Anal. Bioanal. Electrochem., Vol. 15, No. 3, 2023, 240-250
https://www.doi.org/10.22034/abec.2023.1975892.1291

Analytical & Bioanalytical Electrochemistry

Full Paper

Development of Potentiometric Evaluations of Ranitidine in Pure and Pharmaceutical Products

Omar Salih Hassan,[1] Salma Anwer Abdullah,[2] and Amina M. Abass[3,*]

[1]*Department of Chemistry, College of Education for Pure Science, Tikrit University, Tikrit, Iraq*
[2]*Department of Clinical laboratory sciences, College of Pharmacy, Tikrit University, Tikrit, Iraq*
[3]*Department of Chemistry, College of Science, Al-Nahrain University, Al-Jaderia, Baghdad, Iraq*

*Corresponding Author, Tel.: +964-7718916492
E-Mail: aminamohsen75@gmail.com

Received: 4 December 2022 / Accepted with minor revision: 22 March 2023 / Published online: 31 March 2023

Abstract- Ranitidine ion-selective membrane electrodes were fabricated from PVC matrix and ranitidine hydrochloride (RNH-HCl)-phosphotungestic acid (PTA) as the detecting components in the existence of di-n-octyl phthalate (DOPH), di-n-butyl phthalate (DBPH) and dibutyl phosphate (DBP) as the solvent mediator and plasticizing the PVC membrane. The electrodes were prepared with DOPH (electrode 1), and DBPH (electrode 2) gave a Nernstian, stable, and rapid response, which displayed linear response in the concentration range of 1.0×10^{-5}-1.0×10^{-2} mol.L^{-1} and 2.03×10^{-5}-1.0×10^{-2} mol.L^{-1}, with Nernstian slope of 58.73, and 52.50 mV.decade^{-1} for electrode 1 and electrode 2 respectively. Limits of detection 9.30×10^{-6} and 3.70×10^{-6} mol.L^{-1} for electrodes 1 and 2, respectively were also obtained. Individual electrodes were operative at the pH range of 3.0-5.5 and 3.5-5.5. The membrane electrodes showed excellent selectivity for the drug ranitidine in comparison with various inorganic cations. The electrodes showed a cycle of 55,50 days not including major variations in the parameters of the electrodes. Sensor 3 was given a non-Nernstian response equal to 28.76 mV.decade^{-1} and the range of concentration was 2.0×10^{-5}-1.0×10^{-2} mol.L^{-1} with a limit of detection near 3.68×10^{-6} mol.L^{-1}. Ranitidine can be determined effectively in unmixed and pharmaceutical formulations using these designated methods.

Keywords- Ranitidine; Detection limit; Plasticizer; Potentiometric method; Pharmaceutical products

1. INTRODUCTION

The drug ranitidine which is shown in Figure 1, is a histamine H2-receptor antagonist indicated for the treatment of peptic ulcers [1]. Ranitidine hydrochloride (RNH), has a chemical name of N-(2-[(5-(dimethylaminomethyl)furan-2-yl)methylthio]ethyl)–N-methyl-2-nitroethene-1,1–diaminehydrochloride with the molecular formula ($C_{13}H_{22}N_4O_3S$). H2-receptor antagonist drug is used in hypersecretory conditions and peptic ulcers for short-term treatment [2].

