J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 48(3): 1089-1097, 2024
Doi: 10.33483/jfpau.1522582

ORIGINAL ARTICLE / ÖZGÜN MAKALE

DETERMINATION OF ANTIVIRAL-DRUG FAVIPIRAVIR FROM BIOLOGICAL SAMPLES BY USING MOLECULAR IMPRINTED POLYMER-BASED ELECTROCHEMICAL SENSOR

BİYOLOJİK ÖRNEKLERDEN MOLEKÜLER BASKILI POLİMER TABANLI ELEKTROKİMYASAL SENSÖR KULLANILARAK ANTİVİRAL-İLAÇ FAVİPİRAVİRİN TAYİNİ

Çiğdem KANBEŞ-DİNDAR[1]*, Bengi USLU[1]*

[1]Ankara University, Faculty of Pharmacy, Department of Analytical Chemistry, 06560, Ankara, Türkiye

ABSTRACT

Objective: *The molecularly imprinted polymer (MIP) technique was applied in this study for selective, fast, and sensitive electrochemical determination of antiviral drug favipiravir (FAVI).*
Material and Method: *By electropolymerizing the functional monomer o-phenylenediamine (o-PD) on a glassy carbon electrode (GCE) in the presence of a template molecule FAVI, the new MIP-based sensor (MIP@o-PD/GCE) was constructed using cyclic voltammetry (CV). For the removal and rebinding procedures, as well as the optimization of conditions and performance measurement of MIP@o-PD/GCE, differential pulse voltammetry (DPV) was used. The ferrocyanide/ferricyanide redox marker was used to monitor each step of the experimental procedure using DPV.*
Result and Discussion: *MIP@o-PD/GCE has a linear response to FAVI in the range from 10 pM to 90 pM under optimal experimental conditions for human serum samples. The detection limit of MIP@o-PD/GCE was obtained to be 1.80 pM, whereas the quantification limit was found to be 6.23 pM. The designed sensor was successfully applied to a synthetic human serum sample to verify its applicability and validity. Electrochemical sensor selectivity was evaluated by comparing the binding of paracetamol and tenofovir, which are similar to favipiravir, and also oseltamivir and famciclovir, which are other drugs used in the treatment of COVID-19.*
Keywords: *Antiviral drug, electroanalysis, electrochemical sensor, favipiravir, molecularly imprinted polymer*

ÖZ

Amaç: *Bu çalışmada moleküler baskılanmış polimer (MIP) tekniği, antiviral ilaç favipiravirin (FAVI) seçici, hızlı ve hassas elektrokimyasal tayini için uygulanmıştır.*
Gereç ve Yöntem: *Döngüsel voltammetri (CV) kullanılarak, fonksiyonel monomer o-fenilendiaminin (o-PD) bir şablon molekül FAVI varlığında camsı karbon elektrot (GCE) üzerinde elektropolimerize edilmesiyle, yeni MIP tabanlı sensör (MIP@o-PD/GCE) oluşturulmuştur. MIP@o-PD/GCE'nin uzaklaştırma ve yeniden bağlama prosedürlerinin yanı sıra etki edebilecek koşulların optimizasyonu ve performans ölçümü için diferansiyel puls voltametrisi (DPV) kullanılmıştır. Ferrosiyanid/ferrisiyanid redoks işaretleyicisi, DPV kullanılarak deneysel*

* **Corresponding Author / Sorumlu Yazar:** Çiğdem Kanbeş-Dindar
e-mail / e-posta: ckanbes@gmail.com, **Phone / Tel.:** +905050491355

Corresponding Author / Sorumlu Yazar: Bengi Uslu
e-mail / e-posta: buslu@pharmacy.ankara.edu.tr, **Phone / Tel.:** +903122033178

Submitted / Gönderilme : 25.07.2024
Accepted / Kabul : 07.08.2024
Published / Yayınlanma : 10.09.2024

prosedürün her adımını izlemek için kullanılmıştır.
Sonuç ve Tartışma: *İnsan serum numune örnekleri için MIP@o-PD/GCE, optimum deneysel koşullar altında 10 pM ila 90 pM aralığında FAVI'e doğrusal bir yanıt vermektedir. MIP@o-PD/GCE'nin tespit limiti 1.80 pM olarak elde edilirken, miktar belirleme limiti 6.23 pM olarak bulunmuştur. Tasarlanan sensör, uygulanabilirliğini ve geçerliliğini doğrulamak için sentetik bir insan serumu örneğine başarıyla uygulanmıştır. Elektrokimyasal sensör seçiciliği, FAVI ile benzerlik gösteren parasetamol ve tenofovir ile Covid-19 tedavisinde kullanılan diğer ilaçlar olan oseltamivir ve famsiklovirin bağlanması karşılaştırılarak değerlendirilmiştir.*
Anahtar Kelimeler: *Antiviral ilaç, elektroanaliz, elektrokimyasal sensör, favipiravir, moleküler baskılanmış polimer*

