Int. J. Electrochem. Sci., 6 **(2011)** 3508 - 3524

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Construction and Performance Characterization of Ion Selective Electrodes for Potentiometric Determination of Ranitidine Hydrochloride in Pharmaceutical Preparations and Biological Fluids

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Received: 24 May 2011 / *Accepted:* 5 July 2011 / *Published:* 1 August 2011

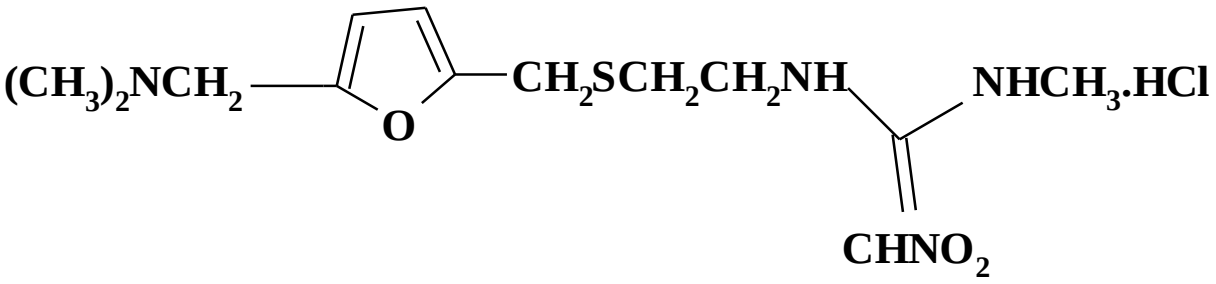
The construction and performance characteristics of ranitidine hydrochloride (RNH) selective electrodes are described. Two types of electrodes: carbon paste and screen printed electrodes were constructed based on the ion-pair formation during potentiometric titration of ranitidine hydrochloride with sodium tetraphenylborate. The electrodes were fully characterized in terms of plasticizer type, response time, lifetime, soaking, titrant, pH and temperature. The CPE and SPE electrodes exhibited Nernstian response for RNH in the concentration range from 1.0×10^{-7} to 1.0×10^{-2} and 1.0×10^{-7} to 1.0×10^{-2} mol L^{-1} with a slope of 55.74±1 and 58.89±1.2 mV $decade^{-1}$, respectively. The detection limit and quantification are found to be 0.07×10^{-7} and 0.23×10^{-7} and 0.09×10^{-7} and 0.32×10^{-7} mol L^{-1} for CPE and SPE, respectively. The standard electrode potentials, $E°$, were determined at 10, 25, 30, 40 and 50 °C and used to calculate the isothermal temperature coefficient ($dE°/dT$) of the two electrodes. Temperatures higher than 50 °C seriously affect the electrodes performance. The direct potentiometric determination of RNH using the proposed sensors gave average recoveries % of 98.00±0.40-98.57±0.37 and 98.68±0.42-99.33±0.31 for CPE and SPE sensors, respectively. The electrodes were applied for potentiometric determination of RNH in pure state and pharmaceutical preparation under batch conditions, urine and serum. Interference studies from a large number of inorganic cations, sugars, glycine and drug excipients are reported. The electrodes gave average selective precision and were usable within the pH range 3-5 and 3-6 for CPE and SPE, respectively. The developed method was found to be simple, accurate and precise when compared with the reported method.

Keywords: Carbon paste electrode, screen printed electrode, ranitidine hydrochloride, potentiometric titration, tablets, urine, serum

1. INTRODUCTION

Ranitidine hydrochloride (RNH) is a histamine H_2-receptor antagonist that inhibits stomach acid production. It is commonly used in treatment of peptic ulcer disease (PUD) and gastroesophageal

reflux disease (GERD). Ranitidine is also used alongside fexofenadine and other antihistamines for the treatment of skin conditions such as hives. Chemically, it is N-[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenedamine HCl. The Systematic (IUPAC) name was N-(2-[(5-(dimethylaminomethyl)furan-2-yl) methylthio]ethyl)-N-methyl-2-nitroethene-1,1-diamine HCl. It has the following structural formula (Scheme 1)



Scheme 1. Structural formula of Ranitidine hydrochloride.

The molecular formula is $C_{13}H_{22}N_4O_3S{\cdot}HCl$, representing a molecular weight of 350.87 g mol^{-1}. It is a white to pale yellow, crystalline substance that is soluble in water. Various analytical techniques have been employed for the quantitative analysis of RNH. Most of these analytical methods are based on high performance liquid chromatography (HPLC) which is applied for determination of RNH and its metabolites in biological fluids [1-6], capillary electrophoresis using UV or capillary electrophoresis-electrochemiluminescent detection [7, 8], and spectrophotometric methods [9-14]. Different electrochemical analytical methods were applied for determination RNH which included voltammetric behaviour [15, 16], coulometric titration [17] and potentiometry using ion-selective electrodes based on liquid-membrane and polyvinyl chloride (PVC)-matrix ion-selective electrodes (ISE) that respond to the cationic forms of RNH [18-21].

Most of these methods, however, utilize expensive instrumentation, suffer from lack of selectivity, involve careful control of the reaction conditions or derivatization reactions, and require time-consuming pretreatment steps, which affect their usefulness for routine analysis. On the other hand, applications of potentiometric sensors in the field of pharmaceutical and biomedical analysis have been advocated [22]. The approach provides simple, fast, and selective technique for determination of various drugs [22-31].

However, as far as the available literature is concerned, very little is known about the use of this technique for RNH quantification [20, 21, 32, 33]. The present work describes preparation; characterization and application of carbon paste (CPE) and screen printed (SPE) electrodes for continuous determination of RNH in pure and pharmaceutical preparations. Performance characteristics of both sensors (CPE and SPE) reveal low detection limit, high sensitivity, good selectivity, fast response, long life span and application for accurate determination of RNH in pharmaceutical preparations.