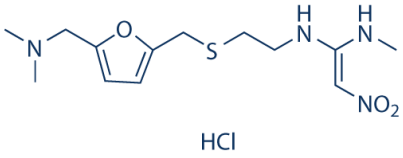

Figure 1. Chemical structure of ranitidine hydrochloride

Potentiometric sensors applied ion-selective membranes, which mixes of a limited number of important elements with the care of a balanced ratio. The variations of the membrane structure for the ion-selective membrane, each quantitative and qualitative, influence on the performance of sensors. Various materials and formations are applied to increase the detection limit of the electrodes, as a result, adjustment of the component of the membrane is of great importance. Additionally, the composition of the membrane can affect the operation of sensors [3]. Ion-selective electrodes (ISEs) are utilized in various formations and in numerous kinds of sensors extending from electrochemical sensors including coulometric, voltammetric, and potentiometric, gated transistor types to optical sensors. Potentiometric ISE is a technique used in designing membrane sensors. They include an ionophore as a ligand capable to favorably primary ions in a lipophilic medium [4,5]. Because of the attendance of ionophore as a highly selective material, the ISE lets evaluation of substances as an ion in free form, in the attendance of other analytes, in complex matrices, as well as samples of blood [6-11]. ISE sensors are used for various applications. It is necessary that sensors are characterized by a high steadiness of operation, containing selectivity, sensitivity in addition to performance, reproducibility and the response time [12-14]. Moreover, it is beneficial, if the sensor manufacture lets miniaturization and production of devices in mass-scale. Many researches showed using phosphotungetic acid (PTA) with drugs as an ion pairing agent in the membrane of electrodes, such as moxifloxacin determination in wastewater effluents [15] or the electrode which contains a complex of Cyclizine (Cy)-Phosphotungstic acid (PT) [16] or a membrane doped with LNP-phosphotungstic acid (LNP-PTA) as an ion pair for evaluation of lisinopril in pharmaceuticals products [17]. Also, there is a report on electrodes for determination of ciprofloxacin hydrochloride depended on an active material of (CFH-PT) [18]. Pilocarpine hydrochloride

with (PCH)-phosphotungstate was prepared too [19]. The purpose of this research was to improve selective, sensitive and confirmed ISEs for the evaluation of RNH in pure form and medication dosage.

2. SUBSTANCES AND PROCEDURES

2.1. Devices

With a pH/mV meter, the electrochemical measurements were done. An external reference electrode was a double junction Ag/AgCl electrode comprising 1M KCl in the outer part. HANNA pH meter was used for pH correction. HANNA pH meter was used for all potentiometric measurements and the measurements were made at 25±1°C with stable stir by a magnetic stirrer. All weights were examined by analytical balance.

2.2. Reagent and materials

From (IRAQ-SDI, Samara) State Company of Drug Industries and Medical Appliance standard drug of ranitidine was provided. Pharmaceutical product ranitidine tablet supplied from Egypt. PVC with high molecular weight type: Breon S110/10B.P chemical UK Ltd. Di-octyl phthalate (DOPH), di-n-butyl phthalate (DBPH), and di-n-butyl phosphate (DBP) were acquired from Fluka and BDH, tetrahydrofuran, HCl, NaOH (Merck, Germany) were used. Phosphotungestic acid (PTA) was used from Sigma-Aldrich. Distilled water was used in all analytical measurements.

2.3. Standard solutions of ranitidine

The standard solution of the drug (0.01 M) (MW= 350.87 $g.mol^{-1}$) was made through dissolving a certain amount of drug in distilled water, working solutions ranging from 1.0×10^{-1}-1.0×10^{-6} $mol.L^{-1}$ were made by thinning of sequential of the solution.

2.4. Ion selective electrodes

2.4.1. Ion-Pairs preparation

By mixing up 50 mL of 1 $mol.L^{-1}$ ranitidine solution with 50 mL of 1 $mol.L^{-1}$ PTA solution, ion pairs were prepared. The precipitate of (RNH-PTA) was filtered, washed thoroughly with distilled water, and dried up at room temperature for 24 hrs. In locked amber glass bottles ion pair was kept.

2.4.2. Structure of membranes

The method for the preparation of membranes is by dissolving suitable weights of the plasticizers (DOPH, DBPH, and DBP) and matrix PVC with the ion pair. With a little volume of THF the matrix is dissolved. The solutions were emptied into a petri-dish, by a filter paper

cover up as well as the solvent was evaporated gradually at room temperature, leaving the casted membranes on electrodes that are the most important part of ion-selective electrodes.

2.4.3. Assembly of ISE

To poly-ethylene tube was attached with a stamped circular membrane in an electrode shape and attached to the end of glass tube. With internal solution filled this electrode which containing of 0.1 M ranitidine. Wire of Ag/AgCl electrode was utilized as an internal reference electrode [20,21]. Then this electrode attached to double junction Ag/AgCl electrode as external reference electrode.

