Antifungal agents are essential drugs used to treat fungal infections caused by various types of fungi. Due to their mechanism of action, these drugs bear serious adverse reactions, interact with a wide range of other drugs, and negatively impact the environment. Therefore, there is a need for accurate, sensitive, and reliable detection methods to minimize and possibly avoid their potentially negative effects. Even though so far classical methods have proven to be effective in detecting these drugs, some of their disadvantages have led the scientific community to focus its efforts on electrochemical methods, as they are simpler to use, more sensitive, and require a smaller quantity of sample and minimal sample pretreatment. This mini-review focuses on electrochemical sensors developed between 2017 and 2022 to detect and quantify antifungal azoles, highlighting their response characteristics, sensitivity, and applicability in real samples analysis.

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Fungi are microorganisms such as yeasts and molds. While most of them can spread without the presence of an animal or human substrate, occasionally they are accidental pathogens. Both healthy and vulnerable individuals, such as immunocompromised ones, are susceptible to fungal infections. Over 600 different types of fungi have been identified as human pathogens, annually infecting billions of people.

Antifungal azoles are a group of drugs used in the management of superficial, subcutaneous, and systemic fungal infections. There are two main groups of antifungal azoles, based on the number of nitrogen atoms in the 5-membered heterocycle: imidazoles and triazoles, consisting of:

**Imidazoles:**
- butoconazole
- clotrimazole
- eberconazole
- econazole
- fenticonazole
- isoconazole
- ketoconazole
- luliconazole
- miconazole
- omoconazole
- oxiconazole
- sertaconazole
- sulconazole
- tioconazole

**Triazoles:**
- albaconazole
- efinaconazole
- fluconazole
- isavuconazole
- itraconazole
- posaconazole
- terconazole
- voriconazole

Antifungal azoles can also be classified by generation. Imidazoles represent the first generation and are usually administered topically, because of their low oral bioavailability and serious side effects. For a while, ketoconazole was available for systemic administration, although it wasn’t preferred because other, more potent, and less harmful molecules were available. Azoles’ second (fluconazole and itraconazole) and third (other triazoles) generations are remarkable due to an extended spectrum of activity, improved safety profiles, and better pharmacokinetic and pharmacodynamic properties. These features make them suitable for systemic use.

Antifungal azoles act by inhibiting cytochrome P450 (CYP450) enzymes, mainly 14α-demethylase—an enzyme with an essential role in the biosynthesis of ergosterol from lanosterol. Ergosterol is an important component of the fungal cell membrane and by decreasing its synthesis, the permeability and fluidity of the cell membrane are altered, and the cellular proliferation of the fungi is disrupted.

At the moment, different antifungal azoles are used in treating invasive fungal infections, depending on their spectrum of activity and aspects such as pharmacokinetic profile, pharmacotoxicology, and available pharmaceutical formulations. For example, fluconazole is recommended in candidiasis, uncomplicated candidemia, and cryptococcosis. On the other hand, itraconazole is primarily endorsed in histoplasmosis and Blastomyces, and as an alternative medication in treating invasive yeast and mold diseases. Voriconazole is the preferred treatment for primary invasive aspergillosis, and more recently in infections caused by *Scedosporium apiospermum* and some *Fusarium* species. Posaconazole is indicated as preventive and salvage therapy for invasive fungal infections and is frequently administered in sequence after amphotericin B treatment in mucormycosis.

Various antifungal azoles are available as topical pharmaceutical formulations (e.g., ointments, creams, gels, lotions, shampoos, powders, nail polish, and others) that can be used on the skin, nails, or mucous membranes to treat candidiasis, dermatophytosis, Malassezia infections, and non-dermatophyte mold infections. The efficacy and, consequently, the necessity of these drugs in the treatment of fungal infections is unquestionable. However, antifungal azoles have certain disadvantages in terms of adverse reactions, drug interactions, and environmental impact.

