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Effect of Different Organized Media on Ion-Selective Electrode (ISE) Determination of Propranolol in Pharmaceutical Dosage Forms

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ABSTRACT

This study examined the effect of different organized media such as β-cyclodextrin and micelle surfactants, either anionic (sodium dodecyl sulphate), cationic (cetrimide) or non-ionic (tween-20 and tween-80), on the potentiometric properties of propranolol polyvinyl chloride selective electrode based on tetraphenyl borate (PRO-TPB) ion-exchanger as an electroactive material. It was found that the Nernstian slope for propranolol over the concentration range of 1×10^{-5} to 10^{-2} M was unaffected by non ionic surfactant, whereas cationic surfactant significantly decreased the Nernstian slope. However, anionic surfactant significantly increased the Nernstian slope. The electrode basic analytical parameters such as measurement range, slope characteristics, detection limit, response time, and selectivity coefficients in relation to some inorganic cations, sugars, amino acids and some β-blockers were investigated in presence or absence of organized media. Electrode was used for the potentiometric determination of propranolol in pharmaceutical preparations with and without organised compounds. The results were consistent with those obtained using a reference method.

Key words: propranolol, organized media, ion selective electrode, polyvinyl chloride, selectivity coefficient, dosage forms

INTRODUCTION

Propranolol hydrochloride, 1-(isopropylamine)-3-(1-naphthyloxy)-2-propanol hydrochloride (PRO) (Figure 1) is a β-adrenergic receptor blocking agent that is prescribed for its antihypertensive, antianxiety, anticonvulsant and antianginal effects[(1)]. Many analytical methods have been reported for usage in pharmaceutical preparation[(2,3)]. Surfactants are usually included as excipients in many drug formulations to improve dissolution rate and increasing drug solubility[(4)]. These aims are based on the ability of surfactant to reduce interfacial tension and contact angle between solid particles and aqueous media.

Ion selective electrodes (ISE) have been used as an attractive and simple technique which requires no prior sample preparation[(5,6)]. Organized media (OM) are amphiphile aggregates or polymers that form anisotropic microstructures in solution. Examples of widely utilized OM include surfactant micelles, crown ethers, and cyclodextrins[(7)]. OM assemblies have a great potential in many areas of analytical chemistry. The use of ISE in aqueous solution containing some surfactants or β-cylodextrin as an organized medium has no unfavourable effect on the response of glass and solid electrodes so far. The presence of such OM may potentially interfere with the response of the polymer membrane. Based on the charge of the hydrophilic group, surfactants can be divided into four types: anionic, cationic, zwitterionic and non-ionic. Both ionic and non-ionic surfactants interact with polymer membrane being divided into the aqueous phase and the membrane phase. Electrodes with polymer membrane for the determination of ionic surfactants[(8-10)] by both direct potentiometric and titration methods have been reported. Thus, ionic surfactants are potential interfer-

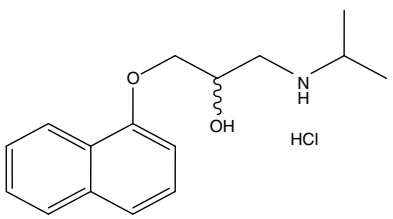

Figure 1. Propranolol hydrochloride

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ences. Although non-ionic surfactant does not respond potentiometrically, they can unfavourably affect the determination of other ionic species. These substances undergo a division into the sample phase and the membrane phase enhancing the extraction of interfering ions from the sample solution to decrease the membrane selectivity. Also, adsorption of the OM molecules on the membrane surface results in potential instability. β-Cyclodextrin (β-CD) is a macrocyclic oligosaccharide consisting of seven D-(+)-glucopyranose units linked by α(1,4) interglucose bonds and shaped like a truncated core with a relatively hydrophobic hollow cylindrical cavity[11,12]. Cyclodextrins are known to form inclusion compounds with many hydrophobic or specially amphiphilic species by capturing different guest molecules in their cavity. This peculiar behavior is responsible for their use in diverse applications such as drug delivery systems, catalysis as well as taste and odor preservatives in food industry.