2. EXPERIMENTAL

2.1. Reagents and materials

All chemicals were of analytical reagent grade unless otherwise specified. Doubly distilled water was used for the preparation of stock solutions of RNH, pure ranitidine hydrochloride (RNH) which was provided by Glaxosmithkline Egypt.

o-Nitrophenyloctylether (*o*-NPOE) was supplied from Fluka (Switzerland), while dioctylphthalate (DOP), dibutylphthalate (DBP) and dioctylsebacate (DOS) were supplied from Merck (Germany) and tricresylphosphate (TCP), polyvinylchloride (PVC relative high molecular weight) and graphite powder (synthetic 1–2 μm) were supplied from Aldrich (USA). Sodium tetraphenylborate (NaTPB) and ammonium reineckate (RN) [$NH_4(Cr(NH_3)_2(SCN)_4).H_2O$] were purchased from Fluka (Switzerland). Phosphomolybdic acid (PMA) $H_3[PMo_{12}O_{40}]$, was purchased from Aldrich (USA). Tetrahydrofuran (THF) supplied from El-Nasr Company (Egypt).

A stock solution (10^{-2} mol L^{-1}) of RNH drug was prepared by dissolving 0.35087 g of RNH in 100 mL bi-distilled water. Other dilute solutions (10^{-3}–10^{-8} mol L^{-1}) were prepared by serial dilution and both the pH and ionic strength was kept constant at 4.5 and 0.05 mol L^{-1}, respectively (adjusted with acetate buffer of pH 3). All the RNH solutions were kept in dark bottles.

A stock solution (10^{-2} mol L^{-1}) NaTPB solution was prepared by dissolving an accurate weighed amount in warm 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 (10^{-2} mol L^{-1}) thallium (I) acetate solution.

The RNH pharmaceutical preparations were Aciloc (Ranitidine hydrochloride, 75 mg tablets, SIGMA Pharm. Ind., Egypt), Rantidol [Ranitidine HCl, 150 mg film coated tablets, El Nasr Pham. Chem. Co., Egypt) and Histac (Ranitidine, 150 mg tablets, RANBAXY, Egypt).

The ion-pair associate was prepared from aqueous medium by adding 25 ml 10^{-2} mol L^{-1} NaTPB solution to 25 ml 10^{-2} mol L^{-1} RNH solution. The resulting ion-pair associated precipitate was filtered, washed thoroughly with distilled water and dried at room temperature. The predicted composition of the ion associate complex has a molar ratio of 1:1 for RNH-TPB and was ascertained by elemental analysis ($[C_{37}H_{43}BN_4O_3S]$; calculated: %C = 70.00; %H = 6.78; %N = 7.57%. Found: %C = 68.64; %H = 6.62; %N = 8.03%). The calculated and observed elemental analysis data for the ion-associate complex are in good agreement with its structure.

2.2. Apparatus

Laboratory potential measurements were performed using a 716 DMS Titrino Metrohm connected with 728 Metrohm stirrers (Switzerland). This Titrino had a combined electrode, which was more convenient to be used, equipped with silver-silver chloride double - junction reference electrode (Metrohm 6.0222.100) in conjugation with different drug ion selective electrode.

Digital multimeter connected to a portable PC and Brand digital burette was used for the measurement of the drug under investigation. Prior to analysis, all glassware used were washed carefully with distilled water and dried in the oven before use.

2.3. Electrode composition and construction

2.3.1. Screen-Printed Electrodes

SPE was prepared according to the method previously reported by the authors [34-37]. SPEs were printed in arrays of six couples consisting of the working and the reference electrodes (each 5x35 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.

A pseudo silver/silver chloride electrode was firstly printed using a home-made polyvinyl chloride ink containing silver/silver chloride (65:35%) which is cured at 60 °C for 30 min. The working electrodes were prepared depending on the method of fabrication.

The working electrode was printed using homemade carbon ink (prepared by mixing 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. Three types of the working electrodes were prepared depending on the method of fabrication. The fabricated electrodes were stored at 4 °C and used directly in the potentiometric measurements.

2.3.2. Polyvinyl chloride (PVC), carbon paste, coated wire and coated graphite electrodes

The cited plain electrodes were constructed as described previously [34-37]. The PVC was filled with $1x10^{-2}$ mol L^{-1} KCl and $1x10^{-3}$ mol L^{-1} of the RNH solution. All the fabricated electrodes (PVC, CPE, CWE and coated graphite electrodes) were soaked in the suspended aqueous solution of RNH-TPB ion pair for 24 h before measurement. With carbon paste electrodes, a new electrode surface was obtained by screwing the piston to eject a part of the paste followed by polishing of the surface with a wet filter paper.

2.3.3. Effect of pH on the electrode response

The effect of pH on the potential values of the CPE and SPE electrodes was studied over the pH range of 1–12 at 1-pH interval. This is done by immersing the electrodes in 10^{-2} and 10^{-4} mol L^{-1} RNH solutions. The pH was gradually increased or decreased by adding aliquots of diluted sodium hydroxide or hydrochloric acid solutions, respectively. The potential obtained at each pH was recorded.

2.3.4. Effect of foreign compounds on the electrode selectivity

The response of the two studied electrodes was also examined in the presence of a number of other related substances.