Regarding the side effects of systemic antifungal azoles, the most significant are gastrointestinal symptoms, hepatotoxicity (ranging from mild abnormalities to hepatic failure), QT prolongation.
(especially ketoconazole, itraconazole, fluconazole, and voriconazole), birth defects risks, and cutaneous reactions. Additionally, because these drugs are substrates and inhibitors of cytochrome P450 enzymes, they interact with a considerable number of drugs, such as antibiotics, antiretrovirals, antipsychotics, sedatives and narcotics, antiepileptics, antidepressants, antimigraine agents, anti-hypertensives, arrhythmics, anticoagulants, and antidiabetic agents, hydropilidemic agents, chemotherapeutics, immunosuppressants and hormonal agents. Therapeutic monitoring of antifungal azoles could lead to a reduction of their toxicity as well as to more efficient treatments. Experts recommend routine therapeutic drug monitoring, especially for voriconazole, itraconazole, and posaconazole therapy.

Besides the risks concerning side effects and drug-drug interactions, antifungal azoles also represent an environmental hazard. These drugs have been correlated with algal growth inhibition, fish endocrine disruption, suppression of cytochrome P450-catalyzed steroidogenesis, modulation of sex differentiation in frogs, and larval growth disruption. According to the Joint Research Centre’s technical report Selection of substances for the 3rd Watch List under the Water Framework Directive, clotrimazole, fluconazole, and miconazole have been selected for monitoring in inland surface waters as they may contribute to antimicrobial resistance. There is a real need for developing high reliable methods for the assay of the active compounds in different pharmaceutical formulations, in biological samples, and in the environment to avoid overdosages, toxic effects, and also environment contaminations which will not be in the benefit of the health of people. Electrochemical methods are cost-effective, and easy-to-use methods, while the sampling can be reduced to just buffering of the samples to be analysed. At this point, it is common to use classical detection methods to quantify antifungal azoles in various samples. The European Pharmacopeia recommends using potentiometric titration for species like fenticonazole, econazole, ketoconazole, isoconazole, bifonazole, fluconazole, and itraconazole, while for voriconazole indicates to use liquid chromatography. A literature survey revealed the use of other methods to determine these compounds, such as high-performance liquid chromatography (HPLC) with UV detection, HPLC-tandem mass spectrometry (HPLC-MS/MS), reversed-phase HPLC (RP-HPLC) with UV detection, sequential injection analysis (SIA) with spectrophotometric detection, spectrophotometry, and capillary electrophoresis (CE).

Although these techniques are widely used due to their robustness, sensitivity, and reliability, they require large amounts of reagents, expensive equipment, sample pretreatment, and specialized personnel. In contrast to chromatographic methods, electrochemical methods are cheap, based on simple principles, and require small amounts of reagents, and minimal sample processing. Furthermore, the equipment can be miniaturized.

Various electrochemical sensors (used in cyclic voltammetry (CV), differential pulse voltammetry (DPV), anodic adsorptive stripping differential pulse voltammetry (AS-DPV), square wave voltammetry (SWV), anodic adsorptive square wave voltammetry (AS-SWV), linear sweep voltammetry (LSV), and chronoamperometry (CA)) were developed to determine ketoconazole, fluconazole, itraconazole, posaconazole, and terconazole. The response characteristics of the proposed sensors are shown in Table 1. By comparing the numbers of contributions on classical and electrochemical methods developed in the period 2017–2022, according to Scopus (Fig. 1) for selected antifungal azoles, a low interest in electrochemical methods can be observed.

This mini-review aims to provide the scientific community, analytical laboratories, clinicians, and authorities with a viable alternative to traditional methods of determination. With its help, they can select the right sensor for the quantification of antifungal azoles depending on the sample matrix, the interfering species present in the sample and other essential aspects.

