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Potentiometric determination of terbinafine hydrochloride antifungal drug in pharmaceutical and biological fluids using ion selective electrodes

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Abstract

The target of this study is focused on the determination of terbinafine hydrochloride (TFHC) as antifungal drug. A potentiometric method based on modified screen-printed and modified carbon paste ion-selective electrodes was described for the determination of TFHC in different pharmaceutical and biological fluids. It is based on potentiometric titration of TFHC using modified carbon paste (MCPE) and screen-printed (MSPE) as end point indicator sensors. The influences of the paste composition, different conditioning parameters and foreign ions on the electrodes performance were investigated and response time of the electrodes has been studied. The electrodes showed Nernstian response of 57.83±0.75, 59.06±0.69, 56.99±0.92 and 58.75±1.06 mV decade^{-1} in the concentration range of 3.8×10^{-7}–1×10^{-2} and 1×10^{-7}–1×10^{-2} mol L^{-1} for MCPE (electrode I and II) and MSPE (electrode III and IV), respectively. The electrodes were found to be usable within the pH range of 3.0–9.0 and 4.0-9.0 exhibited a fast response time (about 9 and 11 s), low detection limit of 3.8×10^{-7} and 1.0×10^{-7} mol L^{-1}, long lifetime (70, 85 and 152, 166 days) for MCPE (electrode I and II) and MSPE (electrode III and IV), respectively. The electrodes were successfully applied for the determination of TFHC in pharmaceutical preparation and biological fluids (urine and serum). The results obtained applying these potentiometric electrodes are comparable with British pharmacopeia. The method validation parameters were optimized and the method can be applied for routine analysis of TFHC drug.

Keywords: Terbenafine HCl, pharmaceutical analysis, Potentiometry, Modified screen-printed electrodes, modified carbon paste electrodes.

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1. Introduction

Terbinafine (Fig 1), chemically (E)-N-(6,6-dimethyl-2-hepten-4-inyl)-N-methyl-1-naphtalenemethanamine is an antifungal agent of the allylamine class that selectively inhibits fungal squalene epoxidase [1].

In other words, Terbinafine inhibits fungal and bacterial cell wall growth, causing the contents of the cell to be unprotected and finally die. Thus, it is applied to the skin in the incidence of dermatophytoses, pityriasis versicolor, and cutaneous candidiasis occurrence or superficial fungal infections like seborrheic dermatitis, tinea capitis, and onychomycosis especially for its short duration therapy [2]. Terbinafine is used for treatment of dermal affections in the form of creams, gels, tablets and solutions. It may cause some side effects such as an allergic reaction, a rash, and changes in vision or blood problems [3].

Some techniques have been reported for the determination of Terbinafine in pharmaceutical formulations including capillary zone electrophoresis [4], HPLC [5, 6], UV−spectrophotometric method [7], polarography [8], voltammetry [9] and non-aqueous methods [10].

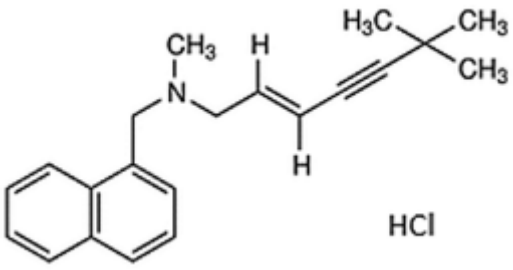

Fig (1): Chemical structure of Terbinafine

Potentiometry with ion-selective electrodes (ISEs) is still one of the most promising analytical tools capable of

determining both inorganic and organic substances in medico-biological practice [11-14]. There is a constant increase in the number of electrodes capable of selectivity identifying various drugs. Suitable ISEs for drugs have enough selectivity towards the drugs over pharmaceutical excipients and they can be useful in the quantitative analysis of the drugs in pharmaceutical preparations without prior separation. In particular, ISEs are useful in the case of drugs which are unstable during prior separation [15].

Potentiometric sensors possess many advantages over traditional methods of analysis and provide accurate, reproducible, fast and regular selective determination of various ionic species. In addition, ISEs allow non-destructive, on line monitoring of particular ions in a small volume of sample without pretreatment [16].

The carbon paste electrodes (CPEs) are suggested as a very useful end point indicator electrode in the potentiometric titration of drugs [17-19]. In comparison with similar PVC and coated wire electrodes, CPEs had the advantages of very low Ohmic resistance, very short response time in addition to the ease of fabrication and regeneration as well as long functional lifetime. Handmade carbon paste (made of carbon powder and liquid binder) was soft non-compatible material and had to be packed into a special electrode holder. It is well known that ISE are one of the few techniques that can measure both positive and negative ions. In fact, a number of ion-selective electrodes for target cations and anions have been reported [20-23].

The present work describes the preparation and potentiometric characterization of terbenafine-carbon paste (TFHC-CPE) and terbenafine-screen-printed electrode (TFHC-SPE) sensor based on potassium tetrakis(4-chlorophenyl)borate (KTpClPB) and multi-walled carbon nanotube (MWCNT) ionophores as electroactive material and plasticizer. These electrodes were found to give accurate results for the determination of terbenafine HCl in different pharmaceuticals preparations and biological fluids (urine and serum).

2. Experimental

Materials

All chemicals and reagents used were of analytical reagent grade and some of them were used as such without any further purification. Distilled water was used throughout all experiments. They included Terbenafine HCl provided by Misr Company for Pharmaceutical Industry, Egypt. Glucose, urea, sucrose, starch, maltose, lactose, Picric acid, glycine, sodium fluoride and chloride salts of calcium, nickel, potassium, aluminum, cadmium, iron, zinc, manganese, copper and cobalt were used as interfering materials.

For making ISE membrane the following reagents were used: o-nitrophenyloctylether (o-NPOE) was supplied from Fluka, while di-n-octyl phthalate (DOP), dibutylphthalate (DBP) and dioctyl sebacate (DOS) were supplied from BDH. In addition, tricresylphosphate (TCP), graphite powder (synthetic 1 – 2µm), multi-walled carbon nanotube (MWCNT) with the highest purity (diameter within 10–20 nm) and polyvinylchloride (PVC relative high molecular weight) were supplied from Aldrich. Potassium tetrakis[4-cholorophenyl]borate (KTpClPB) and Sodium tetraphenylborate (NaTPB) were supplied from Merck and Sigma-Aldrich, respectively.

