Low-level Electrochemical Analysis of Ketoconazole by Sepiolite Nanoparticles Modified Sensor in Shampoo Sample

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Abstract
In this study, the nano-sepiolite modified carbon paste electrode (CCPE) was prepared for the determination of ketoconazole (KC). The effects of pH, the proportion of the electrode modifier, deposition potential, and deposition time were investigated. Ketoconazole shows one irreversible oxidation peak at about the potential value of 0.6–0.7 V at different pH values. CV studies show that the modified electrode performed a catalytic effect on the peak signal of KC compared to the bare electrode. This catalytic behavior of CCPE was used for the development of a sensitive detection method. The impact of pH and scan rates on the anodic peak potentials and currents were examined, and the scan rate results show that the oxidation behavior of KC was controlled by the adsorption process at the CCPE surface. Therefore, adsorptive stripping differential pulse voltammetry (AdsDPV) and adsorptive stripping square wave voltammetry (AdsSWV) methods were developed for KC analysis. The two different linear ranges were obtained as (0.1–1.0) nM and (3.0–10.0) nM for AdsDPV, and (0.1–10.0) nM and (3.0–10.0) nM for AdsSWV, respectively. The detection (LOD) and quantification (LOQ) limits were found to be 0.017 nM and 0.056 nM for AdsDPV and 0.025 nM and 0.083 nM for AdsSWV, respectively. Besides, the proposed new sensor has obtained very high recovery values in the analysis of KC in the pharmaceutical shampoo.

Keywords: Ketoconazole; carbon paste electrode; sepiolite clay; pharmaceutical shampoo

1. Introduction
Ketoconazole is 1-acetyl-4-[(4RS,4SR)-2,4-dichlorophenyl]-2-(1H-imidazol-1-yl methyl)-1,3-dioxalan-4-yl] methoxy) phenyl] piperazine and an imidazole derivative.1 Ketoconazole (KC) has a strong antifungal effect against many fungal, gram-positive microorganisms and yeasts. In addition, KC is used in oral administration as an antifungal drug due to its lower toxicity than most azole antifungals.2 The mechanism of action is caused by damage to the cytoplasmic membrane in the fungus and leads to the disruption of mitochondrial and microsomal enzymes of fungi. KC is used as an active component of antifungal formulations in creams, tablets, and anti-dandruff shampoos.3 KC can cause side effects such as urticaria, angioedema, leukopenia, hemolytic anemia, nausea, and thrombocytopenia.

Determination of ketoconazole due to its importance in biological fluids, pharmaceutical preparations, and also cosmetic products appears to be worthwhile. Various methods have been developed for this purpose, including spectrophotometry,4–7 high-performance liquid chromatography,8–10 and liquid chromatography-triple quadrupole tandem mass spectrometry.11 These methods are often time-consuming and require expensive equipment. Also, due to their low sensitivity, requiring pretreatment steps, such as extraction and separation steps are needed in an organic environment. Electrochemical methods can be considered for the detection of pharmaceutical and cosmetic drugs. Among them, adsorptive stripping voltammetry-based adsorption phenomena can be preferred for the electrochemical detection of pharmaceutical and cosmetic drugs in the terms of sensitivity, trace level analysis, and simplicity.12–15 Modification of electrode with nano-materials can be used for developing electrochemical nano-sensors.16,17 Electrode modification can
catalyze the electron transfer rate between the analyte and electrode. Sepiolite clay used as electrode modifier has ease of adsorption for the polar organic species and ions, imparts the electrical conductivity, and has a catalytic contribution to the electrochemical processes. As well, the intercalation and ion exchange capacity of sepiolite clay expands the sorption capacity and conductivity properties of the working electrodes.\textsuperscript{18,19}

Electrochemical sensors based on nano-sepiolite clay show trace limit of detection, higher effective surface area, conductivity, and adsorption capacity properties. In our previous studies, we have tried the sepiolite mineral alone and combined with other modifiers for inducing novel properties in carbon paste electrodes.\textsuperscript{12,19–21} In this regard, we have developed two different sensitive and selective adsorptive voltammetric stripping methods (AdsDPV and AdsSWV) for the determination of ketoconazole at sepiolite clay modified CPE. The developed methods were successfully applied to the determination of ketoconazole in shampoo samples containing ketoconazole. The developed AdsDPV and AdsSWV methods for determination of KC in a shampoo sample, compared to the other electroanalytical methods based on KC analysis in the cosmetic products\textsuperscript{1,22–24} have the widest linear working range and the lowest limit of detection.