The potentiometric selectivity coefficients were evaluated according to IUPAC guidelines using the separate solutions method [38] in which the potential of cell compromising the CPE and SPE electrodes and a reference electrode is measured with two separate solutions, D and B where D (RNH ions) and B (interfering ion) at the same activity $a_D = a_B$. Selectivity coefficients were calculated by the separate solutions method, where potentials were measured for 10^{-3} mol L^{-1} RNH solution and then for 10^{-3} mol L^{-1} interfering solution, separately, then potentiometric selectivity coefficients were calculated using the following equation [38]:

$$\log K^{pot}_{D,B} = ((E_1 - E_2)/S) + (1 + (Z_1/Z_2) \log a$$

where *S* is the slope of the calibration plot, E_1 is the potential measured in 1×10^{-3} mol L^{-1} RNH (D), E_2 the potential measured in 1×10^{-3} mol L^{-1} of the interfering compound (B), z_1 and z_2 are the charges of the RNH (D) and interfering species (B), respectively.

In addition to the SSM, the selectivity of the investigated electrodes was determined by the matched potential method (MPM) [39]. 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^1_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.

2.4. Application to pharmaceutical dosage form

The contents of tow Aciloc, Rantidol or Histac tablets. An amount of this solution equivalent to 350 mg RNH was accurately transferred separately to a 100 ml volumetric flask and the volume was completed to the mark with acetate buffer (pH 4.5) to prepare 10^{-3} mol L^{-1} solution of RNH. The e.m.f. produced by immersing the prepared CPE and SPE electrodes in conjunction with single junction Ag/AgCl reference electrode in the prepared solutions were determined then the concentration of RNH was calculated from the titration with 10^{-3} mol L^{-1} NaTPB.

2.5. Application to serum and urine

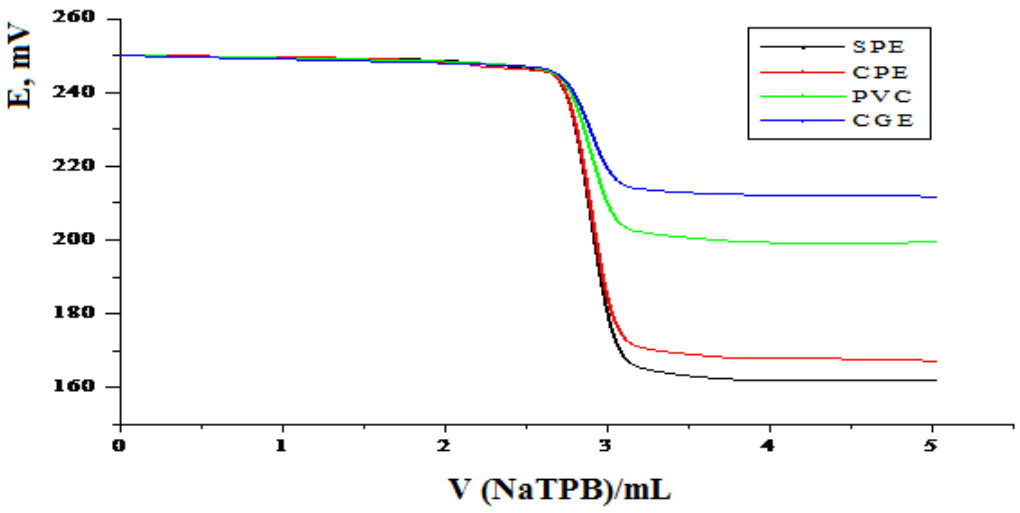
Phosphate buffer was added to urine or serum samples dropwise until a pH of 4.0 is obtained. 5 mL of the pH-adjusted urine or serum was transferred into four small separatory funnels, and then to each was added 5 mL 10^{-2}, 10^{-3}, 10^{-4} and 10^{-5} mol L^{-1} standard drug solution, followed by the addition of 20 mL toluene for urine and 20 mL diethyl ether for serum samples, respectively. After shaking each funnel for 5 min, the aqueous layer was transferred to a centrifuge tube. Centrifuged for 2 min at 1500 rpm, then transferred to a 50 mL volumetric flask and the solution diluted with deionized water to the appropriate level. Apply the procedure described above.

3. RESULTS AND DISCUSSION

The development and application of ion-selective electrodes (ISEs) continue to be of interest for pharmaceutical analysis because they offer the advantages of simple design and operation, fast response, reasonable selectivity, low detection limit, high accuracy, wide concentration range applicability to coloured and turbid solutions, and possible interfacing with automated and computerized systems [40].

3.1. Electrode performance

From the previous experimental investigations [34-37], it is obvious that both CPE and SPE can influence the response performances such as the sensitivity, linear concentration range, the detection limit, the response time *etc*. if other properties of the sensor, *e.g.* selectivity or pH response, are omitted. In this study, the analytical performance of CPE and SPE electrodes is compared with the traditional PVC, CW and coated graphite electrodes. They have the best performance (total potential change, potential break at the end point as well as the response time) in comparison with other electrodes (Figure 1).