These systems were used to study the solubility of some β-blockers[13] and the solubility and complexation of some analgesics[14,15]. However, propranolol has been previously determined using a polyvinyl chloride (PVC) membrane electrode based on ion pair complexes with silicotungstic acid[16] dinonylnaphthalene-sulphonate or tetra(2-chlorophenyl)borate[17] and with phosphotungstic acid[18]. This study explored the effect of different OM on ISE determination of propranolol in its pure form and pharmaceutical dosage forms.

MATERIALS AND METHODS

I. *Materials and Reagents*

All reagents were of analytical grade. Solutions were prepared in bidistilled water. Propranolol hydrochloride was kindly provided by Misr Company for Pharmaceuticals and Chemical Industries. Sodium tetraphenyl borate (TPB) was purchased from Aldrich. Dibutyl phthalate (DBP) was purchased from Loba Chemie and polyvinyl chloride was purchased from Fluka. Pharmaceutical formulation containing PRO and Inderal tablets containing 10 and 40 mg of PRO per tablet were purchased from a local pharmacy.

II. *Preparation of Ion Selective Membrane Electrode*

The precipitate of the PRO-TPB ion associate was prepared from aqueous medium by mixing equal portions of PRO and TPB (50 mL of 10^{-2} M). The precipitate was filtered, washed thoroughly with bidistilled water until chloride was no longer detected in the aqueous phase, and dried at room temperature. The membrane composition (w/w) was 5% (0.0175 mg) PRO-TPB, 47.5% (0.16 mg) DBP and 47.5% (0.16625 mg) PVC. The components were dissolved in about 10 mL of tetrahydrofuran (THF) and the resulting solution was poured into a Petri dish of 7.5 cm diameter and left to dry in air.

A disc of approximately 10 mm in diameter and 3 mm thickness was fixed on the base of a PVC tube with a PVC/THF paste. The tube was partially filled with a solution that contains 10^{-1} and 10^{-3} M of sodium chloride and PRO, respectively. The electrochemical system was as follows:

Ag/AgCl/0.1 M NaCl and 10^{-3} M PRO /membrane/ test solution/ saturated calomel electrode.

III. *Apparatus*

The potential was measured with an Orion model 420A digital pH/mV meter. A Lab Companion circulator thermostat, Model CW-05GL, was used to control the temperature of the test solution.

IV. *Construction of Calibration Graph with and without Organized Media (OM)*

Aliquot volumes containing the PRO in the working concentration range of 10^{-2}-10^{-5}M were quantitatively transferred into 50 mL bidistilled water containing 0 -10^{-6} M of OM. The emf produced by immersing the prepared electrodes in conjunction with single junction calomel reference electrode in the prepared solutions was measured. A calibration curve for E, mV vs SCE and pC was constructed, where C is concentration of the PRO with different concentrations of OM.

V. *Assay Procedure for Tablets*

Ten tablets of each concentration (10 mg and 40 mg) were finely powdered after weighing. A portion of the tablet powder equivalent to 10 and 40 mg of the drug were extracted with 3 × 30 mL portions of bidistilled water. After sonication of each portion for 10 minutes, the extracts were transferred quantitatively into 100 mL measuring flasks and completed with bidistilled water. The final solution was centrifuged (4000 × g) for 15 min and filtered. Aliquots covering the working concentration range 1.35×10^{-5} to 2.70×10^{-3} M were quantitatively transferred into the titration cell. Proceed as described for construction of calibration graph. The nominal content of the tablets were calculated using either the calibration graph or the corresponding regression equation.

