Modified Screen-Printed Microchip for Potentiometric Detection of Terbinafine Drugs

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1. Introduction

Terbinafine represents one of the most commonly prescribed medications in the United States, with more than one million prescriptions. It is a synthetic antifungal medication that mainly fights infections caused by fungus that affect the toenails or fingernails. It is generally taken by the mouth or applied to the skin as an ointment or cream. Chemically, terbinafine’s (C_{21}H_{25}N) name is [(2E)-6,6-dimethylehept-2-en-4-yn-1-yl] (methyl) (naphthalen-1-ylmethyl) amine. It belongs to allyl amine derivatives, which provide broad-spectrum activity against dimorphic fungi, yeasts, dermatophytes, and molds. It is slightly soluble in water but soluble in methanol, ethanol, and methylene chloride. Terbinafine leads to the death of fungal and bacterial cells based on its selective inhibition of the growth of thier cell wall. It is highly lipophilic in nature and tends to accumulate in nails, fatty tissues, and skin.

Based on its therapeutic importance, precise and accurate quantification of terbinafine in human fluids and pharmaceutical formulations is of considerable significance. Several methods have been recently reported for the quantitative determination of terbinafine in different pharmaceutical and real biological samples. Back volumetric titration with sodium hydroxide using potentiometric end point detection and reversed phase HPLC have been reported for the official quantifications of terbinafine in British and American pharmacopeia, respectively [1]. Other than official methods, titration with perchloric acid in acetic acid media [1] and different chromatographic techniques [1–10] have also been reported for the determination of terbinafine.
Spectrophotometric methods (UV-visible) [1, 11, 12], spectrofluorimetric [1, 13], electroanalytical methods [1, 14, 15], capillary electrophoresis [1, 16], and cylinder-plate based microbiological assay [1, 17] have also been reported for terbinafine determination.

To the best of our knowledge, so far, no potentiometric microchips have been reported for the determination of terbinafine drugs in pharmaceutical formulations. However, the development of miniaturized microchips has widespread and growing interest in manufacturing potentiometric sensors with extremely valuable modifying response characteristics as well [18–22]. The microfabrication of miniaturized potentiometric screen-printed microchips represents an important challenge in the expanding field of modern analytical tools [23–26] due to their mass production, integration, and automation feasibility. Such potentiometric microsensors have the advantages of small size, a wide range of applications, high reproducibility, good accuracy, and a small sample volume [27–30].

The objective of this work was to develop a precise, accurate, simple, fast, and reliable screen-printed microchip, which would serve as a potentiometric quantification method for terbinafine in its pharmaceutical formulations. This paper, consequently, describes microfabrication, potentiometric characterization, and analytical application of terbinafine based on potentiometric screen-printed microsensors modified by multiwall carbon nanotubes (MWCNTs). Based on our previous work, a combination of the screen-printed platform substrate with modification of the sensitive element with MWCNTs and the nebulization process of the cocktail coating mixture recently developed results in superior potentiometric response parameters in terms of sensitivity, selectivity, credibility, and versatile applicability [19, 21, 25, 27]. Realization of such microdevices generates new generations of useful and promising microchip sensors for the detection of drugs and biological species from different real samples with high accuracy and precision.

2. Experiment

2.1. Chemicals and Reagents. All the used materials and reagents were of analytical reagent grade, unless otherwise stated. Moreover, double-distilled water obtained from a POLNA water distiller (MERA, Zaklady Automatyki, Poland, 1 MΩ-cm) was used for rinsing the glassware and for the preparation of reagents throughout. All chemicals used in different studies were of analytical reagent grade and purchased from Sigma Aldrich (UK), PubChem (USA), and Merck (USA). The used microelectrode substrates were screen-printed plastic microchips comprising a working carbon electrode (0.25 mm PET, 3 mm/6 mm in diameter, and graphene-modified SPE) and purchased from Suzhou Delta-Biotech (Ltd, China). Purified multiwall carbon nanotubes (MWCNs, id: 5–12 nm, od: 30–50 nm, length: 10–20 μm, and purity: >95%) were obtained from the Chengdu Organic Chemicals Company “COCC,” China. Terbinafine raw material (purity: 99.6%) was a gift supplied by the Egyptian Drug Authority, EDA. Terbinafine drugs with different formulations were collected from local pharmaceutical stores and used in the application studies of the microchip.