**Electrochemical sensors used for the determination of ketoconazole.**—Saleh et al. developed a carbon paste electrode modified with gold nanoparticles (AuNPs/CPE) for ketoconazole determination in pharmaceutical products such as antifungal cream, tablets, and shampoo. The pH effect on the redox behavior of ketoconazole was studied using DPV and CV techniques and a pH-dependent process was revealed. At pH 2.00, two oxidation and two reduction peaks were observed on the CVs. When the pH ranged from 3.00 to 6.00, two oxidation and one reduction peaks were shown. Ultimately, at pH 7.00, only one oxidation peak was observed, indicating an irreversible process at the AuNPs/CPE surface. The electrooxidation of ketoconazole at AuNPs/CPE was studied using CV. The results indicate an adsorption-controlled and irreversible process. SWV measurements showed a linear concentration range of ketoconazole from 1.00 to 80.00 μmol l–1 and a limit of detection (LOD) of 0.10 μmol l–1. The sensor proved to have good stability and repeatability. Furthermore, the AuNPs/CPE was sensitive toward ketoconazole when applied in commercial pharmaceutical formulations. The recovery values obtained ranged from 94.90 to 99.67%.

Haque and collaborators prepared a nitrogen-doped carbon modified glassy carbon electrode (NDC/GCE) to detect ketoconazole from real samples. Nitrogen-doped carbon was conjugated with Nafion to disperse it into an aqueous medium, functionalize the surface of the electrode and stabilize the carbon film. The electrocatalytic activity of the NDC/GCE towards ketoconazole was studied using CV, revealing a quasi-reversible process. An enhanced electrochemical signal was obtained when compared with the bare GCE. When the effect of pH was investigated by CV, the results showed an improved electrochemical signal and good solubility and quasi-reversibility at lower pH (≤4.00). By studying the effect of the scan rate on ketoconazole oxidation, an adsorption-controlled process was confirmed. CV was used to calibrate the sensor, obtaining a linear concentration range of 47.00–752.00 μmol l–1 and a LOD of 3.00 μmol l–1. Moreover, the NDC/GCE is selective towards ketoconazole. The electrochemical behavior of potentially interfering species (such as aerosol 200, maize starch, povidone K30, lactose monohydrate, magnesium stearate, and sodium starch glycolate) was studied. The CVs revealed these molecules do not exhibit electroactive behavior in the potential range studied. The proposed sensor was applied for the determination of ketoconazole in pharmaceutical tablets, obtaining recovery and RSD values of 99.20–106.00% and 0.57 – 4.12%, respectively.

Aydar and co-authors proposed a nano-sepiolite clay modified carbon paste electrode (CCPE). AS-DPV and AS-SWV techniques were employed for calibration studies, resulting in two linear concentrations ranges of 1.00 × 10–4–1.00 × 10–3 μmol l–1 and 3.00 × 10–3–1.00 × 10–2 μmol l–1 for AS-DPV and AS-SWV, respectively. Consequently, the obtained LOD values were 1.68 × 10–5 μmol l–1 for AS-DPV and 2.48 × 10–5 μmol l–1 for AS-SWV. For interference studies, species such as Na+, K+, Mg2+, Co2+, Cu2+, Zn2+, Fe3+, ascorbic acid, glucose, lactose, glycercin, and sodium benzoate in 100-fold concentration of ketoconazole were studied. Na+, K+, Fe3+, ascorbic acid, glucose, lactose, glycercin, and sodium benzoate had an insignificant influence on the peak current. However, in the presence of Mg2+, Co2+, Cu2+, and Zn2+, the ketoconazole oxidation peak disappeared, possibly due to a complexation reaction between ketoconazole and the metals. The CCPE was successfully employed to determine ketoconazole from a shampoo sample. The recovery values ranged from 99.42 to 110.40% and the RSD values from 3.10 to 4.00%.