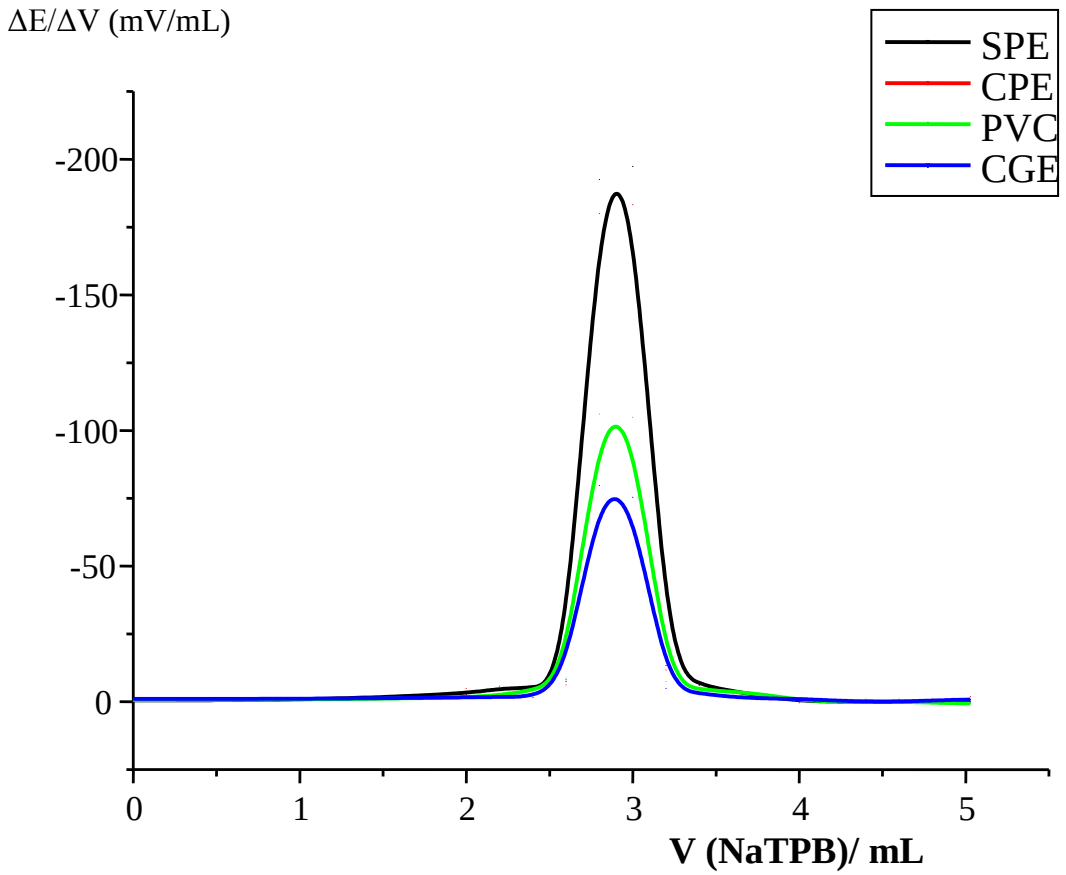


Figure 1. Comparison between the performance of SPE (TCP), CPE (TCP), PVC (TCP) and CGE (TCP) in the potentiometric titration of 3 mL of 10^{-2} (mol L^{-1}) RNH with 10^{-2} (mol L^{-1}) NaTPB.

Table 1. Critical response characteristics of CPE and SPE sensors.

Parameters	CPE	SPE
Slope (mV decade^{-1})	55.74±1.0	58.89±1.2
Intercept	485.01	478.15
Correlation coefficient (r)	0.9631	0.9935
Linear range (mol L^{-1})	1.0×10^{-7} to 1.0×10^{-2}	1.0×10^{-7} to 1.0×10^{-2}
Detection limit (mol L^{-1})	0.07×10^{-7}	0.09×10^{-7}
Response time (s)	4s	4s
Working pH range	3-5	3-6
Life time /day	47	60
Percent recovery (%)±SD	98.00±0.40-98.57±0.37	98.68±0.42-99.33±0.31
Accuracy (%)	98.69	98.95
Standard deviation (%)	1.26	1.89
Repeatability (CV[a] %)	0.67	0.59
Between day variability (CV[b] %)	0.79	0.49
Robustness[b]	98.86±0.75	99.08±0.65
Ruggedness[c]	98.57±0.35	98.97±0.26

[a] Mean of three measurements.
[b] A small variation in method parameters were studied as pH of buffer.
[c] Comparing the results by those obtained by using HANNA 211.

RNH reacts with sodium tetraphenylborate to form a stable RNH-TPB ion-pair complex which is water insoluble but readily soluble in an organic solvent such as tetrahydrofuran. The critical response characteristics of CPE and SPE were determined and results are summarized in (Table 1). The electrodes exhibit a Nernstian response over the concentration range from 1×10^{-2} to 1×10^{-7} and1×10^{-2} to 1×10^{-7} mol L^{-1} for RNH with CPE and SPE, respectively. A slope of 55.74±1.0 and 58.89±1.2 mV $decade^{-1}$ was observed for change in concentration with CPE and SPE, respectively.

3.2. Effect of plasticizer type

In this study, five plasticizers, DOP, DOS, TCP, DBP and *o*-NPOE were used to examine the optimization of the membrane with plasticizer which entailed the use of plasticizer content ratio of 60.0, 64.0, 66.0 and 70.0 wt%, and the use of PVC contents of 39.0, 35.0, 31.5, and 28.0 wt%. The typical potential responses of the electrodes constructed with five plasticizers are given. It is found that, the electrodes plasticized with o-NPOE were superior to DOS, DBP, DOP and TCP with respect to highest total potential change (89 mV) and the highest potential break at the end point ($\Delta E/\Delta V$ = 197 mV). Hence, *o*-NPOE was selected as the plasticizer of the membranes [41]. The same results are previously reported by the authors using SPE [34-37].

