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A New Ritodrine Selective Electrode and its Pharmaceutical Application

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Abstract: A novel ritodrine hydrochloride ion-selective PVC membrane electrode based on ion-pair complex of ritodrine-tetra phenyl borate was prepared with *di-n*-butyl phosphate as a plasticizer. The influences of membrane composition, temperature, pH of the test solution and foreign ions on the electrode performance were investigated. The electrode showed a Nernstian response over a wide ritodrine concentration range (1×10^{-5}-1×10^{-2} M) with a slope of 59.33 mV decade^{-1} and was found to be very selective, precise and usable within the pH range 3-7.5. The standard electrode potentials, $E°$, were determined at different temperatures and used to calculate the isothermal temperature coefficient ($dE°/dT$) of the electrode, which was 0.00075. The electrode was successfully used for potentiometric determination of ritodrine hydrochloride both in pure solutions and in pharmaceutical preparations.

Keywords: Ritodrine hydrochloride, Ion-selective electrode, Pharmaceutical analysis.

Introduction

Ritodrine hydrochloride (RTH), chemically [1-(4- hydroxy phenyl)-2-[2-(4-hydroxy phenyl) ethyl amino] propanol-hydrochloride], is a selective β_2- adrenergic agonist solely used as uterine relaxant. It decreases uterine contractility and is used to arrest premature labour and as an emergency means of alleviating foetal asphyxia during labour[1,2]. A review of literature revealed that several methods have been reported for the determination of ritodrine[3-13]. The chemical structure of ritodrine hydrochloride was depicted in Figure 1.

The aim of the present work, describes a sensitive and reasonably selective poly (vinyl chloride) membrane electrode based on the use of ritodrine - tetra phenyl borate as a novel electroactive material. The electrode exhibit useful analytical characteristics for the direct determination of ritodrine HCl in pure form and in pharmaceutical preparations.

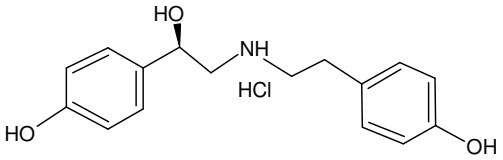

Figure 1. Chemical structure of ritodrine HCl.

Experimental

All chemicals were of analytical grade and double distilled water was used throughout the experiments. Ritodrine hydrochloride, PVC of relative high molecular mass and tetrahydrofuran (THF) were obtained from Sigma -Aldrich, Sodium tetra phenyl borate (Na-TPB) and *di-n*-butyl phosphate (DBP) were obtained form Merck. The pharmaceutical preparations containing ritodrine hydrochloride (Yutopar® tablets10mg\tablet or ampoules 10 mg\mL) were purchased from local drug stores.

Stock ritodrine hydrochloride solution (1×10^{-1} M) was prepared daily by dissolving an appropriate amount of the drug in double distilled water. More dilute solutions were prepared by appropriate dilution. The stock solution and dilutions were kept in dark bottles in the refrigerator. To investigate the selectivity of the proposed electrode towards inorganic cations, sugars and amino acids 1×10^{-2} M salt solutions of each of the following ions were prepared: Na^+, K^+, Li^+, Pb^{2+}, Mg^{2+}, Co^{2+}, Cr^{3+}, Al^{3+} and Fe^{3+}. Also 1×10^{-2} M solutions of glucose, lactose, starch, glycine, aspargine and alanine were prepared.

Preparation of the ion- pair

The ritodrine tetra phenyl borate (RTH-TPB) ion-pair was prepared by mixing 50 mL of aliquots of 1×10^{-2} M RTH and sodium tetra phenyl borate. The resulting precipitate was filtered, washed thoroughly with double distilled water till chloride free (tested using $AgNO_3$ solution) and dried at room temperature for at least 3 days. The chemical composition of the ion- pair as identified by elemental analysis was found to be 1:1 (RTH-TPB). Analysis: Calc. for $[C_{17}H_{22}NO_3]$ $[C_{24}H_{20}B]$: C, 81.05 ; H, 6.97 ; N, 2.31. Found: C, 80.96 ; H, 6.33; N, 2.02.