2.4.4. Calibration of electrode

Standard solutions of ranitidine were prepared as 25 mL of 0.01 mol.L^{-1}, then transmitted to a 50 mL beaker and diluted. The combination of the sensor with reference Ag/AgCl electrode was dipped in the solution, and the cell was utilized for potentiometric measurements. Figure 2 shows the diagram of the cell assembly as follows:

Ag/AgCl-KCl (1 mol.L^{-1})+RNH(1 mmol.L^{-1}) **ll** RNH -PTA-(DOPH or DBPH,DOP)-PVC membrane **ll** test solution **ll** Ag/AgCl-KCl (1 mol.L^{-1})

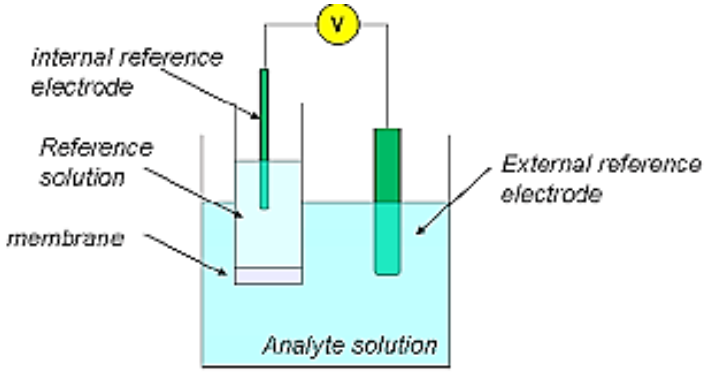

Figure 2. Diagram of the cell for ion selective membrane measurement [22]

The potential measured was schemed versus the minus logarithm of ranitidine concentration. Between measurements, by distilled water, the electrodes were washed away, with filter paper was dried.

2.4.5. pH Effect

pH effect on the response of potential was deliberate by using 10^{-3} mol.L^{-1} ranitidine solution. By utilizing appropriate amounts of 1 mol.L^{-1} HCl or NaOH solution, the pHs of the solutions were adjusted, and the different pH values corresponding to the potential of the reading were recorded.

2.4.6. Selectivity

Using some inorganic mixtures, the response of the electrode was studied via matched potential method [23]. In this method, the potentiometric selectivity coefficient is characterized as the activity proportion of essential and interfering species that give similar changes under same conditions.

$$K=(à\text{-}a) / a_B$$

From the outset, a known activity (à) of the target species solution is added into a reference solution that includes a certain activity (à) of target species. The expected variation (ΔE) is noted straightaway, when an interfering species is added to the reference solution, adding interference is continued till a similar possible change (ΔE) is recorded again [24].

2.4.7. Determination of ranitidine in pharmaceutical dosage forms

Local producing preparations (ranitidine tablet supplied from Egypt), was utilized for the examination of ranitidine by potentiometric strategies assurance. Ten tablets of ranitidine were excellently powdered and precise weighted identical to one tablet weigh, broke up utilizing a similar condition utilized to break down the medication material.

3. RESULTS AND DISCUSSION

3.1. Calibration curves

Potentiometric sensors are known via their simple design and operatory, wide linear range of determination, appropriate selectivity, and generally quick response. The ionophores dependability, straightforwardly influences the reaction, and selectivity of the electrodes can form complexes of inclusion with various atoms and extraordinary adaptability [25]. The potentiometric sensors showed an analytical range as seen in Figure 3 by the linear part of the calibration curve, were 1.0×10^{-5}-1.0×10^{-2} and 2.03×10^{-5}-1.0×10^{-2} mol.L^{-1} for two sensors (RNH-PTA-DOPH) and (RNH-PTA-DBPH). The ranitidine sensor's characteristic slope were 58.73, 52.50 mV.decade^{-1}, the limits of detection were 9.30×10^{-6} and 3.70×10^{-6} mol.L^{-1}.The electrode (RNH-PTA-DBP) was given a little value of slope equal to 28.76 mV.decade^{-1} with a limit of detection 3.68×10^{-6} mol.L^{-1} and the concentration was 2.0×10^{-5}-1.0×10^{-2} mol.L^{-1} (Table 1).

The lifetime of this sensor was 12 days which might be ascribed to the impact of steric, which decreased the bond strength with the electrodynamic compound. It might be on the grounds that the kind of plasticizers utilized, which incorporated a long alkyl tie focused on the phosphate bunch, may reduce the ion exchange between the outer species of drug [26]. The lifetimes were 55, and 50 days for sensors (RNH-PTA-.DOPH) and (RNH-PTA-DBPH), respectively.

