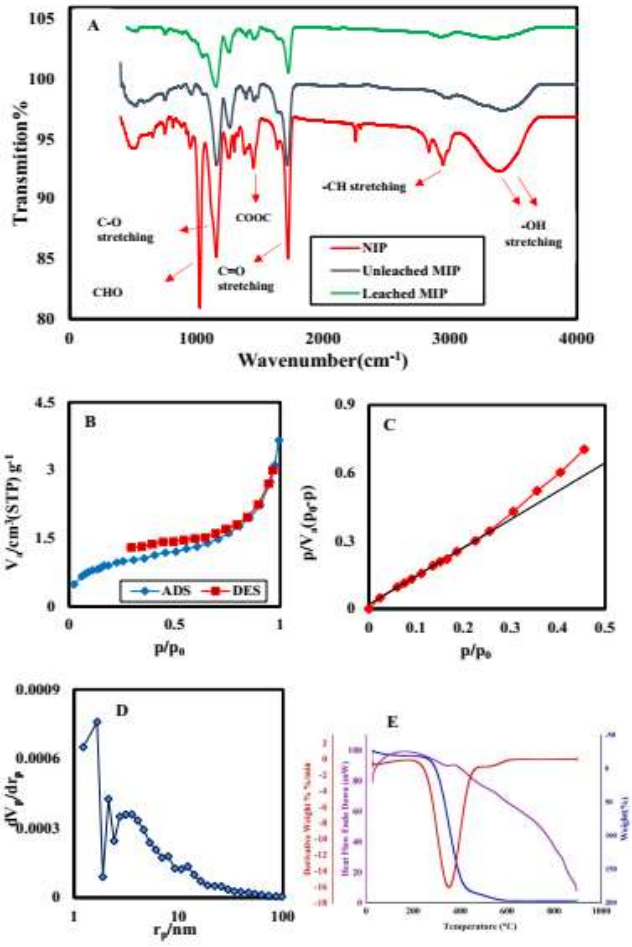



**Fig. 2.** A) FT-IR spectrum of NIP, unleached, and leached MIP samples. B) Nitrogen absorption and desorption; C) BET plot of pore size; D) BJH plot of NIP and MIP. E) Analysis of STA for CLZP MIP.

The thermal stability of MIP is a crucial characteristic that determines its usefulness in various applications. The STA technique was applied to check the thermal stability of MIP, and the results were presented in Fig. 2E. The results revealed two weight losses in the thermogravimetric and derivative thermogravimetry (TG/DTG) analysis pattern. The weight loss observed at 110 °C is related to removing solvent and moisture, while, the second weight loss at 350 °C is related to the destruction of the structure of the as-synthesized MIP. This occurs in a single step and is assigned to the decomposition of the free monomer and the cross-linker [26].

## Investigating the Electrochemical Behavior of CLZP with CPE and Modified Electrodes

In a preliminary study, the electrochemical behavior of CPE and MIP-modified CPE (MIP/CPE) was compared in $[Fe(CN)_6]^{3-/4-}$ aqueous solution containing 0.1 M KCl, as the probe solution. Figure 3A displays the CV results of CPE and MIP/CPE in 10.0 mM $[Fe(CN)_6]^{3-/4-}$. The curve (- - -CPE) shows the redox reaction at the surface of bare CPE. By modifying the CPE with MIP, the peak current of the sensor increased (-MIP/CPE). These results suggest that the presence of MIP on the electrode surface may increase the surface area of the electrode and enhance the peak current.
In addition, to obtain the actual surface area of the MIP/CPE modified electrode and CPE, the CV technique was used with a 10 mM $K_3Fe(CN)_6$ solution as a probe at different scan rates ($v$) [28]. For an irreversible process, the Randles-Sevcik equation was used:

$$I_{pa} = 2.69 \times 10^5\ n^{3/2}\ A\ C_0\ D_R^{1/2}\ v^{1/2} \quad (1)$$

In this formula, $I_{pa}$ is the anodic peak current, n is the electron transfer number, and A is the surface area of the electrode. $D_R$ refers to the diffusion coefficient of the analyte, $C_0$ (M) is the concentration of $K_3Fe(CN)_6$, and ν is the applied scan rate. For 10 mM of $K_3Fe(CN)_6$ solution in 0.1 M of KCl electrolyte, the value of n = 2 and $D_R = 7.6 \times 10^{-6}$ cm$^2$ s$^{-1}$ was considered. Then, the real surface areas were calculated from the slope of the $I_{pa}$ *vs.* $v^{1/2}$. The results showed that the MIP/CPE surface area was 1.86 times as great as the CPE surface area, with values of 0.0426 cm$^2$ and 0.0791 cm$^2$, respectively.

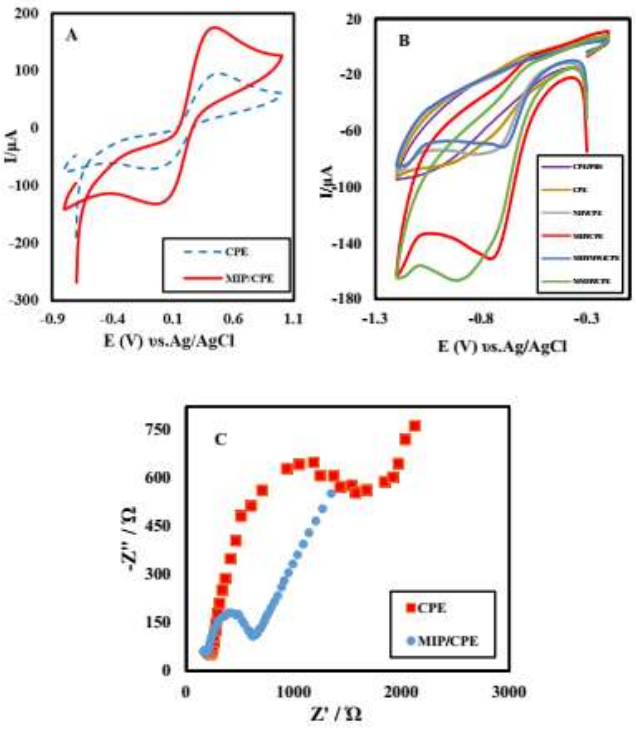



**Fig. 3.** A) CV results of CPE and CPE/MIP in 10.0 mM $[Fe(CN)_6]^{3-/4-}$ containing 0.1 M KCl, scan rate = 100 mV s$^{-1}$. B) Electrochemical behavior of CLZP with CPE and modified electrodes in the presence of 80 µM CLZP. (scan rate = 50 mV s$^{-1}$ and PBS, pH = 7.0). C) Nyquist plots CPE and CPE/MIP of 50 mM Fe $(CN)_6^{3-}$/$Fe(CN)_6^{4-}$ containing 0.1 M KCl solution.

In addition, the electrochemical behavior of the various constructed sensors toward the CLZP drug was investigated in Fig. 3B, over the potential range of -0.2 to -1.20 V, at pH = 7. For this purpose, the CV pattern of the electrodes including bare CPE in PBS, and also CPE and CPE modified with some modifiers such as NIP, MIP, MWCNT, and MMIP in the presence of CLZP (80 µM) were recorded. The MIP/CPE exhibited the highest reduction current (~150 µA) at the potential of -0.74 V. The high electrocatalytic current may be due to the high selectivity of MIP and enhancement of the surface area of the modified sensor [29]. It should be noted that the addition of MNPs resulted in a very wide reduction peak with a current of -166.85 µA at the potential of -0.89 V. Besides, the addition of MWCNT to the MIP/CPE resulted in a reduction peak with a current of -70.53 µA, but

it did not significantly affect the electrocatalytic current or improve the electrode efficiency. Therefore, MIP/CPE was selected as the final working electrode for further studies due to its highest peak current, more optimal potential, and favorable peak shape compared to other electrodes. It is worth noting that when the electrode's surface is saturated with high dosages or various modifiers, the oxidation and reduction processes become more limited. Additionally, the material finds it tough to reach the electrode's surface as the holes gradually fill up, making it difficult to transfer electrons.