Preparation of membrane

The membrane was prepared by dissolving the required amounts of PVC, DBP and ion-pair of total weight 0.20 g in a 5 cm (diameter) Petri dish containing 5 mL THF, covered with a filter paper and the solvent was allowed to evaporate slowly at room temperature.

The electrochemical system

Potentiometric measurements were carried out with a Jenway 3010 pH- meter. A Techne circulator thermostat, Model C-100, was used to control the temperature of the test solution. The electrochemical system is represented as follows: Ag/AgCl/ internal solution /membrane/test solution/KCl salt bridge//SCE. Where the internal solution is a mixture containing equal volumes of 1×10^{-3} M RTH and potassium chloride. Jenway 4330 conductivity meter was used for conductance measurements.

Electrode Calibration

Suitable increments of standard drug solution were add to 50 mL doubly distilled water so as to cover the concentration range from 1×10^{-6} - 1×10^{-2} M. In this solution the sensor and reference electrode were immersed and the e.m.f values were recorded after each addition.

The values were plotted against the negative logarithm of drug concentration (P_{drug}). The electrode was washed with double distilled water and dried between measurements.

Selectivity of the electrode

Selectivity coefficients were determined by the separate solution method[14], in which the following equation was applied.

$$\log K^{pot.}_{RTH,B^{z+}} = \frac{(E_2 - E_1)}{S} + \log[RTH] - \log\left[B^{z+}\right]^{1/z+} \quad (1)$$

Where E_1 and E_2 are the electrode potentials of solutions of the RTH and interfering cation, B^{z+}, respectively (both of the same concentration) and S is the slope of the calibration graph.

Potentiometric determination of RTH

The standard addition method was applied[15], in which a known incremental change is made through the addition of standard solution of the sample. This was achieved by adding known volumes of standard drug solution to 50 mL aliquot water containing various amount of the investigated drug in its pure state or pharmaceutical preparations (tablets or ampoules). The change in potentials was recorded for each increment and used to calculate the concentration of RTH sample solution using the following equation:

$$C_x = C_s \left(\frac{V_s}{V_s + V_x} \right) \left(10^{n(\Delta E/S)} - \frac{V_x}{V_s + V_x} \right)^{-1} \quad (2)$$

Where C_x and V_x are the concentration and volume of the unknown, respectively, C_s and V_s are the concentration and volume of the standard, respectively, S is the slope of the calibration graph and ΔE is the change in potential due to the addition of the standards.

For the analysis of tablets, 20 tablets were accurately weighed and powdered in a mortar; then, the required amount from the tablet powder was taken as sample and dissolved in 10^{-2} M HCl, the solution was completed to 50 mL with distilled water. As for ampoules, the content of 10 ampoules were mixed and the requisite volume was transferred to a 50 mL volumetric flask, the flask was completed to mark with double distilled water.

Conductimetric determination of RTH

A volume containing 10-90 mg of RTH was transferred to a 50.0 mL volumetric flask and made up to the mark with double distilled water. The contents of the volumetric flask were transferred to a beaker and the conductivity cell was immersed. Then 10^{-2} M NaTPB was added and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring. The conductance reading after each addition was corrected for dilution[16] by means of the following equation, assuming that conductivity was a linear function of dilution:

$$\Omega_{corr} = \Omega_{obs} \left[\frac{\nu_1 + \nu_2}{\nu_1} \right] \quad (3)$$

Where Ω is electrolytic conductivity, ν_1 is the initial volume and ν_2 is the volume of the added reagent (corr.= corrected and obs.= observed). A graph of corrected conductivity *vs.* volume of the added titrant was constructed, and the end point was determined.