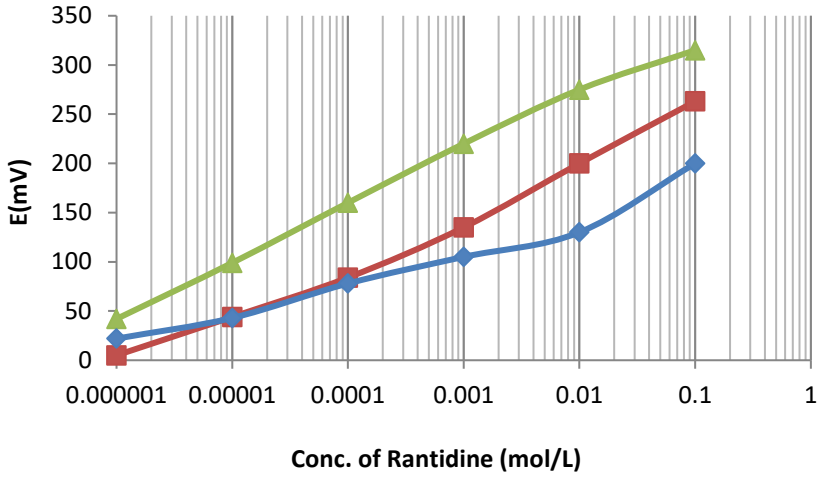

Figure 3. The ranitidine sensor's calibration curves; green curve: DOPH electrode; red curve: DBPH electrode; and blue curve: DBP electrode

Table 1. Analytical properties factors of the suggested ranitidine sensor matrix membrane sensor preparation

Parameters	**Electrode DOPH**	**Electrode DBPH**	**Electrode DBP**
Slope (mV/decade)	58.73	52.50	28.76
Detection limit (mol.L^{-1})	9.30×10^{-6}	3.7×10^{-6}	3.68×10^{-6}
Correlation Coefficient	0.9904	0.9994	0.9936
Range of Linearity (mol.L^{-1})	1.0×10^{-5}-1.0×10^{-2}	2.03×10^{-5}-1.0×10^{-2}	2.0×10^{-5}-1.0×10^{-2}
Working pH range	3.0-5.0	3.5-5.0	2.5-3.5
Reg. Eq. Y = mX + b	Y=22.8 ln(x)+299	Y=25.537ln(x)+394.3	Y=12.508ln(x)+189.8
Life of time(day)	55	50	12

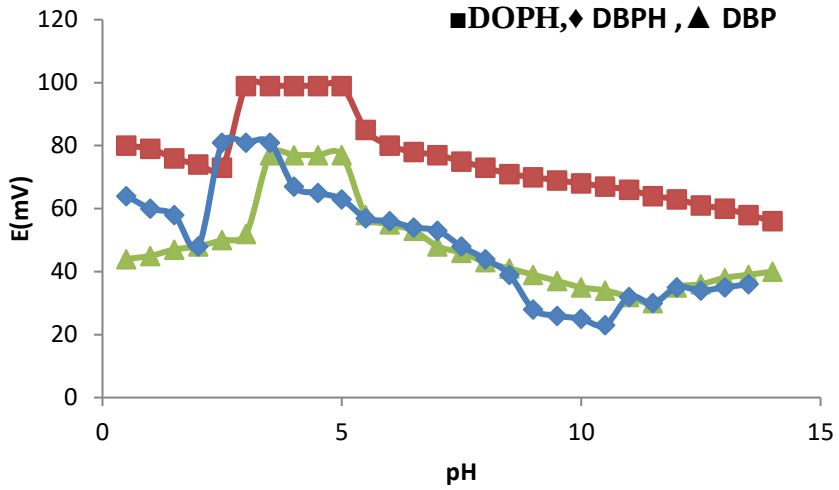

Figure 4. Impact of the sensor reply on the pH in 10^{-3} mol.L^{-1} ranitidine concentration

3.2. Impact of pH

The pH effect on the reply of the suggested sensors was concentrated over the pH scope of 3.0-5.0. As shown in Figure 4, the ranitidine potentials of (RNH-PTA-DOPH) and (RNH-PTA-DBPH) electrodes, these ranges can be utilized as the functioning ranges of pH for the electrode associations. Additionally, it was noticed that above pH 5, non-Nernstian slopes were noticed, which can be credited to the development of the free ranitidine base in the test solution.

