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Construction of Modified Screen-Printed and Carbon Paste Electrodes for Electrochemical Determination of Antihistaminic Diphenhydramine Hydrochloride in Pure and Pharmaceutical Preparations

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The construction and performance characteristics of diphenhydramine hydrochloride (DPH) modified screen printed (SPE) and carbon paste (CPE) electrodes with DPH-tetrapheylborate ion pair (DPH-TPB) (MSPE and MCPE) and with sodium tetraphenyl borate ion pairing agent (NaTPB) (in situ) (ISPE and ICPE) using tricrysylphosphate (TCP) as plasticizer are described. These electrodes exhibit suitable response to DPH in the concentration range of $1x10^{-1}$ to $1x10^{-6}$ mol L^{-1} with lower detection limit of $9.65x10^{-7}$, $9.68x10^{-7}$, $9.78x10^{-7}$ and $9.76x10^{-7}$ mol L^{-1} and response time of about 5, 6, 10 and 11s with Nernstian slope values of 56.20±0.65, 59.14±0.90, 55.86±1.12 and 60.03±1.32 mV $decade^{-1}$ for MSPE, ISPE, MCPE and ICPE, respectively. The fabricated electrodes were used over a period of 2 months under pH range of 2.5-8.0, 3.0-9.0, 2.5-7.0 and 3.0-8.0 for MSPE, ISPE, MCPE and ICPE, respectively. The analytical performance of the SPEs and CPEs compared with respect to selectivity coefficients for DPH relative to a numbers of potential interfering substances were investigated. The method was applied for determination of DPH in pharmaceutical preparations with a percentage recovery of 98.75-99.27, 98.95-99.66, 98.91-99.65 and 97.83-99.17% and and R.S.D = 0.54, 0.29, 0.26 and 0.56 for MSPE, ISPE, MCPE and ICPE, respectively. The results are compared with the official method.

Keywords: Potentiometry, diphenhydramine, ISPE, ICPE, capsules.

1. INTRODUCTION

Diphenhydramin hydrochloride (DPH), (Fig. 1), [2-(diphenylmethoxy)-N,N-dimethylethylamine hydrochloride], is a first generation antihistamine drug. Despite being one of the

oldest antihistamines in the market, it is more effective than even some of the latest prescription drugs [1, 2]. It is widely used as antiallergic, antiemetic and antitussive drug found in many pharmaceutical preparations.

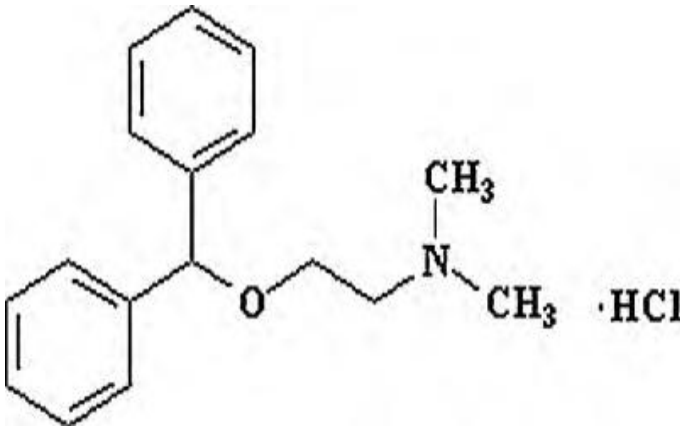


Figure 1. Structural formula of diphenhydramine hydrochloride.

It is usually given orally in a preparation of tablet, capsule or syrup. Several methods have been proposed for determining DPH in pharmaceutical preparations including titrimetry [3–5], electrochemical analysis [6, 7] and spectrophotometry [8–11]. Chromatographic methods have been used such as thin layer chromatography [12], gas chromatography [13] and high performance liquid chromatography [14–16]. The last one is used as an official method since 1990. Many of the above methods suffer from many interfering substances and/or suffer from time-consuming procedure or high coast.

Many electrochemical methods of analysis, according to the type of physical parameters which may be potential, current, or charge involved in the transduction process [17, 18], were suggested. On the other hand, applications of potentiometric sensors in the field of pharmaceutical and biomedical analysis have been advocated [19]. The approach provides simple, fast and selective technique for determination of various drugs [20–25]. Among these methods, potentiometric determination using modified screen-printed electrodes were selected to determine DPH which is the goal for this study. Potentiometric detection based on ion-selective electrodes (ISEs), offers several advantages such as speed and ease of preparation and procedures, simple instrumentation, relatively fast response, wide dynamic range, reasonable selectivity, and low cost [26]. Screen printed electrochemical sensors, which are simple and sensitive, have been reported. They often fabricated according to application of the thick-film technology which results in highly reproducible, efficiency of the large scale production [27–30] and economic fabrication of the electrodes. In continuation to our research work [7], we introduced new potentiometric sensors for selective determination of DPH in pure and pharmaceutical preparations. The method is based on the ion-pair formation between DPH and sodium tetraphenyl borate as electroactive material and tricresylphosphate (TCP) as placticizer in DPH matrix. These sensors exhibit analytical characteristics with near-Nernstian sensitivity, low detection limit and therefore, are useful as indicator electrodes in potentiometric determination of DPH in pure form and in capsules.

2. EXPERIMENTAL

2.1. Reagents and materials

Diphenhydramine hydrochloride (DPH) was kindly provided, as a gift, from National Organization for Drug Control and Research, Giza, Egypt. A pharmaceutical preparation (Sultan, Antihistaminic 50 mg per capsule) was supplied from Pharaonia Company, New Borg El-Arab City, Alexandria, Egypt. Polyvinylchloride (PVC relative high molecular weight) and graphite powder (synthetic 1–2 μm) were supplied from Aldrich (USA) and tricresylphosphate (TCP) was purchased from Sigma-Aldrich (Germany). All the solutions were prepared in de-ionized water. Glucose, lactose, starch, sucrose, fructose, glycine, calcium chloride, ammonium chloride, sodium chloride and cadmium chloride were used. Sodium tetraphenylborate (NaTPB, Sigma-Aldrich, Germany), phosphotungstic acid (PTA, Fluka, Switzerland), phosphomolybdic acid (PMA, Fluka, Switzerland) and reineckate ammonium salt (RAS, Fluka, Switzerland) were used for precipitation of different ion pairs. Cyclohexanone and acetone were supplied from Fluka (Switzerland).

2.2. Apparatus

Laboratory potential measurements were performed using HANNA pH meter model 211 (Romania). Silver-silver chloride double - junction reference electrode (Metrohm 6.0222.100) in conjugation with different drug ion selective electrodes was used. Digital burette was used for the measurement of the drug under investigation. Elemental analysis (C, H, N) were determined using CHNS-932 (LECO) Vario Elemental analyzer. Automatic pipettes Socorex Swiss (50–200 μL and 200–1000 μL) were used to measure the very small volumes whereas glass micropipettes were used to measure the large volumes.

2.3. Pharmaceutical preparations

Diphenhydramine hydrochloride solution (Sultan,) was prepared by grinding the content of fifteen capsules, the weight of the powder assigned to contain 0.7278 g DPH was dissolved in 30 mL de-ionized water, filtered and the solution was completed to the mark (50 mL) with de-ionized water.