Potentiometric titration of RTH

Different weights of the RTH was transferred into a 100 mL beaker and diluted to 50 mL with double distilled water. The resulting solutions were titrated against 10^{-2} M Na-TPB using the investigated electrode as indicator electrode. The same method was applied for the determination of RTH in the pharmaceutical preparations.

Results and Discussion

Composition of the membrane

Five different membrane compositions were investigated. They consist of 5.00, 6.00, 7.00, 8.00 and 10.00% of an ion pair and the ratio of the plasticizer to PVC was always 1:1. Electrode made by using membrane consisting of 7.00% ion pair show the nearest performance characteristic of the Nernstian behavior (slope 59.33 mV decade^{-1}), within the usable concentration range 1×10^{-5} - 1×10^{-2} M of ritodrine (Figure 2).

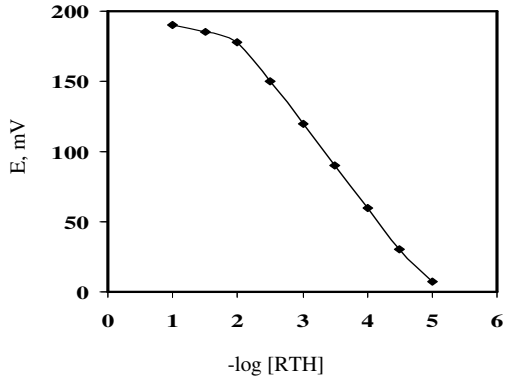

Figure 2. Typical calibration graph of RTH- selective electrode.

The slope increasing with increasing the composition may be attributed to the increase in the ion-exchange process at the solution –membrane interface reaching the near-Nernstian or Nernstian slope at the compositions 7.00%. The response characteristics of the electrode under investigation were determined and results are summarized in Table 2.

Table 1. Composition of different RTH-TPB membranes and slopes of the corresponding calibration graphs at 25 °C.

Composition %(w\w)			slope	RSD*
Ion Pair	DBP	PVC	mV decade^{-1}	
5.00	47.50	47.50	47.05	0.82
6.00	47.00	47.00	53.60	0.55
7.00**	46.50	46.50	59.33	0.92
8.00	46.00	46.00	62.12	1.20
10.00	45.00	45.50	65.02	0.96

**Relative standard deviation(five determinations), **Optimum composition.*

Table 2. Critical response characteristics for RTH-selective electrode.

Parameter	Value
Slope, mVdecade^{-1}	59.33
Correlation coefficient, r	0.9989
Linear range/M	1×10^{-2} - 1×10^{-5}
Working pH range	3 – 7.5
Response time*, s	15
Life time/day	30

**Response time for 10^{-3} M drug/sec.*

The response time of the electrode was tested for 1×10^{-2}-1×10^{-6} M ritodrine hydrochloride solutions. This electrode exhibits a fast dynamic response of about 15 s. When the concentration of drug solution was lower than 1×10^{-5} M, the response time increased to 30 s. The electrode was used for a period of 30 days without significant change in the electrode parameters.

Effect of soaking

The performance characteristics of the electrode were studied as a function of soaking time. For this purpose the electrode was soaked in 1×10^{-3} M of drug solution and the calibration graphs (pRTH *vs*. *E*elec, mV) were plotted after 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 and 6 h. The optimum soaking time was found to be 0.5-2 h, at which the slopes of the calibration curves were 57.0-59.0 mV per concentration decade, at 25 °C. Soaking for longer than 6 h is not recommended to avoid leaching, though very little, of the electro active species into the bathing solution. The electrode should be kept dry in an opaque closed vessel and stored in a refrigerator while not in use. The reproducibility of five repeated measurements on the same solution was ± 1 mV.

Effect of pH

The effect of pH of the ritodrine HCl solutions (1×10^{-3} M, 1×10^{-4} M and 1×10^{-5} M RTH) on the electrode potential was investigated. The solutions were acidified by the addition of very small volumes of 0.1 N HCl acid then the pH value was increased gradually using NaOH (0.1 or 1.0 M) for each pH value, the potential was recorded and thus the potential-pH curves for three ritodrine HCl concentrations were constructed as shown in Figure 3.