3.3. Measurements of selectivity Coefficient for ranitidine sensors

The factors of selectivity for ranitidine membrane sensor regarding meddling particles were concentrated by the separate solution or by the MP (matched potential) strategies revealed previously [27] using the equations [28-30]:

$$\text{Log } K_{\text{pot A,B}} = [(EB - EA) / (2.303RT/zF)] + (1 - zA/zB) \log aA$$

By utilizing the separate solution method, at the EMF value of concentration 1×10^{-3} mol. L^{-1} for ranitidine, the height selectivity of the electrodes to RNH respect to inorganic cations was observed. This might be credited to the distinction in the size of ionic, portability, or porousness of the interfering ions to the membrane as contrasted with RNH [31]. The obtained data are reported in Tables 2,3.

Table 2. Data of selectivity coefficients for ranitidine electrode

Electrode (RNH+DOPH+PTA)					
Concentration of ranitidine					
Ion	**10^{-1}**	**10^{-2}**	**10^{-3}**	**10^{-4}**	**10^{-5}**
Na^{+}	0.03894	5.4116×10^{-3}	5.0671×10^{-4}	2.6826×10^{-5}	1.3593×10^{-6}
K^{+}	0.08576	8.3909×10^{-3}	7.1968×10^{-4}	4.7445×10^{-5}	2.5118×10^{-6}
Ca^{2+}	0.01178	6.1727×10^{-4}	1.6742×10^{-5}	2.5675×10^{-7}	4.6927×10^{-9}
Mg^{2+}	0.01286	1.8077×10^{-4}	1.8276×10^{-5}	3.0599×10^{-7}	5.3526×10^{-9}
Fe^{3+}	0.02465	9.01567×10^{-5}	8.51900×10^{-6}	7.01654×10^{-7}	6.4552×10^{-9}
Al^{3+}	0.09301	8.0124×10^{-5}	8.4508×10^{-6}	4.1298×10^{-7}	6.6507×10^{-9}

Table 3. Data of selectivity coefficients for ranitidine electrode

Electrode (RNH+DBPH+PTA)					
Concentration of ranitidine					
Ion	**10^{-1}**	**10^{-2}**	**10^{-3}**	**10^{-4}**	**10^{-5}**
Na^{1+}	0.01339	1.0477×10^{-3}	8.1941×10^{-5}	5.2675×10^{-6}	1.01500×10^{-6}
K^{1+}	0.01145	1.0074×10^{-3}	1.2127×10^{-4}	4.3298×10^{-6}	1.6247×10^{-6}
Ca^{2+}	0.04073	1.0896×10^{-3}	8.8637×10^{-4}	9.8107×10^{-6}	3.3380×10^{-7}
Mg^{2+}	0.08912	6.8432×10^{-3}	2.0187×10^{-4}	6.5140×10^{-6}	7.4109×10^{-7}
Fe^{3+}	0.05430	5.9129×10^{-3}	4.8197×10^{-4}	5.0164×10^{-6}	3.9154×10^{-7}
Al^{3+}	0.76328	8.9622×10^{-3}	7.7657×10^{-4}	6.0122×10^{-6}	8.1965×10^{-7}

3.4. Analytical applications of the studied electrodes

The proposed sensors were applied for the examination of RNH in pure form and drug formulation measurements (ranitidine produced by Egypt). The outcomes displayed in Table 4 and Table 5 demonstrate the appropriateness of the methods. Statistical analysis for treating the results was applied utilizing potentiometric methods containing direct, standard addition, and multi-standard addition methods. Also, potentiometric titration method which includes titrating RNH *vs.* phosphotungstic acid (PTA) as a titrant was successfully carried out.

Table 4. Evaluation of ranitidine in pure drug utilizing proposed sensors

Type of Electrode	Sample	Response by potentiometric method			
		Direct	SAM*	MSA**	Titration
RNH+DOPH+PTA	1×10^{-3}	0.9550×10^{-3}	0.9846×10^{-3}	0.98103×10^{-3}	0.9612×10^{-3}
	RSD%	3.17	2.24	-	-
	Rec%	95.50	98.46	98.10	96.12
	Er%	-4.50	-1.54	-1.90	-3.88
	1×10^{-4}	0.9693×10^{-4}	0.9848×10^{-4}	0.98107×10^{-4}	0.9723×10^{-4}
	RSD%	2.49	1.59	-	-
	Rec%	96.93	98.48	98.10	97.23
	Er%	-2.49	-1.52	-1.90	-2.77
RNH+DBPH+PTA	1×10^{-3}	0.972710^{-3}	0.9755×10^{-3}	0.9777×10^{-3}	0.9870
	RSD%	1.90	1.15	-	-
	Rec%	97.27	97.55	97.77	98.70
	Er%	-2.73	-2.45	-2.23	-1.30
	1×10^{-4}	0.9733×10^{-3}	0.9766×10^{-4}	0.9787×10^{-4}	0.9864×10^{-4}
	RSD%	3.14	1.78	-	-
	Rec%	97.33	97.66	97.87	98.64
	Er%	-2.67	-1.78	-2.13	-1.36