2. Experimental

2.1. Reagents and Apparatus

Sepiolite clay, graphite powder, mineral oil, and all solvents were supplied from Sigma. Ketoconazole was also supplied from Sigma-Aldrich, and other used chemicals were analytical grade and used without a preliminary purification step. The stock solution of KC (1.0 \cdot 10^{-3} \text{ M}) was prepared by dissolving of KC in a few drops of 0.1 M HCl solution and water. The prepared stock solution was stored in the refrigerator at + 4 °C. 0.04 M Britton-Robinson buffer (pH 9.0) and KC stock solution were used in all analyses. In all voltammetric methods, supporting electrolyte (0.04 M BR buffer pH 9.0) and KC stock solution were added to the electrochemical cell with a total volume of 10.0 mL. The CCPE, reference, and counter electrodes were immersed in the cell. After arranging all the electrode connections, the working solutions were purged with nitrogen gas (99.99% purity) to remove the oxygen and then the voltammograms were recorded in the potential window of 0.2 V–0.9 V by using AdsDPV and AdsSWV.

2.4. Shampoo Sample Preparation

The 0.5 g of Ketoral shampoo was weighed to produce the desired final concentration of the sample. After that, a few drops of 0.1 M HCl and a small amount of doubly distilled water were added. Then, the total volume of pure water to 100 mL was completed, and the solution was prepared to contain 1.9 \cdot 10^{-4} \text{ M} KC. This mixture was incubated overnight at 4 °C to complete the dissolution of the KC. Appropriate volumes of the resulting solution were placed in the voltammetric cell containing 10.0 mL of BR buffer (pH 9.0), and voltammograms were recorded.

3. Results and Discussion

3.1. Surface Characterization of CPE and CCPE

The surface morphological studies of both bare CPE and sepiolite clay modified CPE (CCPE) were carried out using SEM and EDX measurements. The SEM photographs of CPE and CCPE show that the CCPE electrode...
surface has a more porous structure than bare CPE surface (Fig. 1 a,b). Meanwhile, the EDX measurement was performed to confirm the elemental content of the bare CPE and sepiolite modified CPE (Fig. 1 c, d). In Fig. 1 c, only one peak is seen that belongs to the carbon (C) element in CP electrode and Fig. 1 d shows four peaks that belong to the carbon (C), oxygen (O), magnesium (Mg), and silicon (Si), respectively. According to EDX plots and SEM measurements of the electrodes, it can be clearly said that sepiolite clay has remained successfully on the CPE surface.

Cyclic voltammetry (CV) and Electrochemical impedance spectroscopy (EIS) measurements were performed using 5.0 mM Fe(CN)₆³⁻/Fe(CN)₆⁴⁻ in 0.1 M KCl solution to compare the electrochemical properties of CPE and CCPE (Fig. 2 a, b). According to the obtained CV voltammograms in Fig. 2 a, the higher anodic and cathodic peak currents and the lower peak separation (ΔEₚ) values were obtained at the CCPE electrode compared to CPE. Meanwhile, the Nyquist plots of the same electrode surfaces (Fig. 2 b) show that the charge transfer resistance (Rₛ) (about 4000 ohms) of CCPE is smaller than the Rₛ (about 7000 ohms) of CPE. CV and EIS results confirm that the sepiolite clay on the CPE surface provides an electrocatalytic effect on the electron transfer rate.