INTRODUCTION

FAVI also known as 6-fluoro-3-hydroxy-2-pyrazinecarboxamide (Figure 1), is a pro-drug that Fujifilm Toyama Chemical Company in Japan developed for treating influenza [1]. It was invented in 2002 and received approval in 2014 [2]. Following its arrival at the target cell, it undergoes a metabolic pathway that creates its active form, FAVI-ribofuranosyl-5'-triphosphate, within the cell [3]. This molecule is then recognized as a substrate by the RNA-dependent RNA polymerase, which is crucial for viral transcription, and that enzyme is selectively blocked [4].

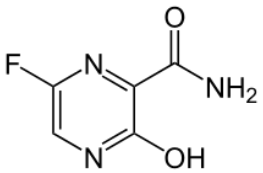

Figure 1. Chemical structure of FAVI

Various research focuses on determining the FAVI (Free Active Pharmaceutical Ingredient) in drugs or biological liquids. The previously conducted research employed several analytical methods, including capillary electrophoresis [5], spectroflourometry [6], liquid chromatography with UV detection [7], liquid chromatography with mass spectroscopy [8,9] spectrophotometry, and voltammetry [10,11]. These studies showed that FAVI could be analysed selectively when chromatographic systems were applied. However, these methods are time-consuming and too many organic solvents were used. Consequently, researchers have created electrochemical approaches as more feasible and eco-friendly alternatives in several investigations. Nevertheless, there is little empirical evidence demonstrating the resolution of the selectivity issue in these strategies. Furthermore, they lack the necessary sensitivity for analyzing biological materials. Hence, it is imperative to establish a more refined and discerning analytical technique. Within this particular framework, the integration of electrochemistry with molecular imprinting polymer technology presents a very efficient and practical resolution.

Biomimetic recognition elements, or MIP are polymer matrices with specific recognition sites for target molecules, or templates. Specific spots that identify the target molecule are created during the polymerization process. Subsequently, using the suitable solvent, these areas are permitted to create the suitable hollow spaces for identifying purposes. MIP technology is often used with electrochemical analysis techniques to selectively determine drug compounds.

The aim of this study was to develop a selective MIP surface using an electrochemical polymerisation technique for the stable and selective determination of FAVI from biological media. The stable, selective, and sensitive surface was optimized by adjusting essential parameters such as polymerization cycle, monomer: drug ratio, removal duration, and rebinding time. Subsequently, the linear operating range of the selective sensor surface was determined. Finally, we examined the sensor's linear working range in serum medium to demonstrate the applicability of the sensor for biological matrices.

MATERIAL AND METHOD

Instruments

A traditional three-electrode cell powered by AUTOLAB (Netherlands) was used to conduct the electrochemical experiments, namely CV and DPV. Our system was executed on a PC with the help of the NOVA 2.1.4 software. A reference electrode made of saturated Ag/AgCl (3 M KCl), a Pt plate counter electrode, and a GCE (3 mm diameter, BASi) were used in a standard three-electrode setup. The precision balance was calibrated by Ohaus Instruments (Shanghai, China) to measure the acquired quantities. A pH meter with a precision of ±0.05 was used to test the solutions' pH levels (Mettler-Toledo pH/ion S220, Switzerland). The removal and rebinding operations were carried out using a Thermo-Shaker (Biosan TS 100).

Reagents

The FAVI standard solution was made using distilled water and thereafter kept in a refrigerator. Methanol (99.8%), sodium hydroxide (>97%), acetic acid (AA) o-PD (≥98%), and sodium acetate trihydrate (>99%) were obtained from Sigma-Aldrich. For electrochemical measurements, the acetate buffer solution (pH 5.2) was prepared by using double-distilled water. All prepared solutions were stored at 4◦C in a refrigerator. The human serum stock solution (derived from male AB plasma) was purchased from Sigma-Aldrich in St. Louis, MO, USA.

