Hindawi
Journal of Chemistry
Volume 2022, Article ID 9114162, 8 pages
https://doi.org/10.1155/2022/9114162

Research Article

Modified Screen-Printed Microchip for Potentiometric Detection of Terbinafine Drugs

Menna El-Beshlawy[1] and Hassan Arida[2]

[1]*Department of Chemistry, Faculty of Women, Ain Shams University, Cairo, Egypt*
[2]*Department of Pharmaceutical Chemistry, College of Pharmacy, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia*

Correspondence should be addressed to Hassan Arida; aridaha@hotmail.com

Received 16 August 2022; Revised 10 November 2022; Accepted 15 November 2022; Published 22 November 2022

Academic Editor: Mahmood Ahmed

The development of miniaturized microchips has widespread and growing interest in manufacturing potentiometric sensors with extremely valuable modifying response characteristics. In this context, here, we demonstrate microfabrication, electrochemical evaluation, and analytical applications of disposable thin-film potentiometric microsensors responsive to terbinafine antifungal medication. Miniaturized microchips have been realized by integration of the sensitive layer membrane modified by carbon nanotubes onto the surface of the plastic screen-printed microchip support using a new approach, which has been recently developed. The sensitive membrane comprises terbinafine HCl: ammonium heptamolybdate complex ion pair as ionophore, o-nitrophenyl octyl ether as a solvent mediator, potassium tetrakis (4-chlorophenyl) borate as an anion excluder, and polyvinyl chloride as support. The microsensor based on this plasticised sensitive membrane provides the Nernstian response and covers a wide concentration range of terbinafine of 10^{-8}–10^{-2} mole·L^{-1}. The merits offered by the elaborated terbinafine microchip over the bulk-based electrode include reasonable sensitivity (58.5 mV/concentration decade), fast response time (~30 s.), long-term stability (4 months), integration, and automation feasibility. Furthermore, microfabricated terbinafine chips were successfully applied to the measurements of the investigated medication in some real samples with high accuracy (96.9%) and precision (<3%).

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-dimethylhept-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, 1.0 $M\Omega \cdot cm^{-1}$) 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 91-72) 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 microelectrode 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, were fabricated and examined as terbinafine potentiometric microsensors. The metal

Figure 1: The photographic picture of the screen-printed microchip assembly.

Table 1: Sensitive layer composition of the terbinafine microchip assembly.

Ionophore composite, 14 mg		ONPOE (mg)	PVC (mg)
CNTs (%)	Ionophore (%)		
5	95	114	66

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 prior the nebulization process and for 3, 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 prior the nebulization process and for 3, 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 prior the nebulization process and for 3 min between the successive nebulization steps, to spread out the nanoparticles. The microfabricated chip assembly was used in the characterization and application studies of terbinafine analysis. Prior measurements, the microchip assemblies were soaked in 10^{-2} mole·L^{-1} terbinafine solution for one hour. In addition, the chips were store dry in air when not in use.

A cocktail coating mixture containing the nanocomposite sensitive element was deposited on the surface of a thin-film screen-printed plastic microchip substrate using the nebulization methodology, which has been recently developed (Figure 2). Prior to the deposition of the sensitive layer, the surface of the thin-film gold microchip substrate was treated chemically and electrochemically, respectively. The realized microchip was used as a working electrode in conjunction with a Ag/AgCl commercial reference electrode in potentiometric measurements. The potentiometric characterization and analytical application studies of the terbinafine microsensor assembly were performed according to the IUPAC recommendation.

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 heptamolybdate 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.