2.2. Instrumentation. Electrochemical characterization measurements were carried out at room temperature using an Orion (model 720) pH/mV meter and a Lab companion HP-3000L magnetic stirrer. An Orion (model 9172) combination pH electrode was used for all pH experiments. Microsensor based on “terbinafine: ammonium heptamolybdate” as ion pair complex, carbon nanotubes as modifier, and screen-printed microchip as support, was used as working electrode sensitive for Terbinafine. This micro-electrode was applied in conjunction with an Orion single junction reference electrode for all potentiometric measurements.

2.3. Synthesis of the Sensitive Membrane Layer. The sensitive layer mixture was prepared for each assembly by thoroughly mixing the potassium tetrakis (4-chlorophenyl) borate anion excluder, plasticised ionophore (terbinafine: ammonium heptamolybdate ion pair complex, carbon nanotube composite), and poly (vinyl chloride) support in tetrahydrofuran (THF) as a solvent in a small beaker. Before being used as a sensitive membrane coat, the cocktail coating mixture was then transferred into a homemade manual small nebulizer and sonicated for 2 h.

2.4. Screen-Printed Terbinafine Microchip. The microfabrication of the disposable plastic screen-printed electrode integrated with the organic membrane sensitive layer was reported using a cost-effective, fast, and simple new approach [19, 21, 23], as described in our previous projects. In this technique, plastic disposable screen-printed microchips (Figure 1) were rinsed in double-distilled water and left to dry in the air at room temperature before being used as electrode substrates in all microchip assemblies. Two assemblies of the microchip containing different constituents of the sensitive membrane, as summarized in Table 1, were fabricated and examined as terbinafine potentiometric microsensors. The metal contacts of the screen-printed microchip substrate were properly covered using tissue paper before the deposition of the sensitive layer. In a fume hood, small aliquots (few microlitre) of the organic membrane sensitive layer were nebulized successively onto the surface of screen-printed microchips for a few seconds. After each successive nebulization step, the very thin layer of the sensitive membrane deposited on the surface of the chip substrate was then left in the air for 2–3 min for solvent volatilization. Nebulization steps were successively repeated several times until a uniform layer of the organic membrane sensitive coat covering the substrate surface was obtained. To spread out nanoparticles, the cocktail coating sensitive mixture was sonicated for 2 h. The cocktail coating sensitive mixture was sonicated for 2 h. The cocktail coating sensitive mixture was sonicated for 2 h. The cocktail coating sensitive mixture was sonicated for 2 h. The cocktail coating sensitive mixture was sonicated for 2 h. The cocktail coating sensitive mixture was sonicated for 2 h. The cocktail coating sensitive mixture was sonicated for 2 h. The cocktail coating sensitive mixture was sonicated for 2 h. The cocktail coating sensitive mixture was sonicated for 2 h. The cocktail coating sensitive mixture was sonicated for 2 h.
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| Ionophore composite, 14 mg CNTs (%) | ONPOE (mg) | PVC (mg) |
|-----------------------------------|------------|----------|
| 5                                 | 95         | 114      | 66       |

3. Results and Discussion

3.1. Electrochemical Characterization of Terbinafine Microchips. The terbinafine screen-printed microchip modified with MWCNTs was realized using a simple, fast, and cheap approach, which has been recently developed [19, 21]. It was found that the modification of the sensitive membrane layer of the potentiometric microchip-based electrodes with MWCNTs significantly improved the performance properties of the chip due to unique electronic and mechanical properties of carbon nanotubes [25, 27]. MWCNT materials possess a greater surface area, excellent biocompatibility, and facilitate redox reactions with rapid electron-transfer rates, and consequently, they are significantly used in the development of electrochemical microsensors [19, 21, 25, 27]. The performance characteristics including sensitivity, selectivity, response time, detection limit, the effect of pH, and the linear range of the elaborated new microsensor modified with MWCNTs were measured using the microfabricated assembly according to the IUPAC recommendations.

Prior to the microfabrication of the chip assembly, the chemical structure of the prepared terbinafine: ammonium heptamolybdiate ion pair complex was analysed using FTIR spectroscopy. The results obtained for the ion pair (spectra a) and for the terbinafine drug (spectra b) are presented in Figure 3. As can be seen, new peaks appear at 3450 cm⁻¹ and 951 cm⁻¹ in curve “a” (ion pair spectra) when compared with curve “b” (drug spectra). These peaks are the characteristic absorption peaks of N-H groups in the quaternary ammonium ion derivative. The FTIR spectra showed that the functional groups of the synthesis product correspond to the terbinafine ion pair, which confirms the formation of the proposed ionophore ion pair complex.
To evaluate the analytical performance of the elaborated microchip of the terbinafine drug, the potential of the designed assembly was recorded after successive immersion in different concentrations of terbinafine from 10^{-9}–10^{-2} mole·L^{-1}, and the obtained calibration graph is presented in Figure 4. The calibration plot showed that the linear detection response covers the range from 10^{-8}–10^{-2} mole·L^{-1}, with a Nernstian sensitivity of 58.5 ± 0.5 mV/concentration decade and a detection limit of 5×10^{-9} mole·L^{-1}.