2.4. Preparation of modified screen printed and carbon paste electrodes

SPEs were printed in arrays of six couples consisting of the indicator electrodes (each 5×35 mm). 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 cut by scissors. The indicator electrodes were prepared depending on the method of fabrication. The indicator electrode was printed using homemade carbon ink (prepared by mixing 225 mg TCP, 0.625 g of polyvinyl chloride (8%), 0.375 g carbon powder and the different amount of contents of 2.5-30 mg ion pairs or ion pairing reagents) and cured at 50 °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. Three types of the indicator electrodes were prepared depending on the method of fabrication. The fabricated electrodes were stored at 4 °C and used directly in the potentiometric measurements [31–33].

The carbon paste electrode is prepared by intimate mixing accurately weight (500 mg) of highly pure graphite powder, plasticizer (0.2 ml of TCP) and the content amount of (2.5-12.5 mg) ion pairs or ion pairing reagents. This matrix was thoroughly mixed in the mortar and the resulted past was used to fill the electrode body [31–33]. 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.

2.5. Ion pairs preparation

Different DPH-IPs were precipitated by dropwise addition of the ion pairing solution to 50 ml of DPH solution (10^{-2} mol L^{-1}) with continuous stirring for 15 min. The precipitated IPs were then filtered off, washed several times with de-ionized water and dried at 50 ºC. The chemical compositions of the different ion pairs (IPs) were confirmed by elemental analysis.

2.6. Calibration of sensors

Standard DPH solutions having concentrations of 10^{-1} to 10^{-6} mol L^{-1} were prepared. The potential in mV of each sample solution was directly measured using the sensors. The logarithmic values of concentrations (log[DPH]) were plotted versus measured potentials. Slopes of the resulting calibration curves were calculated.

3. RESULTS AND DISCUSSION

3.1. Elemental analysis

Table. 1. Composition of ion pairs.

Ion pair types (DPH-reagent)	Calculated values			Found values			Stoichiometric ratio
	%C	%H	%N	%C	%H	%N	
DPH-TPB	85.48	7.30	2.43	85.85	7.41	2.21	1:1
DPH-PTA	16.79	1.81	1.15	17.23	1.97	1.10	3:1
DPH-PMA	23.62	2.55	1.62	24.38	2.75	1.50	3:1
DPH-RN	42.51	5.06	16.53	42.88	4.53	17.30	1:1

The DPH-TPB, DPH-PTA, DPH-PMA and DPH-RN ion pairs which have white, white, light green and light violet colours, resulted from reaction between DPH and Na-TPB, PTA, PMA and RN ion pairing agents, respectively, can be used as modifier in DPH sensors. Table 1 shows that the calculated and observed analysis data for the ion-associate complexes are in good agreement with their suggested formulae.

3.2. Optimization of the electrode performance

Modified (using DPH-TPB, DPH-PTA, DPH-PMA and DPH-RN ion pairs) and in situ modified (using Na-TPB, PTA, PMA and RN ion pairing agents) electrodes were prepared and optimized by testing the nature and content of modifier, effect of pH, response time, temperature of DPH solution, life time of sensors and finally applications.

3.2.1. DPH-ISEs modified with the IPs

3.2.1.1. Effect of the ion-pair type.

Table. 2. Critical response characteristics of MSPE, ISPE, MCPE and ICPE sensors.

Parameters	Modified sensors				Unmodified sensors [7]	
	MSPE	ISPE	MCPE	ICPE	SPE	CPE
Slope (mVdecade^{-1})	56.20±0.65	59.14±0.90	55.86±1.12	60.03±1.32	55.20±1.0	54.70±1.0
Intercept	670.20	631.67	439.67	418.80	545.4	543.8
Correlation coefficient (r)	0.9998	0.9992	0.9989	0.9986	0.9494	0.9616
Linear range (mol L^{-1})	1x10^{-6}-1x10^{-1}	1x10^{-6}-1x10^{-1}	1x10^{-6}-1x10^{-1}	1x10^{-6}-1x10^{-1}	1x10^{-6}-1x10^{-1}	1x10^{-6}-1x10^{-1}
Detection limit (mol L^{-1})	9.65x10^{-7}	9.68x10^{-7}	9.78x10^{-7}	9.76x10^{-7}	9.7x10^{-7}	9.8x10^{-7}
Response time (s)	5	6	10	11	10	16
Working pH range	2.5 – 8	3-9	2.5 – 7	3 - 8	3-8	3-7
Life time (day)	71	76	57	62	63	55
Isothermal coefficient (V/ºC)	0.00034	0.00032	0.00021	0.00036	0.00038	0.00030
Percent recovery(%) ±SD	98.75±0.43-99.27±0.34	98.95±0.19-99.66±0.20	98.91±0.29-99.65±0.32	97.83±0.76-99.17±0.20	97.88±0.54-99.13±0.43	97.28±0.64-99.03±0.62
Accuracy (%)	99.17	99.31	99.28	98.66	98.55	98.26
Standard deviation (%)	1.86	1.13	0.90	1.93	2.08	2.58
Repeatability (CV^{a} %)	0.54	0.29	0.26	0.56	0.76	01.07

Different fabricated electrodes (SPEs and CPEs) were modified in bulk with different IPs; DPH-TPB, DPH-RN, DPH-PTA or DPH-PMA, as electroactive components. The fabricated electrodes show Nernstian responses towards DPH with different slopes depending on the nature of the IP used. Electrodes modified with DPH-TPB ion pair showed high sensitivity with respect to others indicated by the highest slope (56.20±0.65 and 55.86±1.12 mV decade^{-1} for MSPE and MCPE sensors, respectively). The other electrodes gave calibration graphs with lower slope values. The result is better than of those previously reported for unmodified electrodes (55.2 and 54.7 mV decade^{-1} for unmodified SPE and CPE, respectively) (Table 2) [7], PVC membrane (51.0 mV decade^{-1}) [6a] or

61.0, 54.0 and 51.0 mV decade^{-1} for CWE (Cu), CWE (Cu/CuS) and PVC membrane [6b], respectively.

3.2.1.2. Effect of the ion-pair content.

The influence of the DPH-TPB ion exchanger content (sensing material) on the electrode performance was studied. For this purpose, various electrodes were prepared containing different amounts of the ion pair amounts to 2.5–30 mg for MSPE and 2.5–12.5 mg for MCPE (Figure 2).

