Preparation and Potentiometric Study of Ranitidine Hydrochloride Selective Electrodes and Applications

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Ranitidine hydrochloride selective electrodes were constructed based on ranitidine tetraiodo bismuthate (III) ion pair in PVC matrix membrane. The used plasticizers were di-butylphthalate (DBPH), di-octylphtalate (DOPH), di-butylphosphate (DBP) and tri-butylphosphate (TBP). The electrodes based on DOPH, DBP and TBP gave the same linear response in between 10^{-5} and 10^{-1} M, while the one based on DBPH ranged between $0.5 \cdot 10^{-5}$ and 10^{-1} M. The slopes of the calibration curves were in between 22.25 and 41.20 mV per decade with correlation coefficients in between 0.9951 and 0.9990. The best detection limit was $6.30 \cdot 10^{-6}$ M for the DOPH electrode. The interferences of various cations and drugs were studied using the separate solution method. *The optimum pH and lifespan of the electrodes were also studied.*

Keywords: ion-selective electrode, potentiometry, ranitidine, drug analysis

Ranitidine is a H_2-receptor antagonist drug prescribed for the treatment of duodenal ulcer. A survey of current literature reveals that liquid chromatography, capillary electrophoresis and spectrophotometric methods have been reported for the determination of ranitidine hydrochloride in human plasma and commercial formulations [1-7].

Electrochemical methods have an important part in biological and pharmaceutical analysis due to their simplicity, quickness and accuracy when compared to other analytical methods [8-13]. Ion-selective electrodes (ISE) have enough selectivity towards the active substance over pharmaceutical excipients and they can be used for their quantitative analysis in pharmaceutical preparations without prior separations.

Few studies have been reported for ranitidine hydrochloride quantitative analysis in pharmaceutical formulations based on ion-selective membrane electrodes only. Ion-selective membrane electrodes for ranitidine hydrochloride have been constructed based on ranitidine-tetrakis-(3-chlorophenyl)borate,ranitidine-tetraphenyl-borate and ranitidine-phosphotungstate as electroactive compound [14-16].

We report in this paper the construction of several ranitidine hydrochloride electrodes based on tetra-iodobismutate (III) as ionophore using various plasticizers. The properties of those electrodes, the effect of pH, and the selectivity coefficient were studied.

Experimental part

Materials and methods

All potentiometric measurements were carried out using a Hanna 301 digital pH/millivoltmeter. A ranitidine selective electrode was used as indicating electrode in conjunction with a Radelkis OP-0830P calomel electrode (SCE) as reference electrode.

All used chemicals were analytical grade. Bismuth (III) subnitrate, potassium iodide, tetrahydrofuran (THF), *di*-butylphthalate (DBPH), *di*-octylphtalate (DOPH), *di*-butylphosphate (DBP) and *tri*-butylphosphate (TBP) were commercially available (Fluka). Polyvinylchloride (PVC) of relatively high molecular weight was used. Ranitidine hydrochloride reference substance was purchased from Dar Al Dawa-Jordan. All pharmaceutical formulations were purchased from a local pharmaceutical company.

There were prepared 10^{-1} M stock solutions for each of the following substances: NH_4Cl, NaCl, $CaCl_2$, $MgCl_2$, $AlCl_3$, chlorpheniramine maleate, nizatidine, famotidine, vitamin B_1 and citric acid. Dilute solutions were prepared by subsequent dilution of those stock solutions.

Potassium tetraiodobismutate (III) solution was prepared by mixing a potassium iodide solution with bismuth (III) subnitrate solution in hydrochloric acid medium [17].

For the synthesis of the ion pair complex, 0.1 g ranitidine hydrochloride was dissolved in 100 mL water, the pH was adjusted to 1.0 with 2 M hydrochloric acid and lastly the potassium tetraiodobismutate (III) solution was added in small portions with stirring.

The resulting precipitate, ranitidine-tetraiodobismutate (III), was separated using a G4 filtering crucible; it was then washed with saturated solution of the precipitate and dried at 60°C.

Construction of the electrode

Several membrane compositions were investigated by varying the ratio of PVC, plasticizer, and the membrane active material [18-21]. The membrane with a composition of 1 % ionophore, 68 % plasticizer and 31 % PVC generated a stable potential response.