RESULTS AND DISCUSSION

I. *Response Characteristics, Response Time, Detection Limit and Reproducibility*

The electrochemical performance characteristics of propranolol electrode were systematically evaluated according to IUPAC guidelines[19]. The response of different membranes containing different percentages of PRO, TPB, and DBP (Table 1) were linear over

the concentration range of 1×10^{-2} - 1×10^{-5} M (Figure 2). It was evident that the electrode containing 5%(w/w) PRO : TPB exhibited a calibration plot of Excellent Nernstian slope (57.53 mV per concentration decade, at 25°C) over a relatively wide range of PRO concentration (1.0×10^{-2} - 3.4×10^{-5} M). The electrode provided stable emf reading within 10-20 s for 10^{-2}-10^{-4} M drug solutions. In dilute solutions > 10^{-4} M the response time were 30-40 s. Consequently, the above electrode was selected for carrying out all the studies.

II. *Effect of pH*

The effect of pH of the test solution (10^{-3}, 5×10^{-4} and 10^{-4} M, PRO) on the response of the electrode potential was investigated based on changes in pH over the range of 1.5-12.5. The pH was changed by adding very small volumes of 0.1 M hydrochloric acid or 0.1 M sodium hydroxide (Figure 3). At all concentrations, the electrode potential was stable and practically unaffected by the pH change over the working pH range 2.5-8.5, above which the potential reading decreased sharply. This behavior might be attributed to the precipitation of the free base of PRO as a result of its low solubility in alkaline solutions (pH > 9), which lead to a consequent decrease in its available concentration. The pH of 5.6 was used for all the experiments.

III. *Effect of Different Organized Media*

The effect of surfactants on the calibration graphs of the propranolol electrode was studied. Cationic, anionic

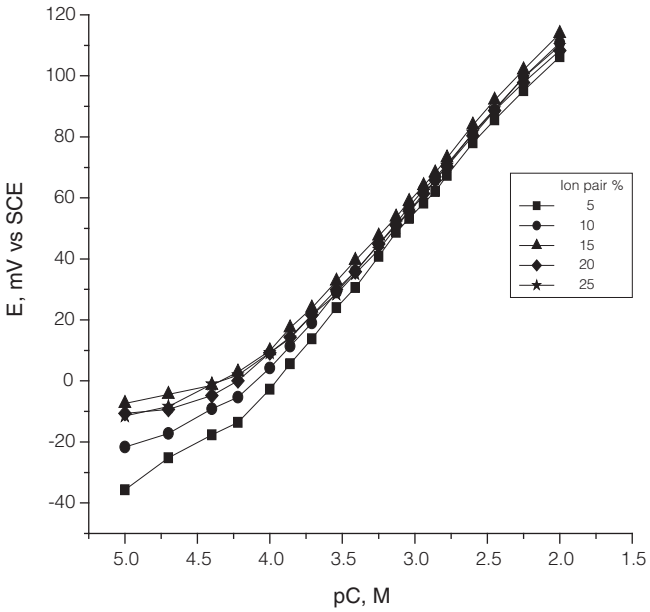

Figure 2. calibration curves of PRO electrode with membrane containing different percentage of ion pair (w/w).

Table 1. Slopes of the calibration curves and the detection limit for PRO electrode with different percentages of membrane composition at 25°C

Electrode number	Membrane Composition%			Slope mV/M decade	RSD %	Detection limit (M)
	PVC	DBP	Ion Pair			
1	47.5	47.5	5	57.53	0.61	3.98×10^{-5}
2	45	45	10	55.35	0.69	4.47×10^{-5}
3	42.5	42.5	15	49.84	0.71	5.25×10^{-5}
4	40	40	20	50.70	0.68	7.94×10^{-5}
5	37.5	37.5	25	50.89	0.65	7.94×10^{-5}

Table 2. Effect of different concentrations of organized media on the detection limit with the slope of linear part of calibration curves at 25°C