3.3. Response time

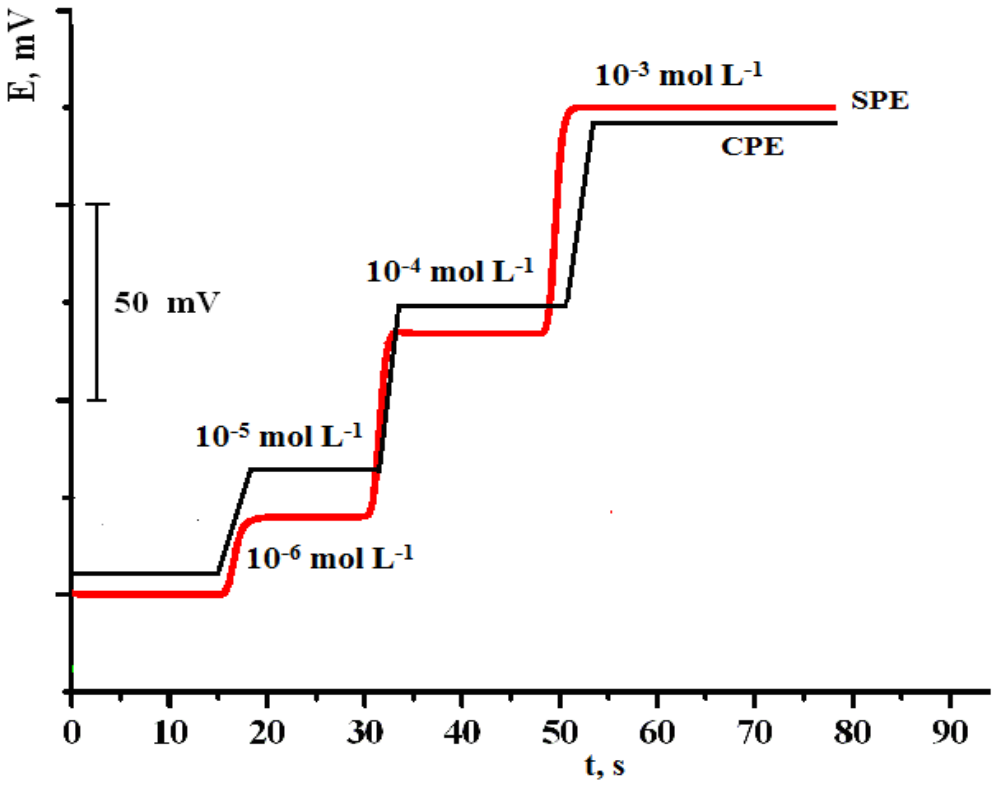


Figure 2. Dynamic response of CPE and SPE sensors: a) 1×10^{-6}, b) 1×10^{-5}, c) 1×10^{-4}, d) 1×10^{-3} (mol L^{-1}) RNH.

The time required for the electrode to reach a steady potential response within ±1 mV after successive immersion of series of RNH solutions, each having a 10-fold difference in concentration, was measured [38]. The response time of the electrodes were tested for 1×10^{-1}-1×10^{-6} mol L^{-1} RNH solutions. The sequence of measurements was always from low to high concentrations. The electrode response time is found to be 4s (Figure 2) and the equilibrium potentials essentially remained constant for over 15 min. This fast and stable potential reading is reflected on the time needed for complete titration process as it is only about 3-5 min.

3.4. Effect of titrant

3 ml of 10^{-2} mol L^{-1} drug solution was transferred to a 10 ml volumetric beaker then this solution was potentiometrically titrated against different titrants including NaTPB, RN and PMA using CPE and SPE as a sensing electrodes where the total potential change and the potential break for each titrant were calculated.

RNH reacts with PMA, NaTPB and RN in the molar ratio of 3:1, 1:1 and 1:1, respectively. The highest total potential change is obtained using NaTPB as a titrant with good reproducibility compared with other titrants.

3.5. Effect of pH

The effect of pH of the RNH test solution (10^{-2} and 10^{-4} mol L^{-1}) on the electrode potential was investigated by following the variation of potential with change in pH by the addition of very small volumes of HCl and/or NaOH (0.1–1 mol L^{-1} of each; Figure 3).

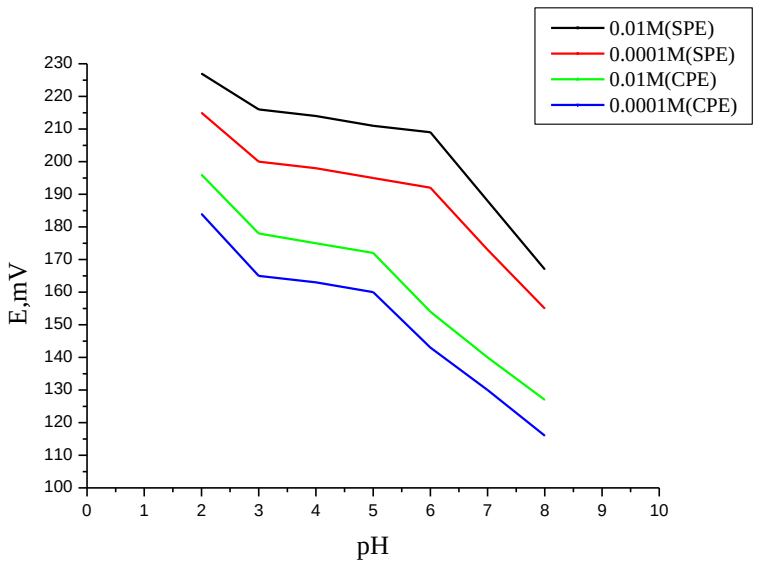


Figure 3. Effect of pH on potential/mV of 1.0×10^{-2} and $1x10^{-4}$ (mol L^{-1}) RNH solutions using CPE and SPE.

As is obvious, within the pH range 3–6, the electrodes potentials are practically independent of pH, and in this range, the electrodes can be safely used for RNH determination. The increase in mV reading at pH less than 3 can be due to penetration of H^+ into the membrane surface [34-37] or a gradual increase of protonated species and dependence of the e.m.f values on the pH of the solution. At higher pH values (pH > 6.0), 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 [34-37]. The decrease in potential readings at pH > 6.0, on the other hand, can be probably attributed to penetration of OH^- ions into the gel layer of the electrodes.

