Int. J. New. Chem., 2024, Vol. 11, Issue 2, pp. 113-122.

International Journal of New Chemistry
Published online 2024 in http://www.ijnc.ir/.
Open Access

Print ISSN: 2645-7236

Online ISSN: 2383-188x

Original Research Article

Electrochemical Sensor for Ketoconazole Determination with Molecularly Imprinted Polymer-Carbon Ceramic Electrode (MIP/CCE)

Sohrab Ershad*[1], Somayeh Dadmanesh, Mehdi Hosseinzadeh[2]

[1] Payame Noor University (PNU), P.O BOX 19395-4697, Tehran, Iran

[2] Mehdi Hosseinzadeh, Marand Faculty of Technical and Engineering, University of Tabriz, Tabriz, Iran

Received: 2023-10-01 *Accepted: 2023-11-25* *Published: 2023-11-30*

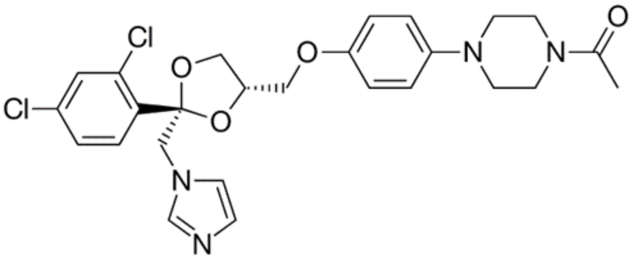
ABSTRACT

Using a molecularly imprinted polymer (MIP) as a recognition element, a selective voltammetric sensor for ketoconazole (KC) was designed and constructed. MIP was synthesized using methacrylic acid as a functional monomer and KC as a template, and then into the carbon paste electrode as a ketoconazole sensor, was incorporated. A new chemically modified electrode containing MIP compound on the surface of a glassy carbon electrode (GCE) by sol-gel method was obtained. The electrochemical behavior of the resulting modified electrode by cyclic voltammetry method in detail was investigated. The obtained film electrode had very good stability and thus exhibited a good electrocatalytic response for KC oxidation. A sharp catalytic oxidation peak was observed at around 53 mV in the MIP/CCE electrode and GCE, a small oxidation peaks current at about 63 mV was observed. The diffusion coefficient and transfer coefficient (α) for the electrocatalytic oxidation of KC were also studied under experimental conditions.

Keywords: Carbon Ceramic Electrode (CCE), Cyclic Voltammetry, Ketoconazole (KC), Molecularly Imprinted Polymer (MIP)

Introduction

Ketoconazole, cis-1-acetyl-4-[4-[2-(2,4-dichlorophenyl)-2-(1H-imidazole-1-ylmethyl)-1,3-dioxolon-4-yl] methoxy] piperazine (KC, Scheme 1), has been used as a broad-spectrum and effective antifungal drug [1] for the treatment of a wide variety of super facial and systematic mycoses [2, 3]. It has the advantage of producing stable blood levels after oral administration over other imidazole derivatives [4]. Due to the critical importance of determining ketoconazole in biological fluids, and pharmaceutical preparations, several chromatographic [5-11] and spectroscopic techniques [12-20] have been reported for its quantitative determination.



scheme 1. Chemical structure of ketoconazole

The literature reports on the electrode processes of the drug despite its analytical importance, the electrochemical behavior of ketoconazole is quite sparse [21]. In 1992, Fijalek et al. described a polarographic method for the determination of ketoconazole on dropping mercury electrodes in the range of 1-30 mg/mL using a phosphate buffer pH 7.45 [21].

In this article, we studied the voltammetric oxidation of ketoconazole in chloroform solution on the glassy carbon, platinum, and gold electrodes. It should be noted that, despite its potential toxicity and relatively high volatility, chloroform is reported as a very suitable solvent for the extraction and determination of ketoconazole from biological [12, 16, 20] and pharmaceutical samples (tablets and creams). Dopamine and catechol were detected by the sensor, whereas potentially interfering and analog compounds, including resorcinol, phenol, serotonin, hydroquinone, and Ketoconazole had a minimal effect (e3%) on the detection and identification of either analyte. Bare gold electrodes and non-imprinted hybrid electrodes did not respond to catechol at concentrations lower than 0.5 mM. Finally, the catalytic properties of the sensor were found to be consistent with Michaelis-Menten kinetics and were characterized by the chronoamperometry method.