In addition, to investigate and compare the electrochemical behavior of the unmodified and MIP/CPE-modified electrodes, the electrochemical impedance spectroscopy (EIS) technique was also performed [30]. For this purpose, the EIS patterns were recorded in a probe solution containing 50.0 nM $Fe(CN)_6^{3-}/Fe(CN)_6^{4-}$ (1:1) containing 0.1 M KCl [29]. The Nyquist plots of the CPE and CPE/MIP are shown in Fig. 3C. As can be seen, the MIP/CPE modified electrode had a smaller semicircle at lower frequencies compared to the unmodified CPE. Moreover, as indicated by the semicircle diameter of the CPE, the charge transfer resistance ($R_{ct}$) was found to be higher than that of the electrode with MIP/CPE.

## Optimization of the pH and Modifier Dosage

To find the best pH for the electrocatalytic determination of CLZP, the electrochemical behavior of CLZP on the surface of the MIP/CPE was investigated at different pH values (2.0-10.0) in the presence of 80 µM CLZP, at a scan rate of 50 mV $s^{-1}$. The curves of the peak current *vs.* the reduction potential and also the potential changes in terms of pH changes were presented in Fig. 4. According to the CV results, the reduction peak at -0.53 V shifted to more negative potentials as the pH values increased, indicating that proton ions played a critical role in the CLZP reduction mechanism [31]. The maximum reduction peak current was observed at pH = 7, subsequently decreasing. Thus, pH = 7 was chosen as the optimum value to investigate the electrochemical behavior of the CLZP, using the designed MIP/CPE sensor. A linear correlation was established between the reduction peak potential of CLZP and pH, with an excellent correlation coefficient $R^2 = 0.9967$ (Fig. 4C). Meanwhile, in the graph of E *vs.* pH values, due to the slope value (0.0541) close to the Nernstian slope it can be concluded that the reduction mechanism of CLZP was based on equal $H^+/e^-$ transfer [32]. The proposed mechanism was also presented in Scheme 2.

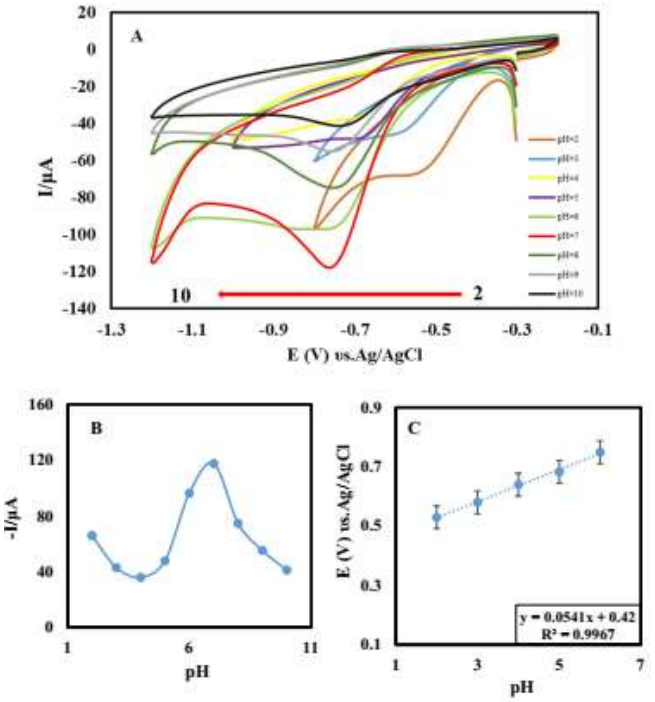
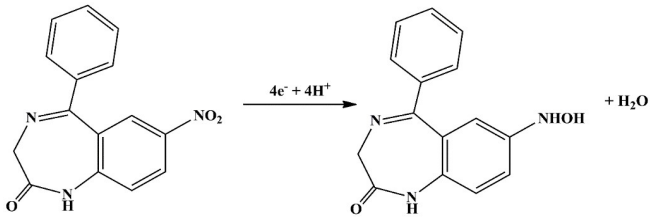



**Fig. 4.** A) CV of CPE/MIP in 80 µM CLZP at different pH, 50 mV $s^{-1}$. B) The graph of changes in peak current according to pH. C) Linear diagram of potential in terms of pH in the presence of 80 µM CLZP.