Pharmaceutical samples

Mycomic tablets 250 mg (sample 1; Future Pharmaceutical Industries, Badr City, Egypt), Lamifen Tablets 250 mg (sample 2; EGPI Company, Obour City, Egypt) and Terbinajed Cream 0.1% (sample 3; Jedco International Pharmaceuticals Co., Puplic Free Zone, Nasr City, Cairo, Egypt).

Apparatus

Laboratory potential measurements were performed using Jenway 3505 pH-meter. Silver-silver chloride double-junction reference electrode (Metrohm 6.0726.100) in conjugation with different ion selective electrode was used. pH measurements were done using Thermo-Orion, model Orion 3 stars, USA. Prior to analysis, all glassware used were washed carefully with distilled water and dried in the oven before use.

Standard solutions

Terbenafine HCl solution

Stock terbenafine HCl solution (1.0×10^{-2} mol L^{-1}) was prepared by dissolving the proper weight of the drug (327.89 mg) into smaller amount of distilled water, heated with stirring till the drug completely dissolved. The resulting solution was then made up to 100 mL with distilled water in a measuring flask.

Tetraphenylborate solution (TPB^-)

1×10^{-2} mol L^{-1} NaTPB solution was prepared by dissolving 1811 mg into 500 mL distilled water, adjusted to pH = 9 by adding sodium hydroxide and completed to the desired volume with water. The resulting solution was standardized potentiometrically against standard (1×10^{-2} mol L^{-1}) thallium (I) acetate solution [24].

Interfering ions solutions

A 10^{-3} mol L^{-1} standard solution each of glucose, urea, sucrose, starch, maltose, lactose, Picric acid, glycine, sodium fluoride and chloride salts of calcium, nickel, potassium, aluminum, cadmium, iron, zinc, manganese, copper and cobalt were prepared by dissolving the proper weights into 100 mL bidistilled water.

Electrode preparation

Carbon paste electrode preparation

The sensing electrodes were prepared by intimate mixing accurately weight 500 mg of highly pure graphite powder and plasticizer (0.2 mL of DOP, TCP, DBP, DOS or o-NPOE). This matrix was thoroughly mixed in the mortar and the resulted past was used to fill the electrode body [25, 26]. A fresh surface was obtained by gently pushing the stainless-steel screw forward and polishing the new carbon-paste surface with filter paper to obtain a shiny new surface.

Preparation of the Terbenafine-modified screen-printed electrodes

Modified SPEs were printed in arrays of six couples consisting of the working and the reference electrodes (each 5 × 35 mm) following the procedures previously described [27-34]. A polyvinyl chloride flexible sheet (0.2 mm) was used as a substrate which was not affected by the curing temperature or the ink solvent and easily cutted by scissors.

The working electrodes were prepared depending on the method of fabrication. The working electrode was printed using homemade carbon ink (prepared by mixing 2.5-15 mg Potassium tetrakis[4-cholorophenyl]borate (KTpClPB), 15 mg multi-walled carbon nanotube (MWCNT), 450 mg o-NPOE, 1.25 g of polyvinyl chloride 8% and 0.75 g carbon powder). They were printed using homemade carbon ink and cured at 50 ^{o}C for 30 min. A layer of an insulator was then placed onto the printed electrodes, leaving a defined rectangular shaped (5 × 5 mm) working area and a similar area (for the electrical contact) on the other side. Fabricated electrodes were stored at 4 ^{o}C and used directly in the potentiometric measurements.

Procedures

Study of the experimental conditions

Identification of slope of the studied electrode:

The electrochemical performance characteristics of the studied Terbenafine HCl selective electrode were evaluated according to IUPAC standards [35].

Sensors calibration was carried out by measuring the potential of 10^{-7}–10^{-2} mol L^{-1} drug solutions starting from low to high concentrations. The potentials were plotted as a function of drug concentrations. Sensors life spans were examined by repeated monitoring of the change in the potential break and total potential jump of the drug titration periodically. The detection limit was taken at the point of intersection of the extrapolated linear segment of the drug calibration graph.

The dynamic response times of the Carbon paste electrode (CPE) and screen-printed electrode (SPE) was tested for the concentrations of 10^{-6}–10^{-3} mol L^{-1} TFHC solutions. The sequence of measurements was from low to high concentrations. The time required for the electrodes to reach value within ±2 mV from the final equilibrium potential after increasing Terbenafine HCl concentration level by ten folds was measured.

Effect of pH on the electrodes response

To examine the effect of pH on the electrode responses, the potential was measured at specific concentration of the TFHC solution (1.0×10^{-3} and 1.0×10^{-5} M) from the pH value of 1.0 up to 11.0 (concentrated NaOH or HCl solutions were employed for the pH adjustment) by ion selective electrode. The results showed that the potential remained constant despite the pH change in the range of 3 to 9 which indicates the applicability of this electrode in the specified pH range.

Effect of temperature

The effect of temperature on the performance of the potentiometric electrodes was evaluated in a thermostat at different temperatures ranged from 10-60 °C [23, 36, 37].

Analytical applications

Determination of Terbenafine HCl in pharmaceutical dosage forms

Ten tablets of Lamifen® (250 mg/tablet) were finely powdered. An accurate weight containing 0.327 g Terbenafine HCl was dissolved in 100 mL distilled water to obtain a standard stock solution. Working solutions in the range of 1.0×10^{-7}-1.0×10^{-2} mol L^{-1} for standard addition method and direct determination method were prepared by serial dilutions with distilled water.

Potentiometric determination of Terbenafine in pharmaceutical preparations

Terbenafine was determined in pure solution and pharmaceutical preparations using the developed electrode under both batch conditions (standard addition). In standard addition method, known increments of 10^{-2} mol L^{-1} standard Terbenafine solution were added to 25 mL aliquot of sample solution where the change in the potential readings was recorded for each increment and used to calculate the concentration of Terbenafine in sample solution.