Figure 1. SEM images of CPE (a) and CCPE (b), EDX elemental mapping of CPE (c) and CCPE (d)

Figure 2. a) CV voltammograms b) Nyquist plots of CPE and CCPE in 5.0 mM Fe(CN)₆³⁻/Fe(CN)₆⁴⁻ in 0.1 M KCl solution.
3. 2. Optimization of Sepiolite Content

The optimum amount of sepiolite clay was determined to use in the preparation of the modified CCPE electrode. For this purpose, clay modified electrodes were prepared in such a way that the amount of sepiolite clay was 3.3%, 5.0%, 6.7%, 8.3%, and 10.0%. The signals were recorded using the CV method at a scan rate of 0.1 V/s in a BR buffer solution. The peak current of KC increased up to 6.7% and decreased sharply at the higher amount of sepiolite (Fig. 3). It indicates that 6.7% was the optimum amount of sepiolite concentration. The electrode based on nano-sepiolite clay shows the higher peak current as compared to bare CPE because of the high conductivity and catalytic effect to the electron-transfer rate of sepiolite clay.20

3. 3. Electrochemical Behavior of KC

The cyclic voltammograms of 1.0 µM KC demonstrated the oxidation signals of KC at 0.597 V and 0.582 V potentials at CPE and CCPE electrodes in BR buffer solution (pH 9.0), respectively (Fig. 4). The CCPE sensor produced a better current response and sharper peak shapes compared to the bare electrode. The presence of sepiolite clay in the modified electrode improved the sensitivity of the method and the electro-catalytic effect on the redox signals of KC.

3. 4. Cyclic Voltammetric Studies

The effect of the scan rate on the redox properties of KC was investigated by using the CV method. For this purpose, cyclic voltammograms were recorded at scan rates in the range 0.005–0.4 V/s in the presence of 1.0 \( \times \) 10^{-6} M KC on scanning from 0.2 V to 0.9 V towards positive potential region on CCPE electrode (Fig. 5). These voltammograms were used for determining whether the electrochemical ox-

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**Figure 3.** CVs of 1.0 µM KC in BR buffer solution on CCPE with different quantities of sepiolite clay (pH 9.0; scan rate: 0.10 V/s).

**Figure 4.** CVs of 1.0 µM KC at CPE and CCPE electrodes (υ: 0.1 V/s, 0.04 M BR buffer, pH 9.0).

**Figure 5.** CVs of 1.0 µM KC with increasing scan rates in BR buffer at pH 9.0. Insets: logυ-logI_p graph.
oxidation behaviors are reversible, irreversible, or quasi-reversible. As shown in Fig. 5, only one anodic peak at about 0.60 V was observed. No peak was observed in the reverse scan potentials. In addition, as the scan rate increased, the oxidation signal of KC is shifted to more positive potential values, and this phenomenon shows that the oxidation peak of KC exhibits irreversible redox behavior.

To monitor the electrochemical process (adsorption or diffusion-controlled) of KC, we used CV technique. In this context, the log $i_p$-log $v$ graph was plotted, and the slope value of the log $i_p$-log $v$ graph is 0.78 for the oxidation peak of KC. According to this result, it can be said that the adsorption phenomenon is dominant in the electrochemical behavior of ketoconazole. The fact that pre- or post-peaks are observed in the cyclic voltammograms of KC at high scan rates is another indication that adsorption does occur on the electrode surface. $i_p$ vs. $v^{1/2}$ graph is nonlinear, which indicates electrochemical reaction is not diffusion controlled.