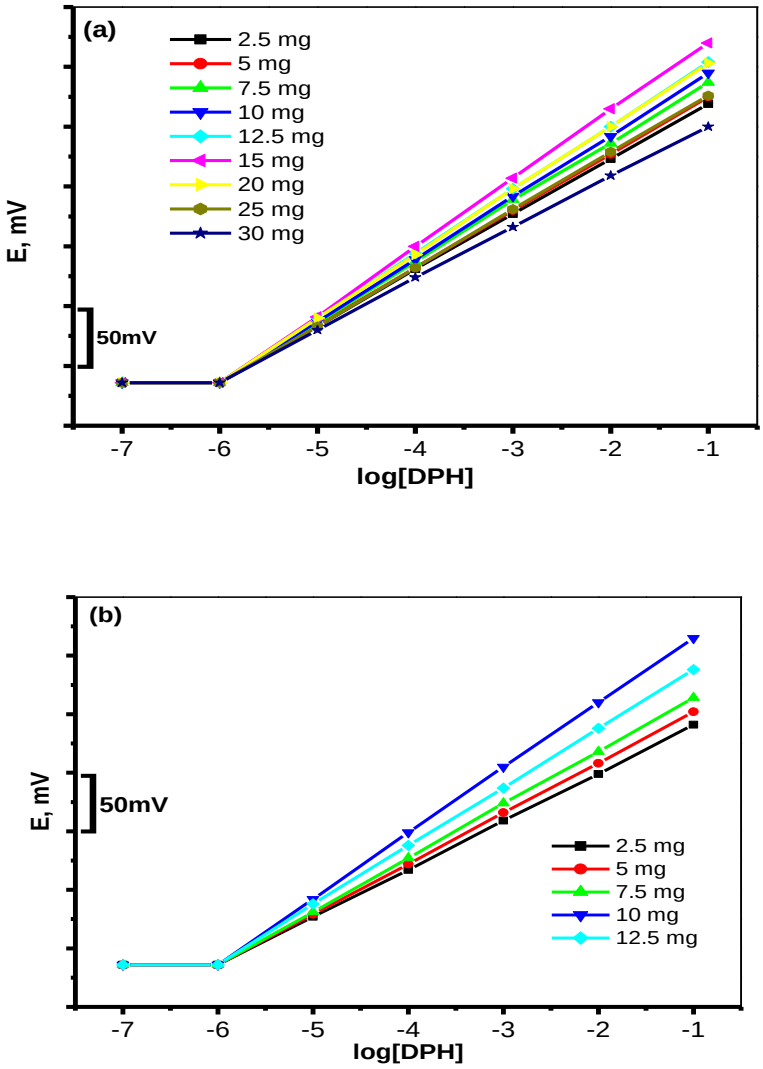


Figure 2. Effect of IP content on calibration of in situ (a) SPE (b) CPE

It was obvious that, as the ion-pair content increases, the slope of the calibration curve increases till certain point (optimum IP content is found to be 15 and 10 mg for SPE and CPE sensors, respectively) then decreases for all types of the studied electrodes. This is also supported by the high slope values of the calibration curve in the tested concentration range from 10^{-6} to 10^{-1} mol L^{-1}

(56.20±0.65 and 55.86±1.12 mV decade^{-1}) for MSPE and MCPE sensors, respectively. This means that the performance characteristics of the MSPE and MCPE sensors increased with the increase of the ion pair content.

3.2.2. In situ DPH-ISEs

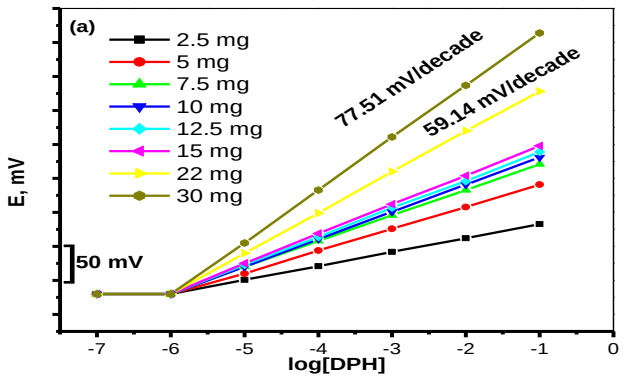
Suitable ion-pairing agent is incorporated in the electrode matrix. The advantage of this technique lies in the fact that time required for the electrode fabrication (no need for IP preparation) will be reduced and expansion of the application of ISEs for the determination of drug that cannot be precipitated as a suitable IPs will be done.

3.2.2.1. Effect of the ion-pairing agent type.

Electrodes containing different ion-pairing agents (NaTPB, RN, PTA and PMA) were prepared, and then used for the determination of DPH. It is obvious from the calibration results that electrodes modified with NaTPB were found to have the highest slope values of 59.14±0.90 and 60.03±1.32 mV decade^{-1} for ISPE and ICPE sensors, respectively. The result is better than of those previously reported for unmodified electrodes (Table 2) [7], PVC membrane or coated wire electrodes [6].

3.2.2.2. Effect of the ion-pair agent content.

The effect of the counter ion-pair agent content on the performance of the SPE and CPE electrodes containing 2.5–30 and 2.5–12.5 mg of NaTPB as an ion-pairing agent were studied (Figure 3). They were prepared. It was found that 22 and 10 mg of NaTPB were the best contents that gave the highest slope values of 59.14±0.90 and 60.03±1.32 mV decade^{-1} for ISPE and ICPE electrodes, respectively.



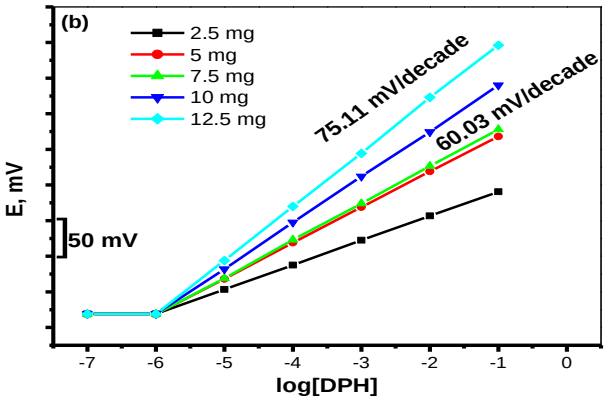


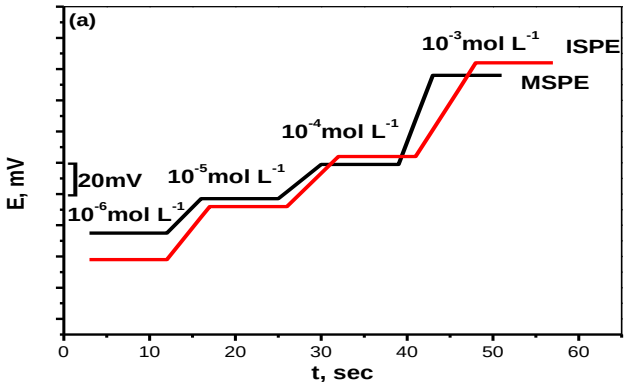
Figure 3. Effect of ion-pairing agent content on calibration of in situ (a) SPE (b) CPE

3.3. Performance of sensors

3.3.1. Calibration plots

The potentiometric response characteristics of DPH-ISEs (SPE and CPE) using different modes of preparation namely modification with ion pairs (MSPE and MCPE) and in situ modification (ISPE and ICPE)), were evaluated according to IUPAC recommendations [35]. Data obtained in Table 2 show that the developed sensors can be successfully applied for the potentiometric determination of DPH with linear response from 10^{-6} to 10^{-1} mol L^{-1} and Nernstian cationic slopes depend on the type of the electrode and the method of preparation. This concentration range is wider than the previously reported data using PVC membrane (10^{-2}-$3.5x10^{-5}$ mol L^{-1}) [6a], coated wire electrode ($5.0x10^{-5}$-10^{-2} mol L^{-1}) [6b] and unmodified SPE and CPE (10^{-6}-10^{-2} mol L^{-1}) [7]. The lower limit of detection (LOD) of the electrode in batch mode was defined as the concentration range of DPH corresponding to the intersection of the two extrapolated linear segments of the calibration graph, equals to 9.68×10^{-7}, 9.65×10^{-7}, 9.78×10^{-7} and 9.76×10^{-7} mol L^{-1} for ISPE, MSPE, MCPE and ICPE electrodes, respectively. These detection limits are lower than those previously reported [6, 7].