Preparation of the MIP and Non-Imprinting Polymer (NIP) Based Electrochemical Sensors

The GCE was subjected to ultrasound for twenty minutes in a mixture of one-to-one methanol and two-part distilled water before the electrochemical polymerization (EP) procedure. The next step was to use a polishing pad to clean the electrode surface with alumina slurry. The surface was then rinsed with double-distilled water and let to dry at room temperature. To prepare the MIP@o-PD/GCE, the GCE was immersed in the polymeric film solution (5 mM o-PD, 2 mM FAVI in 0.1 M pH 5.2 acetate buffer) and electropolymerized scanning between -0.2 and 0.8 V for 20 cycles with 50 mV/s scan rate(Figure 2A). The polymeric film was prepared in the same protocol without FAVI to prepare the NIP-based sensor.

After the EP of the functional monomer o-PD and the template FAVI on the GCE surface, the imprinted electrode was rinsed with double-distilled water. Removal of template molecule FAVI was performed by immersing the imprinted GCE into a solution containing methanol and 1 M AA (2:3, v/v) for 5 min using a Thermo-Shaker at 550 rpm and room temperature. Afterward, the rebinding process was carried out by incubating the MIP-based electrode in different concentrations of FAVI for 5 min using a Thermo-Shaker at 550 rpm and room temperature. Before incubation of each different concentration, the electrode was washed with distilled water for 30 s.

In order to compare the analytical performance of the MIP-based electrochemical sensor, the NIP-based sensor was employed. Using the identical experimental procedure and circumstances as described above, but without the addition of FAVI during the EP stage, NIP-based GCE was synthesized. A GCE in NIP and MIP-based electrochemical sensors were used to conduct electrochemical measurements in a solution containing 5 mM $[Fe(CN)_6]^{3-/4-}$ and 0.1 M KCl (1:1). The methods used were CV and DPV.

RESULT AND DISCUSSION

Polymerization of MIP and NIP

Firstly, in order to perform the electrochemically selective determination of FAVI, the most widely used monomer in the literature, o-PD, was used and a MIP layer was formed on the surface of the electrode by electropolymerisation method as shown in Figure 2A. At this stage, the optimal parameters often seen in current studies, namely a monomer-to-template ratio of 10:1 and a polymerization cycle of 20, were selected[15]. Subsequently, analysis was conducted using the DPV method at each stage in the presence of a redox agent, and the change on the electrochemical surface was found to be shown in Figure 2B, where the highest current value is first obtained from the electrode surface. However, when the polymer coating increases, the surface becomes closed due to the insulating

properties of the polymer, making electron transport more difficult, and resulting in a significant decrease in current value. Later, the target molecule, namely FAVI, was removed in the presence of a suitable solvent to create selective cavity voids on the surface, resulting in the formation of voids that allow electron transfer. As a result, the current value of the redox marker has increased. Later, to demonstrate the determination of FAVI from the desired environment, cavity voids were created on the surface of the electrode. The surface was then incubated in a solution containing FAVI for 15 minutes. As seen in the image, when FAVI selectively settled into the cavity voids, there was a decrease in the current signal of the redox marker due to a decrease in electron transfer from the surface.