Silva et al. fabricated a carbon black and chitosan-stabilized gold nanoparticles modified glassy carbon electrode (CB–CTS–AuNPs/GCE) to detect ketoconazole from pharmaceutical...
| Analyte       | Electrode     | Electrochemical method | Linear concentration range (μmol l⁻¹) | Detection limit (μmol l⁻¹) | Sample matrix | References |
|--------------|---------------|------------------------|---------------------------------------|----------------------------|---------------|------------|
| Ketoconazole | AuNPs/CPE     | SWV                    | 1.00 – 80.00                          | 0.10                       | Cream         | 37         |
|              |               |                        |                                       |                            | Tablet        |            |
|              |               |                        |                                       |                            | Shampoo       |            |
| NDC/GCE      | CV            |                        | 47.00–752.00                          | 3.00                       | Tablet        | 38         |
|              | AS-DPV        |                        | 1.00 × 10⁻⁴–1.00 × 10⁻¹               | 1.68 × 10⁻⁵                | Shampoo       | 39         |
|              | AS-SWV        |                        | 3.00 × 10⁻³–1.00 × 10⁻²               | 2.48 × 10⁻⁴                |               |            |
|              |               |                        |                                       |                            | Tablet        | 40         |
|               |               |                        |                                       |                            | Cream         |            |
|               |               |                        |                                       |                            | Serum         |            |
| Fluconazole  | CILE\Fe_3O_4@PA-Ni@Pd-Cs | DPV            | 0.01–5.00                             | 3.50 × 10⁻³                | Tablet        | 41         |
|              |               |                        |                                       | 10.00–400.00              |              |            |
|              |               |                        |                                       |                            | Urine         |            |
|              |               |                        |                                       |                            | Serum         |            |
| Itraconazole | NiO-ZnO/MWCNT-COOH/GCE | DPV            | 2.50 × 10⁻²–2.20                      | 4.10 × 10⁻³                | Urine         | 42         |
|              |               |                        |                                       |                            | Serum         |            |
|              | BDDE          | SWV                    | 7.90 × 10⁻⁻²–1.20                     | 1.79 × 10⁻²                | Tap water     | 43         |
|              |               |                        |                                       |                            | River water   |            |
|              |               | AS-DPV                | 26.70–103.80                          | 12.76 × 10⁻²               | ——            | 44         |
|              |               | AS-SWV                | 1.50 × 10⁻³–0.70                      | 1.36 × 10⁻³                | Tableted      | 45         |
|              |               |                        |                                       |                            | Spiked plasma |            |
|              |               | GCE                    | 26.70–103.80                          | 27.28                      | ——            | 46         |
|              | CNTs-SPE      | LSV                    | 6.39 × 10⁻²–1.82                      | 2.11 × 10⁻²                | Pure form     | 47         |
|              |               |                        | 4.64 × 10⁻²–0.71                      | 1.53 × 10⁻²                | Spiked plasma |            |
|              |               |                        | 5.48 × 10⁻²–0.78                      | 1.81 × 10⁻²                | Dried blood spots |    |
|              | BDDE          | SWV                    | 5.70 × 10⁻²–84.40 × 10⁻²              | 7.78 × 10⁻³                | Tap water     | 43         |
|              |               |                        |                                       |                            | River water   |            |
|              | HMDE          | DPV                    | 7.13 × 10⁻³–7.13 × 10⁻²               | 2.14 × 10⁻³                | Oral suspension | 48     |
|              | O-BDDE        | DPV                    | 0.20–4.00                             | 0.40                       | ——            | 49         |
|              |               | GCE                    | 4.00–100.00                           |                            |              |            |
| Terconazole  |               |                        | 1.00–100.00                           | 0.50                       |              |            |
|              |               | PGE                    | 1.00–10.00                            | 1.23                       |              |            |
|              |               |                        | 10.00–100.00                          |                            |              |            |