Determination of Terbenafine HCl in biological fluids

Different quantities of TFHCl was added to 2 ml serum or 4 ml urine and they were transferred to a 100 ml volumetric flask, completed with water and small volumes (0.1–2 ml) of 0.01 mol L^{-1} HCl to the mark to give solutions of pH ranging from 4 to 6 and concentrations of 1.0×10^{-4} to 5.0×10^{-3} mol L^{-1} of TFHCl. These solutions are subjected to the potentiometric determination using direct, calibration and standard additions method for TFHCl determination [38].

3. Results and discussion

ISEs employing modified carbon paste (MCPEs) and screen-printed electrodes (MSPEs) based on Potassium tetrakis[4-cholorophenyl]borate (KTpClPB) and multi-walled carbon nanotube (MWCNT) as neutral ionophores were found to be highly responsive to TFHC in respect to several other cations. Therefore, the performance of the electrodes for $TFHC^{+}$ was firstly studied in detail. In order to test the ISE performance, several characteristics were investigated, including: selectivity, sensitivity, response time, working pH range, lifetime of the electrodes at different concentrations of the drug, and the effect of the paste composition.

Optimization of the paste composition

Due to the fact that sensitivity and selectivity of potentiometric transducers depends mainly on the sensing material. Very selective interactions could be obtained by designing of sensing materials complementary to the size and charge of a particular ion. Therefore, KTpClPB and MWCNT may be used advantageously as sensor's ionophore because the template' shape is printed on it [16]. The increase in the content of MWCNT improves the conductivity of the electrodes, increases the transduction of the chemical signal to electrical signal and therefore increases the sensitivity of the electrodes. Thus, five MCPEs and MSPEs were prepared to determine the best electrode contents. The proportions of KTpClPB:MWCNT ionophore were varied as 5-15 mg (w/w)%. The potentiometric titration was carried out for each electrode and the resulting potential breaks at the end point were found to be 374, 378, 389, 398 and 387, and 334, 339, 367 and 354 mV mL^{-1} for modified MCPE and MSPE sensors, respectively. These electrodes gave sharp and reproducible inflection at the end point (398 and 354 mV mL^{-1} for modified CPE (electrode I) and SPE (electrode III) sensors, respectively. These results indicated that the highest potential break at the end point was evaluated using 12.5 mg of [KTpClPB:MWCNT] ionophore for MCPE (electrode I) and MSPE (electrode III) sensors,

respectively. But when increasing the amount of ionophore over 12.5 mg, the total potential change decreased as shown in Fig (2).

Sensor performance characteristics

The synthesized KTpClPB and MWCNT were incorporated in (MCPE and MSPE) electrodes and dispersed into (TCP and o-NPOE) plasticizer and were tested as sensing materials in the proposed potentiometric sensors. The electrochemical cell of the fabricated sensors for TFHC determination could be illustrated diagrammatically as follows: Ag/AgCl double junction reference electrode/sample test solution//sensors//10^{-2} mol L^{-1} TFHC (in 0.01 M HCl)/Ag/AgCl internal reference wire.

Characterization of the main analytical features for the studied sensors was followed according to IUPAC recommendations [35, 39]. Sensors I, II, III and IV displayed cationic responses of 57.83±0.75, 59.06±0.69, 56.99±0.92 and 58.75±1.06 mV $decade^{-1}$ (Fig. (3)). The sensor prepared with TFHC- KTpClPB and MWCNT paste. The validity of the proposed potentiometric method for determining TFHC was assessed according to IUPAC recommendations[35] by measuring the range, lower limit of detection (LOD), accuracy, repeatability, intermediate precision, linearity (correlation coefficient) and sensitivity (slope). Data obtained with five determinations each of TFHC is the limits of detection (LODs) for TFHC ranged from 3.8×10^{-7} mol L^{-1} for electrodes I, II and 1.0×10^{-7} mol L^{-1} for electrodes III, IV (Table 1).

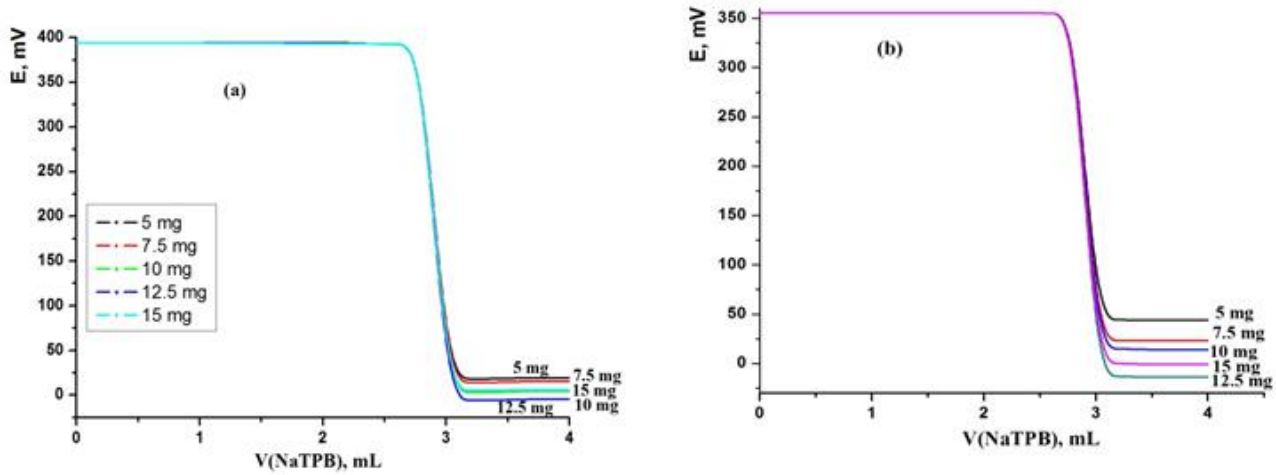

Fig (2): Effect of ionophore contents on (a) TFHC-MCPE and (b) TFHC-MSPE electrodes using TCP plasticizer.