SAM* (Standard Addition Method)
MSA*(Multi Standard Addition Method)

Table 5. Evaluation of ranitidine in pharmaceutical forms utilizing proposed sensors

Type of Electrode	Sample	Response by potentiometric method			
		Direct	SAM*	MSA**	Titration
RNH+DOPH+PTA	1×10^{-3}	0.9598×10^{-3}	0.9751×10^{-3}	0.9803×10^{-3}	0.9612×10^{-3}
	RSD%	3.23	1.72	-	-
	Rec%	95.98	97.51	98.03	96.12
	Er%	-4.02	-249	-1.97	-3.88
RNH+DBPH+PTA	1×10^{-3}	0.9677×10^{-3}	0.9798×10^{-3}	0.9790×10^{-3}	0.9723×10^{-4}
	RSD%	2.55	1.53	-	-
	Rec%	96.77	97.98	97.90	97.23
	Er%	-3.23	-2.02	-2.10	-2.77

SAM* (Standard Addition Method)
MSA*(Multi Standard Addition Method)

The Figures 5A-D show the potentiometric methods for pure drug and Figures 6A,B and 7 show the potentiometric methods for pharmaceutical forms.

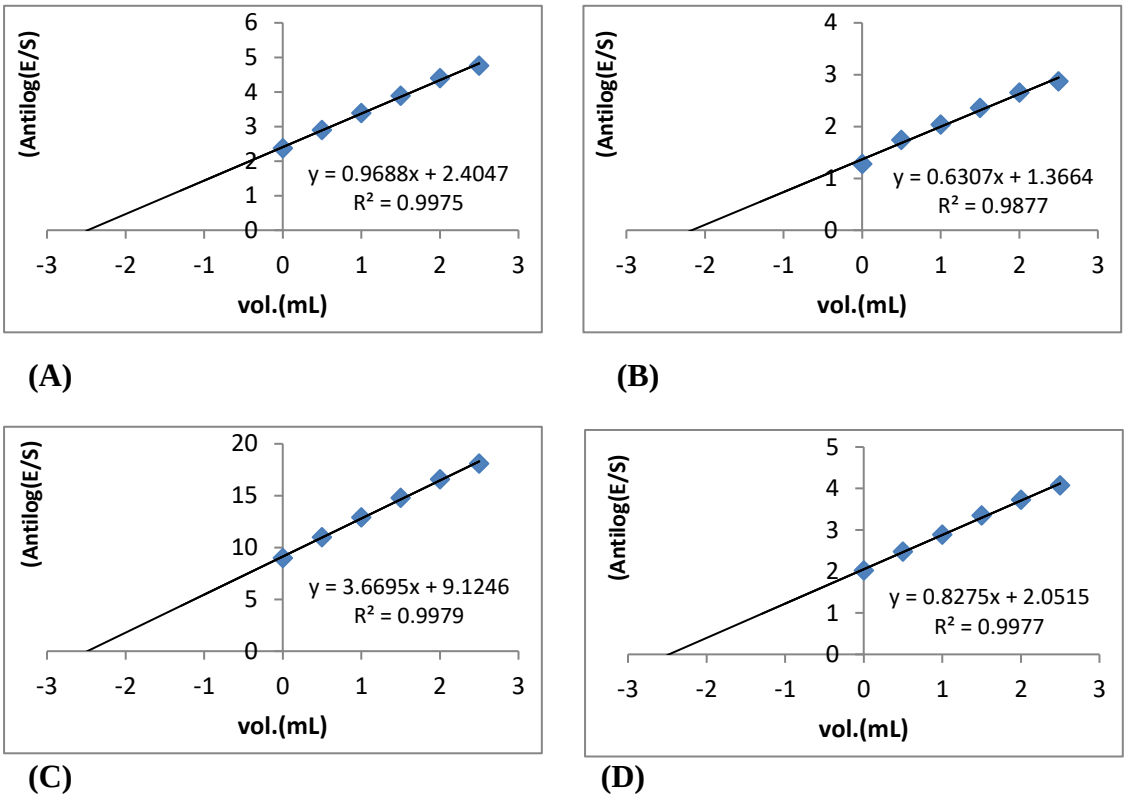