AuNPs/CPE = gold nanoparticles modified carbon paste electrode.
NDC/GCE = nitrogen-doped carbon modified glassy carbon electrode.
CCPE = nano-sepiolite clay modified carbon paste electrode.
CB–CTS–AuNPs/GCE = carbon black and chitosan-stabilized gold nanoparticles modified glassy carbon electrode.
CILE\Fe_3O_4@PA-Ni@Pd-Cs = chitosan and Ni@Pd core–shell nanoparticles immobilized on Fe_3O_4@polyaniline yolk-shell composites modified carbon ionic liquid electrode.
NiO-ZnO/MWCNT-COOH/GCE = carboxylated multiwalled carbon nanotubes and NiO-ZnO composite modified glassy carbon electrode.
BDDE = boron-doped diamond electrode.
AgNPsΔGO@GCE = silver nanoparticles-decorated graphene oxide nanocomposite modified glassy carbon electrode.
SDS-GR/CPE = sodium dodecyl sulfate modified graphene-carbon paste electrode.
GCE = glassy carbon electrode.
CNTs-SPE = multi-walled carbon nanotubes modified screen-printed electrode.
HMDE = hanging mercury drop electrode.
O-BDDE = oxygen terminated boron-doped diamond electrode.
PGE = pyrolytic graphite electrode.
formulations and biological samples. An irreversible redox process controlled by diffusion was revealed when the oxidation of ketoconazole was studied at CB–CTS–AuNP/GCE using CV. Using SWV, a linear concentration range of 0.10 to 2.90 μmol l⁻¹ and a LOD of 4.40 × 10⁻³ μmol l⁻¹ ketoconazole were obtained. The calculated sensitivity value of the proposed sensor was 3.60 μA L⁻¹ μmol⁻¹. Interference studies were carried out employing SWV in 1:1 and 1:10 ketoconazole solutions containing microcrystalline cellulose, lactose monohydrate, magnesium stearate, and crospovidone. The results indicated these species did not interfere with ketoconazole’s determination. The applicability of the sensor was studied in pharmaceutical samples (tablet and cream) and synthetic biological samples (urine and serum). For the pharmaceutical formulations, the results were compared with UV–vis spectrophotometry, obtaining errors of 10.30% and 3.80%. The recovery values for the biological samples ranged from 106.00 to 109.00%. 40

A number of voltammetric sensors were proposed for the analysis of ketoconazole. Comparing the response characteristics obtained using the proposed sensors for the assay of ketoconazole, 37–40 the lowest limit of detection was achieved by the sensor based on CCPE, when the AS-DPV was used; the linear concentration ranges are not wide for any of the proposed sensors. High sensitivity and selectivity are needed, as well as for samples from environment such as water analysis, there is a real need of low limits of determination to be able to determine it with high precision.

Electrochemical sensors used for the determination of fluconazole.—Zad and collaborators 41 developed a carbon ionic liquid electrode modified with chitosan and Ni@Pd core–shell nanoparticles immobilized on Fe₃O₄@polyaniline yolk-shell composites (CILEFe₃O₄@PA-Ni@Pd-Cs) for the determination of fluconazole in pharmaceutical tablets and biological samples (urine and serum). CV was used to investigate the effect of pH and scan rate on the electrochemical response of fluconazole at the proposed sensor. The obtained results suggest the oxidation of fluconazole is a diffusion-controlled one-electron transfer process. The calibration of the sensor was performed using DPV and CA methods. Two linear concentration ranges were obtained with DPV, one from 0.01 to 5.00 μmol l⁻¹ and another one from 10.00 to 400.00 μmol l⁻¹, and a LOD of 3.50 × 10⁻³ μmol l⁻¹. For CA, the linear concentration range was between 0.25 and 345.37 μmol l⁻¹ with a LOD of 0.08 μmol l⁻¹.

For interference studies, the influence of species like K⁺, Na⁺, Ca²⁺, NH₄⁺, Mg²⁺ in 500-fold excess, phenol, hydroquinone, p-nitrophenol, 2,4-dinitrophenol in 150-fold excess, and histidine, aspartic acid, glucose, and urea in 100-fold excess was analyzed. The measurements revealed none of these species interfered in the determination of fluconazole, proving the CILEFe₃O₄@PA-Ni@Pd-Cs has a good selectivity towards fluconazole. When applied in real samples, the recovery values obtained ranged from 96.40 to 102.10% and the RSD ranged from 1.17 to 3.10%. 41 Although, fluconazole is widely used in treatments, only this electrochemical method of analysis was developed for the searched period; therefore more highly sensitive and highly selective methods of analysis must be developed for this active substance.