To minimize this effect, one of the most promising approaches is the use of chemically modified electrodes (CME). Various methods have been applied to modify the electrode, such as covalent bonding [19, 20] electrochemical polymerization [21, 22], and mixing with carbon paste [23, 24]. One of the successful and promising techniques is the use of chemically modified electrodes (CMEs) that contain selected specific redox mediators immobilized on the surface of the conventional electrode. For this reason, the sol-gel process seems very suitable for coating thin films on complex shapes. The pore size and porosity of these films can be controlled to ensure that the permeability of the film remains high and maximizes the specific surface area. Furthermore, the sol-gel process involves condensation of appropriate monomeric precursors, low-temperature hydrolysis, and includes suitable organic moieties that that are not stable at high temperatures. [25]. But so far, the CMEs containing MIP that were prepared by the sol-gel method for Ketoconazole have not been reported. In this study, we used a facile and effective sol-gel immobilization method to fabricate an electrode for the electro catalytic oxidation of KC. This electrode consists of silicon dioxide gel films doped with MIP, which largely preserves its electrochemical activity, structure, and electro catalytic properties. Several voltammetric studies report better performance in sensitivity [26, 27] and detection limits due to the unique physicochemical properties of MIP [27]. There are numerous publications on electrochemical catalytic studies of the MIP [26-29]. Nevertheless, there are limited studies on MIP modified hybrid electrodes, which can provide potential new approaches for better reproducibility and sensitivity of the electrochemical determinations of biochemical or chemical compounds, including KC. As a part of our continuous work on the electrochemical studies in recent years [30-32], in this report, the electro catalytic study of KC was investigated using MIP modified sol-gel electrode by mechanical attachment. The obtained oxidation peaks indicate that the MIP modified ceramic carbon electrode has an acceptable electrochemical behavior in terms of reproducibility and sensitivity.

Experimental

Reagents and Solutions

Methyl trimethoxy silane (MTMOS), Ketoconazole, hydrochloric acid (HCl), and methanol were of analytical grade provided by Merck. Potassium chloride was used to prepare the background electrolyte solution. Using phosphate buffer, the pH value of different solutions was adjusted to 7. To prepare the solutions, distilled water was used.

Instrumentation

A GC electrode was used as the working electrode. All potentials in the text refer to saturated Ag/AgCl (saturated KCl) and serve as the reference electrode (all electrodes obtained from Azar Electrode Co., Urmia, Iran), a platinum wire was used as a counter electrode. Electrochemical measurements were performed using an Autolab potentiostat/galvanostat model PGSTAT 30 (Metrohm, Utrecht, Netherlands), and a system was run using GPES 4.9 software on a PC.

Preparation of Molecular Imprinting Polymer

Polymerization solution content was: 0.23 mmole ketoconazole, 0.12 mmole methacrylic acid, 16 mmole ethylene glycols dimehtacrylate, and 0.3 mmole isobutyronitrile in 25/75 toluene/acetonitrile solvent.

Preparation of Modified Electrode

MIP provided by Article [33] and briefly, the technique of immobilizing MIP on GC electrode is given as follows. The GC electrode with emery paper (p 2000) and then by 0.05 µm alumina powder was polished. The electrode was washed in water and then with absolute ethanol for 5 minutes sonicated, and then dried at 25ºC. First, MIP (5 mg) was dissolved in 1 ml of methanol until a clear solution was reached and completely homogenized by sonication for 5 minutes. Then, 0.9 ml of the resulting solution was mixed with 0.1 ml hydrochloric acid (0.1 M) and 0.6 ml (MTMOS) and stirred until a homogeneous gel solution was obtained. The resulting clear solution was aged for 30 min at room temperature, and then 10 µl of the freshly prepared solution onto the surface of the GC electrode was pipetted. The gel films were dried at room temperature for 24 hours and ready to use.