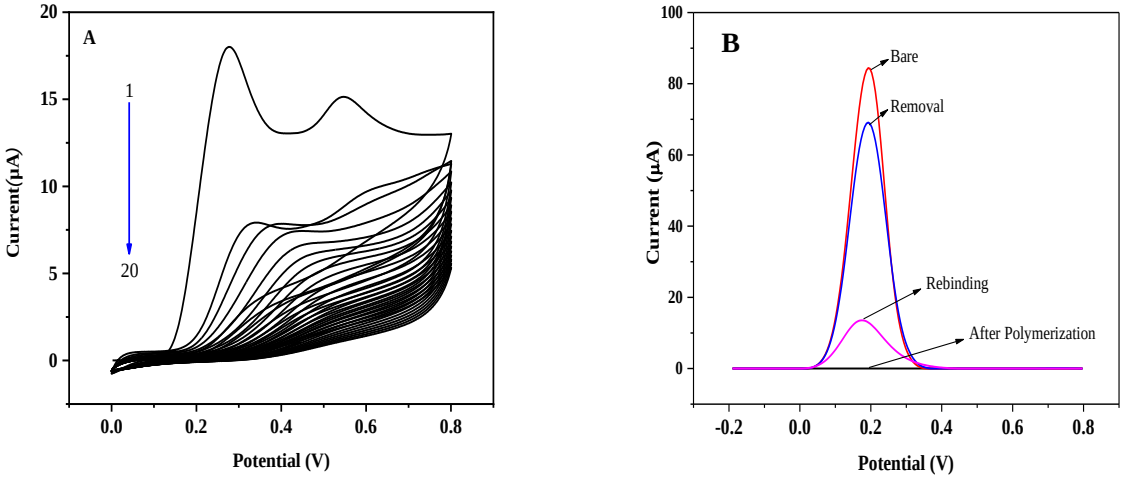

Figure 2. Cyclic voltammograms during electropolymerization of 5 mM o-PD in the presence of 2 mM FAVI in 0.5 M acetate buffer, pH 5.2 (Scan rate: 50 mV/s, 20 cycles) (A); Differential pulse voltammograms (B) Bare GCE: red. FAVI-MIP/GCE after electropolymerization (black), template removal (blue), rebinding in buffer (pink)

Optimization of Important Sensor Parameters

Following the successful demonstration of the feasibility of creating a selective surface using o-PD, several parameters such as the number of polymerization cycles, monomer: template ratio, removal time, and rebinding times were fine-tuned to establish a durable and consistent selective surface. Only the optimum parameters were modified in each phase, while the remaining values were kept fixed. The polymerization cycle was analyzed to determine the total number of cycles when the surface was fully coated with the polymer. According to Figure 3A, the highest current value after removal was obtained when the electrode surface was coated by MIP solution for 20 cycles. For this purpose, the monomer-drug ratio was four different monomer: drug ratios (10:1; 5:1; 1:1; and 2.5:1) were tested, and the peak current as a 68 µA was obtained at 2.5:1 (Figure 3B). Different removal solutions including: 0.1 M AA, ethanol, methanol, and methanol: AA (2:3) were tried to remove FAVI from the cavities formed during polymerization. The results obtained are close to each other for each solution media. However, it did not rebind after ethanol use and the methanol: AA (2:3) show the highest reproducibility. By using methanol:AA mixture as removal solution, removal time optimization was performed to remove FAVI in the most appropriate time without damaging the polymer surface and the most appropriate removal time was found to be 5 minutes (Figure 3C). The optimization of the incubation period of FAVI is a crucial component in the MIP sensor. A 100 µM solution of FAVI was used at this step, with an incubation duration of 5 minutes determined as the most suitable (Figure 3D).

Selectivity of FAVI -MIP Electrode Surface

The selectivity of the electrochemical sensor was assessed by comparing the affinity of paracetamol and tenofovir, which are comparable to FAVI, as well as oseltamivir and famciclovir, which are additional medications used in the management of Covid-19. A one-to-one ratio was used for all

drugs. It was found that the incubation in these solutions did not result in any notable alteration in the sensor (Figure 4). Recovery values of paracetamol, oseltamivir, tenofovir, and famciclovir were 97.25, 104.85, 98.35, and 102.14, respectively. The 97.25-102.14% recovery indicated that the interfering agents did not significantly affect the FAVI/MIP/GCE analytical performance.