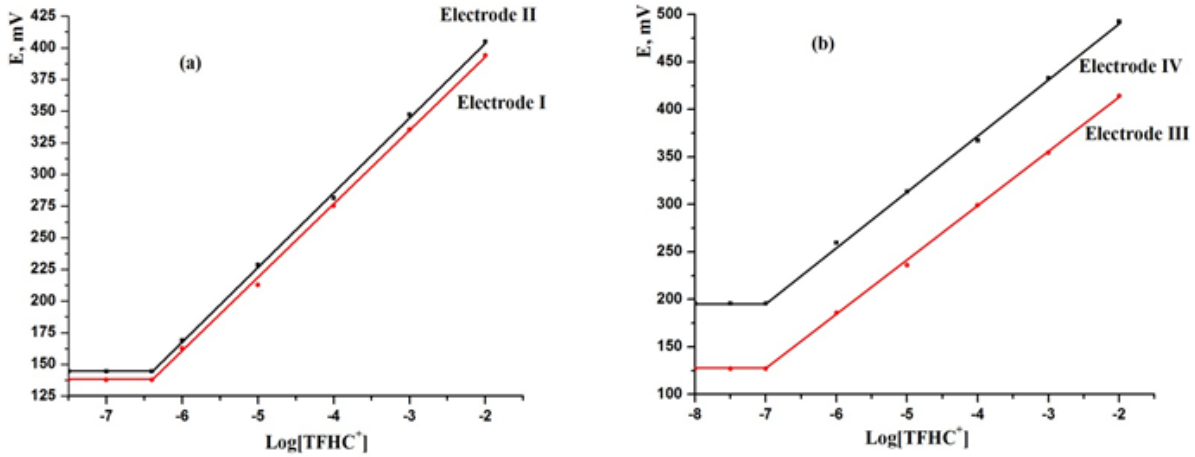

Fig (3): Calibration graphs using (a) TFHC-MCPE and (b) TFHC-MSPE electrodes.

Table (1): Response characteristics of TFHC-MCPE (electrode I and II) and TFHC-MSPE (electrode III and IV) potentiometric sensors.

Parameter	TFHC- MCPE		TFHC –MSPE	
	Electrode I (TCP)	Electrode II (o-NPOE)	Electrode III (TCP)	Electrode IV (o-NPOE)
Slope (mV decade^{-1})	57.83±0.75	59.06±0.69	56.99±0.92	58.75±1.06
Usable range (mol L^{-1})	$3.8 \times 10^{-7} - 1.0 \times 10^{-2}$		$1.0 \times 10^{-7} - 1.0 \times 10^{-2}$	
Detection limit (mol L^{-1})	3.8×10^{-7}		1.0×10^{-7}	
Response time (s)	9		11	
Working pH range	3.0 - 9.0		4.0 - 9.0	
SD of slope (mV decade^{-1})	0.271	0.157	0.294	0.163
Intercept (mV)	510.58±1.15	522.56±1.01	524.31±1.44	607.57±0.17
Life time (days)	70	85	152	166
Accuracy (%)	99.91	99.93	99.80	99.86
Precision (%)	0.160	0.142	0.183	0.153
Temp	0.000271	0.000642	0.000388	0.000492

Effect of Plasticizer

The solvent mediator, in particular, has a dual function: it acts as a liquifying agent, making the paste material workable, that is enabling homogenous solubilization and modifying the distribution constant of the ion-exchanger used and sustaining these characteristics on continued use. The proportion of solvent mediator must be optimized in order to minimize the electrical asymmetry of the paste in order to keep the sensor as clean as possible and to stop leaching to the aqueous phase. For a plasticizer to be adequate for use in sensors, it should gather certain properties and

characteristics such as having high lipophilicity, high molecular weight, low tendency for exudation from the paste matrix, low vapor pressure and high capacity to dissolve the substrate and other additives present in the paste [25]. To spot a suitable plasticizer for constructing this electrode, we tested five plasticizers, with a range of characteristics. This was evaluated by using five different plasticizers (DOP, DBP DOS, o-NPOE and TCP) in the preparation of MCPE and MSPE the response of these electrodes to TFHC concentration were examined. Electrodes I, II, III and IV as shown in Fig (4). From the obtained results it is clear that the use of o-NPOE as a plasticizer resulted in the best sensitivity and linear range for all the used electrodes. This can be attributed to its high dielectrical constant in comparison with the other plasticizers.

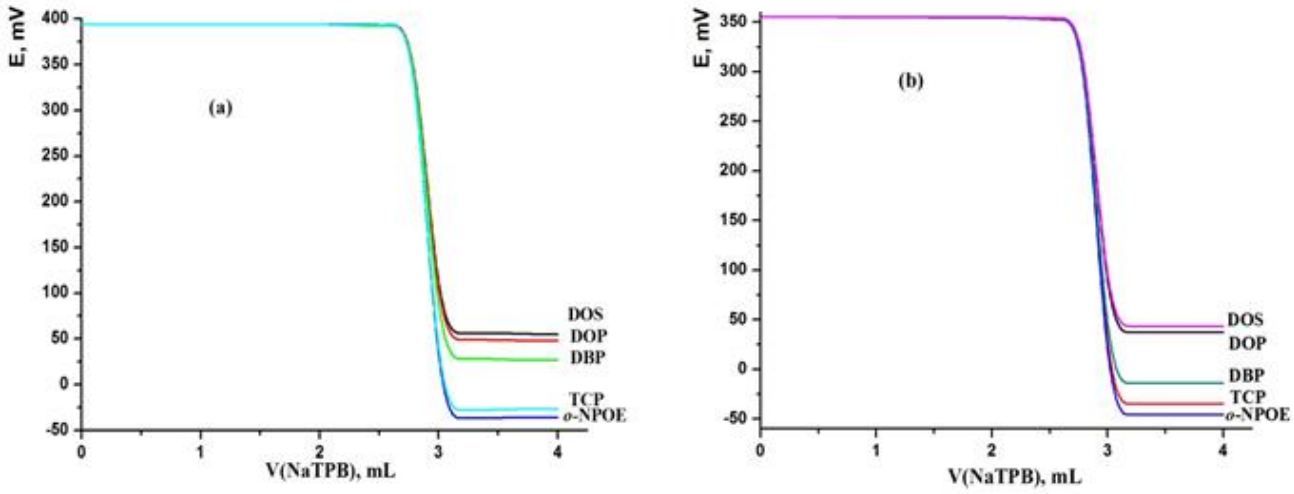

Fig (4): Effect of plasticizer type on the performance of (a) TFHC-MCPE and (b) TFHC-MSPE electrodes.