A mixture was prepared by dissolving 1 mg of ranitidine-tetraiodobismutate (III), 31 mg of PVC and 68.0 mg of plasticizer in 3 mL of tetrahydrofuran. The mixture was poured into a 30 mm diameter glass ring placed on a glass plate, and allowed to evaporate for 24 h at room temperature. The membrane obtained as 0.25-0.35 mm thick film was removed from the glass plate, and a 10 mm diameter disk was cut out and fixed to the end of a 100 mm long PVC tube by using a PVC/THF solution. The Ag/AgCl electrode and 10^{-3} M ranitidine hydrochloride solution were used as reference electrode and internal filling solution for the electrode, respectively.

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The assembled electrodes were conditioned by soaking in 10^{-5} M ranitidine hydrochloride solution for 2 h before use. When not in use, the electrodes were stored in air.

Results and discussions

Ranitidine hydrochloride-tetraiodobismutate was a stable water insoluble ion-pair complex, though readily soluble in organic solvents such as dimethylformamide. The complex was incorporated into a PVC membrane with the following plasticizers: *di*-butylphthalate (membrane I), *di*-octylphtalate (membrane II), *di*-butylphosphate (membrane III) and *tri*-butylphosphate (membrane IV). The characteristics of the electrodes were assessed on the basis of their calibration curves. The physical properties of these membranes were as follows: yellow, non-crystalline, flexible and clear.

Effect of pH

The effect of *p*H on electrode response was examined by measuring the variation of potential of the cell for three different ranitidine hydrochloride solutions (10^{-4}, 10^{-3} and 10^{-2} M). A representative plot for the DOPH electrode is shown in figure 1. The results of the *p*H ranges of the ranitidine hydrochloride selective electrodes are listed in table 1.

When used at higher *p*H, free bases precipitated in aqueous test solutions and, consequently, the concentration of unprotonated species gradually increased. As a result, lower potential readings were recorded.

Total ionic strength

A value of 0.1 for the ionic strength was found to be optimum for samples below 10^{-1} M and it was obtained by dilution using 1 M potassium nitrate. The measured potential was uninfluenced by ionic strength for 10^{-1} M ranitidine hydrochloride solutions.

Response time

The response time for all the electrodes at concentrations ranging from 10^{-5} to 10^{-1} M is listed in table 2.

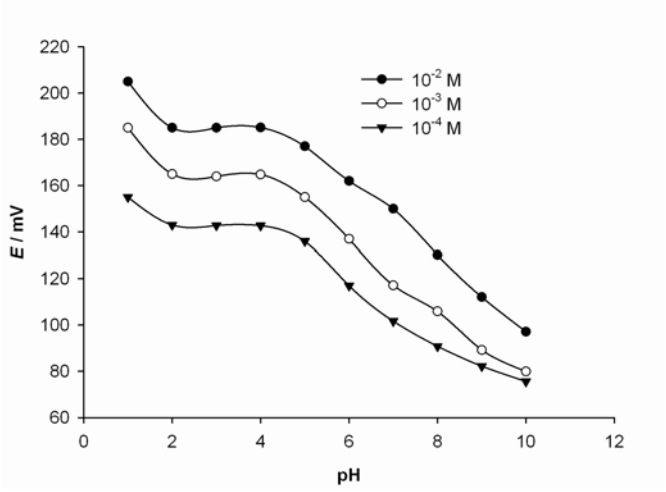

Fig.1. Effect of pH on DOPH electrode response

Table 1
pH RANGE FOR RANITIDINE ELECTRODES

Membrane no.	Plasticizers	pH range
I	DBPH	3.0 - 6.0
II	DOPH	2.0 - 4.0
III	DBP	2.0 - 6.5
IV	TBP	1.0 - 6.5

The response time varied from 1.5 to 25 s depending on the analyte concentration and it did not depend on whether the potentials were recorded from low to high concentrations or vice versa.. The response time was around 25 s for 10^{-5} M ranitidine hydrochloride solution; for higher concentrations the response time was shorter. The signal stability was good.