The response time defined as the time needed by the chip assembly to achieve a stable potential was found to be less than (30 s) over all calibration graph. This study was conducted by successive immersing of the chip assembly in a series of terbinafine concentration from 10^{-9}–10^{-2} mole·L^{-1} starting from low to high concentration. The time required for the chip to reach the steady potential within ±1 mV from its final value was recorded, and the results obtained are presented in Figure 5. As can be seen, the chip quickly (≤30 s) reached its equilibrium response in the whole tested terbinafine concentration range. Moreover, the potential values of the dynamic response revealed that linear Nernstian behavior covers the terbinafine concentration range of the calibration plot. These emphasized the reliability, credibility, and repeatability of the realized chip for accurate and precise quantification of terbinafine drugs.

The long-term stability of the elaborated terbinafine microchip was determined by frequent calibration of the assembly, and the performance parameters of the chip were collected after each calibration. These studies revealed that the lifetime of the realized terbinafine chip was more than 4 months. During this period, performance parameters are almost the same without any significant changes, and these findings are in good agreement with those obtained for similar screen-printed microchips fabricated by the same methodology [19, 21, 25, 27].

To examine the influence of pH on the chip response, the potential of the assembly was detected at two different concentrations of terbinafine solutions (1 × 10^{-5} and 1 × 10^{-4} mole·L^{-1}) from a pH value of 4.5 up to 9.5. In this study, small aliquots of concentrated solutions of sodium hydroxide and nitric acid were utilized in pH adjustment, and the results obtained are presented in Figure 6. The results obtained revealed that the potential of the chip was not affected by change in pH of the test solution in the pH range of 7–9, and consequently, tris-HCl buffer (1 mole·L^{-1} and pH
8) was used in the characterization studies of the terbinafine microchip. The potential of the terbinafine microchip provided higher and lower response below and above this range, which attributes to protonation of the drug at lower pH values and degradation of the ion pair sensitive material at higher pH values, respectively.

Basically, selectivity is the most important parameter of sensor characteristics, which determine the specificity of the primary investigated ion in the presence of interfering ions. It is the relative response of the proposed sensor for principal ions over other interfering ions present in solution. Therefore, the potentiometric selectivity coefficient of the terbinafine microchip was determined using a separate solution method (SSM) [14] by separate calibration for terbinafine as well as all studied interfering ions in the concentration range of $10^{-9} - 10^{-2}$, as presented in Figure 7. The values of the selectivity coefficient for all studied interfering species were calculated, and the results obtained are summarized in Table 2. The selectivity coefficient values of the microsensor confirmed that the elaborated microchip offered very high selectivity for terbinafine drugs in the presence of many investigated interfering ions. This
Table 2: Selectivity coefficients of the terbinafine microchip in the presence of interfering ions.

| Interfering ions       | \( \log(K_{\text{pot,}j}^{\text{Ter}}) \) |
|------------------------|-----------------------------------------|
| Potassium hydrogen tartrate | 6.1                                      |
| Potassium hydrogen phthalate | 2.2                                      |
| Sodium salicylate       | 6.25                                     |
| Sodium acetate          | 2.1                                      |
| Sodium L-glutamate      | 2.8                                      |
| Sodium succinate        | 4.9                                      |
| Sodium nitrate          | 4.6                                      |
| Sodium phosphate        | 4.9                                      |
| Sodium carbonate        | 4.8                                      |
| Sodium chromate         | 4.8                                      |
| Sodium sulphate         | 5.2                                      |
| Bidistilled water       | -250                                     |
| Tris-HCl, pH=8          | -200                                     |
| -150                    | -100                                     |
| -50                     | 0                                        |
| 50                      | 100                                      |
| 150                     |                                          |

Figure 8: The layer effect study on the response of the terbinafine microchip from \(10^{-5}\) mole-L\(^{-1}\) terbinafine in bi-distilled water and tris-HCl buffer, pH 8.