3.3.2. Response time



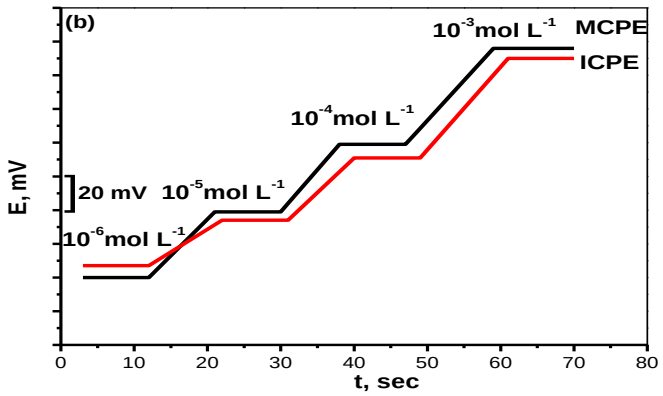
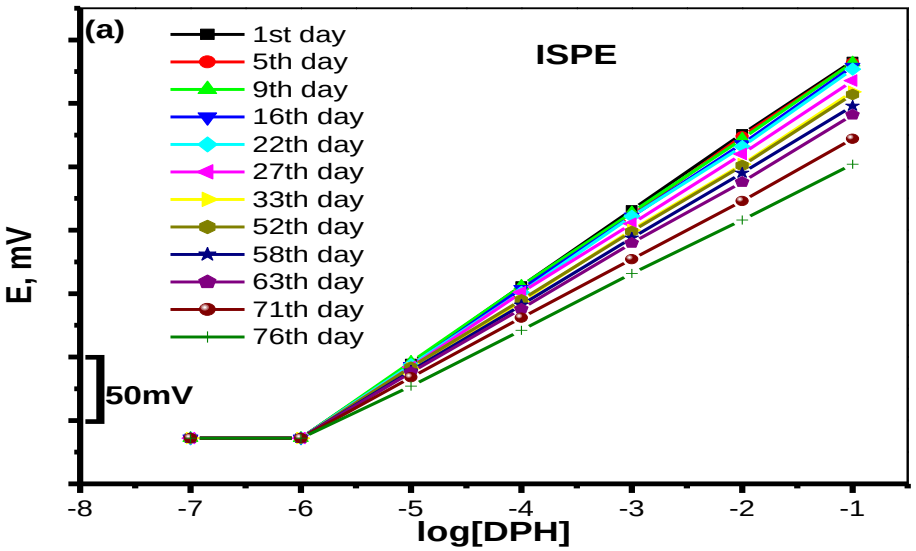


Figure 4. Dynamic response time DPH sensors: (a) SPE and (b) CPE sensors.

The response time of a fabricated sensor is of critical importance. It is the average time required for the electrode to reach a steady potential response within ±1 mV of the final equilibrium value after successive immersion of a series of DPH solutions, each having a 10- fold difference in concentration, is investigated [35–37]. The response time of the SPEs (MSPE and ISPE) and CPEs (MCPE and ICPE) sensors was defined as t_{95} for the slope of the calibration curve of DPH solution when the DPH concentration was rapidly increased from 1.0×10^{-6} to 1.0×10^{-1} mol L^{-1} (Fig. 4). It is found that the response time of the fabricated MSPE, ISPE, MCPE and ICPE is 5, 6, 10 and 11 s, respectively, and the equilibrium potentials essentially remained constant for over 10 min. The result is better than those previously reported for unmodified electrodes (10 and 16 s for SPE and CPE, respectively) (Table 2) [7], PVC membrane (≤ 20s) [6a] and CWE (≤10s) [6b].