Dynamic response time behavior of the proposed electrode

It is well known that the dynamic response time of modified carbon paste (MCPE) and screen-printed electrodes (MSPE) is one of its most important characteristics. To measure the dynamic response time of the electrode the concentration of the test solution was changed in steps from 1.0×10^{-6} - 1.0×10^{-3} mol L^{-1}. The average time required for the electrode to reach a potential response within ± 1.0 mV of the final equilibrium value after successive immersion in a series of $TFHC^{+}$ ion solutions, each increasing in concentration by a factor of 10-fold, the response times 9 for MCPE (Electrode I and II) and 11 for MSPE (Electrode III and IV), respectively (Fig (5)).

Effect of pH on electrode performance

The pH dependence of the best modified carbon paste and screen-printed electrodes based on KTpClPB and MWCNT ionophores was examined at a 1.0×10^{-3} and 1.0×10^{-5} mol L^{-1} concentration of $TFHC^{+}$ ion. The pH of the solution was varied by the small addition of a 0.1 mol L^{-1} solution of either HCl or NaOH. The potential remains constant over the pH range for proposed MCPE 3.0–9.0 and 4.0–9.9 for MSPE. Therefore, the same was taken as the working pH range of the electrodes. The significant change in potential response observed at decrease in mV readings at pH < 3 may be due to the interference of hydronium ion. On the other hand, the observed potential drift at higher pH values (pH > 9.0), free-base precipitated in the test solution and consequently, the concentration of unprotonated species gradually increased. As a result, lower e.m.f. readings were recorded as shown in Fig (6).

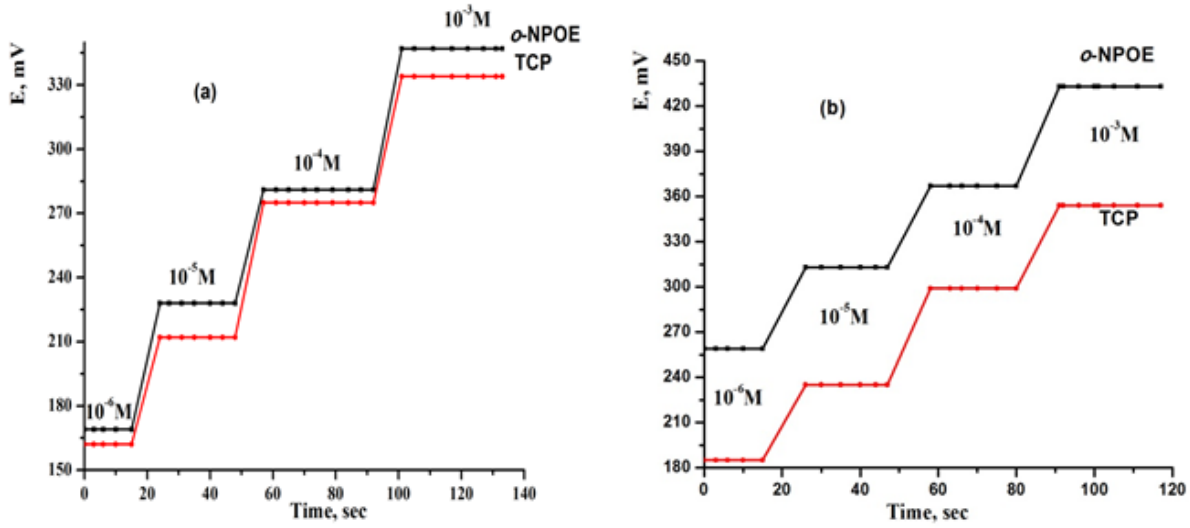

Fig (5): Dynamic response time of TFHC electrodes of (a) TFHC-MCPE and (b) TFHC-MSPE electrodes.