Electrochemical sensors used for the determination of itraconazole.—Chen et al. 42 produced a glassy carbon electrode modified with carboxylated multi-walled carbon nanotubes and NiO-ZnO composite (NiO-ZnO/MWCNT-COOH/GCE) for imatinib and itraconazole simultaneous determination from biological samples (human urine and serum). When studying the effect of pH and scan rate on the itraconazole redox process using CV, it was observed the reaction reaction is an irreversible adsorption-controlled process that involves two electrons and one proton. The linear concentration range of itraconazole recorded using DPV was 2.50 × 10⁻²–2.20 μmol l⁻¹ with a LOD of 4.10 × 10⁻³ μmol l⁻¹. Species such as 120-fold excess glucose, 100-fold excess ascorbic acid, uric acid, dopamine, lysine, serine, valine, and 25-fold excess Na⁺, K⁺, Cl⁻, Ca²⁺, Mg²⁺, and bovine serum albumin did not interfere with the simultaneous determination of the two analytes. When applied in real samples, the obtained recovery and RSD values were in the range 97.00–101.00% and 2.10–3.20%, respectively. 42

Mielech–Łukasiewicz and Starczewska 43 used a boron-doped diamond electrode (BDDE) to determine itraconazole from water samples (tap and river water). By studying the effect of pH and scan rate on the itraconazole oxidation using CV it was revealed the reaction is a mixed diffusion and adsorption process that involves one electron. The analytical curve was determined using the SWV

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**Figure 1.** Schematic representation of contributions on classical and electrochemical methods developed in the period 2017–2022, according to Scopus.
that the current potential has not shifted significantly. The measurements have also revealed that the itraconazole using CV showed two current peaks at pH 2. A linear concentration range of 1.50 μmol l⁻¹ and a LOD of 1.79 × 10⁻² μmol l⁻¹ was used to carry out the sensor calibration, obtaining a linear concentration range of 2.60–103.80 μmol l⁻¹ and a 12.76 × 10⁻² μmol l⁻¹ LOD.

El-Desoky and Khattab developed a sodium dodecyl sulfate modified graphene-carbon paste electrode (SDS-GR/CPE) for itraconazole determination in pharmaceutical formulation and human plasma samples. Evaluation of the effect of pH on the oxidation of itraconazole using CV showed two current peaks at pH = 2.00 that gradually decrease and eventually disappear completely at pH values greater than 5.00. The measurements have also revealed that the current potential has not shifted significantly, indicating a process that doesn’t involve any proton. By investigating the effect of the scan rate on the process at the electrode surface it was observed that the first peak corresponds to a diffusion-controlled process while the second, the main peak, indicates an adsorption-controlled process. The total number of electrons involved in the process was calculated to be 2. A linear concentration range of 1.50 × 10⁻² to 0.70 μmol l⁻¹ and a LOD of 1.36 × 10⁻³ μmol l⁻¹ were obtained using the AS-SWV method. For the interference studies, species such as metal ions (Ca²⁺, Mg²⁺, Fe³⁺, Zn²⁺, Cd²⁺, Pb²⁺), vitamins (A, C and E), other drugs (ibuprofen, ketoprofen, and ketorolac) and uric acid were selected. The results showed no interference on the determination of itraconazole in presence of 1400-fold metal ions, 1000-fold vitamins A and E and other drugs, 800-fold vitamin C and 600-fold uric acid. The sensor was applied to determine itraconazole from tablets obtaining recovery values in the range 98.30–101.25% and RSD below 2.50%. When applied in spiked human plasma, recovery values between 98.85 and 101.13% and RSD below 2.50% were recorded.

Jakhar and Sharma used a glassy carbon electrode (GCE) to determine itraconazole. The effect of pH and scan rate on the redox reaction of itraconazole at GCE was studied using CV. The results showed an irreversible adsorption-controlled process involving 2 electrons and one proton. AS- DPV and AS-SWV techniques were used to validate the analytical process, thus obtaining two linear concentration ranges and LODs: 26.70–103.80 μmol l⁻¹ and a 27.28 μmol l⁻¹ LOD for AS-DPV and 26.70–152.80 μmol l⁻¹ and a 33.82 μmol l⁻¹ LOD for AS-SWV.