### 3.5. Influence of pH

The pH is a crucial parameter that can affect the peak currents and redox mechanism at the electrode surface in voltammetry. Therefore, the effect of pH on the peak current of KC was investigated by using the CV method. The oxidation peak currents of $1.0 \cdot 10^{-6}$ M KC were measured at different pH (2.0 – 12.0) to determine the optimum pH. Fig. 6. shows that the highest peak current was obtained at pH 9.0. This pH value was chosen to perform the electroanalytical study. To investigate the transferred electron number (n) in the electrooxidation of KC for the irreversible process, we used the following Eq. (1).25

$$E_{pa} - E_{pa}/2 = \frac{47.7}{an}$$

Here, $E_{pa}$ is anodic peak potential, $E_{pa}/2$ is the half peak potential, $a$ is the electron transfer coefficient. The $a$ is taken to be 0.5 for an irreversible process. In this study, the number of electrons transferred (n) was found to be 2.28. This result is in good accordance with the previously estimated number of electrons of KC at pH 9.0.26 Therefore, the oxidation process of KC involves a two-electron transfer process, and the tentative oxidation peak of KC was attributed to the oxidation of the imidazole group with the loss of electrons to form the ketone structure.

### 3.6. Optimization of Experimental Conditions for AdsDPV and AdsSWV Methods

Experimental conditions such as deposition potential and time are vital parameters affected by the electrochemical signal of organic compounds. For this purpose, deposition potentials were changed in the range 0.0–1.0 V for AdsDPV and AdsSWV methods (Fig. 7 A, C). This study has shown that 0.1 V and 0.4 V provided the highest peak current for AdsDPV and AdsSWV, respectively. Therefore, these deposition potentials were used in all subsequent experiments.

Similar trials for deposition time were evaluated in deposition time ranging from 0.0 to 180 s (keeping deposition potentials) (Fig. 7 B, D). It was observed that $I_p$ values increase rapidly until 75 s, and then they decrease rapidly for AdsDPV method (Fig. 7B). The optimum value of deposition time was chosen as 75 s. Similarly, the deposition time where the highest peak current was observed was selected as 45 s for AdsSWV (Fig. 7D).

Figure 6. CVs of 1.0 µM KC in different pH values Inset: pH-$i_p$ graph.

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3.7. Calibration Studies and Validation of Optimized Methods

The applicability of AdsDPV and AdsSWV techniques as analytical methods for the analysis of KC was studied by measuring the anodic current as a function of the KC concentration. Calibration curves were constructed for both methods at pH 9.0. Considering the slopes of calibration graphs, the results obtained AdsDPV is more sensitive than by AdsSWV (Fig. 8A-B and Table 1). It was decided that the CCPE electrode could determine KC in the two different linear concentrations ranges of 0.1−1.0 nM and 3.0−10.0 nM for the AdsDPV and AdsSWV methods.

The following equations calculated the LOD and LOQ values:

\[
\text{LOD} = \frac{3s}{m}, \quad \text{LOQ} = \frac{10s}{m}
\]  

Where, \( s \) is the standard deviation for the studied KC concentration (1.0 \cdot 10^{-9} \text{ M}), and \( m \) is the slope of the calibration chart.

The LOD and LOQ values for AdsDPV were 0.017 nM and 0.056 nM; the AdsSWV was 0.025 nM and 0.083 nM respectively (Table 1). A survey of the literature reveals that LOD and LOQ values of KC are the lowest results so far.

AdsDPV and AdsSWV methods developed for KC determination on the CCPE electrode were compared to the results obtained by voltammetric methods in the literature (Table 2). The linear working range, LOD, and LOQ values obtained by the CCPE electrode were found to be superior to those reported methods.

The repeatability, reproducibility, and stability of the modified electrode were investigated. Reproducibility of peak current and potential values (intra-day and inter-day) were determined by using AdsSWV and AdsDPV methods. The percentage of relative standard deviation (%RSD) values is shown in Table 1. %RSD values are less than 5.0%. These results indicate excellent repeatability. However, the reproducibility of the CCPE sensor was tested using five different electrodes prepared on the same day. The %RSD values of reproducibility were calculated as 2.58% and 4.62% for AdsSWV and AdsDPV, respectively.