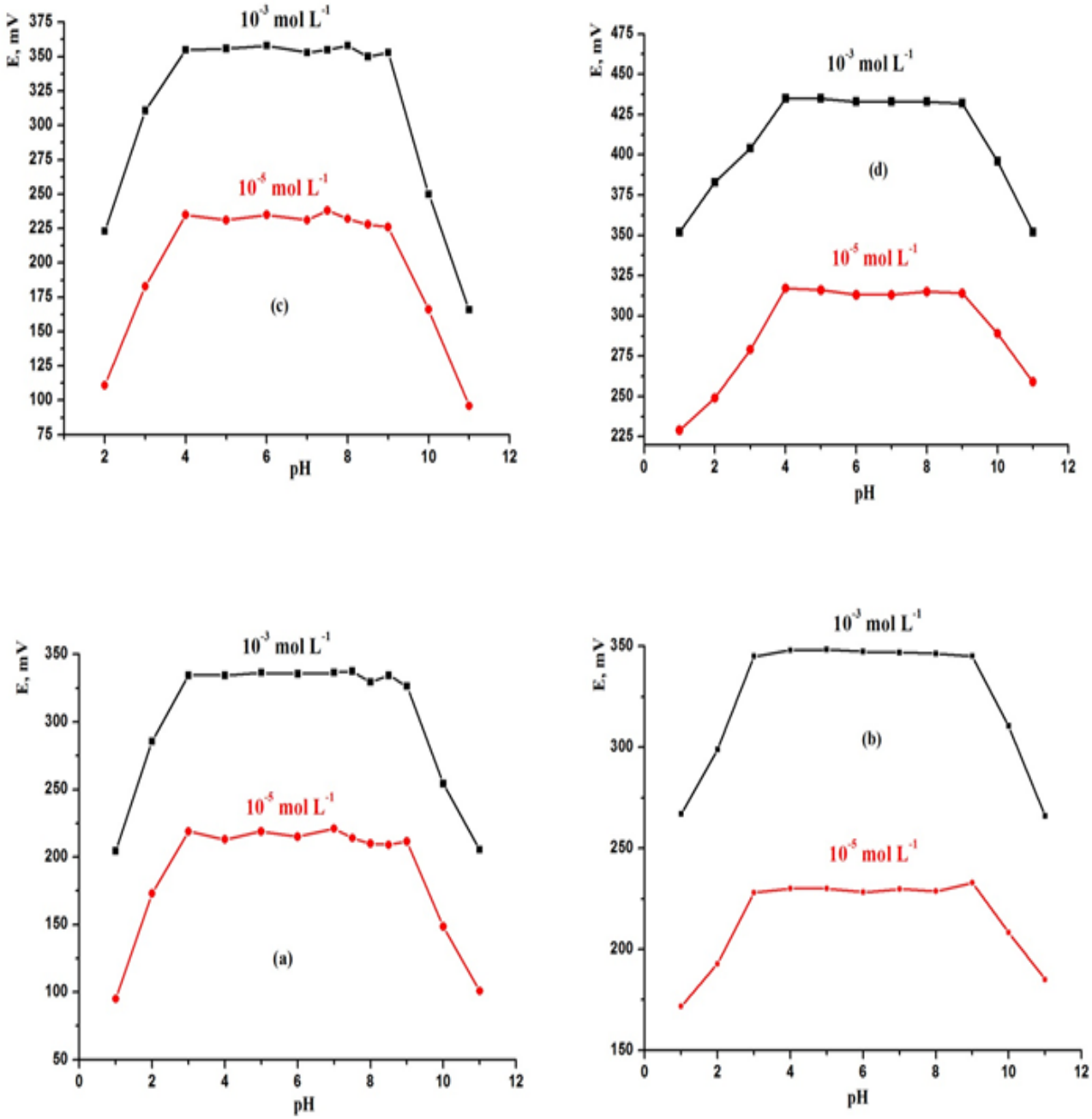

Fig (6): Effect of pH of the test solution on MCPEs [(a) electrode (I) and (b) electrode (II)] and MSPEs [(c) electrode (III) and (d) electrode (IV)].

Effect of Temperature of the Test Solution

Calibration graphs (electrode potential (E_{elec}) versus p[TFHC]) were constructed at different test solution temperatures (20–60 ˚C) using MCPE and MSPE. For the determination of the isothermal coefficient (dE^o/dt) of the electrode, the standard electrode potentials (E^o) against the normal hydrogen electrode at different temperatures were obtained from calibration graphs as the intercepts at p[TFHC] = 0 (after subtracting the values of the standard electrode potential of the silver-silver chloride double-junction reference electrode at these temperatures) and were plotted versus (t-25), where t was the temperature of the test solution in ˚C. A straight-line plot was obtained according to Antropov's equation [36]:

$$E^o = E^o(25) + (dE^\circ/dt)\,(t - 25)$$

where $E^o(25)$ is the standard electrode potential at 25 ºC, the slope of the straight-line obtained represents the isothermal coefficient of the electrodes (0.000271, 0.000642, 0.000388 and 0.000492 mV/ºC) for electrodes (I), (II), (III) and (IV), respectively (Fig. (7)). The value of the obtained isothermal coefficient of the electrodes indicated that the electrodes had fairly high thermal stability within the investigated temperature range. The investigated electrodes were found to be usable up to 50 ˚C without noticeable deviation from the Nernstian behavior.