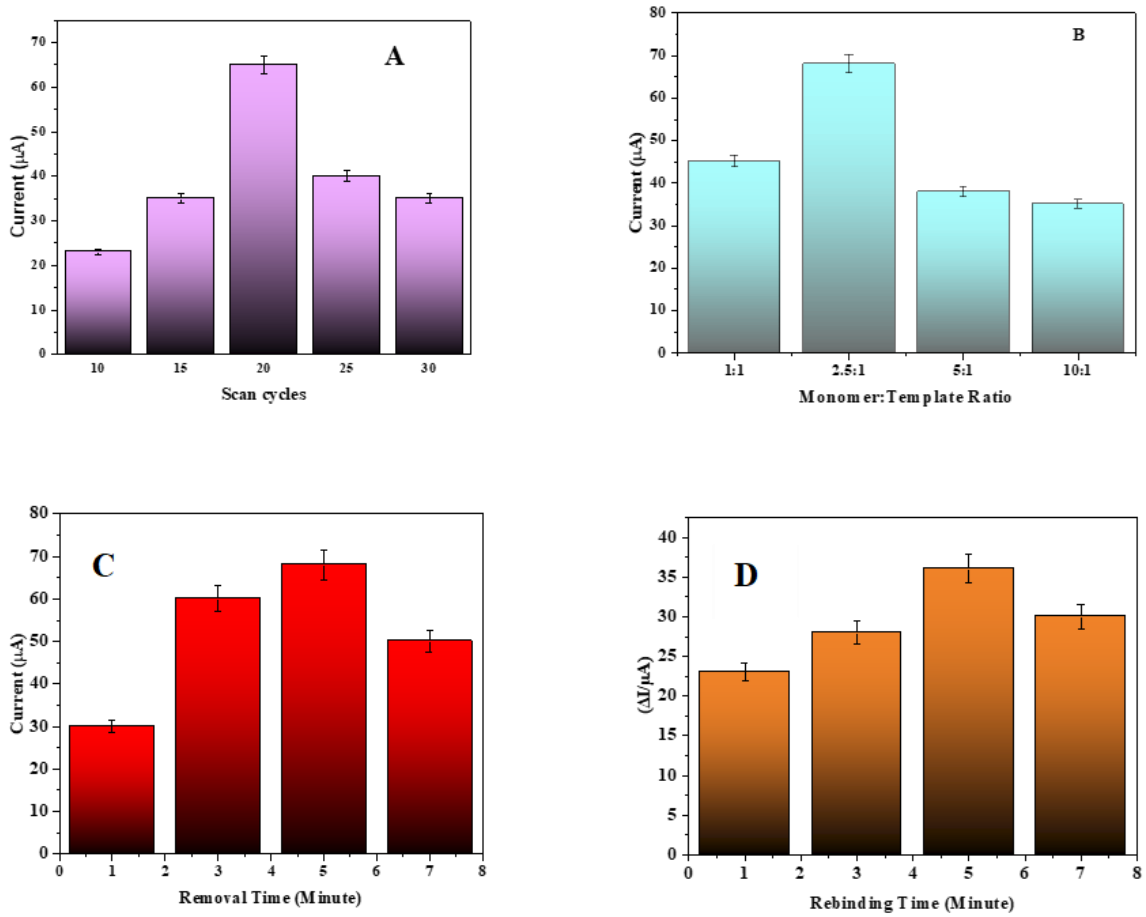

Figure 3. The optimization studies of electropolymerization scyle (A), monomer: template ratio(B), removal time (C), rebinding time (D), for development of MIP(FAVI)/GCE

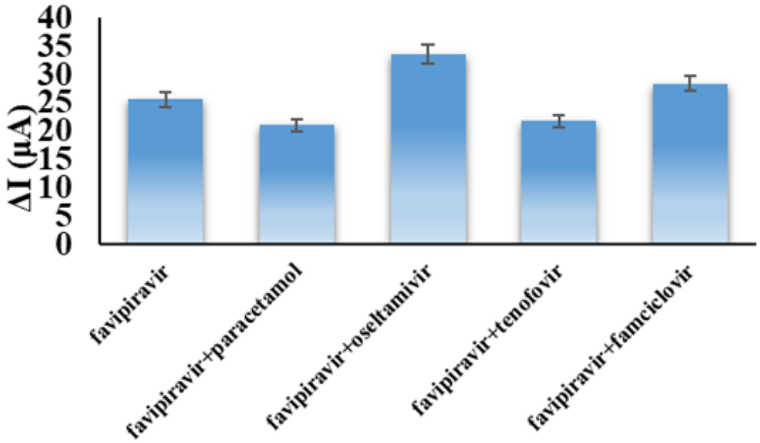

Figure 4. The structure of FAVI, FAVI:paracetamol (1:1), FAVI:oseltamivir (1:1), FAVI:tenofovir (1:1), FAVI:famciclovir (1:1)

Electroanalytical Applications

To investigate the analytical performance of MIP-modified GCE was incubated in different standard FAVI concentrations and the voltammograms obtained are shown in Figure 5A. Also, the analytical performance of MIP-modified GCE was evaluated by incubating it in various serum FAVI concentrations. The resulting voltammograms can be displayed in Figure 5C. The calibration curve was generated by plotting the ΔI current value against the variable FAVI standard concentration (Figure 5B) and the varying FAVI serum concentration (Figure 5D). Figure 5B and Figure 5D also shows the signals obtained after incubation with NIP-modified GCE at different FAVI concentrations to compare the selectivity of the sensor. The linearity was achieved for standard FAVI solutions and serum samples in the concentration range of 20–100 pM and 10-90 pM, respectively (Figure 5). While by using standard FAVI concentration, the related equation between peak current and concentration was founded as ΔI (μA) = 0.4562 *C* (pM) – 23.85 (*r* = 0.9924), by utilizing spike human serum FAVI solution, the related equation between peak current and concentration was described as ΔI (μA) = 0.5213 *C* (pM) – 21.63 (*r* = 0.9948).