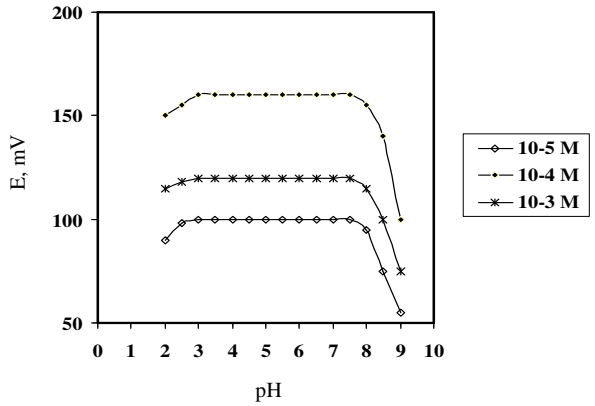

Figure 3. Effect of pH on the potential response of RTH-selective electrode for different concentrations.

The change in pH had a negligible effect in the pH range 3-7.5 and thus in this range the electrode can safely be used for ritodrine HCl determination. The decrease in the potential reading with pH above the mentioned range can be attributed to the formation of the free base of the drug and disappearance of the protonated species[17,18].

Conductimetric studies of pure solution of drug

Conductance measurements have been used successfully in quantitative conductimetric titration of system in which the conductance of the solution varies before and after the equivalence point. The system under investigation showed a regular rise in conductance up to the equivalence point where a sudden change in the slope occurred. The results of the drug determination (Table 3) showed that good recoveries and low standard deviations were

obtained. The optimum concentration ranges for RTH determination were 10.00 - 90.00 mg with mean recovery value of 100.06 with coefficients of variation of 0.10 - 0.88, at which sharp inflections and stable conductance readings were obtained.

Table 3. Conductimetric determination of ritodrine HCl in pure solution.

Ritodrine HCl		
Taken, mg	Recovery, %	R.S.D., %
10	100.10	0.10
20	100.75	0.75
60	100.84	0.83
80	99.50	0.50
90	99.11	0.88

Selectivity of the electrode

The influence of some possible interfering inorganic cations, sugars and amino acids on the RTH- electrode was investigated. The resulting selectivity coefficients are summarized in Table 4. The selectivity coefficients revealed that the proposed electrode are highly selective. The inorganic cations did not interfere due to the differences in their ionic size, mobility and permeability. Also, the smaller the energy of hydration of the cation facilitated a greater response of the membrane. In the case of sugar and amino acid, the high selectivity is mainly attributed to the difference in polarity and lipophilic nature of their molecules relative to ritodrine hydrochloride.

Table 4. Selectivity coefficients of the RTH-selective electrode calculated by the separate solution method (1×10^{-3} M of both ritodrine and the interferent) at 25 °C.

Interferent	$K^{pot}_{RTH,B^{Z+}}$	Interferent	$K^{pot}_{RTH,B^{Z+}}$
Na^+	2.3×10^{-3}	Fe^{3+}	9.1×10^{-4}
K^+	4.7×10^{-3}	Glucose	3.2×10^{-2}
Li^+	8.9×10^{-3}	Lactose	9.8×10^{-2}
Pb^{2+}	3.5×10^{-4}	Starch	7.6×10^{-2}
Mg^{2+}	6.2×10^{-2}	Glycine	6.3×10^{-4}
Co^{2+}	5.1×10^{-4}	Aspargine	5.2×10^{-4}
Cr^{3+}	9.2×10^{-3}	Alanine	2.9×10^{-4}
Al^{3+}	5.7×10^{-4}		