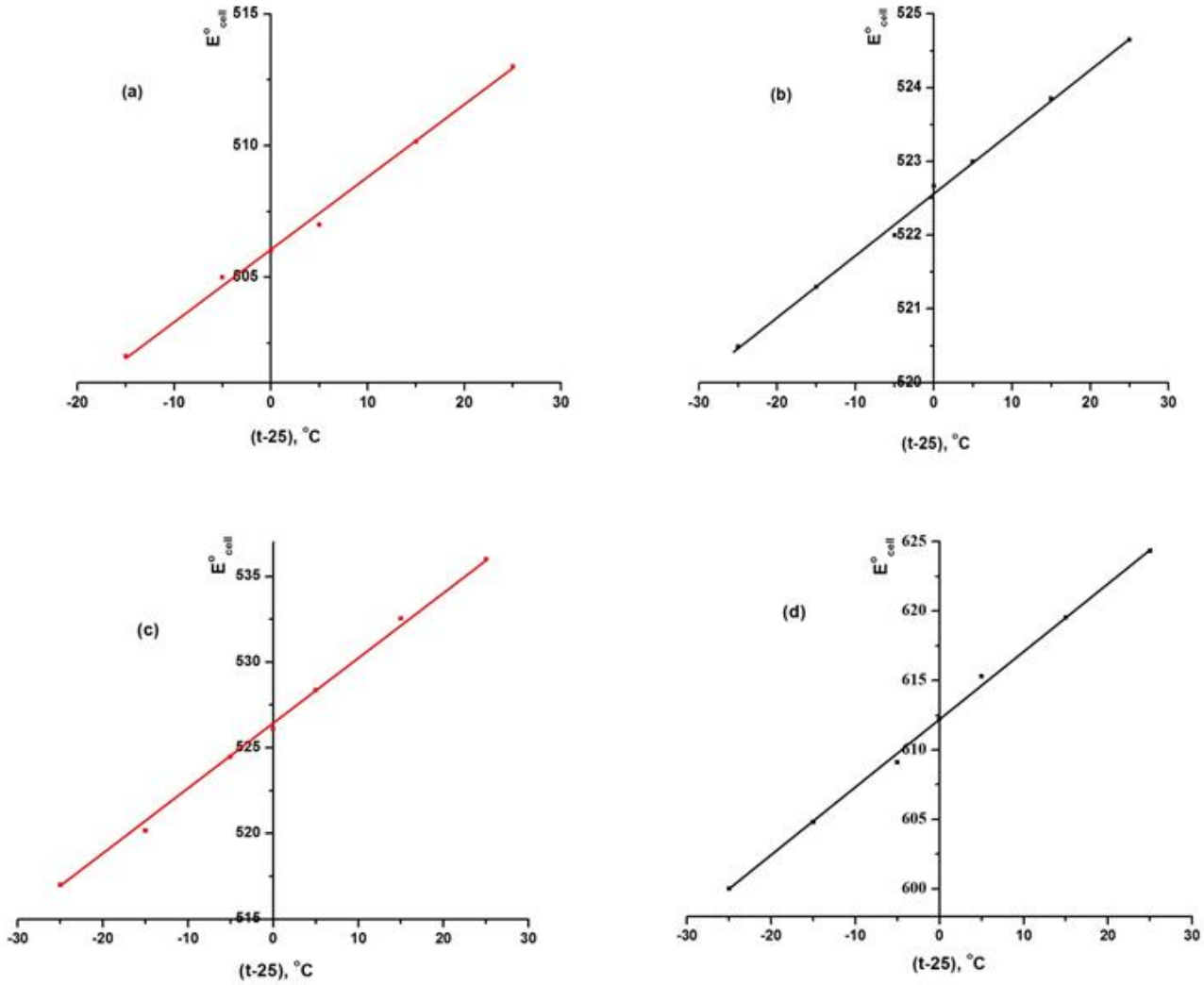

Fig (7): Effect of temperature on the performance of MCPEs [(a) electrode (I) and (b) electrode (II)] and MSPEs [(c) electrode (III) and (d) electrode (IV)].

Lifetime

The lifetime of the electrodes was determined by recording its potential at an optimum pH value and plotting its calibration curve each day. It was observed that there was no significant change in the slope and detection limit (DL) of the electrodes on the following day. The KTpClPB:MWCNT paste electrode was tested over a

period of 70, 85, 152 and 166 days to investigate its stability for electrodes (I), (II), (III) and (IV), respectively. During these periods, the slope of the calibration graph varied within ±1 mV/decade (Fig (8)). After these periods the electrochemical behaviour of the sensors gradually deteriorated. This is possibly due to the decrease in the quantity of plasticizer and ionophore in the prepared electrodes.

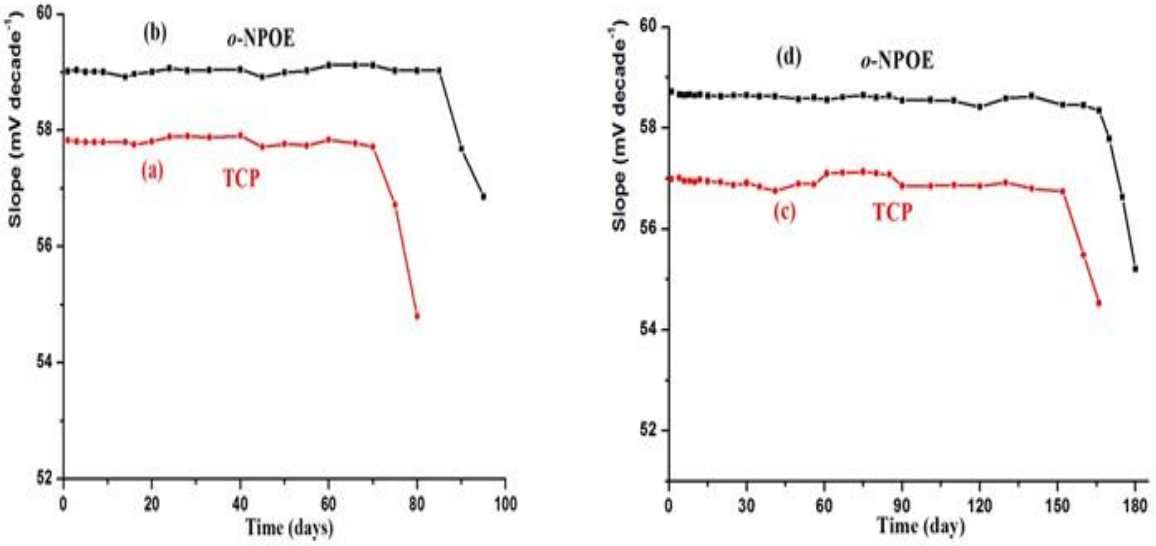

Fig (8): Effect of life time on the performance of MCPEs [(a) electrode (I) and (b) electrode (II)] and MSPEs [(c) electrode (III) and (d) electrode (IV)].

Selectivity of the electrodes

The potentiometric selectivity coefficients of the TFHC electrodes were determined using two methods: the separate solution method and the matched potential method [40]. While determining selectivity coefficients by means of SSM, the following equation was used:

$$\log K^{pot}_{A,B} = ((E_B-E_A)/S) + (1-(Z_A/Z_B)) \log a_A$$

where, E_A is the potential measured in 1×10^{-3} mol L^{-1} TFHC (A), E_B the potential measured in 1×10^{-3} mol L^{-1} of the interfering compound (B), Z_A and Z_B are the charges of the TFHC (A) and interfering species (B), respectively, and S is slope of the electrode selectivity coefficients of the terbenafine selective electrodes calculated by the modified separate solution method at 25 ˚C.

While the selectivity coefficients for many nitrogenous compounds such as starch, sugars and glycine were obtained by the matched method which was totally independent on the Nicolsky equation. The following equation was applied:

$$K^{pot}_{TFHC,B} = (a\,'_{TFHC} - a_{TFHC}) / a_B$$

The influence of some inorganic anions, cations, glycine and sugars on the TFHC-electrodes was investigated (Table 2). The values of the selectivity coefficients obtained using the MPM method are more reliable, particularly when the calibration curves in the interfering ions solutions do not have a theoretical course. The selectivity coefficients values of the electrodes I, II, III and IV reflected a very high selectivity of the investigated electrodes for the TFHC cation. The inorganic cations did not interfere owing to the differences in ionic size, and consequently their mobilities and permeability, as compared with those of $TFHC^+$ (Table 2).