To investigate the stability of the CCPE sensor, we recorded the KC signals on different days. After the first ten days, it was found that the sensor signal retains 98.42% and 99.02% of the initial value. When the current and potential values of C oxidation signal obtained up to 40 days were examined, it was observed that peak current and potential values of KC decreased by 5.0% compared to its...
Figure 8. A. AdsDPV and B. AdsSWV voltammograms recorded in 0.04 M BR buffer (pH 9.0) for increasing KC concentrations under optimized conditions. Inset: Calibration graphs for KC.

Table 1. The statistical results of the regression analysis obtained with AdsSWV and AdsDPV methods at the CCPE electrode.

| Regression parameters                      | CCPE            |
|-------------------------------------------|-----------------|
| AdsSWV                                    | AdsDPV          |
| Potential, V                              | 0.58            | 0.52            |
| Linear working range, nM                  | 0.1–1.0         | 0.1–1.0         |
| 3.0–10.0                                  | 3.0–10.0        |
| The slope of calibration graph, µA/µM     | 27.51           | 49.47           |
| The intercept of calibration graph, µA     | 0.011           | 0.018           |
| Limit of detection (LOD), nM              | 0.036           | 0.060           |
| Limit of quantification (LOQ), nM         | 0.025           | 0.017           |
| Regression coefficient (R²)               | 0.997           | 0.992           |
| Repeatability of peak potential, RSD*% (intra-day) | 0.991   | 0.993           |
| Repeatability of peak potential, RSD*% (inter-day) | 0.76      | 0.68            |
| Repeatability of peak current, RSD*%       | 3.22            | 3.72            |
| Repeatability of peak current, RSD*% (intra-day) | 4.51      | 4.63            |
| Reproducibility of peak current, RSD*%     | 4.44            | 4.04            |
| Reproducibility of peak potential, RSD*%   | 2.58            | 4.62            |
| Reproducibility of peak potential, RSD*%   | 0.83            | 0.82            |

*RSD is the relative standard deviation of 5 replications.
original values. According to this result, it can be said that the stability of the prepared clay CPE electrode is maintained for up to 40 days. The prepared sensor was kept at +4 °C after all experiments.

3.8. Interferences

The interference effect of some electroactive species, which can be found in cream and drug substances, has been investigated in voltammetric AdsDPV and AdsSWV methods developed for the determination of KC. For this purpose, the concentration of Na⁺, Mg²⁺, K⁺, Co²⁺, Fe³⁺, Cu²⁺, Zn²⁺, ascorbic acid, glucose, lactose, glycerin, and sodium benzoate was added to 100 times the concentration of KC. The percent changes in the peak current of KC in the presence of Na⁺, K⁺, Fe³⁺, ascorbic acid, glucose, lactose, glycerin, and sodium benzoate was found to be less than 5% compared to its original signal. The obtained results indicate that these species did not have any interference effect. The results obtained in the presence of Mg²⁺, Co²⁺, Cu²⁺, and Zn²⁺ showed that these species had a high interference effect in the electrochemical determination of KC. When these cations were added in the presence of KC, the oxidation peak of KC was observed to disappear. This result may be attributed to the formation of a complex between these metals and KC.28, 29

3.9. Real Sample Analysis and Recovery Studies

To determine the accuracy of the two methods developed, we performed a recovery study using a shampoo (Ketoral shampoo 2.0% KC). In Table 3, for AdsSWV and AdsDPV methods, the recovery values were found in the range of 99.5% to 110.4% indicating that the accuracy of the methods is really satisfactory.

To evaluate the accuracies and precisions of the two developed AdsDPV and AdsSWV methods, student t-test and F-test were applied to the data obtained from the recovery study. The results show that (Table 3) there are no meaningful differences in terms of accuracy and precision between these two methods.