Results and discussion

Electrocatalytic Oxidation of KC at the MIP Modified GC Electrode

Using cyclic voltammetry, the electrochemical properties of the MIP modified GC electrode were studied with sol-gel technique, Typical cyclic voltammograms of MIP-modified and bare GC electrodes by sol-gel techniques in phosphate buffered electrolyte solution (pH 7.0) in 0.1 M KCl solutions at a scan rate of 10 mV s^{-1} are shown in Figure 2. As shown in the resulting figure, the oxidation peak areas observed for the MIP modified GC electrodes are much larger than the bare GC electrode.

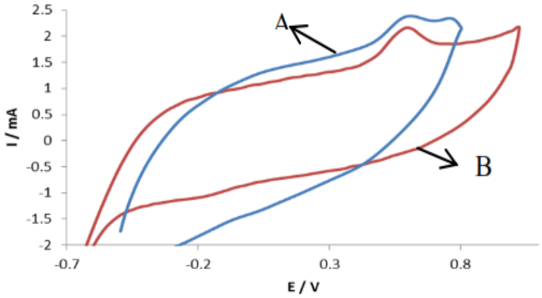


Figure 2. Cyclic voltammograms for 1.0 mM KC at (A) MIP/CCE electrode (B) bare GC electrode in 0.1 M KCl solutions in phosphate buffer electrolyte solution (pH 7.0) at scan rate 50 mV s^{-1}.

As can be concluded and inferred from the linear graphs of peak current (i_p) versus square root of the scan rate ($\nu^{1/2}$) for KC, the nature of the oxidation process in the studied buffer system is under diffusion control. Cyclic voltammograms of MIP/CPE electrode in 0.1 M phosphate buffer with pH 7.0 at scan rates: 10, 20, 30, 40, 50, 60, 70, and 80 mVs^{-1} containing 1 mM KC are indicated in Fig 3A.

According to Figure 3A, the anodic currents increase, and as the scan rate increases the peak potential shifts. From plotting the peak current values against $\nu^{1/2}$ (Fig. 3B), the following linear relationship has resulted:

$$I_p = 2 \times 10^{-4} + 3 \times 10^{-4}\, v^{1/2}\ (\mathrm{mV}^{1/2}\ \mathrm{s}^{-1/2}),\ R^2 = 0.9957$$

This behavior indicates the control of the oxidation reaction by the diffusion process. Therefore, for an irreversible diffusive process according to the following equation:

$$I_p = 3.01 \times 10^5 n\, [(1\text{-}\alpha)\, n_\alpha]^{1/2} ACD^{1/2}\, v^{1/2}$$

and considering (1-α) $n_\alpha = 0.361$ (see below), D = 4.09 × 10^{-6} cm^2 s^{-1} (see chronoamperometric studies), A = 0.123 cm^2, the total number of electrons participating in the KC anodic oxidation process is estimated as n=1.84 ≈ 2.

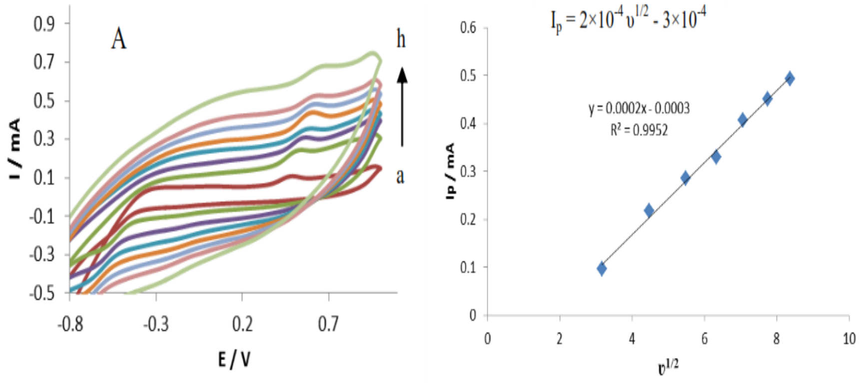


Figure 3. (A) Cyclic voltammograms of MIP modified GC electrodes in 0.1 M KCl solutions in phosphate buffer electrolyte solution (pH 7.0) containing 1 mM KC at scan rates of (a) 5, (b) 10, (c) 20, (d) 30, (e) 40, (f) 50, (g) 60, (h) 70, (i) 80, (g) 90 and (k) 100 mV s^{-1} (B) dependence of the peak current with square root of the scan rate.