3.3.3. Life time



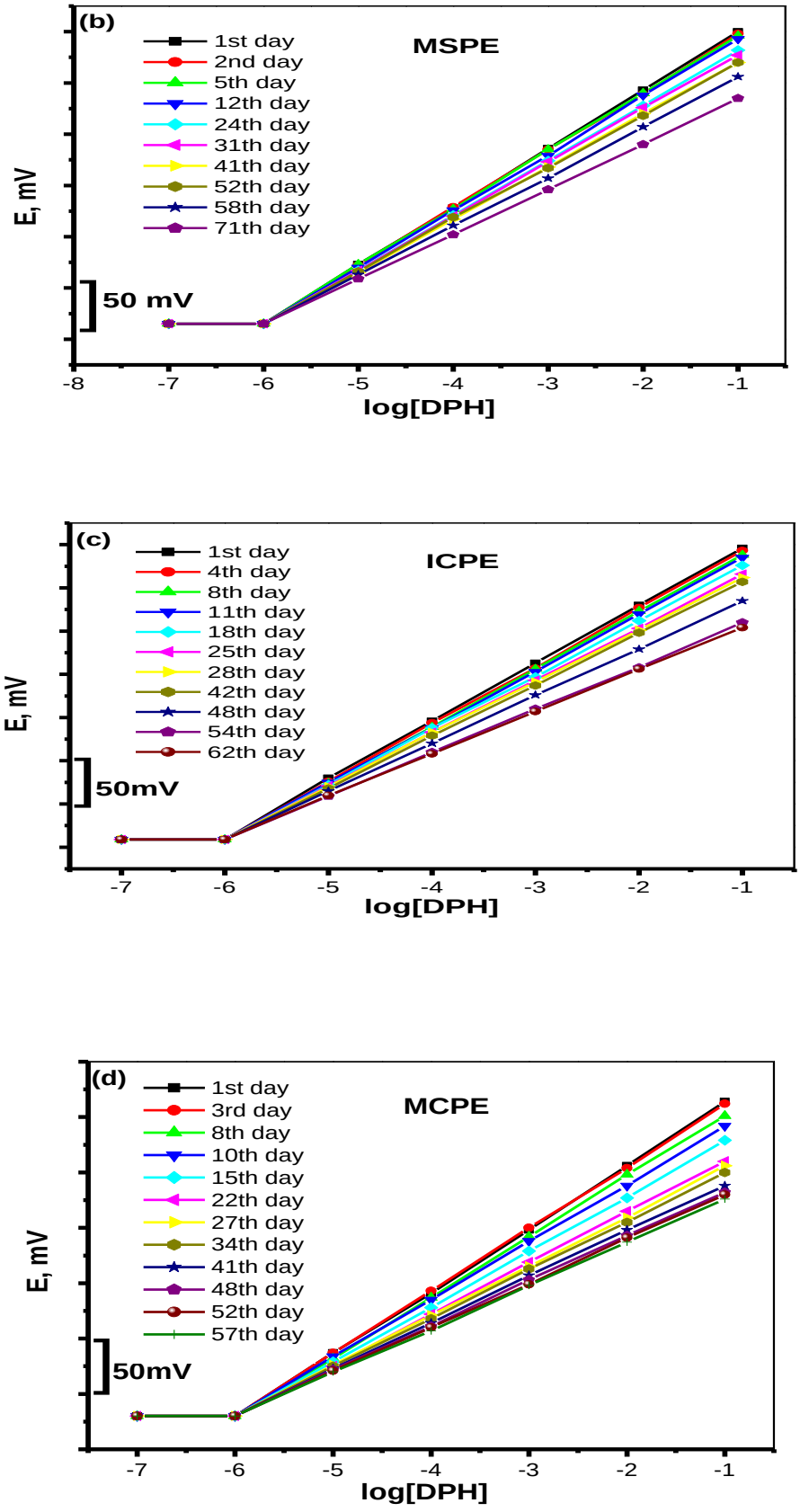


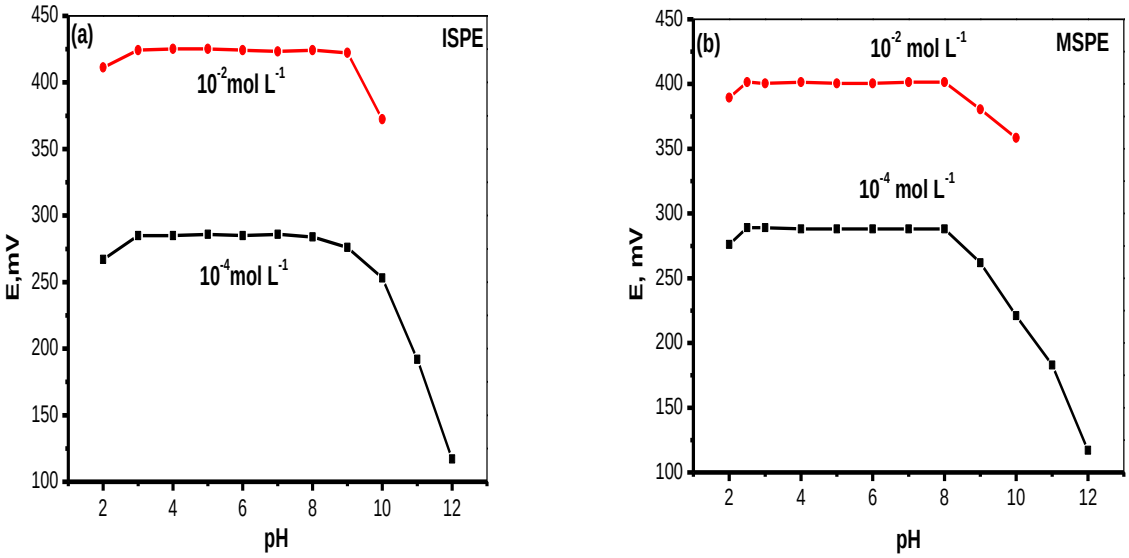
Figure 5. Life time of DPH-ISE sensors (a) In situ SPE (b) Modified SPE, (c) In situ CPE (d) Modified CPE.

The performance of the fabricated modified SPE and CPE potentiometric sensors has been calibrated on different days ranged from one day to 76 days for modified SPE and 62 days for modified CPE and the measurement of the slope is recorded daily. The data obtained for DPH-ISEs are shown in Fig. 5. For modified SPE sensors, it is clear that these ISPE and MSPE electrodes have a life time up to 76 and 71 days, respectively. While ICPE and MCPE sensors are usefully used up to 62 and 57 days, respectively.

This indicates that all the fabricated sensors have high mechanical durability and good adherent to the PVC substrate. Both dry and wet ion-sensitive membranes adhere very tightly to the conductive track and the substrate material. Mechanical separation of these layers is impossible as the consecutive thick-films forming the sensor contain the same polymer matrix material. For the determination of the storage stability, SPE sensor fabricated in the same production cycle has been used. Although the electrode is a disposable device, a longer stability test is also investigated and the electrodes are successfully used for at least 50 consecutive measurements. The result is better than of those previously reported for unmodified electrodes which have duration times of 63 and 55 days for SPE and CPE, respectively [7] (Table 2).

3.3.4. Effect of pH

The effect of pH on the modified SPE and CPE sensors performance was evaluated using different concentrations of $1.0x10^{-2}$ and $1.0x10^{-4}$ mol L^{-1} of DPH within the pH range 2–12. It is carried out by addition of small volumes of HCl and/or NaOH solution (0.1–1 mol L^{-1} of each) to the titration medium using SPE (MSPE and ISPE) and CPE (MCPE and ICPE) potentiometric sensors. It is obvious that, within the pH range from 2.5 to 8.0, 3.0 to 9.0, 2.5 to 7.0 and 3.0 to 8.0 [31–33, 38, 39] for MSPE, ISPE, MCPE and ICPE, respectively, the electrodes potential is practically independent of pH. In this range, the electrodes; SPE and CPE, can be safely used for DPH determination (Fig. 6).



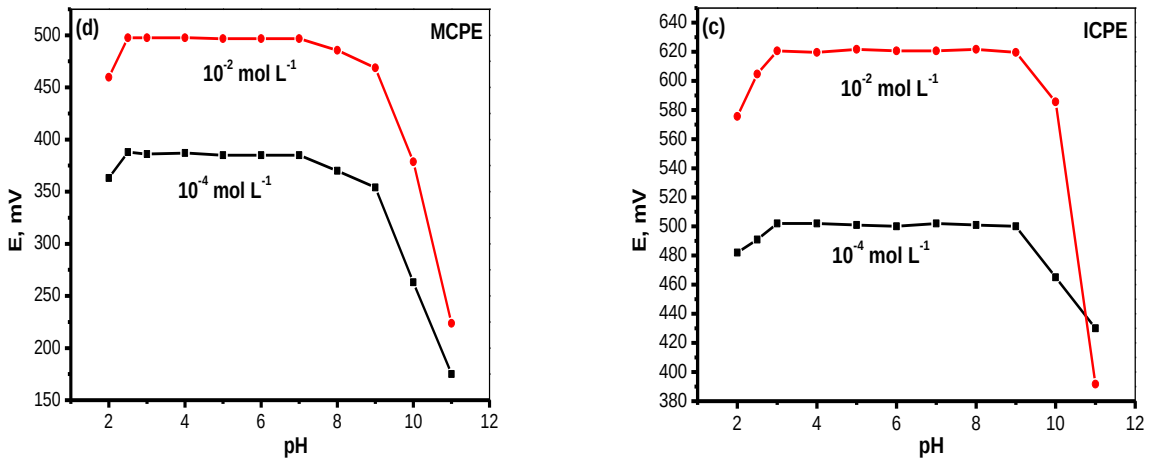


Figure 6. Effect of pH on DPH-ISE sensors: (a and b) SPE (in situ and modified) and (c and d) CPE (in situ and modified)

The increase in mV readings at pH < 2.5 may be due to interference of hydronium ion. At higher pH values (pH > 8.0), free base precipitates in the test solution and consequently, the concentration of unprotonated species gradually increased. As a result, lower e.m.f. readings were recorded. Therefore, pH = 3 is recommended for the subsequent studies. The result indicates that these modified electrodes are pH independent over a wide pH range than those previously reported [6, 7].