Linearity

The response characteristics of the ranitidine electrodes measured at pH 3.0 achieved with buffer solution are listed in table 3 [22]. The stability of the electrodes was monitored continuously for 10^{-3} M ranitidine hydrochloride solution by measuring the potential drift for 7 days. The standard deviations of the potential drift obtained for these 7 days were equal to ±4, ±3, ±6, and ±2 mV for membranes no. I, II, III, and IV.

A typical calibration plot for electrode II is shown in figure 2 (pC = - log C).

As the graph shows, the calibration curves were linear over the concentration range of 10^{-5}-10^{-1} M with a slope of 41.20 mV per decade and the correlation coefficient R = 0.9990. The regression equation for the calibration curve was found to be E/mV = - 41.20·pC + 267.81.

A graphical method (fig.3) was applied for calculating the limit of quantification defined as the intersection of the regression line for the linear domain with the range when the electrode response is relatively constant [23]. The limit of quantification for electrode II was $6.30 \cdot 10^{-6}$ M (2.21μg·mL^{-1} ranitidine hydrochloride).

When DOPH was used as plasticizer the electrode gave the best response. The electrode II had good stability and was used for the quantitative determination of ranitidine hydrochloride from pharmaceutical products.

Precision

Repeatability was investigated by measuring the potential of nine replicate samples of 10^{-4}, 10^{-3} and 10^{-2} M ranitidine hydrochloride solutions, and the mean standard deviation was 2.04 %. Inter-day precision was assessed by analyzing the same three concentrations over three consecutive days, resulting in mean standard deviation of 2.48 %.

Accuracy

The accuracy of the electrode II was assessed by analyzing three standard solutions (10^{-4}, 10^{-3} and 10^{-2} M ranitidine hydrochloride) using direct potential method. The

Conc (M)	Electrode I	Electrode II	Electrode III	Electrode IV
1.0×10^{-1}	2.9	1.8	1.5	1.5
1.0×10^{-2}	8.6	11.1	7.7	6.8
1.0×10^{-3}	13.0	16.0	15.5	16.6
1.0×10^{-4}	21.6	23.8	18.9	19.2
1.0×10^{-5}	24.9	25.0	22.3	24.4

Table 2
RESPONSE TIMES FOR RANITIDINE HYDROCHLORIDE ELECTRODES

Parameters	Electrodes			
	I	II	III	IV
Plasticizers	DBPH	DOPH	DBP	TBP
Slope mV/decade	29.90	41.20	26.48	21.54
Correlation coefficient	0.9987	0.9990	0.9981	0.9951
Linearity range (M)	0.5×10^{-5}-1.0×10^{-1}	1.0×10^{-5}-1.0×10^{-1}	1.0×10^{-5}-1.0×10^{-1}	1.0×10^{-5}-1.0×10^{-1}
Detection limit (M)	6.80×10^{-6}	6.30×10^{-6}	7.10×10^{-6}	7.80×10^{-6}
Potential drift (mV/day)	4	3	6	2
Life time (days)	~ 55	~ 60	~ 50	~ 50