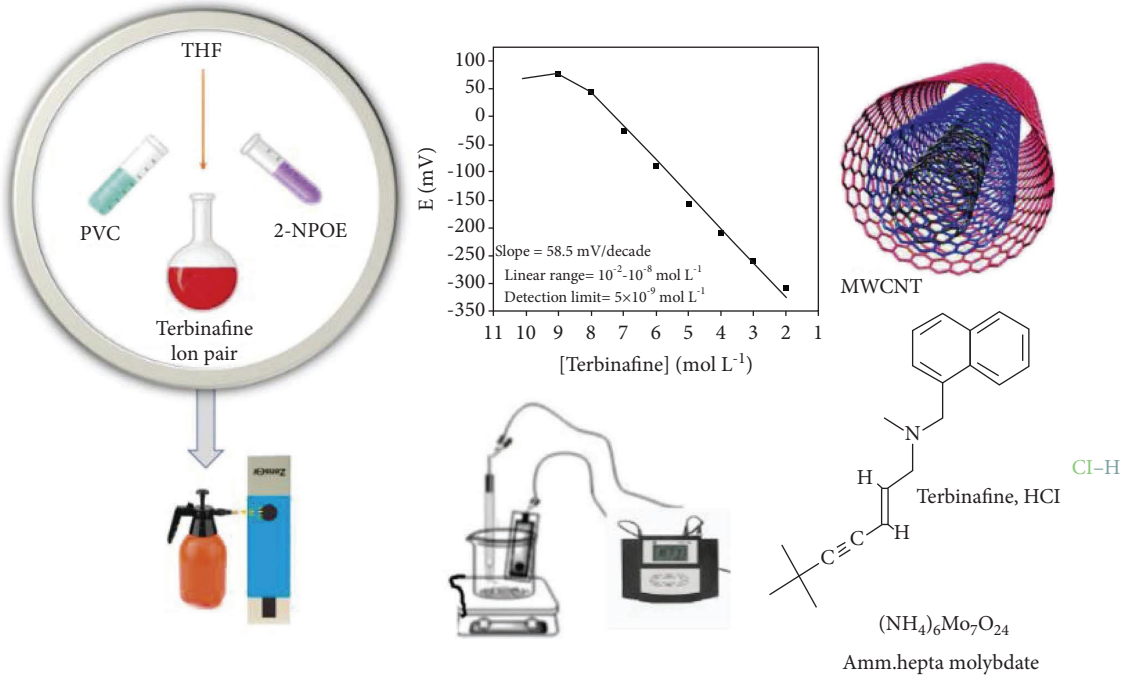

Figure 2: Representative illustration for the microchip fabrication process.

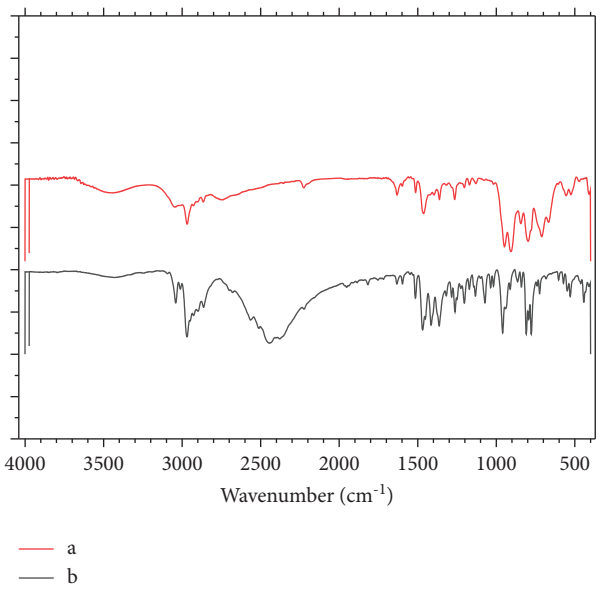

Figure 3: FTIR spectra terbinafine: ammonium heptamolybdate ion pair (a) and terbinafine drug (b).

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^{-10}–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

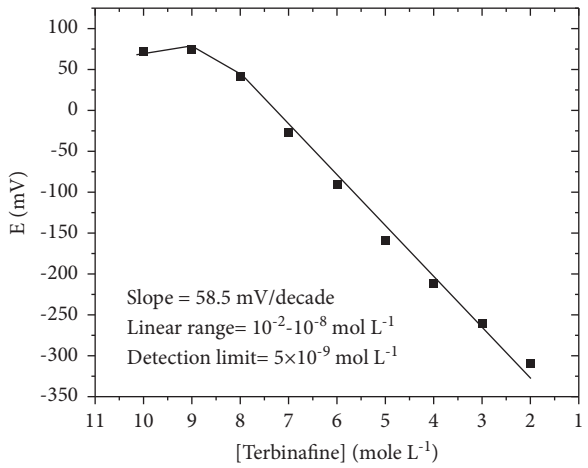

Figure 4: Potentiometric calibration response of the terbinafine screen-printed microchip.

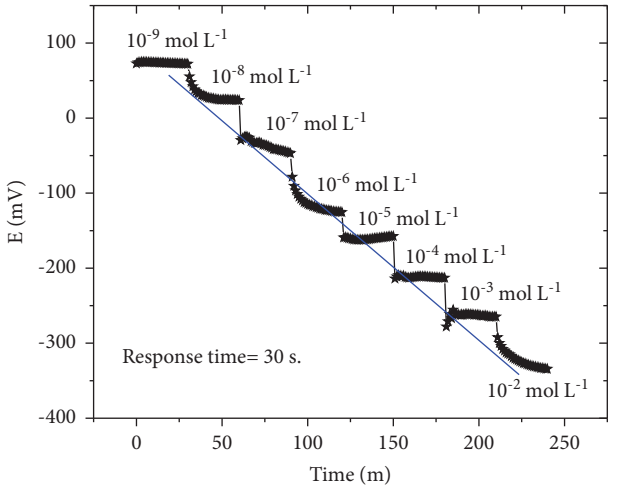

Figure 5: Dynamic response of the terbinafine screen-printed microchip.