3.3.5. Effect of temperature

Calibration graphs (electrode potential (E_{elec}) versus p[DPH]) were constructed at different test solution temperatures (10, 25, 30, 40, 50 and 60 °C). For the determination of the isothermal coefficient (dE^0/dt) of the SPE and CPE electrodes, the standard electrode potentials (E^0) against the normal hydrogen electrode at the different temperatures were obtained from calibration graphs as the intercepts at p[DPH] = 0 (after subtracting the values of the standard electrode potential of the calomel 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 is obtained according to Antropov's equation [40, 41].

$$E^0 = E^0_{(25)} + (dE^0/dt)(t - 25)$$

Where $E^0_{(25)}$ is the standard electrode potential at 25 °C. The slope of the straight-line obtained represents the isothermal coefficient of the MSPE, ISPE, MCPE and ICPE electrodes which are found to be 0.00034, 0.00032, 0.00021 and 0.00036 V/°C, respectively. The value of the obtained isothermal coefficient of the electrodes indicates that they have fairly high thermal stability within the investigated temperature range. The investigated electrodes were found to be usable up to 60 °C without noticeable deviation from the Nernstian behaviour. The relative sensitivity of modified SPE and CPE towards the temperature may be due to the change in the conductivity of the electrodes with increasing the temperature which will affect the potential reading. The result is better than of those previously reported for unmodified electrodes (0.00038 and 0.0003 V/°C for SPE and CPE, respectively) (Table 2) [7] and PVC membrane (0.00156 V/°C) [6a].

3.3.6. Selectivity

The selectivity behaviour is obviously one of the important characteristics of SPE and CPE sensors in which reliable measurement of the target drug is determined to be possible or not. The selectivity coefficient, $\log K^{pot}_{D,B}$, of the SPE and CPE were determined employing separate solution method (SSM) with the rearranged Nicolsky equation [38, 42]:

$$\log K^{pot}_{D,B} = \frac{(E_1 - E_2)}{S} + \left(1 + \frac{z_1}{z_2}\right) \log a$$

where, E_1 is the potential measured in 1.0×10^{-3} mol L^{-1} DPH (D), E_2 the potential measured in 1.0×10^{-3} mol L^{-1} of the interfering compound (B), z_1 and z_2 are the charges of the DPH (D) and interfering species (B), respectively, and S is slope of the electrode calibration plot. The results obtained are summarized in Table 3.

Table 3. Potentiometric selectivity coefficient of SPE and CPE sensors.

Interfering ion (B)	$K^{pot}_{D,B}$							
	MSPE		ISPE		MCPE		ICPE	
	SSM	MPM	SSM	MPM	SSM	MPM	SSM	MPM
Glucose	---------	2.50×10^{-5}	------	5.00×10^{-6}	---------	1.20×10^{-4}	---------	3.20×10^{-6}
Fructose	---------	3.90×10^{-5}	--------	3.24×10^{-6}	---------	3.98×10^{-4}	---------	1.09×10^{-6}
Lactose	---------	5.01×10^{-5}	--------	2.90×10^{-6}	---------	1.23×10^{-4}	---------	3.80×10^{-6}
Sucrose	---------	3.55×10^{-5}	--------	4.70×10^{-6}	---------	1.00×10^{-4}	---------	5.60×10^{-6}
Starch	---------	7.24×10^{-5}	--------	4.70×10^{-6}	---------	2.88×10^{-4}	---------	5.04×10^{-6}
Glycine	---------	3.55×10^{-5}	---------	1.50×10^{-6}	---------	8.71×10^{-4}	---------	8.28×10^{-6}
Na^+	9.55×10^{-5}	---------	4.60×10^{-6}	---------	6.03×10^{-4}	---------	9.54×10^{-6}	---------
NH_4^+	9.12×10^{-5}	---------	1.30×10^{-6}	---------	1.59×10^{-4}	---------	4.73×10^{-6}	---------
K^+	9.21×10^{-5}	---------	3.45×10^{-6}	---------	7.54×10^{-4}	---------	7.22×10^{-6}	---------
Cd^{2+}	3.16×10^{-5}	---------	2.24×10^{-6}	---------	3.63×10^{-4}	---------	1.38×10^{-6}	---------
Ca^{2+}	1.45×10^{-5}	---------	3.24×10^{-6}	---------	6.17×10^{-4}	---------	1.97×10^{-6}	---------
Ni^{2+}	6.13×10^{-5}	---------	9.09×10^{-6}	---------	5.36×10^{-4}	---------	4.17×10^{-6}	---------
Co^{2+}	7.21×10^{-5}	---------	9.37×10^{-6}	---------	6.13×10^{-4}	---------	3.51×10^{-6}	---------
Fe^{3+}	1.31×10^{-4}	---------	2.13×10^{-5}	---------	9.89×10^{-4}	---------	8.98×10^{-6}	---------
Al^{3+}	1.97×10^{-4}	---------	1.94×10^{-5}	---------	9.78×10^{-4}	---------	1.10×10^{-5}	---------
Cr^{3+}	2.01×10^{-4}	---------	3.01×10^{-5}	---------	1.08×10^{-3}	---------	1.12×10^{-5}	---------

In addition to the SSM, the selectivity of the investigated electrodes was determined by the matched potential method (MPM) [44]. In this method, the potentiometric selectivity coefficient is defined as the activity ratio of primary and interfering ions that give the same potential change under identical conditions.

At first, a known concentration ($C`_D$) of the drug ion solution is added into a reference solution that contains a fixed concentration (C_D) of drug ions, and the corresponding potential (ΔE) is recorded. Next, solution of an interfering ion is added to the reference solution until the same potential change (ΔE) is recorded. The change in potential produced at the constant background of the drug ion must be the same in both

$$K^{pot}_{D,B} = (C`_D - C_D)/C_B$$

where C_B is the concentration of the interfering ion.

In pharmaceutical analysis, it is important to test the selectivity toward the excipients and the fillers added to the pharmaceutical preparations. A reasonable selectivity toward DPH in the presence of many carbohydrates and nitrogenous compounds such as amines, glycine, and some inorganic cations was observed. The results showed no serious interference by a number of pharmaceutical excipients, diluents and active ingredients commonly used in the drug formulations (e.g. glucose, lactose, maltose, fructose, starch and sucrose) at concentration as high as a 10–100-fold molar excess over DPH. This is clear from the results obtained for the pharmaceutical preparations Table 3 that these excipients do not interfere. Therefore, the sensors have been found to be chemically inert to other substances. The result is better than of those previously reported for unmodified electrodes.

3.4. Analytical applications

3.4.1. Potentiometric determination of DPH drug in pharmaceutical preparation

The potentiometric calibration methods are applied for the determination of DPH in pharmaceutical preparation using modified SPE and CPE sensors plasticized with TCP (Table 4).

Table 4. Potentiometric determination of DPH in Sultan capsules by different modes of DPH-ISE sensors.