Table 3
PARAMETERS OF RANITIDINE HYDROCHLORIDE SELECTIVE ELECTRODES

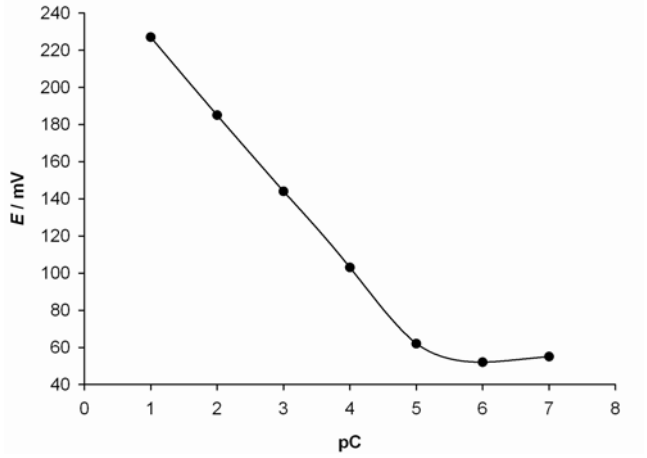

Fig.2. Calibration curves for electrode II

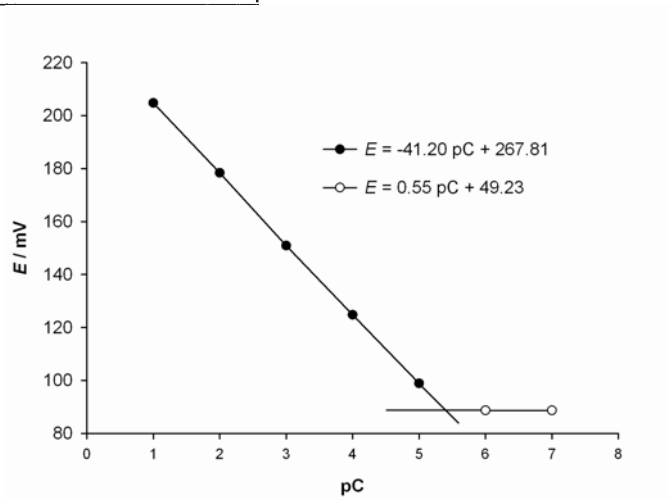

Fig.3. Limit of quantification for electrode II

Interfering species	K	Interfering species	K
NH^{4+}	1.18×10^{-1}	Chlorpheniramine maleate	3.01
Na^{+}	1.05×10^{-1}	Nizatidine	2.68
Ca^{+2}	1.63×10^{-2}	Famotidine	3.77×10^{-1}
Mg^{+2}	8.03×10^{-3}	Vitamin B1	7.4×10^{-3}
Al^{+3}	1.75×10^{-3}	Citric acid	2.8×10^{-3}

Table 4
SELECTIVITY COEFFICIENT OF ELECTRODE II

obtained data proved the average recovery and the standard deviation to be 100.59 and 1.37 %, respectively.

Robustness

The robustness of the method was assessed by comparison of the intra and inter-day assay results for ranitidine hydrochloride measured by two analysts. The mean standard deviations values for intra and inter-day assays of ranitidine performed in the same laboratory did not exceed 3.05 %. The robustness of the method was also investigated under a variety of conditions such as small changes of *p*H, laboratory temperature and provenience of chemicals. The percent recoveries of ranitidine were good.

Electrode selectivity

The selectivity of electrode II was investigated by the separate solution method and the potentiometric selective coefficients (K), were calculated by equations (1) and (2) [24]:

$$logK = \frac{E_{(II)}-E_{(I)}}{P} + log[A^{+}] - log[I^{z+}] \quad (1)$$

$$K = 10^{\frac{\Delta E}{P}} \cdot \frac{[A^{+}]}{[I^{z+}]} \quad (2)$$

Two separate drug solutions of the same concentration 10^{-3} M were prepared for the primary ion (A^{+} - ranitidine) and the interfering secondary ion (I^{z+}). Their potentials E_I (for A^{+}) and E_{II} (for I^{z+}) were measured (P - slope of the calibration curve).

As the results revealed in table 4 show, the tested inorganic cations and the organic compounds (except chlorfeniramine maleat and nizatidine), do not interfere. Moreover, the excipients found in ranitidine hydrochloride tablets or injectable solutions do not interfere with the determination of ranitidine.

Sample analysis

The direct potentiometric method was applied for the determination of ranitidine hydrochloride in pharmaceutical

tablets (150 mg ranitidine hydrochloride per tablet) and injectable solution (50 mg per 2 mL vial).

The limit values and the relative standard deviation obtained by using ranitidine selective PVC membrane electrode method were 150.55 ± 0.31 mg per tablet and 0.19% (n = 9) respectively. For injectable solution the results obtained were 50.37 ± 0.16 mg per 2 mL vial and 0.31% (n = 9) respectively.

The results are within the limits specified by the 10th Edition Romanian Pharmacopoeia (150 ± 7.50 mg per tablet and 50 ± 2.50 mg per 2 mL injectable solution).

Conclusions

Ranitidine hydrochloride selective electrodes based on ion pair complex of ranitidine-tetraiodobismutate using various plasticizers were constructed. The best ranitidine electrode was obtained when DOPH was used as plasticizer. This electrode was used for drug determination in pharmaceutical preparations. The electrode based on DOPH gave the best results and it was not influenced by any of the studied interferents. The proposed analytical method proved to be simple, quick and accurate.

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