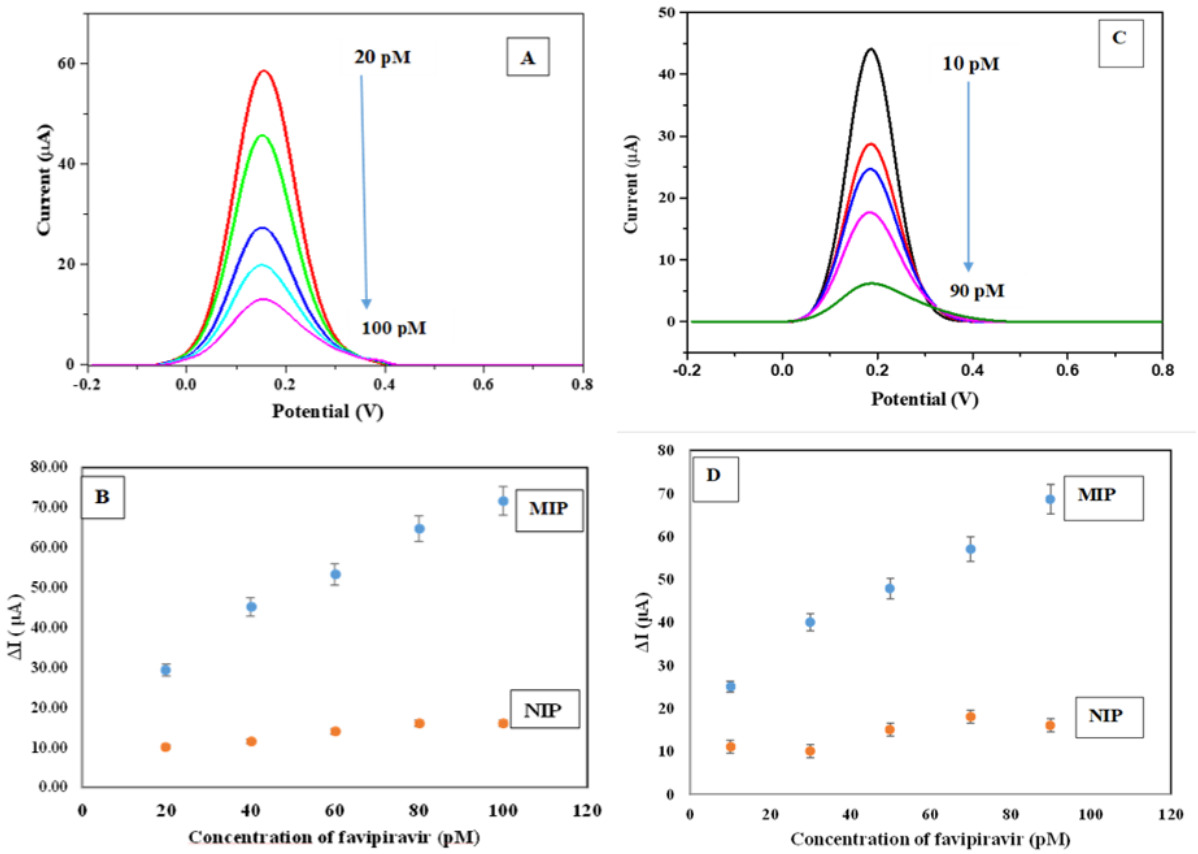

Figure 5. DP voltammograms of MIP-FAVI/GCE with different FAVI concentrations in (A) buffer solution, and (C) commercial serum solution. The calibration curve of FAVI with MIP-FAVI/GCE and NIP/GCE in (B) standard solution, and (D) commercial serum solution

Statistical data of the calibration are given in Table 1. Repeated measurements of FAVI peak potential and peak current within and between days demonstrate the sensitivity of the developed method. The formulas 3 s/m and 10 s/m were used to determine the LOD and LOQ values, where "s" is the standard deviation of the response and "m" is the slope of the calibration curve. The LOD and LOQ values (Table 1) showed the sensitivity of the method. The proposed methods are simple to use and are based on human serum obtained reproducible results that were sensitive enough to detect FAVI in samples (Table 1).

The performance of the developed method was also compared with previous analytical methods

(Table 2) and it was found that the developed method was the superior in terms of sensitivity, while most of the other methods involved time-consuming preconcentration, high consumption of harmful and organic solvents and expensive equipment.

Furthermore, the recovery studies were performed with commercial serum samples (Table 3). Recovery and RSD % results have proven the accuracy and precision of MIP@FAVI/GCE.