In the case of the assay of itraconazole, the sensor based on SDS-GR/CPE showed the lowest detection limit; the linear concentration range was of maximum two decades of concentration. Widening the linear concentration range will facilitate determination of itraconazole from different types of samples. From environment (water analysis) to pharmaceutical samples (different formulations containing a variety of dosages of itraconazole), to more complex types of samples such as biological samples. Also, there is a need in lowering the limit of determination of itraconazole, needed especially for its analysis in biological samples and in water samples.

**Electrochemical sensors used for the determination of posaconazole.**—Hassan and collaborators fabricated a multi-wall carbon nanotube modified screen-printed electrode (CNTs-SPE) for posaconazole determination in pharmaceutical dosage forms and biological samples. By studying the effect of scan rate on the redox reaction using CV, a diffusion with a weak adsorption-controlled irreversible process was revealed. The analytical performances of the sensor were studied using LSV on pure form posaconazole, spiked plasma, and dried blood spots, obtaining the following linear concentration ranges and LODs: 6.39 × 10⁻¹ to 8.82 μmol l⁻¹ and a LOD of 2.11 × 10⁻² μmol l⁻¹ for posaconazole pure form; 4.64 × 10⁻³ to 0.71 μmol l⁻¹ and a LOD of 1.53 × 10⁻² μmol l⁻¹ for spiked plasma; 5.48 × 10⁻² to 0.78 μmol l⁻¹ and a LOD of 1.81 × 10⁻² μmol l⁻¹ for dried blood spots. The study of the electrochemical behavior of other antifungal agents (such as sertaconazole, ketoconazole, voriconazole, oxiconazole, clotrimazole, miconazole, isocarnazole, tindazole, itraconazole, and luliconazole) indicate no significant potential interaction on the posaconazole determination at CNTs-SPE. The analytical applications of the proposed sensor were tested on posaconazole pure form, pharmaceutical dosage form (suspension), and biological samples (plasma and dried blood spots), obtaining mean recovery values of 100.37 ± 0.75% for the pure form, 99.31 ± 0.77% for dosage form, 94.39 ± 3.25% for plasma, and 87.96 ± 4.00% for dried blood spots. Moreover, the sensor was successfully applied for pharmacokinetic studies of posaconazole biological samples.

Mielech-Lukasiewicz and Starczewska used a BDDE for posaconazole determination from water samples. pH and scan rate effect studies carried out using CV indicate an irreversible diffusion-controlled process involving one electron. SWV technique was selected to investigate the analytical performances of the sensor, obtaining a linear concentration range from 5.70 × 10⁻² to 84.40 × 10⁻² μmol l⁻¹ and a LOD of 7.78 × 10⁻³ μmol l⁻¹. The following species were used for the interference studies in concentrations of 10-fold, 50-fold, 100-fold, and 500-fold excess: Na⁺, K⁺, Cu²⁺, Ca²⁺, Fe³⁺, Mg²⁺, Cd²⁺, Zn²⁺, Pb²⁺, Cl⁻, SO₄²⁻, NO₃⁻, Triton X-100, sodium dodecyl sulfate, tetrabutylammonium bromide, and methylparaben did not interfere with the determination of posaconazole. The results showed that 100-fold excess of Fe²⁺, Cu²⁺, and over 100-fold excess of Triton X-100, sodium dodecyl sulfate, tetrabutylammonium bromide, and methylparaben interfere with the determination of posaconazole. Similarly, 5-fold excess of triclosan and ketoconazole interfere with the analysis. However, clotrimazole and voriconazole did not interfere, as their oxidation peaks are outside the potential range selected in the study. The analysis of water samples (tap and river water) provided recovery values in the range 94.00–102.80% with RSD values below 3.60%.