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

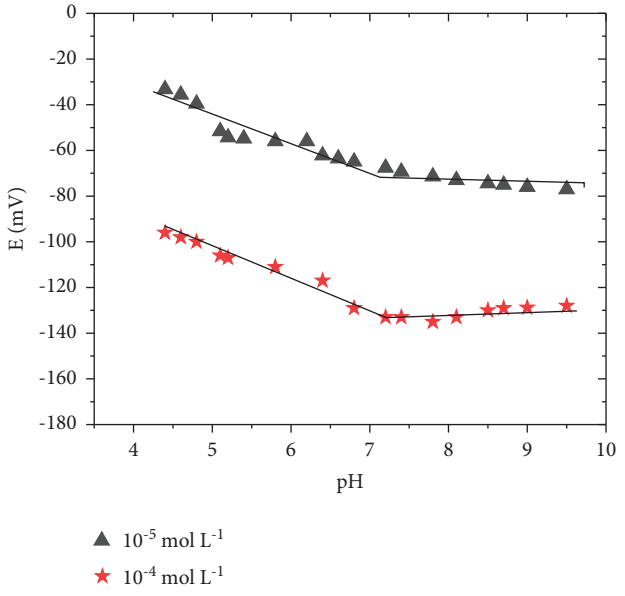

Figure 6: The effect of pH on the potentiometric response of the terbinafine microchip.

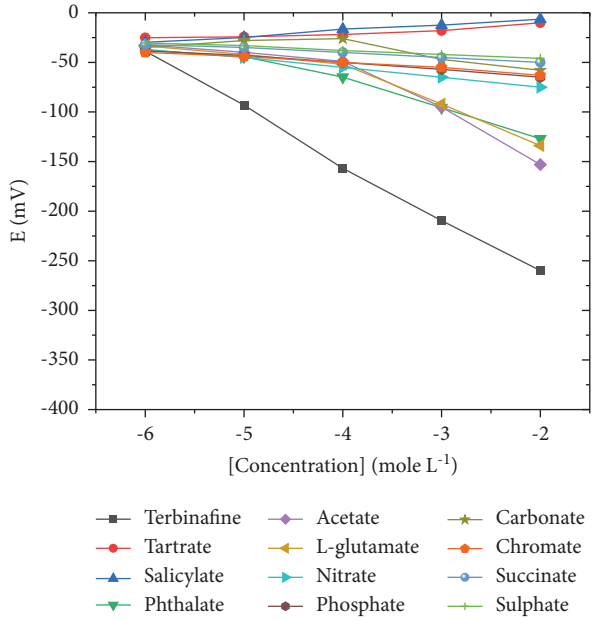

Figure 7: Potentiometric response of the microchip to terbinafine and different interfering ions.

concentration range of 10^{-6}–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 ($K^{pot}_{Ter,j}$)
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

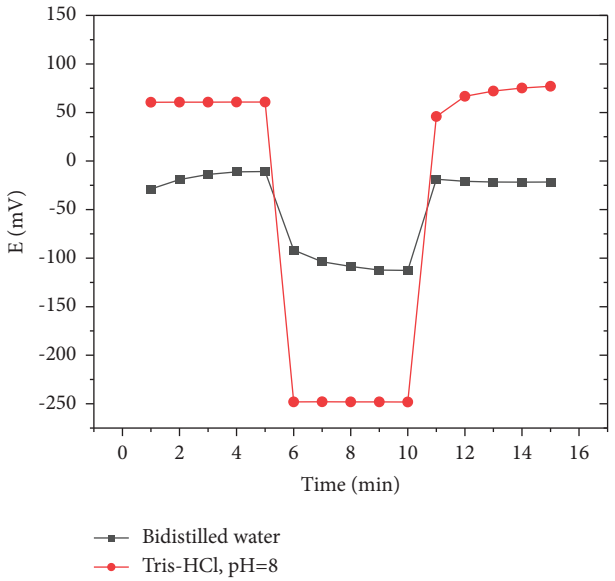

Figure 8: The layer effect study on the response of the terbinafine microchip from 10^{-5} mole·L^{-1} terbinafine in bi-distilled water and tris-HCl buffer, pH 8.