Table (2): Potentiometric selectivity coefficients of some interfering ions using MCPE [I and II] and MSPEs [III and VI] Sensors.

Interfering ions	$-\log K^{MPM}_{TFHC^+, B}$			
	MCPE		MSPE	
	Electrode I	Electrode II	Electrode III	Electrode VI
Urea	5.01	5.11	4.98	5.08
Starch	4.82	4.92	4.81	4.88
Glucose	4.94	4.99	4.92	4.93
Fructose	4.47	4.80	4.38	4.78
Lactose	4.63	4.69	4.59	4.63
Sucrose	4.73	4.76	4.68	4.73
Maltose	4.66	4.72	4.61	4.73
Glycine	5.23	5.33	5.22	5.31
Picric acid	5.49	5.53	5.48	5.52
	$-\log K^{SSM}_{TFHC^+, B}$			
Al^{3+}	3.61	3.75	3.54	3.70
Fe^{3+}	2.72	3.81	2.60	3.78
Ca^{2+}	3.20	3.48	3.09	3.44
Zn^{2+}	3.46	3.52	3.38	3.51
Mn^{2+}	3.58	3.66	3.49	3.63
Cu^{2+}	2.65	3.73	2.61	3.69
Co^{2+}	3.06	3.12	3.01	3.08
Ni^{2+}	3.26	3.30	3.22	3.27
Cd^{2+}	3.44	3.54	3.38	3.55
Na^{+}	4.08	4.18	3.99	4.13
K^{+}	4.21	4.33	4.19	4.30

Potentiometric determination of Terbenafine hydrochloride in pure solutions and in its pharmaceutical formulations

The studied electrodes have been successfully used for the potentiometric determination of terbenafine hydrochloride in bulk drug solutions and in its pharmaceutical preparations. Three replicate determinations at different concentration levels were carried out to test the precision of methods. Results obtained were compared with the official method [41] (Table 3). The data reported in Table (3) indicated that results obtained by the two reported methods are in good agreement; however, the proposed method is more selective, rapid, simple and less time consuming. In addition, the proposed methods were used for determination of the studied drug in pharmaceutical preparations (Table 3).

Table (3): Potentiometric determination of TFHCl in pharmaceutical formulations using MCPEs (electrodes I and II) and MSPEs (electrodes III and IV).

Sample No.	[TFHCl] mg mL^{-1} Pharmaceutical Preparation					RSD(%) Pharmaceutical Preparation				
	British Pharmacopeia	I	II	III	IV	British Pharmacopeia	I	II	III	IV
1	0.522	0.520	0.527	0.519	0.525	0.842	0.887	0.701	0.892	0.724
2	0.554	0.552	0.559	0.550	0.557	0.735	0.746	0.641	0.756	0.661
3	0.588	0.589	0.592	0.586	0.590	0.952	1.002	0.798	1.011	0.803

SD values for Pharmaceutical Preparation (British Pharmacopeia = 0.099-0.326), (electrode I = 0.101-0.376) (electrode II = 0.042-0.241), (electrode III = 0.112- 0.436) and (electrode IV = 0.061- 0.263).

F-test = (electrode I = 1.1 – 1.9), (electrode II = 0.2 – 0.9), (electrode III = 0.8 – 1.6) and (electrode IV = 0.3 – 1.1). (Tabulated F value at 95% confidence limit = 4.87 for n = 4).

t-test = (electrode I = 1.3 – 2.1), (electrode II = 0.3 – 1.1), (electrode III = 0.9 – 1.9) and (electrode IV = 0.6 – 1.4). (Tabulated t value at 95% confidence limit = 2.032 for n = 4).

Application to urine and human serum

Terbenafine can be determined in urine and human serum by using potentiometric determinations and the results obtained are summarized in Table (4). The accuracy of the proposed potentiometric method was reported as investigated by the determination of TFHC in spiked terbenafine samples prepared from serial concentrations of TFHC reference standards. The proposed method can therefore be applied to the determination of TFHC alone and in pharmaceutical preparations or in biological fluids without fear of interferences caused by the excipients expected to be present in tablets or the constituents of body fluids.

Table (4): Determination of TFHC in spiked urine and human serum using MCPEs (Sensor II) and MSPEs (Sensor IV)

Sample	Statistical parameters	(Electrode II)			(Electrode IV)		
		Direct method	Calibration graphs	Standard addition method	Direct method	Calibration graphs	Standard addition method
urine	Mean recovery (%)	99.33	99.01	98.96	99.20	98.88	98.77
	N	5	5	5	5	5	5
	Variance	0.64	0.55	0.76	0.68	0.59	0.72
	RSD (%)	0.23	0.33	0.45	0.38	0.42	0.55
serum	Mean recovery (%)	99.60	99.42	99.01	99.30	99.00	98.99
	N	5	5	5	5	5	5
	Variance	0.36	0.47	0.55	0.39	0.41	0.57
	RSD (%)	0.28	0.39	0.50	0.41	0.51	0.62

4. Conclusions

Two kinds of potentiometric (MCPEs and MSPEs) electrodes were constructed for determination of TFHCl and a comparison was made between them. The sensors show favorable performance characteristics with short response times (9 and 11 s), low detection limits of 3.8×10^{-7} and 1.0×10^{-7} over the concentration range from 3.8×10^{-7} – 1.0×10^{-2} and 1.0×10^{-7} - 1.0×10^{-2} for MCPEs and MSPEs electrodes respectively. Clearly, the MSPE electrode shows a lower detection limit due to its diminished current flux. The sensors were effectively used for determination of TFHCl in pharmaceutical preparations. The proposed electrodes were successfully applied to the determination of terbenafine hydrochloride in pharmaceutical preparation, urine and human serum. The analytical method proposed proved to be a simple, rapid and accurate method.

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