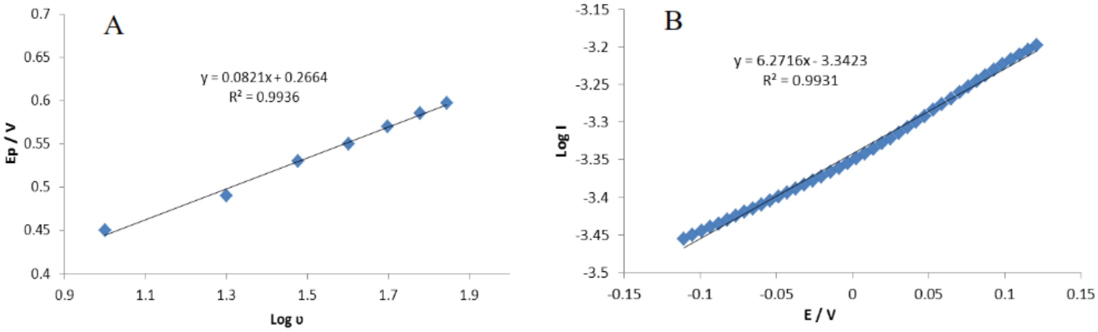


Figure 4. (A) Plot of Ep vs. log ν. (B) Tafel plot derived from data of the rising part of the E vs. log I curve at a scan rate of 20 mV s^{-1}.

As seen in Figure 4A, to obtain information about the rate-determining step, the peak potential (Ep) is proportional to log υ. The slope of Ep vs. log υ is 0.106 mV. Based on the equation for the irreversible diffusion-controlled process, the tafel slope may be estimated:

$E_p = (b \log v)/2 + \text{constant}$

So, b = 0.164 V. This result is close to what is obtained from the polarization measurement. Assuming a transfer coefficient of α = 0.64, this slope indicates that the transfer of one electron is rate-limiting. The tafel slope, b, can be a result by another technique. A tafel plot was plotted

(Fig. 4B). Derived from current vs. voltage curve rise data with a scan rate of 10 mV s^{-1}, A slope of 6.271 V^{-1} is obtained indicating that the rate-limiting step is one electron transfer using the following equation: (assuming a transfer coefficient of $\alpha = 0.64$)

The electrocatalytic oxidation of KC at the MIP/CPE electrode was investigated by chronoamperometry. According to Figure 5, the chronoamperograms obtained for a series of KC solutions with different concentrations are shown.

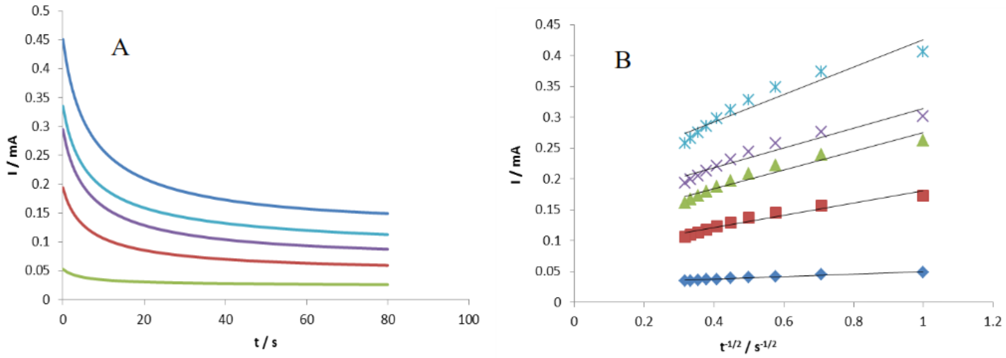


Figure 5. (A) Chronoampromteric response of a MIP modified electrode in 0.1 M phosphate buffer solution (pH 7.0) containing different concentrations of KC for a potential step of 200 mV vs. SCE in the range of 1, 2, 3, 4 and 5 mM (B) Plot of plot of I versus $t^{-1/2}$ obtained from chronoampromteric experiments. The inset shows the relationship between the KC concentration and the slope of the linear segments.