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^{-8}–10^{-2}	10^{-7}–10^{-2}	7×10^{-6}–10^{-2}
Slope (mV/decade)	58.5 ± 0.5	56.99–59.06	57.8
Detection limit (mole·L^{-1})	5×10^{-9}	1×10^{-7}	6.5×10^{-6}
Lower limit of the linear range (mole·L^{-1})	1×10^{-8}	1×10^{-7}	7×10^{-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	Recovery (%)	
		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 bi-distilled 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^{-2} 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.

Acknowledgments

This work was supported by Taif Universityunder Researcher Supporting Project (number TURSP-2020/30), Taif University, Taif, Saudi Arabia.

References

[1] B. Kanakapura and V. K. Penmatsa, "Analytical methods for determination of Terbinafine hydrochloride in pharmaceuticals and biological materials: a review," *Journal of Pharmaceutical Analysis*, vol. 6, no. 3, pp. 137–149, 2016.

[2] H. Kassem and M. A. Almardini, "High performance liquid chromatography method for the determination of terbinafine hydrochloride in semi solids dosage form," *International Journal of Pharmaceutical Sciences Review and Research*, vol. 21, pp. 58–61, 2013.

[3] A. Bhadoriya, P. A. Shah, P. S. Shrivastav, K. D. Bharwad, and P. Singhal, "Determination of Terbinafine in human plasma using UPLC– MS/MS: application to a bioequivalence study in healthy subjects," *Biomedical Chromatography: Biomedical Chromatography*, vol. 33, no. 8, pp. e4543–e4549, 2019.

[4] S. Cox, J. Hayes, M. Hamill et al., "Determining terbinafine in plasma and saline using HPLC," *Journal of Liquid Chromatography & Related Technologies*, vol. 38, no. 5, pp. 607–612, 2015.

[5] M. P. Tagliari, G. Kuminek, S. H. M. Borgmann, C. D. Bertol, S. G. Cardoso, and H. K. Stulzer, "Terbinafine: optimization of a LC method for quantitative analysis in pharmaceutical formulations and its application for a tablet dissolution test," *Quimica Nova*, vol. 33, no. 8, pp. 1790–1793, 2010.

[6] B. V. Suma, K. Kannan, V. Madhavan, and C. R. Nayar, "HPTLC Method for determination of Terbinafine in the Bulk drug and Tablet dosage form," *International Journal of ChemTech Research*, vol. 3, pp. 742–748, 2011.

[7] F. Belal, M. K. Sharaf El-Din, M. I. Eid, and R. M. El-Gamal, "Micellar liquid chromatography coupled with fluorometric detection for the determination of terbinafine in dosage forms

and plasma," *Journal of Chromatography & Separation Techniques*, vol. 8, pp. 1–9, 2017.

[8] K. K. Patel and V. V. Karkhanis, "A validated HPTLC method for determination of Terbinafine hydrochloride in pharmaceutical solid dosage form," *IJPSR*, vol. 3, no. 11, pp. 4492–4495, 2012.

[9] P. D. Goswami, "Stability-indicating RP-HPLC method for analysis of Terbinafine hydrochloride in bulk and in tablet dosage form," *International Journal of Pharmacy and Pharmaceutical Sciences*, vol. 5, pp. 536–540, 2013.

[10] T. K. Majumdar, R. Bakhtiar, D. Melamed, and F. L. S. Tse, "Determination of Terbinafine (Lamisil) in human hair by microbore liquid chromatography/tandem mass spectrometry," *Rapid Communications in Mass Spectrometry*, vol. 14, pp. 1214–1219, 2000.

[11] S. G. Cardoso and E. E. S. Schapoval, "UV spectrophotometry and nonaqueous determination of terbinafine hydrochloride in dosage forms," *Journal of AOAC International*, vol. 82, no. 4, pp. 830–833, 1999.

[12] P. D. Goswami, "Validated spectrophotometric method for the estimation of Terbinafine hydrochloride in bulk and in tablet dosage form using inorganic solvent," *Der Pharmacia Lettre*, vol. 5, pp. 386–390, 2013.

[13] F. Belal, M. K. Sharaf El-Din, M. I. Eid, and R. M. El-Gamal, "Spectrofluorimetric determination of terbinafine hydrochloride and linezolid in their dosage forms and human plasma," *Journal of Fluorescence*, vol. 23, no. 5, pp. 1077–1087, 2013.