*Scheme 2.* The electro-reduction mechanism of the CLZP on MIP/CPE

In addition, to study the effect of MIP dosage on the sensor response, various sensors with different percentages of MIP in the paste compositions were constructed (Fig. S1). For this purpose, the amount of paraffin oil and graphite powder was kept constant, however, the MIP values were

changed (2-6%). The best response was obtained for the sensor that was modified with 4% of the MIP modifier. It is possible that the reduced current response observed at over 4% of MIP is caused by the insulating surface of the MIP and the polymer's non-conductivity in high MIP percentages in the CPE. This has resulted in a significant reduction in the sensor's sensitivity [33].

## The Effect of Scan Rate

To investigate how scan rate affects the electrochemical behavior of CLZP drug on the surface of the MIP-modified electrode, the applied scan rate was varied from 10 to 250 mV $s^{-1}$ under optimum conditions.

Based on the data presented in Fig. 5, it can be observed that the peak current of CLZ reduction ($i_{pc}$) increased as the scan rate increased. A linear relationship between the $i_{pc}$ and $v$ is established with an excellent regression coefficient value ($R^2$ = 0.995). The linearity between the $i_{pc}$ and $v^{0.5}$ is also examined ($R^2$ = 0.953).

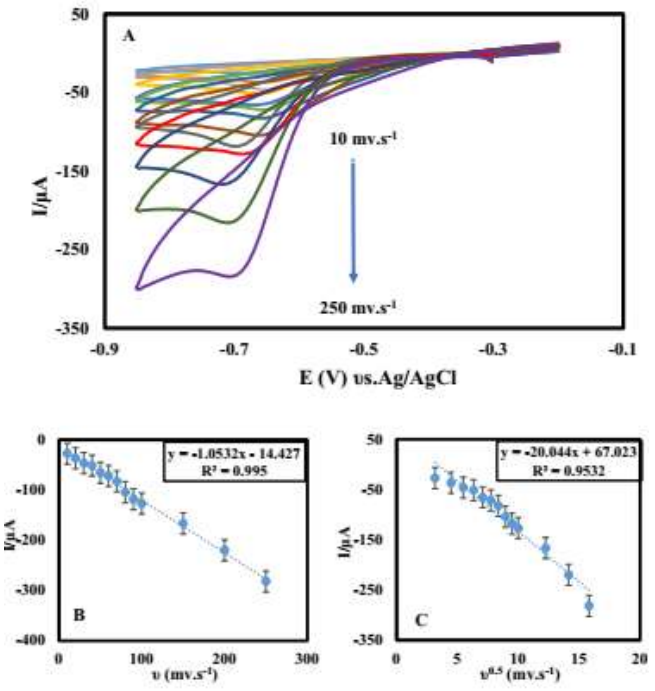



**Fig. 5.** CV patterns of CLZP reduction in the presence of CPE/MIP electrode at scan rates of 10 to 250 mV $s^{-1}$. The Plot of current changes versus scan rate for the modified CPE/MIP electrode in the presence of 80 µM CLZP.

The established relationship for the CLZP reduction on the electrode surface suggests that the electron transfer process is controlled by an absorption process. When the mass transfer is based only on the difference in chemical potentials of the analyte, it can be concluded that the resulting flow is caused by the permeation process [30]. Besides, the observed shift to more negative potentials in the reduction peak may be due to some kinetic limitations at a high scan rate of potential [33].

As known, the Tafel's region is the area that demonstrates the kinetic electron transfer between the electrode surface and the analyte species. This provides valuable information regarding the mechanism of the electrochemical reaction occurring at the electrode surface. Tafel's equation is expressed as logi = b $E_p$ + a, where i is the current density, $E_p$ is the applied potential to the electrode, and a and b are constants. The results obtained from the equation (log I = -3.54 Ep-0.668, and n = 4) and using the slope of the equation [(1 - α) nF/2.303RT], the charge transfer coefficient (α) was found to be 0.69.