3.6. Effect of temperature of the test solution

Calibration graphs (electrode potential (E_{elect}) versus p[RNH]) were constructed at different test solution temperatures (10, 25, 30, 40, 50 and 60 °C). The values of the obtained isothermal coefficient of the CPE and SPE is 0.001 and 0.0035 V/°C, respectively, indicate that the electrodes have a high thermal stability within the investigated temperature range (Figure 4). The investigated electrodes were found to be usable up to 50 °C without noticeable deviation from the Nernstian behaviour.

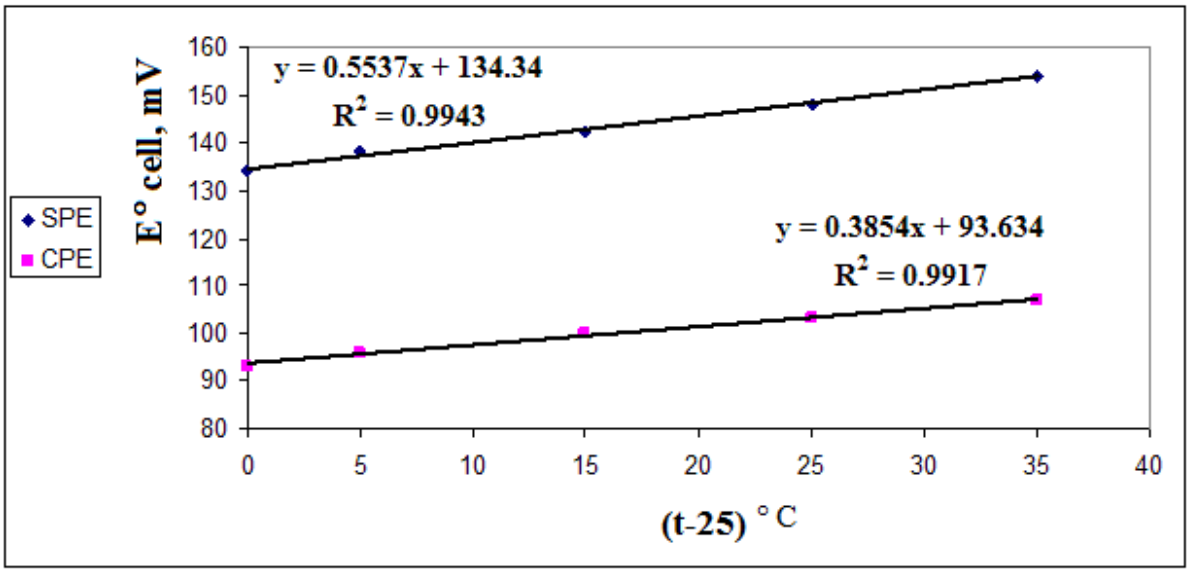


Figure 4. Variation of the cell e.m.f. with the temperature for the CPE and SPE sensors.

3.7. Selectivity of CPE and SPE sensors

The influence of various basic substances on the response of CPE and SPE sensors was investigated by measuring the potentiometric interference from many sugars, inorganic cations and

glycine. The selectivity coefficients were determined by the separate solution method. The results obtained are summarized in (Table 2).

Table 2. Potentiometric selectivity coefficient of o-NPOE plasticized CPE and SPE.

Interfering ions (B)	$K^{pot}_{D,B}$			
	CPE		SPE	
	SSM	MPM	SSM	MPM
Glucose	$1.28x10^{-6}$	----	$2.19x10^{-6}$	----
Lactose	$1.28x10^{-6}$	----	$2.23x10^{-6}$	----
Fructose	$1.33x10^{-6}$	----	$2.27x10^{-6}$	----
Maltose	$1.39x10^{-6}$	----	$2.37x10^{-6}$	----
Starch	$1.45x10^{-6}$	----	$2.45x10^{-6}$	----
Sucrose	$2.48x10^{-6}$	----	$2.62x10^{-6}$	----
Glycine	$1.23x10^{-6}$	----	$2.10x10^{-6}$	----
p-Aminophenol	$2.28x10^{-6}$	----	$2.38x10^{-6}$	----
Ascorbic acid	$1.81x10^{-5}$	----	$1.31x10^{-5}$	----
Ca^{2+}	----	$1.14x10^{-4}$	----	$3.61x10^{-5}$
NH_4^+	----	$1.45x10^{-6}$	----	$1.73x10^{-6}$
K^+	----	$2.28x10^{-6}$	----	$3.78x10^{-6}$
Na^+	----	$1.39x10^{-6}$	----	$3.93x10^{-6}$
Cd^{2+}	----	$3.73x10^{-5}$	----	$4.00x10^{-5}$

A reasonable selectivity toward RNH in the presence of many nitrogenous compounds such as amines, amino acid, 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 RNH. The inorganic cations did not interfere due to the differences in their mobilities and permeabilities as compared with RNH cation. With respect to glycine, the high selectivity is mainly attributed to the difference in polarity and lipophilic character of their molecules relative to RNH.

3.8. Effect of soaking

Figure (5) shows the effect of soaking time of the SPE and CPE electrodes. The performance characteristics of the CPE and SPE electrodes were studied as a function of soaking time. For this purpose the electrodes were soaked in ion pair and the potential break were plotted after 15 min, 30 min, 1h, 2h and 24h, respectively. The optimum soaking time was found to be without soaking at which the slope of the calibration curve was 55.74±1 and 58.89±1 mV $decade^{-1}$, at 25 ºC for CPE and SPE, respectively.