For a potential step of 100 mV vs. SCE, increasing the KC concentration was associated with increasing anodic currents.

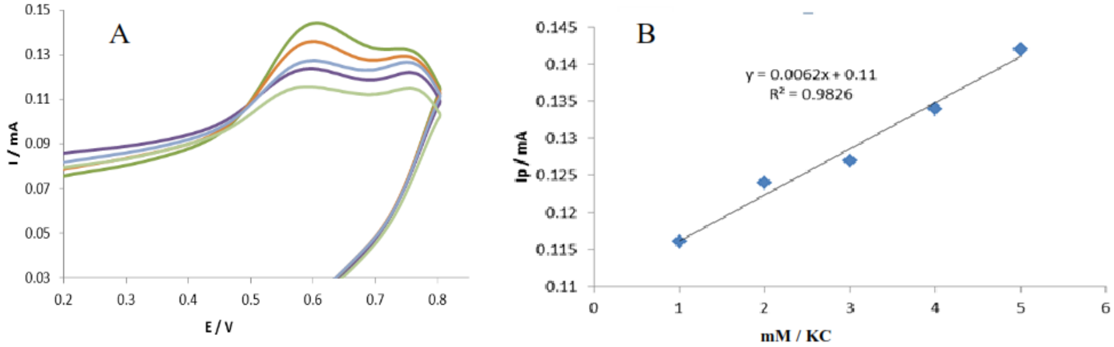


Figure 6. (A) Cyclic voltammograms for increasing concentrations of KC from 1 to 7 (a to g) mM (1~5) in buffer solution (pH 7.0) containing 0.1 M KCl solutions on MIP/CPE electrode. Scan rate was 50 mV s^{-1}. (B) Calibration plot for concentrations of KC from cyclic voltammograms.

In addition, with increasing KC concentration in the range of 1 to 7 mM, the level of Cottrell current measured for 80 seconds increases. In chronoamperometric studies, the KC diffusion coefficient can be determined in the modified electrode. Using the Cottrell equation, the relationship between current and time can be described [34].

$$I = n FAD^{1/2}C/л^{1/2}t^{1/2}$$

Where C is the bulk concentration (mol cm-3), and D is the diffusion coefficient (cm^2 s^{-1}). The plot of I versus $t^{-1/2}$ is linear, and the value of D can be obtained from the slope calculation. The experimentally obtained straight-line plots were then plotted versus KC concentration (Fig. 5B, inset), from which the diffusion coefficient of 4.09×10^{-6} cm^2 s^{-1} was calculated for KC.

The cyclic voltammograms at various KC concentrations are illustrated and a plot of the peak current values as a function of the concentration was also drawn in Figure 6B. In the concentration range of 1~5 mM KC, the plot was linear.

Conclusions

GC electrode coated with a thin film layer of MIP doped sol-gel, acts as an electrocatalyst for KC oxidation. The obtained film towards the oxidation of KC in phosphate buffer aqueous solution with a pH value of 7.0, shows excellent electrocatalytic behavior.

Acknowledgment

We gratefully acknowledge the support of this work by the Marand Payame Noor University (PNU)council.

References

[1] R.F.M. de Almeida, F.C.Santos, K. Marycz, et al. Sci Rep., 9, 16214 (2019).

[2] F. C. Odds, L. J. R. Milne, J. C. Gentles, E. H. Ball, J. Antimicrob. Chemother., 6, 97(1980).

[3] E. W. Gascoigue, G. J. Barton, M. Michaels, W. Mendlermans, J. Heykants, Clin. Res. Rev., 1, 177(1981).

[4] C. G. Meredith, A. L. Moldonado, K. V. Speeg, Drug Metab. Dispos., 13, 156 (1985).

[5] M. Wróblewska, K. Winnicka, Int. J. Mol. Sci., 22, 11326 (2021).

[6] S. Ghurghure, S. S.Garad, S. Birajdar, Curr Trends Biotechnol Pharm.,5,71(2023).

[7] S.K. Muchakayala, N.K.Katari, K.K. Saripella, V.M. Marisetti, L.P. Kowtharapu, Sustain. Chem. Pharm., 36, 101247(2023).

[8] H. Yu, L. Zhang, M. L. D. Yang, G. He, Pharm., 16, 1349 (2023).