4. Conclusions

This study demonstrates that the sepiolite clay modified carbon paste electrode was tested as a sensor for ketoconazole analysis. The ultra-sensitive detection of KC was carried out for the first time by using anodic adsorptive stripping methods. The effect of modifying agent combination, pH, deposition time, and potential values were in-

| Method | Added Amount, nM | Found Amount, nM | Average | Recovery, % | RSD, % | t-test | F-test |
|--------|----------------|----------------|---------|-------------|-------|--------|--------|
| AdsSWV | 3.0            | 3.3; 3.1; 2.3; 3.2; 3.1 | 2.98 ± 0.129 | 99.5 | 4.3 | $t_{d1} = 1.80$ | $F_{d1} = 1.50$ |
|        | 5.0            | 5.1; 5.4; 5.3; 5.2; 5.0 | 5.23 ± 0.188 | 104.6 | 3.5 | $t_{d2} = 0.57$ | $F_{d2} = 3.06$ |
|        | 7.0            | 7.2; 7.6; 8.1; 7.3; 8.2 | 7.73 ± 0.438 | 110.4 | 5.6 | $t_{d3} = 1.89$ | $F_{d3} = 2.42$ |
| AdsDPV | 3.0            | 3.1; 3.2; 2.3; 3.3; 3.1 | 3.14 ± 0.155 | 104.9 | 4.9 | $t_{d4} = 1.80$ | $F_{d4} = 1.50$ |
|        | 5.0            | 5.2; 5.0; 5.3; 5.4; 4.7 | 5.13 ± 0.163 | 102.7 | 3.1 | $t_{d5} = 0.57$ | $F_{d5} = 3.06$ |
|        | 7.0            | 6.0; 7.9; 6.8; 6.9; 7.3 | 6.96 ± 0.591 | 99.42 | 8.4 |

$t_k = 2.31$ (N-2 = 8 at 95% confidence level); $F_k = 6.39$ (N₁-1 = 4 and N₂-1 = 4 at 95% confidence level)

*1, 2 and 3 represent the data obtained at concentrations of 3.0, 5.0 and 7.0 nM, respectively.
vestigated for the determination of KC. The electrochemical determination of KC was successfully developed on the surface-modified electrode in the shampoo sample. No significant interference was found in the analysis of KC except for some cations. The linear working ranges, LOD, and LOQ values obtained by the developed methods were found to be superior to the methods in the literature. The acceptable recovery and low relative standard deviation data demonstrated that the accuracy and precision of the developed methods were satisfactory.

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5. References

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Povzetek

V predstavljeni študiji smo pripravili elektrodo iz ogljikove paste, modificirano z nano-sepiolitom (CCPE) in jo uporabili za določitev ketokonazola (KC). Raziskali smo vpliv pH, deleža elektrodnega modifikatorja, depozicijskega potenciala in časa depozicije. Ketokonazol daje samo en ireverziblni oksidacijski vrh pri vrednosti potenciala okrog 0,6–0,7 V pri različnih vrednostih pH. CV študija je pokazala, da modificirana elektroda katalitsko učinkuje na maksimalni signal KC v primerjavi z golo elektrodo. To katalitsko obnašanje CCPE smo uporabili za razvoj občutljive metode detekcije. Raziskali smo vpliv pH in hitrosti preleta na maksimalni anodni potencial in tok. Rezultati za hitrost preleta pokažejo, da je oksidacijsko obnašanje KC kontrolirano s procesom adsorpcije na površino CCPE. Zaradi tega smo za analizo KC razvili metodi adsorpcijske inverzne diferencialne pulzne voltametrije (AdsDPV) in adsorpcijske inverzne pravokotno-pulzne voltametrije (AdsSWV). Za AdsDPV smo dobili dve različni linearni območji: (0,1–1,0) nM in (3,0–10,0) nM, za AdsSWV pa (0,1–10,0) nM in (3,0–10,0) nM. Meje zaznave (LOD) in meje določitve (LOQ) smo določili kot 0,017 nM in 0,056 nM pri AdsDPV ter 0,025 nM in 0,083 nM pri AdsSWV. Predlagani novi senzor je dosegal zelo visoke izkoristke oz. točnost pri analizi KC v farmacevtskem šamponu.