Figure 5. A) Standard addition method for DBPH of ranitidine solution at 10^{-4} mol.L^{-1}; B) Standard addition method for DOPH of ranitidine solution at 10^{-4}M; C) Standard addition method for DBPH of ranitidine solution at 10^{-3} mol.L^{-1}; D) Standard addition method for DBPH of ranitidine solution at 10^{-4} mol.L^{-1}

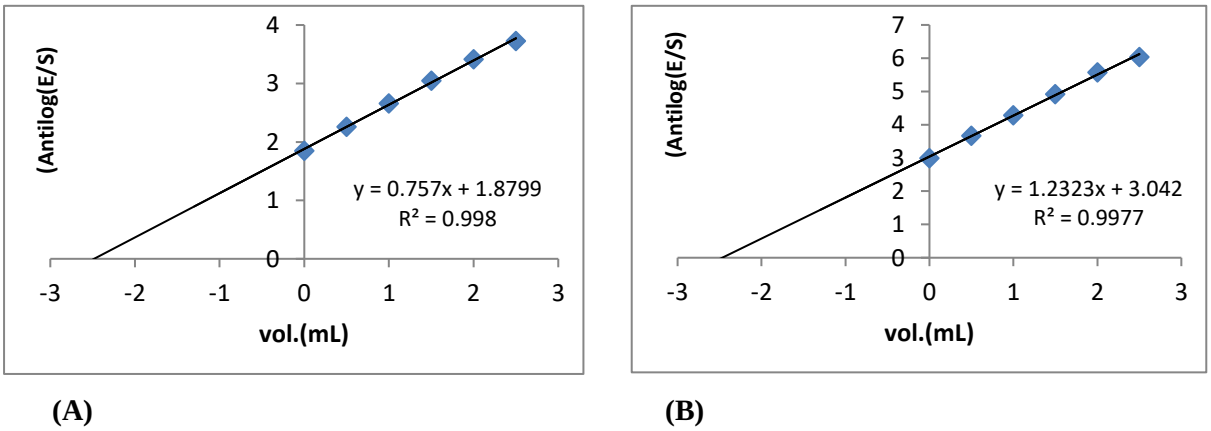

Figure 6. A) Standard addition method for DOPH of ranitidine solution at 10^{-3} mol.L^{-1}; B) Standard addition method for DOPH of ranitidine solution at 10^{-4} mol.L^{-1}

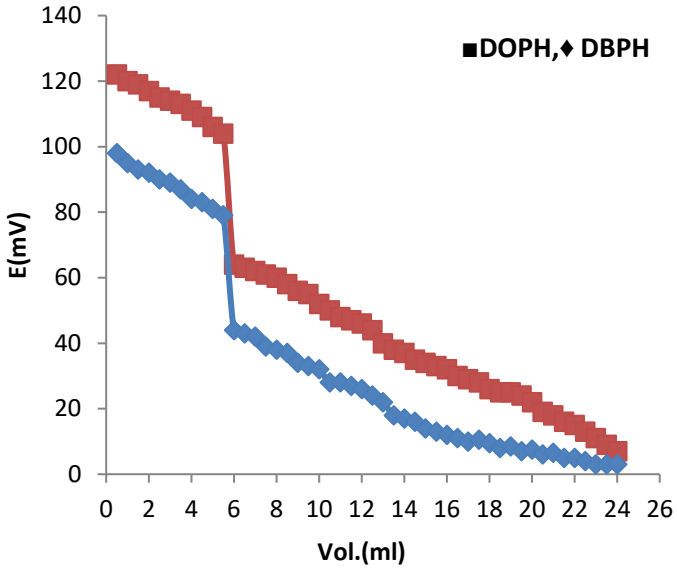

Figure 7. Potentiometric titration for DOPH, DBPH of ranitidine solution at 10^3 mol.L^{-1}

It is determined that the suggested sensors can be applied successfully to evaluate the drug RNH in pure and pharmaceutical formations. The result was recorded in Table 4 for pure drug and Table 5 for pharmaceutical form of ranitidine.