## Determination of CLZP Using the MIP-modified Electrode: Linear Range, Detection Limit, Quantification Limit, and Selectivity

After optimization of the affecting parameters, the MIP/CPE was applied to determine the CLAP drug using the DPV technique, quantitatively. The linearity between the drug concentration and peak current was studied under optimum conditions. The results (Fig. 6A) show that the peak current of the sensor was increased as the CLZP concentration increased continuously, at pH = 7.0 $v$ = 50 mV $s^{-1}$, and E = -0.60 V. The present study also provides a low detection limit of 0.26 µM according to the 3Sb/m equation (n = 5); where m and Sb are the calibration curve's slope and the blank solution's standard deviation, respectively. Moreover, a quantification limit (LOQ) of 0.87 µM was also calculated using the 10Sb/m equation, for this sensor. To investigate the selectivity of the designed sensor in the presence of other drugs, the CV technique was performed for CLZP determination in a binary solution containing a constant concentration of CLZP drug and 20-fold of other drugs including diclofenac, aciclovir, brufen, dimenhydrinate, lidocaine, methocarbamol, paracetamol, and piroxicam (Fig. S2 and Fig. 6C, D). The results indicated that

the reduction of CLZP at the surface of MIP/CPE was not significantly affected (<±5%), in the presence of high concentrations of the other drugs.

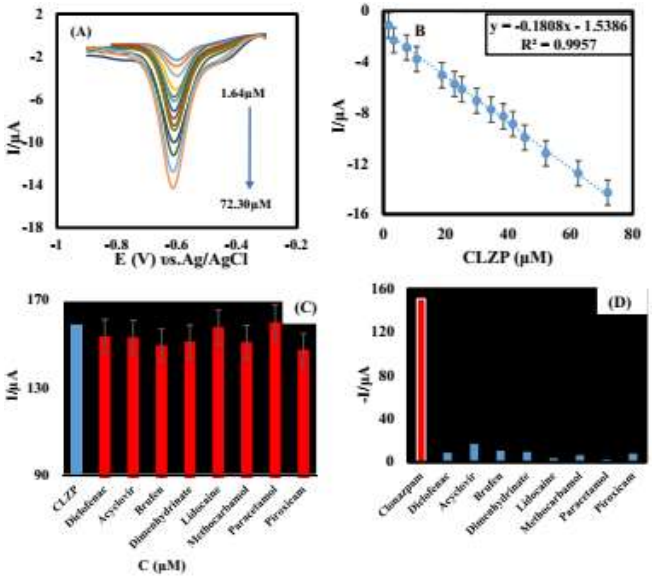



**Fig. 6.** A) DPV patterns of CLZP recorded at different concentrations. B) the corresponding linear calibration range, C) The results of selectivity recorded by CV technique in the presence of different drugs (20-fold) at 80 µM CLZP, 100 mV $s^{-1}$, and PBS, pH = 7.0. D) the response of the MIP/CPE toward various drugs.

## Repeatability, Reproducibility, and Stability of MIP/CPE Sensor

The relative standard deviation (RSD) is a measure of the precision and repeatability of a method. A low RSD value indicates that the determinations are consistent and close to each other, which in turn signifies high precision and repeatability of the method.

To check the repeatability of a sensor, a specially designed MIP/CPE sensor was used to determine the concentration of five CLZP solutions, all with the same concentration. The results showed an acceptable repeatability (RSD = 2.8%) for five replicates of CLZP determination, using the typical MIP/CPE sensor.

To assess the reproducibility of the sensor, five electrodes with the same composition were prepared by different operators on different days to determine an aqueous solution containing a constant concentration of CLZP. The obtained RSD (3.6%) indicates good reproducibility of the sensor.