Concentration (M)	Tween-20		Tween-80		Sodium dodecyl sulphate		Cetrimide		β-cyclodextrin	
	Detection limit (M)	Slope	Detection limit (M)	Slope	Detection limit (M)	Slope	Detection limit (M)	Slope	Detection limit (M)	Slope
10^{-6}	1.51×10^{-4}	56.55	1.45×10^{-4}	57.05	7.41×10^{-5}	56.18	1.02×10^{-4}	57.07	4.17×10^{-4}	50.21
10^{-5}	1.62×10^{-4}	57.12	1.58×10^{-4}	57.40	8.51×10^{-5}	56.48	1.05×10^{-4}	56.88		47.47
10^{-4}	1.78×10^{-4}	57.01	1.78×10^{-4}	57.16	1.20×10^{-4}	57.53		2.06		46.58
10^{-3}	1.86×10^{-4}	57.47	1.86×10^{-4}	56.83		115.84		2.34		37.94
10^{-2}	1.95×10^{-4}	57.33	1.91×10^{-4}	57.10		124.03		5.56		25.67

and neutral surfactants and β-cyclodextrin which form inclusion compounds with many amphiphilic species[20] were used. In the case of non-ionic surfactant tween-20 and tween-80, no significant changes were noted in the linear slope of the calibration graph and the detection limits (Table 2). The electrode potential slightly became more negative as the concentration of surfactant increased. Also, tween-80 shifted more than tween-20, possibly due to the hydrophobic adsorptive forces between the membrane surface and the surfactant molecules and different molecular weights of the two surfactants.

The effect of 1×10^{-6} to 1×10^{-2} M of β-cyclodextrin on the calibration curve of the electrode was investigated. It was observed that the electrode potential of the calibration curves decreased gradually departing from Nernestian value 59 mV as β-cyclodextrin concentration increased. The hydrophobic nature of the internal core of the β-cyclodextrin molecule was responsible for the formation of inclusion complex with the drug in solution[21] . This resulted in decreasing drug concentration for interaction with the electrode as indicated by the significant decrease in the electrode potential (Figure 4).

Cationic surfactant cetrimide at concentration below 1×10^{-5} M slightly increased the electrode potential due to the repulsion effect between the counter ion and the positive head of the micelle surfactant. However, further increase of cetrimide concentration greater than (CMC)s 1×10^{-5} M/L made the electrode lost its performance entirely as shown in Figure 5. This effect might be attributed to the competitive replacement of the drug with the more lipophilic cationic surfactant. The detection limit of the calibration graph moved towards higher values (from 3.98×10^{-5} to 1.05×10^{-4} M) of PRO.

Our results showed that 1×10^{-6} and 1×10^{-4} M of anionic surfactant sodium dodecyl sulphate slightly decreased the electrode potential. This behaviour could be attributed to neutralization of the electric charge on the micelle by the counter-ion which strongly adsorbed on the electrode membrane leading to a decrease in the counter-ion concentrations. Meanwhile, the presence of SDS at a concentration greater than (CMC) 1×10^{-3} M greatly reduced the electrode potential to more negative values as shown in Figure 6. Duplication of the linear

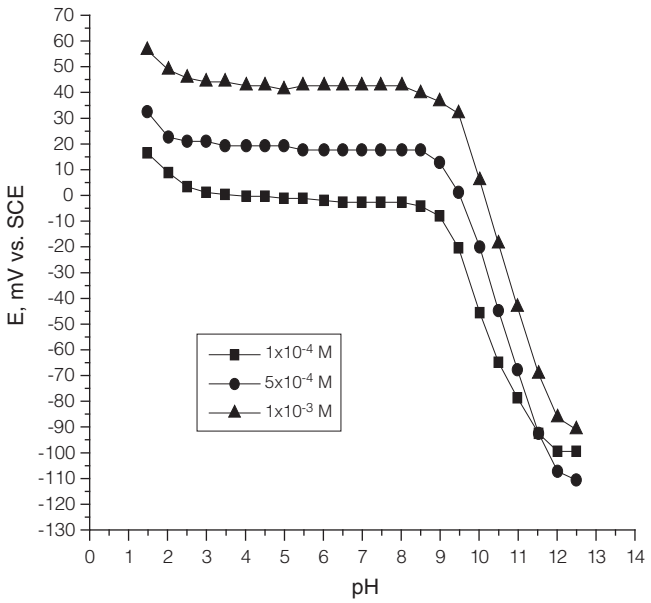

Figure 3. Effect of pH on the electrode potential in the presence of different concentrations of the drug.