Table 3: Terbinafine microchip potentiometric parameters.

| Parameters                           | Terbinafine chip | Ion selective electrode | Membrane sensor |
|--------------------------------------|------------------|-------------------------|-----------------|
| Electrode phase                      | Microchip        | Bulk electrode          | Bulk electrode  |
| Linear range (mole-L\(^{-1}\))      | \(10^{-6} - 10^{-2}\) | \(10^{-7} - 10^{-2}\)  | \(7 \times 10^{-6} - 10^{-2}\) |
| Slope (mV/decade)                    | 58.5 ± 0.5       | 56.99–59.06             | 57.8            |
| Detection limit (mole-L\(^{-1}\))   | \(5 \times 10^{-9}\) | \(1 \times 10^{-7}\)  | \(6.5 \times 10^{-6}\) |
| Lower limit of the linear range (mole-L\(^{-1}\)) | \(1 \times 10^{-8}\) | \(1 \times 10^{-7}\) | \(7 \times 10^{-6}\) |
| pH range                             | 7–9              | 3–9                     | 3–6             |
| Lifetime (months)                    | ≥4               | 5.5                     | 1.5             |
| Response time (s)                    | ≤30              | 9                       | 15              |

Table 4: Quantification of terbinafine in drug formulations and spiked urine (RSD, <3%).

| No | Sample                        | Lamifen | Terbin |
|----|-------------------------------|---------|--------|
| 1  | Bi-distilled water            | 97.8    | 98.4   |
| 2  | Tris-HCl, 1 mole-L\(^{-1}\), pH 8 | 96.0    | 95.0   |
| 3  | Spiked urine                  | 97.0    | 97.3   |
|    | Average recovery              |         | 96.9   |
indicates that interfering ions have extremely low permeability through the sensitive membrane fabricated for terbinafine drug primary ions, and they would not significantly disturb the response of the realized terbinafine chip assembly.

To investigate the influence of the water layer effect on the response of the realized microsensor, the potentiometric water layer test of the terbinafine microchip assembly was performed by recording the potential of the chip versus time intervals after successive immersing of the chip in blank (water and tris-HCl buffer) solution followed by immersing the chip in 10⁻⁵ mole L⁻¹ of terbinafine prepared in bidistilled water and tris-HCl buffer, respectively. The results obtained, which are presented in Figure 8, revealed a lack of potential drift of the microchip response. The microsensor showed stable behavior, fast equilibrium, and consequently high stability and reliability of the realized terbinafine microchip assembly. These findings were attributed to the microfabrication methodology of the chip assembly which was based on the nebulization approach and recently developed [19, 21].

The performance response parameters of the realized terbinafine microchip assembly in comparison with the bulk electrodes published are summarized in Table 3. It should be noted that the performance properties (slope, detection limit, and linear range) of the chip are better than those reported for terbinafine bulk electrodes [14, 15]. This behavior is attributed to the incorporation of the MWCNTs into the sensitive element, which improves the conductivity of the sensor, increases the transduction of the chemical signal to the electrical signal, and therefore increases the sensitivity of electrodes [19, 21]. Moreover, the realized terbinafine microchip assembly provided small size, miniaturization, integration, and automation feasibility.

3.2. Analytical Applications of the Terbinafine Microchip. The elaborated microchip assembly has been successfully used in the determination of terbinafine in some real samples of drug formulations (Terbin 250 mg and Lamifen 250 mg) and in spiked urine as well. In this study, five tablets of each drug formulation were dissolved and treated as reported in our previous work [21]. Drug concentrations were measured using the calibration method, and three replicate measurements were used for each analysis. The accuracy of the proposed method was determined, and the results obtained are collected in Table 4. The proposed method can therefore be applied to the quantification of terbinafine in its drug formulations and biological real samples with an accuracy of 96.9% and without fear of interferences caused by excipients expected to be present in drug formulations or the constituents of urine.

4. Conclusions

Microfabrication, electrochemical characterization, and analytical applications of the terbinafine drug microchip assembly have been demonstrated. In comparison with the published terbinafine electrodes, the realized chip showed advanced performance parameters with a fast response time (≤30 s), low detection limit (5 × 10⁻⁹ mole L⁻¹), Nernstian behavior (58.5 ± 0.5 mV/decade) covering the linear range of 10⁻⁸–10⁻⁵ mole L⁻¹, and relatively long-life span ≥4 months. The elaborated chip has been successfully applied to the quantification of terbinafine in some drug formulations and spiked urine. The analytical method based on the realized chip assembly approved to be a simple, fast, cheap, precise, and accurate method of analysis of terbinafine. In addition, the merits offered by the realized terbinafine microchip assembly include small size, miniaturization, integration, and automation feasibility.

Data Availability
No additional data were used to support the study.

Conflicts of Interest
The authors declare that there are no conflicts of interest with regards to this work.

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