The stability of MIP/CPE was tested in intra-day and inter-day modes by examining the use of MIP/CPE to analyze CLZP for 6 h and 6 days, respectively. The results showed that the sensor is highly time-stable during both intra-day (RSD = 2.08%) and inter-day (RSD = 1.28%) periods, indicating its reliability over time (Fig. S3).

## Application of the Sensor for the Determination of CLZP in Different Real Samples

In order to verify the effectiveness of the designed sensor, the presence of the CLZP drug was identified in some real samples, including drinking water, tablets, urine, and human blood samples. The standard addition method was used for the determination of CLZP and the results were obtained by repeating the tests three times. The results are tabulated in Table 1 and Fig. S4. It has been observed that this sensor is an efficient method for the recovery and determination of CLZP in various real samples, even with complex matrices. As shown in Table 1, the recovery percentages ranged from 95 to 101.25%, indicating the high efficiency of the modified electrode for detecting CLZP in real samples.

# CONCLUSION

A research study was conducted to apply a modified CPE (Carbon Paste Electrode) with different modifiers including MIP (Molecularly Imprinted Polymer), MMIP (Magnetic MIP), NIP (Non-imprinted Polymer) and MIP/MWCNT (Molecularly Imprinted Polymer/Multi-walled Carbon Nanotube) for the detection of CLZP (Clonazepam) drug. The response characteristics of each modified electrode were studied using the cyclic voltammetry (CV) technique. The MIP/CPE sensor showed the best response characteristics including selectivity, sensitivity, peak current, and potential reduction compared to other modified electrodes. In addition, the sensor had good repeatability (RSD = 3.6%) and high time-stability (RSD = 1.28%). The use of MIP for modification of CPE resulted in selective detection of CLZP drugs in the presence of other drugs. The sensor's characteristics were compared to other techniques for CLZP detection (Table 2). The sensor's advantages include simple

**Table 1.** Determination of CLZP in Different Real Samples (N = 3)

| Sample | Added (μM) | Found (μM) | Recovery (%) |
|---|---|---|---|
| Drinking water | 0.00 | 0.00 | - |
| | 50.00 | 49.34 | 98.68 |
| | 70.00 | 68. 20 | 97.43 |
| Urine | 0.00 | 1.20 | - |
| | 30.00 | 31.00 | 99.36 |
| | 50.00 | 50.20 | 98.05 |
| Blood | 0.00 | 0.00 | - |
| | 30.00 | 29.60 | 98.66 |
| | 60.00 | 58.90 | 98.17 |
| Tablet  | 0.00 | 1.40 | - |
| | 4.00 | 5.20 | 96.30 |
| | 8.00 | 9.50 | 101.06 |

**Table 2.** Comparing the Characteristics of the Design MIP-based Sensor for Determination of CLZP with Different Methods

| Method | Modifier/Electrode | Linear range (μM) | Detection limit (μM) | $R^2$ | Ref. |
|---|---|---|---|---|---|
| Potentiometric | ISE | 1.0-10.0 | 2.50 | - | [32] |
| Spectrophotometry | ligand-exchange | 1.0-13.0 | 0.76 | - | [33] |
| LSV[a] | CNFs/CNPs/GCE | 1.0-10.0 | 0.08 | - | [34] |
| SWV[b] | HMDE[d] | 0.10-10.0 | 0.01 | 0.9995 | [35] |
| DPP[c] | DME | 0.24-10.0 | - | - | [36] |
| dc Polarographic | DME | 31.7-95.0 | - | - | [37] |
| DPV | MSN/$C_3N_4$/CNH/GCE | 0.82-76.90 | 0.0025 | 0.9972 | [38] |
| CV | AuNPs/ITO | 1-9 | 0.55 | 0.9993 | [39] |
| DPV | MIP/CPE | 1.64-72.3 | 0.26 | 0.9957 | This work |

[a]Liner sweep voltammetry. [b]Square wave voltammetry. [c]Differential pulse polarography. [d]Hanging mercury drop electrode.

preparation, reconstruction of electrodes, fast response time, appropriate detection limit, and applicability in complex real samples are the practical advantages of this designed sensor.

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