4. CONCLUSION

The ranitidine selective electrode used in the quantification of RNH shows high accuracy, selectivity, sensitivity, and long lifetime. The constructed electrode succeeds to determine RNH in pure solutions, and pharmaceutical preparations without the fear that the presence of interference from excipients in pharmaceutical preparations affect the accurate quantification of RNH. The proposed potentiometric procedure proved its capability for adequate quantification of RNH with low cost and simple techniques to construct electrodes.

REFERENCES

[1] B.D. Priya, B.V. Lakshmi, V. Bhavya, V. Ramya, D. Aparna, T. Prasanthi, and A.L. Rao J. Pharm. Res. 1 (2017) 000128.
[2] A.A. Ghali, Int. J. Pharm. Res. 12 (2020).
[3] K. Maksymiuk, E. Stelmach, and A. Michalska, Membranes 10 (2020) 266.
[4] E. Bakker, P. Bühlmann, and E. Pretsch, Chem. Rev. 97 (1997) 3083.
[5] P. Bühlmann, E. Pretsch, and E. Bakker, Chem. Rev. 98 (1998) 1593.
[6] A.J. Bandodkar, and J. Wang, Trends Biotechnol. 32 (2014) 363.
[7] M.M. Balach, C.H. Casale, and A.N. Campetelli, Biophys. Rev. 11 (2019) 995.
[8] C.I.L. Justino, A.C. Duarte, and T.A.P. Rocha-Santos, Trends Anal. Chem. 85 (2016) 36.

[9] Q. Zhang, X. Wang, V. Decker, and M.E. Meyerhoff, ACS Appl. Mater. Interfaces 12 (2020) 25616.
[10] R. De Marco, G. Clarke, and B. Pejcic, Electroanalysis 19 (2007) 1987.
[11] C. Zuliani, and D. Diamond, Electrochim. Acta 84 (2012) 29.
[12] X.U. Zou, J.H. Cheong, B.J. Taitt, and P. Bühlmann, Anal. Chem. 85 (2013) 9350.
[13] X.U. Zou, X.V. Zhen, J.H. Cheong, and P. Bühlmann, Anal. Chem. 86 (2014) 8687.
[14] J. Bobacka, Anal. Chem. 71 (1999) 4932.
[15] S.A. Abdel-Gawad, H.A. Arab, A. Ahmed, A.A. Albassam, Chemosensors 10 (2022) 146.
[16] S. Rani, and B.K. Sarma, Int. J. Development Res. 8 (2018) 18176.
[17] N.N. Rajendraprasad, and K. Basavaiah, J. Anal. Science and Technol. 10 (2019) 37.
[18] A.M. Abass, Baghdad Science Journal, 14 (2017) 787.
[19] A.M. Abass, ANJS 20 (2017) 13.
[20] J. Moody, S. Nassory, and R. Thomas, Talanta 26 (1979) 873.
[21] J. Moody, S. Nassory, and R. Thomas, Hung. Sci. Instrum, 41 (1977) 23.
[22] V.A. Naik**,** Int. J. Applied Res. Sci. Engin. International Conference on Emerging Technologies in Engineering, Biomedical, Medical and Science (ETEBMS - November 2016).
[23] Y. Umezawa, P. Bühlmann, K. Umezawa, K. Tohda, and S. Amemiya, Pure Appl. Chem. 72 (2000) 1851.
[24] R. Thomas, Pure Appl. Chem. 73 (2001) 31.
[25] F. Faridbod, M. R. Ganjali, R. Dinarvand, P. Norouzi, S. Riahi, Sensors 8 (2008) 1645.
[26] E.M. Zahran, A. New, V. Gavalas, and L.G. Bachas, Analyst 139 (2014) 757.
[27] S. Khalil, and S.S. Al Harthi, Int. J. Electrochem. Sci. 15 (2020) 9223.
[28] N.M. Mohamed, Y.M. Issa, N. Shehata, H.S. Mohamed, and S.A. Ahmed, Adv. J. Chem. A 3 (2020) 24.
[29] J.A. González-Franco, A. Ruiz, and J.A. Ortuño, Chemosensors 10 (2022) 116.
[30] A.V. Kopytina, K. E. Germana, K.Y. Zhizhina, A.V. Tyuremnova, T.V. Zhukovac, and E. G. Ilin, J. Anal. Chem. 75 (2020) 829.
[31] N.A. Abdallah, Sens. Mater. 28 (2016) 797.