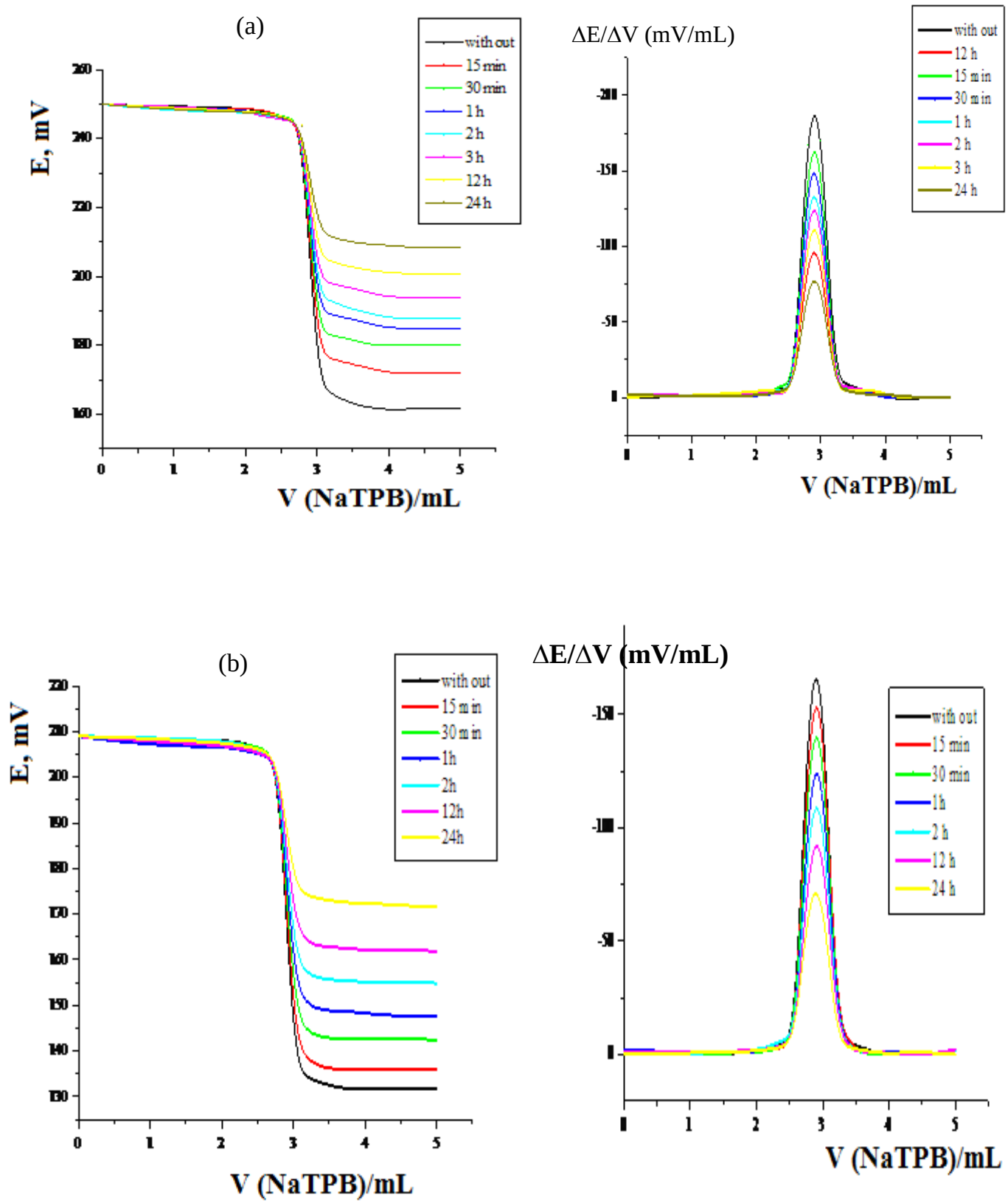


Figure 5. The effect of soaking time on the SPE (a) and CPE (b) performance in the potentiometric titration of 3 mL of 10^{-2} (mol L^{-1}) RNH with 10^{-2} (mol L^{-1}) NaTPB.

3.9. Quantification of RNH

3.9.1. Potentiometric determination of RNH drug in pharmaceutical preparation

Specificity is the ability of the method to measure the analyte response in the presence of all the potential interference. The response of the analyte with chloropheneramine maleate, were compared with the response of pure RNH. It was found that assay results were changed. Therefore, two tablets of each pharmaceutical product (Ranitidine 150, 75 mg) were weighed, dissolved in bi-distilled water, the mixture was filtered, transferred accurately to 100 mL measuring flask, shaked and finally determined by the proposed sensors.

The screen printed carbon paste electrodes are fabricated as previously reported by the research group [34-37]. In order to assess the validity of the prepared electrodes, the potentiometric titration method is applied for the determination of RNH in pharmaceutical preparation using SPE and CPE plasticized with TCP. The application of proposed method for the potentiometric determination of RNH in pharmaceutical preparation gave good results as shown in (Table 3). The results are compared with the standard method and have shown that the SPE and CPE have good efficiency as regard of sensitivity, index of retrieving and repetition.

As the conventional method for determination of RNH (titration in non-aqueous solvents) was difficult and time-consuming as well as using of expensive solvents, but this method (potentiometric determination) is easy, fast and inexpensive. One of the important applications of these drug-selective electrodes would have the study and investigation of RNH.

Table 3. Potentiometric determination of $1x10^{-2}$ (mol L^{-1}) RNH drug in pharmaceutical formulation (Ran150, Ran) against $1x10^{-2}$ (mol L^{-1}) NaTPB using CPE and SPE plasticized with TCP.