Table 1. Correlation data for FAVI calibration generated using DPV in from standard solution and serum

Parameters	**Standard**	**Serum**
Linearity dynamic range (pM)	20-100	10-90
Slope ($\mu A\ pM^{-1}$)	0.4562	0.5213
Intercept (μA)	23.85	21.62
Correlation coefficient (*r*)	0.9924	0.9948
LOD (pM)	2.22	1.80
LOQ (pM)	7.53	6.23
Intra-day precision of peak current (Relative Standard Deviation, RSD%)*	1.78	3.56
Inter-day precision of peak current (RSD%)*	2.43	4.70

*LOD and LOQ values were calculated based on the lowest value of the calibration range. For serum the intra-day precision of the peak current and the inter-day precision of the peak current values were calculated based on the midpoint of the calibration. Each value is the average of five experiments

Table 2. Comparison with other previously reported analytical methods to study the analytical performance of FAVI determination

Method	**LOD**	**Linearity range**	**Applications**	**References**
Spectrofluorometry	0.06 μM	0.25-1.78 μM	Tablets and human plasma	[6]
LC-MS/MS	37.5 μM and 28.6 μM for positive and negative modes	30-318 μM and 39-318 μM for positive and negative modes	Human plasma	[9]
Capillary Electrophoresis	1.59 μM	1.59-19.09 μM	Plasma and urine	[5]
AdSSWV (BDDE)	18 nM	64-6400 nM	Tablets and human urine	[16]
SWV (MnO_2-rGO/SPE)	9.0 nM	10-55000 nM	Tablets and plasma	[17]
DPV (MIP)	**1.80 pM**	10-90 pM	**Human serum**	***Proposed method***

* MnO_2-rGO: Manganese oxide-reduced graphene oxide; SPE: screen printed electrode;BDDE: boron doped diamond electrode

Table 3. Results of DPV recovery studies by using MIP sensor from serum samples

Parameters	**Serum**
Added concentration (pM)	10.00
Found concentration (pM)	10.14
Average recovered %	101.4
Number of experiments	5
RSD % recovery	5.08

Conclusion

This study attempts to design a molecularly imprinted polymer using the advantages of easy preparation of an electrochemical sensitive sensor. FAVI was used to template molecule. Optimized electrochemical MIP sensors were used to analyze FAVI from human serum samples. Results showed that developed electrochemical MIP sensors provide simple, low cost and sensitive determination of FAVI. The effect of some interfering agents onto the FAVI signal was also evaluated and and a change of less than 5% in the FAVI response was observed. In order to analyze serum samples with easier sample preparation and cheaper apparatus, this approach seems to be promising.

AUTHOR CONTRIBUTIONS

Concept: C.K.D., B.U.; Design: C.K.D., B.U.; Control: C.K.D., B.U.; Sources: C.K.D., B.U.; Materials: C.K.D., B.U.; Data Collection and/or Processing: C.K.D., B.U.; Analysis and/or Interpretation: C.K.D., B.U.; Literature Review: C.K.D., B.U.; Manuscript Writing: C.K.D., B.U.; Critical Review: C.K.D., B.U.; 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.