Electrode type	[DPH] taken µg mL^{-1}	[DPH] µg mL^{-1} found		Recovery %		SD (RSD%)[a]		Standard official method[c]			
		calibration	SAM	calibration	SAM	calibration	SAM[b]	[DPH] taken µg mL^{-1}	[DPH] found µg mL^{-1}	Recovery (%)	RSD%[a] (n = 5)
MSPE	4.87	4.91	4.83	100.82	99.18	0.022(0.45)	0.053 (0.61)				
	8.75	8.64	8.71	98.74	99.49	0.072(0.83)	0.042 (0.48)				
ISPE	4.87	4.85	4.79	99.59	98.36	0.031(0.64)	0.061 (0.58)	20.00	19.55	97.75	0.44
	8.75	8.66	8.64	98.97	98.74	0.035(0.40)	0.027 (0.31)				
MCPE	4.87	4.84	4.81	99.38	98.77	0.037(0.75)	0.047 (0.29)				
	8.75	8.63	8.63	98.63	98.63	0.033(0.39)	0.049 (0.56)				
ICPE	4.87	4.94	4.78	101.44	98.15	0.033(0.67)	0.055 (0.37)				
	8.75	8.89	8.41	101.6	96.11	0.078(0.87)	0.039 (0.47)				

[a] Average of five replicate (n = 5)
[b] Standard addition method
[c] With TCP plasticizer and Sultan as pharmaceutical product

The results are compared with the standard official method and have shown that the proposed SPE and CPE electrodes has good efficiency as regard of sensitivity, index of retrieving and repetition. As the conventional method for determination of DPH (extraction method) [43] was difficult and time-

consuming as well as using of expensive solvents, but this method (potentiometric determination) is easy, fast and inexpensive (Table 4). One of the important applications of these drug-selective electrodes would have the study and investigation of DPH.

3.4.2. Intra and inter assays

Table. 5. Inter- and Intra-days by using of different DPH-ISE sensors:

Drug	Electrode type	[DPH] Taken, µg mL^{-1}	Intra-day				Inter-day			
			Found, µg mL^{-1}	Recovery%	SD	RSD%	Found, µg mL^{-1}	Recovery%	SD	RSD%
Pure form	MSPE	3.50	3.49	99.71	0.014	0.41	3.52	100.6	0.017	0.49
		6.20	6.17	99.52	0.041	0.66	6.21	100.2	0.034	0.54
		12.50	12.54	100.3	0.051	0.41	12.43	99.44	0.068	0.55
	ISPE	3.50	3.51	100.3	0.014	0.40	3.51	100.3	0.008	0.23
		6.20	6.15	99.19	0.034	0.55	6.16	99.36	0.041	0.66
		12.50	12.58	100.6	0.058	0.46	12.44	99.52	0.070	0.57
	MCPE	3.50	3.49	99.71	0.025	0.71	3.49	99.71	0.014	0.41
		6.20	6.23	100.5	0.024	0.46	6.11	98.55	0.065	1.07
		12.50	12.53	100.2	0.029	0.47	12.39	99.12	0.086	0.70
	ICPE	3.50	3.45	98.57	0.047	1.35	3.54	101.1	0.042	1.19
		6.20	6.25	100.8	0.060	0.96	6.18	99.68	0.025	0.40
		12.50	12.42	99.36	0.063	0.51	12.49	99.92	0.017	0.56
Sultan tablet	MSPE	2.90	2.89	99.66	0.017	0.59	2.87	98.97	0.032	0.56
		5.25	5.19	98.86	0.023	0.44	5.17	98.48	0.042	0.65
		11.20	11.27	100.6	0.037	0.32	11.27	100.6	0.026	0.44
	ISPE	2.90	2.91	100.3	0.023	0.78	2.83	97.59	0.072	0.88
		5.25	5.19	98.86	0.020	0.39	5.31	101.1	0.045	0.67
		11.20	11.13	99.38	0.037	0.37	11.12	99.29	0.031	0.47
	MCPE	2.90	2.88	99.31	0.018	0.63	2.93	101.0	0.037	0.71
		5.25	5.18	98.66	0.020	0.39	5.17	98.48	0.061	0.93
		11.20	11.09	99.02	0.039	0.58	11.11	99.20	0.040	0.53
	ICPE	2.90	2.89	99.66	0.039	1.36	2.86	98.62	0.042	1.17
		5.25	5.37	102.3	0.036	0.67	5.18	98.67	0.039	0.79
		11.20	11.24	100.4	0.034	0.30	11.16	99.64	0.028	0.56

For the developed drug electrodes, four different calibration runs of pure and pharmaceutical solutions are performed in the same day (Intra) and on four different days (Inter), in order to evaluate the reproducibility of the results obtained. Data listed in Table 5 give statistical summary of each of the calibration series using the SPE and CPE sensors. The results obtained indicate the high accuracy and reproducibility of the proposed method.

4. VALIDATION OF THE PROPOSED POTENTIOMETRIC METHOD USING MODIFIED SPE AND CPE SENSORS.

4.1. Accuracy

The accuracy of the proposed potentiometric method using modified SPE and CPE sensors is investigated by the determination of DPH in sultan samples prepared from serial concentrations of DPH reference standards. The results summarized in Table 2, show that the proposed method is an

accurate one, as indicated by the percentage recovery values, for the determination of DPH in its pharmaceutical preparations without interferences from the coformulated adjuvants.

4.2. Linearity

Under the optimal experimental conditions, linear relationships exist between the electrode potential (mV) and the log [DPH]. The regression data, correlation coefficients (r) and other statistical parameter are previously listed in Table 2.

4.3. Precision

The precision of the proposed potentiometric method using modified CPE and SPE sensors, measured as percentage relative standard deviation (RSD%) was tested by repeating the proposed method for determination of DPH in its pharmaceutical preparations of "two batches" to five replicates [3, 40]. The RSD% values for the repeated determinations of 6.40 mg mL^{-1} were 1.35, 1.09, 1.14 and 1.36% for determination of DPH in sultan capsules using MSPE, ISPE, MCPE and ICPE sensors. The above RSD values are less than 2% indicating good precision of the proposed method.

4.4. Detection limit

The detection limit of the investigated DPH drug was calculated according to IUPAC recommendation [3, 40]. The detection limit is defined as the concentration at which the measured potential differs from that predicted by the linear regression by more than 18 mV. The values previously reported in Table 2, indicate that the proposed modified SPE and CPE sensors are sensitive to detection of very small concentrations of DPH.

5. CONCLUSION

The potentiometric procedure proposed here eliminates the prior separation steps that are usually necessary in the determination of DPH in pharmaceutical preparations. Additionally, the proposed method has some important advantages: the electrodes proved to be successful, providing a rapid, simple and low cost potentiometric method for the determination of DPH in pure solutions and in pharmaceutical preparations. It ensures a good accuracy for the DPH assay due to the possibility to control the ion activity continuously and also a fast assay of DPH capsules.

The accuracy of the method is indicated by excellent recovery and low standard deviation. Screen printing technique which is especially suitable due to its simplicity, low cost, high reproducibility and efficiency of the large scale production (commercialization). The all results here are better than of those previously reported PVC membrane electrodes [7] (Table 6).

Table 6. Comparison of the proposed potentiometric method with the existing methods for the determination of DPH.