[14] T. A. Ali, S. M. Abdelsabour, H. Eldessouky, G. G. Mohamed, and Y. S. Elsayed, "Potentiometric determination of Terbinafine hydrochloride antifungal drug in pharmaceutical and biological fluids using ion selective electrodes," *J. Bas. & Environ. Sci.*vol. 5, pp. 80–92, 2018.

[15] F. Faridbod, M. R. Ganjali, and P. Norouzi, "Potentiometric PVC membrane sensor for the determination of terbinafine," *International Journal of Electrochemical Science*, vol. 8, pp. 6107–6117, 2013.

[16] F. S. Felix, L. M. C. Ferreira, P. d. O. Rossini, C. L. do Lago, and L. Angnes, "Quantification of Terbinafine in pharmaceutical tablets using capillary electrophoresis with contactless conductivity detection and batch injection analysis with amperometric detection," *Talanta*, vol. 101, pp. 220–225, 2012.

[17] S. G. Cardoso and E. E. Schapoval, "Microbiological assay for Terbinafine hydrochloride in tablets and creams," *International Journal of Pharmaceutics*, vol. 203, no. 1-2, pp. 109–113, 2000.

[18] H. Zeng, N. Gao, Y. Yin, and M. Zhang, "Recent progress in improving the performance of in vivo electrochemical microsensor based on materialsin vivo electrochemical microsensor based on materials; A review," *Current Opinion in Electrochemistry*, vol. 33, p. 68, Article ID 100957, 2022.

[19] H. Arida and M. Aldosari, "Organic membrane-based screen printed microchip for potentiometric determination of lead," *US Patent*, vol. 10, pp. 295–497, 2019.

[20] A. K. M. S. Inam, M. A. Costa Angeli, B. Shkodra et al., "Flexible screen-printed electrochemical sensors functionalized with electrodeposited copper for nitrate detection in water," *ACS Omega*, vol. 6, no. 49, pp. 33523–33532, 2021.

[21] M. Alfadhel, M. Alrobaian, and H. Arida, "Fabrication of new potentiometric microsensor for metformin based on modified screen-printed microchip," *International Journal of Electrochemical Science*, vol. 16, pp. 1–11, Article ID 210660, 2021.

[22] M. Z. Yang, C. L. Dai, and C. C. Wu, "A zinc oxide nanorod ammonia microsensor integrated with a readout circuit on-a-Chip," *Sensors*, vol. 11, no. 12, pp. 11112–11121, 2011.

[23] M. Shohayeb, H. Arida, G. Mersal, and M. El-Badawy, "Development of a nanotechnology-based screen-printed biosensor for detection of schistosoma mansoni antibodies," *International Journal of Electrochemical Science*, vol. 11, pp. 1337–1344, 2016.

[24] G. Ogata, Y. Ishii, K. Asai et al., "A microsensing system for the in vivo real-time detection of local drug kinetics," *Nature Biomedical Engineering*, vol. 1, no. 8, pp. 654–666, 2017.

[25] H. Arida, A. Al-Hajry, and I. Maghrabi, "New micro-sensor chip integrated with potassium zinc hexacyanoferrate(II) nano-composite for potentiometric determination of cesium (I)," *International Journal of Electrochemical Science*, vol. 10, pp. 10478–10490, 2015.

[26] J. Gallardo-Gonzalez, A. Baraket, S. Boudjaoui et al., "A highly sensitive potentiometric amphetamine microsensor based on all-solid-state membrane using a new ion-par complex," *Proceedings*, vol. 481, pp. 1–4, 2017.

[27] H. Arida, "Novel pH microsensor based on a thin film gold electrode modified with lead dioxide nanoparticles," *Microchimica Acta*, vol. 182, no. 1-2, pp. 149–156, 2015.

[28] T. Li, A. T. Evans, S. Chiravuri, R. Y. Gianchandani, and Y. B. Gianchandani, "Compact, power-efficient architectures using microvalves and microsensors, for intrathecal, insulin, and other drug delivery systems," *Advanced Drug Delivery Reviews*, vol. 64, no. 14, pp. 1639–1649, 2012.

[29] C. Zanetti, S. Spitz, E. Berger et al., "Monitoring the neurotransmitter release of human midbrain organoids using a redox cycling microsensor as a novel tool for personalized Parkinson's disease modelling and drug screening," *Analyst*, vol. 146, no. 7, pp. 2358–2367, 2021.

[30] R. Ehret, W. Baumann, M. Brischwein et al., "Multiparametric microsensor chips for screening applications," *Fresenius' Journal of Analytical Chemistry*, vol. 369, no. 1, pp. 30–35, 2001.