Sample	[RNH], Proposed Method								Official Method [RNH]			
	CPE				SPE							
	Taken (mg mL^{-1})	Found (mg mL^{-1})	Recovery (%)±SD	RSD (%)	Taken (mg mL^{-1})	Found (mg mL^{-1})	Recovery (%)±SD	RSD (%)	Taken (µgmL^{-1})	Found (µg mL^{-1})	Recovery (%)±SD	RSD (%)
Rantidol	10.50	10.32	98.29±0.18	1.79	10.50	10.44	99.43±0.24	2.27	10.00	9.95	99.50±0.18	1.89
Histac	10.50	10.27	97.81±0.26	2.52	10.50	10.39	98.95±0.16	1.54	10.00	9.84	98.40±0.25	2.53
Aciloc	10.50	10.40	99.05±0.15	1.49	10.50	10.42	99.24±0.22	2.07	10.00	9.75	97.50±0.21	2.19

Aciloc (75 mg tablets), Rantidol (150 mg film coated tablets) and Histac (150 mg tablets).

3.9.2. Application to serum and urine

The proposed potentiometric method was applied successfully for determination of RNH in biological fluids such as human serum and urine. The results obtained are summarized in Table 4.

Table 4. Determination of RNH in pure form "spiking technique" in human urine and serum using CPE and SPE.

Sample	Statistical parameters	CPE			SPE		
		Direct method	Calibration graphs	Standard addition method	Direct method	Calibration graphs	**Standard addition method**
Human urine	Mean recovery (%)	97.94	98.62	98.28	98.28	99.06	98.66
	N	5	5	5	5	5	5
	Variance	0.849	0.428	0.801	0.604	0.869	0.459
	SD	0.797	0.693	0.895	0.469	0.398	0.874
	SE	0.546	0.924	0.365	0.521	0.540	0.631
	RSD (%)	0.877	0.714	0.901	0.494	0.411	0.889
Human serum	Mean recovery (%)	98.73	98.69	97.69	98.83	98.06	97.96
	N	5	5	5	5	5	5
	Variance	0.458	0.537	0.801	0.772	0.951	0.359
	SD	0.672	0.546	0.689	0.589	0.879	0.576
	SE	0.432	0.364	0.536	0.653	0.433	0.452
	RSD(%)	0.759	0.576	0.709	0.621	0.900	0.605

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

4.1. Accuracy

The accuracy of the proposed potentiometric method using CPE and SPE sensors is investigated by the determination of RNH in spiked rantidol samples prepared from serial concentrations of RNH reference standards. The results summarized in Table 1, show that the proposed method is an accurate one, as indicated by the percentage recovery values, for the determination of RNH 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[RNH]. The regression data, correlation coefficients (r) and other statistical parameter are previously listed in Table 1.

4.3. Precision

The precision of the proposed potentiometric method using CPE and SPE sensors, measured as percentage relative standard deviation (RSD%) was tested by repeating the proposed method for determination of RNH in its pharmaceutical preparations of "three batches" to eight replicates [42, 43]. The RSD% values for the repeated determinations were 0.94, 1.06 and 0.75% for determination of RNH in Aciloc, Rantidol and Histac tablets using CPE and 0.86, 0.87 and 0.69% using SPE. The above RSD values are less than 2% indicating good precision of the proposed method.

4.4. Robustness and Ruggedness

The robustness of this proposed method was done by investigating to what extent the capacity of the method remains unaffected by a small but a deliberate variation in method parameters and hence provides an indication of its reliability during normal usage [42, 43]. The ruggedness of the proposed method was done by investigating the reproducibility of the results obtained by the analysis of the same samples under different conditions such as different instruments, laboratories and analysts. The results obtained using another model of pH-meter (HANNA 211, Romania) were compared with those obtained using Jenway 3505 pH-meter. The results obtained are close and also reveal validity of the method (Table 1).

4.5. Detection limit

The detection limit of the investigated RNH drug was calculated according to IUPAC recommendation [42, 43]. 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 1, indicate that the proposed CPE and SPE sensors are sensitive to detection of very small concentrations of RNH.

5. CONCLUSION

The potentiometric method developed for the determination of RNH has proved to be good and advantageous over the previous reported analytical methods due to their sensitivity, rapidity and accuracy (Table 5).

Table 5. Critical response characteristics of CPE and SPE sensors.

Parameters / 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 membrane	59.70	5.0×10^{-4} to 1.0×10^{-1}	2.80×10^{-4}	< 20	------	180	**[19]**
PVC membrane (batch system) RN-TPB#	57.1	2.0×10^{-5} to 1.0×10^{-2}	1.26×10^{-5}	10-20	4-9	180	**[20]**
RN-PT#		1.03×10^{-5} to 1.0×10^{-2}					
PVC membrane (FIA system)* RN-TPB#	60.0	1.0×10^{-5} to 1.0×10^{-2}	5.62×10^{-6}	10-20	2.5-8.5	180	**[20]**
RN-PT#		1.0×10^{-5} to 1.0×10^{-2}					
PVC membrane		10^{-2} to 10^{-6}			2-7		**21**
CPE	55.74±1.0	1.0×10^{-7} to 1.0×10^{-2}	0.07×10^{-7}	4	3-5	47	**Present work**
SPE	58.89±1.2	1.0×10^{-7} to 1.0×10^{-2}	0.09×10^{-7}	4	3-6	60	**Present work**

* FIA means flow injection analysis

RN-TPB and RN-PT are ranitidine-tetraphenylborate or ranitidine-phosphotungstate ion-associates, respectively.

The good recoveries and low relative standard deviation reflect the high accuracy and precision of the proposed method. Moreover, the procedure is simple, easy to operate and it is inexpensive determination to make the electrodes, therefore, an excellent tool for the routine determination of RNH in quality control laboratories as a fast assay in its pharmaceutical preparations and biological fluids.

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