Electrode type	Slope (mV decade^{-1})	Linear range (mol L^{-1})	Detection limit (mol L^{-1})	Response time (s)	Working pH range	Life time (day)	Reference
PVC (DPH-TPB)	51.0	$3.5x10^{-5}$-$1x10^{-2}$	$3x10^{-5}$	≤ 20	2-7.5	----	(6a)
CWE (Cu)	61±2	$5x10^{-5}$-$1x10^{-2}$	----	≤ 10	----	----	(6b)
CWE (Cu/CuS)	54±3	----	----	Instanta-neous	----	60	6b)
PVC (DPH-TPB)	51±2	----	----	Instanta-neous	2-7	60	(6b)
CPE	54.70±1.0	$1x10^{-6}$-$1x10^{-2}$	$9.8x10^{-7}$	16	3 - 7	55	(7)
SPE	55.20±1.0	$1x10^{-6}$-$1x10^{-2}$	$9.7x10^{-7}$	10	3 - 8	63	(7)
MCPE (DPH-TPB)	55.86±1.12	$1x10^{-6}$-$1x10^{-1}$	$9.78x10^{-7}$	10	2.5 - 7	57	Present work
MSPE (DPH-TPB)	56.20±0.65	$1x10^{-6}$-$1x10^{-1}$	$9.65x10^{-7}$	5	2.5 - 8	71	Present work
ICPE	60.03±1.32	$1x10^{-6}$-$1x10^{-1}$	$9.76x10^{-7}$	11	3 - 8	62	Present work
ISPE	59.14±0.90	$1x10^{-6}$-$1x10^{-1}$	$9.68x10^{-7}$	6	3 - 9	76	Present work

References

1. J.E.F. Reynolds, Martindale the Extra Pharmacopoeia, 30th ed, Pharmaceutical Press, London, 1993, pp. 937–938.
2. A.R. Gennaro, Remington: the Science and Practice of Pharmacy, Mack Publishing Company, Pennsylvania, 1995, pp. 1225–1226.
3. The Pharmacopoeia of the United States of America, 18th ed, United States Pharmacopoeial Convention, Inc, Easton, 1970.
4. M.M. Tuckerman, K. Acel, T. Bican-Fister, J. Billow, I.S. Gibbs, Assay of official injections of amine salts, *J. Pharm. Sci*. 61 (1972) 448.
5. British Pharmacopoeia, HMSO, London, 1993, p. 886.
6. (a) A. Erdem, M. Ozsoz, L. Kirilmaz, E. Kilinc, T. Dalbasti, *Electroanalysis* 9 (1997) 932. (b) A.F. Shoukry, S.S. Badawy and Y.M. Issa. *J. Electroanal. Chem*. 233 (1987) 29.
7. E.Y.Z. Farag, G.G. Mohamed, W. G. El-Sayed, *Bioelectrochemistry* 82 (2011) 79.
8. P. Tipparat, S. Lapanantnoppkhun, J. Jakmunee, K. Grudpan, *J. Pharm. Biomed. Anal*. 30 (2002) 105.
9. A.M. El-Didamony, M.A. Moustafa, *Arabian J. Chem*. 3 (2010) 265.
10. The United States Pharmacopoeia, 21st ed, United States Pharmacopoeial Convention, Inc, Rockville, 1985, pp. 340.
11. A.G. Davidson, S.M. Hassan, *J. Pharm. Sci*. 73 (1984) 413.
12. E.E. Muller, J. Sherma, *J. Liq. Chromatogr. Relat. Technol*. 22 (1999) 153.
13. S.V. Raj, S.U. Kapadia, A.P. Argekar, *Talanta* 46 (1998) 221.
14. The United States Pharmacopoeia, 24th ed, United States Pharmacopoeial Convention, Inc, Rockville, 2000, pp. 583–584.
15. D. DiGregorio, J. Sherma, *J. Liq. Chromatogr. Relat. Technol*. 22 (1999) 1599.
16. L. Ye, J.T. Stewart, *J. Liq. Chromatogr. Relat. Technol*. 19 (1996) 711.
17. D.A. Skoog, F.J. Holler, T.A. Nieman, Principles of Instrumental Analysis, 5th ed, Harcourt Brace College Publishers, 1998, pp. 564–588.
18. J. Wang, Analytical Electrochemistry, 2nd ed Wiley VCH, New York, 2000.
19. V.V. Cosofret, R.P. Buck, Pharma. App. of Membrane Sensors, CRC Press, Florida, 1992.
20. [20] V.K. Gupta, Manoj K. Pal, Ashok K. Singh, *Electrochim. Acta* 55 (2010) 1061.

21. V.K. Gupta, M.K. Pal, A.K. Singh, *Electrochim. Acta* 54 (2009) 6700.
22. R.N. Goyal, V.K. Gupta, S. Chatterjee, *Biosens. Bioelec*. 24 (2009) 1649.
23. V.K. Gupta, A.K. Singh, B. Gupta, *Anal Bioanal. Chem*. 389 (2007) 2019.
24. V.K. Gupta, A.K. Singh, B. Gupta, *Chem. High Throughput Screening* 10 (2007) 560.
25. V.K. Gupta, A.K. Singh, B. Gupta, *Chem. High Throughput Screening* 10 (2007) 583.
26. A.A. Ensafi, A.R. Allafchian, *J. Pharm. Biom. Anal*. 47 (2008) 802.
27. R. Paciorek, P. Bieganowski, M. Maj-Zurawska, *Sens. Actuators* B 108 (2005) 840.
28. L. Tymecki, S. Glab, R. Koncki, *Sensors* 6 (2006) 390.
29. K.C. Honeychurch, J.P. Hart, *Trends Anal. Chem*. 22 (2003) 456.
30. M.F. Bergamini, D.P. Santos, M.V.B. Zanoni, *Bioelectrochemistry* 77 (2010) 133.
31. E. Khaled, G.G. Mohamed, T. Awad, *Sens. Actuators* B 135 (2008) 74.
32. G.G. Mohamed, T.A. Ali, M.F. El-Shahat, A.M. Al-Sabagh, M.A. Migahed, E. Khaled, *Anal. Chim. Acta* 673 (2010) 79.
33. G.G. Mohamed, T.A. Ali, M.F. El-Shahat, A.M. Al-Sabagh, M.A. Migahed. *Electroanalysis* 22 (2010) 2587.
34. V.V. Egorov, A.A. Bolotin, *Talanta* 70 (2006) 1107.
35. R.P. Buck, E. Lindner, *Pure Appl. Chem*. 66 (1994) 2527.
36. K. Kalcher, I. Svancara, R. Metelka, K. Vytras, A. Walcarius, in: C.A. Grimes, E.C. Dickey, M.V. Pishko (Eds.), *Encyclopedia of Sensors, American Scientific Publishers, Stevenson Ranch*. 4 (2006) 283–430.
37. K. Vytras, J. Jezkova, V. Dlabka, J. Kalous, *Sci. Pap. Univ. Pardubice, Ser*. A, 3, 1997, p. 307.
38. A.M. Othman, N.M.H. Rizk, M.S. El-Shahawi, *Anal. Chim. Acta* 515 (2004) 303.
39. S.S.M. Hassan, E.M. Elnemma, W.H. Mahmoud, A.H.K. Mohammed, *J. Appl. Electrochem*. 36 (2006) 139.
40. S.M. Ghoreishi, M. Behpour, M. Nabi, *Sens. Actuators* B 113 (2006) 963.
41. L.I. Antropov, Theoretical Electrochemistry, Mir Publisher, Moscow, 1977.
42. S.S.M. Hassan, W.H. Mahmoud, A.M. Othman, *Talanta* 44 (1997) 1087 (and references cited therein).
43. W.S. Hassan, M.M. El-Henawee, A.A. Gouda, *Spectrochim. Acta* A 69 (2008) 245.
44. Y. Umezawa, P. Buhlmann, K. Umezawa, K. Tohda, S. Amemiya, *Pure Appl. Chem*. 72 (2000) 1851.