[9] A. M. Dipietra, V. Cavrini, V. Anderisano, R. Gatti, J. Pharm. Biomed. Anal., 10, 873(1992).

[10] B. Gjorgjeska, J. Pharm. Pharmacol., 2, 226 (2014).

[11] M.S. Lopes, T.A. Catelani, A.L.C.S. Nascimento, et al. J Therm Anal Calorim., 141, 1371 (2020).

[12] R. T. Sane, R.V. Tendolkar, D. P. Gangal, K. D. Ladage, R. M. Kothurkar, Indian J. Pharm. Sci., 50, 347 (1988).

[13] S. Liawruangrath, K. Prasertboonyai, Anal. Lett., 54, 364 (2021).

[14] M. A. Abounassif, B. M. El-Shazly, Anal. Lett., 22, 2233(1989).

[15] A. Viviane, S.T. N. Saifullah, N. A. Kharis, N. A. Endro, Res J Pharm Technol., 5,4795 (2022).

[16] S. Saurabh, S. Shrivastava R. Tiwle, J. Adv. Pharm. Res., 3, 792 (2020).

[17] P. Pashazadeh-Panahi, M. Hasanzadeh, R. Eivazzadeh-Keihan, J. Mol. Recognit., 33, 2830(2020).

[18] K.P. Kannaiah, A. Sugumaran, Quim. Nova., 45, 23 (2022).

[19] H. R. Zare, S. M. Golabi, J. Solid State Electrochem.,4,87 (2000).

[20] P. Pinyou, V. Blay, L.M. Muresan, T. Noguer, Mater. Horiz., 6,1336 (2019).

[21] W. Zhang, S. Liu, Y. Zhang, X. Ding, B. Jiang, Y. Zhang, Biosens. Bioelectron., 131, 200 (2019).

[22] G. Moreno, F. Pariente, E. Lorenzo, Anal. Chim. Acta., 420 29 (2000).

[23] S.Tajik, H. Beitollahi, R. Hosseinzadeh, A. Aghaei Afshar, et al. Nanomater., 6, 4641 (2021).

[24] A.K. Ortiz-Martínez, L.A. Godínez, C. Martínez-Sánchez, J.D. García-Espinoza, I. Robles, Electrochim. Acta., 390, 138861(2021).

[25] M. Zidan, W. T. Tan, Z. Zainal, A. H. Abdullah, J. K. Goh, Int. J. Electrochem. Sci., 5, 501(2010).

[26] S.I. Khan, P.S. Thakur, A.C. Dongapure, J. Pharm. Negat., 13, 1391(2022).

[27] Y. Zhang, G.I. Waterhouse, Z.P. Xiang, J. Che, C. Chen, W. Sun, Food chem., 326, 126976 (2020).

[28] S. Balayan, N. Chauhan, R. Chandra, U. Jain, Biointerface Res. Appl., Chem, 6, 38 (2022).

[29] S. Ershad, L.A. Saghatfroush, J. Khodmarz, S.G. Telfer, Int. J. Electrochem. Sci., 6 3997 (2011).

[30] S. Ershad, J. Khodmarz, Int. J. Electrochem. Sci., 5 1302 (2010).

[31] S. Ershad, L.A. Saghatfroush, G.Karim nejad, S. Kangari, Int. J. Electrochem. Sci., 4 846 (2009).

[32] M.R. Majidi, A. Jouyban, K. Asadpoure-Zeynali, Electrochim. Acta., 52, 6248 (2007).

[33] J.J. Ruiz, A. Aldaz, M. Domı´nguez, Can. J. Chem., 55 2799(1977).

[34] A.J. Bard, L.R. Faulkner, Electrochemical methods, Fundamentals and Applications, Wiley, New York**, 1980**.

HOW TO CITE THIS ARTICLE

Sohrab ershad, Somayeh Dadmanesh, Mehdi Hosseinzadeh, “**Electrochemical Sensor for Ketoconazole Determination with Molecularly Imprinted Polymer-Carbon Ceramic Electrode (MIP/CCE)**” International Journal of New Chemistry., 2024; 11(2), 113-122. DOI: 10.22034/ijnc.2023.2015078.1363