REFERENCES

1. Assis, L.C., de Castro, A.A., de Jesus, J.P.A., da Cunha, E.F.F., Nepoviomava, E., Krejcar, O., Kuca, K., Ramalho, T.C., La Porta, F.A. (2021). Theoretical insights into the effect of halogenated substituent on the electronic structure and spectroscopic properties of the Favipiravir tautomeric forms and Its implications for the treatment of COVID-19. RSC Advances 11(56), 35228-35244. [CrossRef]
2. Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., Liao, X., Gu, Y., Cai, Q., Yang, Y., Shen, C., Li, X., Peng, L., Huang, D., Zhang, J., Zhang, S., Wang, F., Liu, J., Chen, L., Chen, S., Wang, Z., Zhang, Z., Cao, R., Zhong, W., Liu, Y., Liu, L. (2020). Experimental treatment with favipiravir for COVID-19: An open-label control study. Engineering, 6(10), 1192-1198. [CrossRef]
3. Joshi, S., Parkar, J., Ansari, A., Vora, A., Talwar, D., Tiwaskar, M., Patil, S., Barkate, H. (2021). Role of favipiravir in the treatment of COVID-19. In International Journal of Infectious Diseases, 102, 501-508.
4. Furuta, Y., Gowen, B.B., Takahashi, K., Shiraki, K., Smee, D.F., Barnard, D.L. (2013). Favipiravir (T-705), a novel viral RNA polymerase inhibitor. In Antiviral Research, 100, Issue 2, 446-454. [CrossRef]
5. Safari, E., Seyfinejad, B., Farajzadeh, M.A., Afshar Mogaddam, M.R., Nemati, M. (2024). Acid-base reaction-based dispersive solid phase extraction of favipiravir using biotin from biological samples prior to capillary electrophoresis analysis. RSC Advances, 14(27), 19612-19618. [CrossRef]
6. Megahed, S.M., Habib, A.A., Hammad, S.F., Kamal, A.H. (2021). Experimental design approach for development of spectrofluorimetric method for determination of favipiravir; a potential therapeutic agent against COVID-19 virus: Application to spiked human plasma. Spectrochimica Acta-Part A: Molecular and Biomolecular Spectroscopy, 249, 119241. [CrossRef]
7. Bulduk, İ. Gungor, S. Aydın, B.S. Sagkan, R.I (2021). Comparison of HPLC and UV spectrophotometric methods for quantification of favipiravir in pharmaceutical formulations. Iranian Journal of Pharmaceutical Research, 20(3), 57-65. [CrossRef]
8. Challenger, E., Penchala, S.D., Hale, C., Fitzgerald, R., Walker, L., Reynolds, H., Chiong, J., Fletcher, T., Khoo, S., Else, L. (2023). Development and validation of an LC-MS/MS method for quantification of favipiravir in human plasma. Journal of Pharmaceutical and Biomedical Analysis, 233, 115436. [CrossRef]
9. Eryavuz Onmaz, D., Abusoglu, S., Onmaz, M., Yerlikaya, F.H., Unlu, A. (2021). Development and validation of a sensitive, fast and simple LC-MS / MS method for the quantitation of favipiravir in human serum. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences, 1176, 122768. [CrossRef]
10. El-Wekil, M.M., Hayallah, A.M., Abdelgawad, M.A., Abourehab, M.A.S., Shahin, R.Y. (2022). Nanocomposite of gold nanoparticles@nickel disulfide-plant derived carbon for molecularly imprinted

electrochemical determination of favipiravir. Journal of Electroanalytical Chemistry, 922, 116745. [CrossRef]

11. Kanbeş Dindar, Ç., Bozal-Palabiyik, B., Uslu, B. (2022). Development of a diamond nanoparticles-based nanosensor for detection and determination of antiviral drug favipiravir. Electroanalysis, 34(7), 1174-1186. [CrossRef]
12. Ozcelikay, G., Karadas-Bakirhan, N., Taskin-Tok, T., Ozkan, S.A. (2020). A selective and molecular imaging approach for anticancer drug: Pemetrexed by nanoparticle accelerated molecularly imprinting polymer. Electrochimica Acta, 354, 136665. [CrossRef]
13. Ozcelikay, G., Kurbanoglu, S., Bozal-Palabiyik, B., Uslu, B., Ozkan, S.A. (2018). MWCNT/CdSe quantum dot modified glassy carbon electrode for the determination of clopidogrel bisulfate in tablet dosage form and serum samples. Journal of Electroanalytical Chemistry, 827, 51-57. [CrossRef]
14. Majidian, M., Ozcelikay, G., Cetinkaya, A., Unal, M.A., Nazır, H., Atici, E.B., Ozkan, S.A. (2023). Nanomaterial-based electrochemical sensing platform for the determination of Olaparib. Electrochimica Acta, 449, 142198. [CrossRef]
15. Bozal-Palabiyik, B., Erkmen, C., Uslu, B. (2019). Molecularly ımprinted electrochemical sensors: Analytical and pharmaceutical applications based on ortho-phenylenediamine polymerization. Current Pharmaceutical Analysis, 16(4), 350-366. [CrossRef]
16. Allahverdiyeva, S., Yunusoğlu, O., Yardım, Y., Şentürk, Z. (2021). First electrochemical evaluation of favipiravir used as an antiviral option in the treatment of COVID-19: A study of its enhanced voltammetric determination in cationic surfactant media using a boron-doped diamond electrode. Analytica Chimica Acta, 1159, 338418. [CrossRef]
17. Mohamed, M.A., Eldin, G.M.G., Ismail, S.M., Zine, N., Elaissari, A., Jaffrezic-Renault, N., Errachid, A. (2021). Innovative electrochemical sensor for the precise determination of the new antiviral COVID-19 treatment Favipiravir in the presence of coadministered drugs. Journal of Electroanalytical Chemistry, 895, 115422. [CrossRef]