Khalil et al. used a hanging mercury drop electrode (HMDE) for the analysis of posaconazole from a pharmaceutical oral suspension sample. The reduction of posaconazole was studied using CV and the results indicate an irreversible process. The analytical performances of the sensor were carried out using DPV, obtaining a linear concentration range of 7.13 × 10⁻³–7.13 × 10⁻² μmol l⁻¹ and a LOD of 2.14 × 10⁻³ μmol l⁻¹. The HMDE was applied for posaconazole determination in a pharmaceutical sample, obtaining a recovery value of 100.80% and an RSD of 1.36%.

The lowest limit of detection was achieved for the assay of posaconazole by using the sensor based on HMDE, although the wider linear concentration range was achieved by the sensor based on CNTs-SPE. There is a need to develop more sensitive electrochemical sensors, presenting also a wider linear concentration range.
μ two linear concentration ranges were obtained, one from 0.20 to 4.00 μmol l⁻¹ with a LOD 1.23 μmol l⁻¹ LOD. The best limits of detection for the assay of terconazole were achieved using the sensors based on O-BDDE and GCE, with the widest linear concentration range given by the sensor based on O-BDDE. In this case there is a need to develop new electrochemical sensors for the assay of terconazole with higher selectivity, and sensitivity, and wider linear concentration range.

Electrochemical methods vs. chromatographic methods developed for the assay of ketoconazole, fluconazole, itraconazole, posaconazole, and terconazole.—Development of electrochemical methods for analysis of pharmaceutical compounds facilitated always cost-effective analysis of the active substance, as well as fast determinations with a minimum sampling, namely buffering and/or sample dissolution in water or an organic solvent to facilitate the analysis. Also, the electrochemical instrumentation is easy to use. Table II provides a comparison of the response characteristics obtained using chromatographic methods of analysis (classical methods of analysis) and electrochemical methods, in terms of linear concentration range and LOD.

Table II shown the advantages of using electrochemical methods of analysis also in terms of LOD and linear concentration range: lower limits of detection were obtained using the electrochemical sensors, and electrochemical sensors facilitated determinations of ketoconazole, fluconazole, itraconazole, posaconazole, and terconazole at lower concentrations than the chromatographic methods of analysis.

Future perspectives for electrochemical sensors utilization in electroanalysis of antifungal azoles.—While between 2017 and 2022 there was a limited number of papers published for some of the antifungal azoles (fluconazole, itraconazole, posaconazole, terconazole) based pharmaceutical compounds, all presenting limited working concentration ranges, and sometimes high limits of determination, and low selectivity, there is a real need to further develop electroanalytical methods of analysis based on highly reliable sensors, able to be used on wider linear concentration ranges. Increasing the number of electroanalytical methods of analysis from classical methods of electroanalysis to modern ones (e.g., stochastic sensing) is a need. Avoid cross-contamination by using screen-printing disposable sensors will facilitate determination of antifungal azoles in the environment is a need. Development of intelligent sensors as described by Chandhary et al. and of intelligent measurement systems as described by Osman et al. will facilitate automatically control of fabrication lines of antifungalazole drugs, and also their automatically detection in the environment. While electrochemical sensors were widely used for the assay of vitamins, and profen drugs, one should increase the number of sensors and electrochemical methods able to facilitate fast, reliable determination of azole based antifungal active compounds in different matrices, e.g., pharmaceutical compounds, biological samples, and environment (e.g., water).

Conclusions

The sensors discussed in this work represent reliable determination methods for antifungal azoles. Most of them were successfully used in various sample matrices, which demonstrates their potential applicability to larger scales, from drug quality control to pharmacokinetic studies and environmental monitoring. Very low detection limits were observed for most of the proposed sensors. The linear concentration range needs improvement for the assay of antifungal azoles to cover from trace amounts to high amounts that may be found in pharmaceutical formulations, cosmetics, biological samples as well as in the environment.

Acknowledgments

This work was supported by a grant of the Ministry of Research, Innovation and Digitization, CNCS/CCCDI—UEFISCDI, project number PN-III-P4-ID-PCE-2020-0059, within PNCDI III.

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