Effect of temperature of the test solution

To study the effect of temperature, the electrode potential of 10^{-6}–10^{-2} M drug solutions were determined in 15, 20, 25, 30 and 35 °C and the calibration graphs were constructed. The slope, usable concentration range and the standard electrode potentials ($E°_{elec.}$) obtained from the calibration plots as the intercepts at –log[RTH]= 0 corresponding to each temperature is reported in Table 5. From the table, it is obvious that the electrode gave a good Nernstian response in the temperature range 15-25 °C, the slop of the electrode jump to a very high value (100.02 mVdecade^{-1}) at 35 °C which may be attributed to decomposition of the ion pair. The obtained $E°_{elec.}$ values were used to determined the isothermal coefficient ($dE°/dT$) of the electrode using the following equation[19].

$$E°=E°_{25}+(dE°/dT)(t-25) \quad (4)$$

A plot of E^{o} *vs*. (*t* - 25) gave a straight line, the slope of which was taken as the isothermal temperature coefficient. It amounts to 0.00075 V per °C, revealing a fairly good thermal stability of the electrode.

Table 5. Performance characteristics of RTH-selective electrode at different temperatures**.**

Temperature, °C	Slope mVdecade^{-1}	Usable range \ M	*E*°elec.(mV)
15	54.20	1.53×10^{-6}– 2.20×10^{-2}	-160. 02
20	58.55	1.60×10^{-6}– 1.32×10^{-2}	-130.24
25	60.21	1.78×10^{-6}– 2.78×10^{-2}	- 85.65
30	79.22	1.89×10^{-6} – 3.64×10^{-2}	-69.34
35	100.02	4.60×10^{-6}–1.64×10^{-2}	-43.22

Analytical applications

The investigated electrodes were found to be useful in the potentiometric determination of RTH in pure solutions and in the pharmaceutical preparations. The mean recovery and the relative standard deviation values are summarized in Table 6. The data indicated that there was no interference from the excipients used in the formulations of the tablets and ampoules. The results of the pharmaceutical preparations were compared with the officinal method of United States Pharmacopoeia[20] and are shown in Table 6. The results are in good agreement with those obtained from the officinal method. A statistical analysis of the results by Student's *t*- and *F*-tests showed no significant difference in the accuracy and precision between the proposed and officinal methods

Table 6. Determination of ritodrine HCl in pure form and in pharmaceutical preparations using RTH-selective electrode.

	Pure Solution		pharmaceutical preparations			
			Yutopar tablets		Yutopar ampoules	
	Standard addition	Potentiometric titration	Standard addition	Potentiometric titration	Standard addition	Potentiometric titration
Taken*, mg	5	5	5	5	5	5
	10	10	15	15	15	15
	20	20	25	25	25	25
Recovery, %	98.40	99.54	96.41	100.11	100.60	100.62
	100.21	96.11	103.22	99.33	96.42	100.22
	96.50	100.23	101.13	100.20	99.50	104.21
R.S.D.**, %	0.25	0.32	0.33	0.24	0.16	0.30
	0.26	0.28	0.36	0.27	0.19	0.24
	0.20	0.31	0.34	0.34	0.35	0.28

**Taken mg per 50 mL. **Relative standard deviation (five determinations).*

Table 7. Statistical analysis of the results obtained for the determination of ritodrine HCl using RTH-selective in comparison with officinal method.

	Methodes	Parameters			
		Mean Recovery, %	S.D.	*t*-value*	*F*-value **
Yutopar tablets	Standard addition	100.25	0.30	2.03	2.11
	Potentiometric titration	99.88	0.22	1.42	3.09
	Officinal Method	99.70	0.70		
Yutopar ampoules	Standard addition	100.04	0.25	1.57	1.46
	Potentiometric titration	101.68	0.21	1.87	2.98
	Officinal Method	99.97	0.66		

**Tabulated value, 2.78. **Tabulated value, 6.39.*

Conclusion

The new ritodrine HCl selective PVC based membrane electrode exhibited the advantages of simple design and operation, reasonable selectivity, fast response and reproducibility. Further, the electrode can be used to determine ritodrine hydrochloride by direct potentiometry in pure form and in pharmaceutical preparations.

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