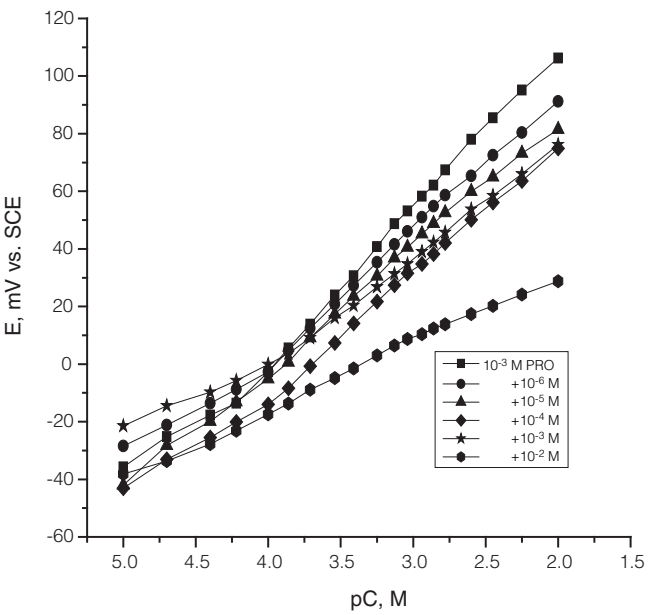

Figure 4. Effect of different concentrations of β-cyclodextrine on the calibration curve of electrode containing 5% (w/w) ion pair.

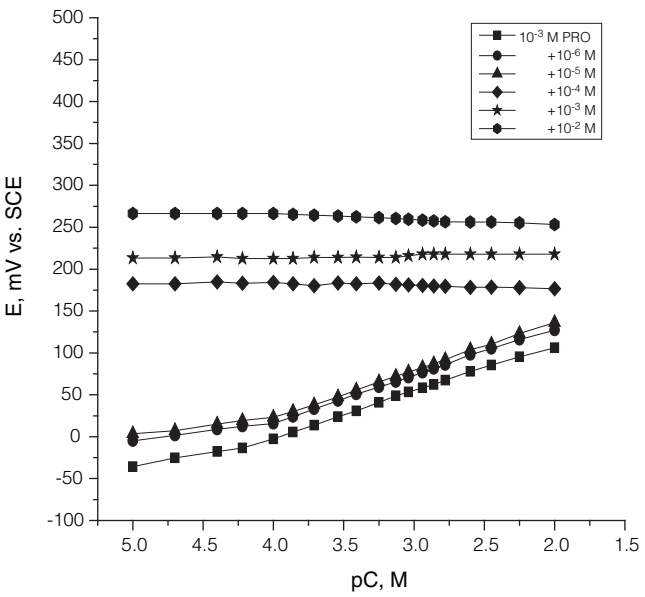

Figure 5. Effect of different concentrations of cetramide on the calibration curve of electrode containing 5% (w/w) ion pair.

slope of the calibration graph at 1×10^{-3} and 1×10^{-2} M SDS concentrations proved this effect.

Generally, the surfactants in increased concentrations led to decrements in concentration readouts for PRO (Table 2) regardless of their electrical charges. This effect indicated preliminary adsorption of surfactant on the surfaces of ion sensitive organic membrane, before the target ions start to diffuse. This consideration is in accordance with the fact that surfactant molecules tend to locate at interfaces since they are amphiphilic in nature[22]. Thus sodium dodecyl sulphate, cetrimide, tween-20 and tween-80 were expected to locate at the interface between the membrane and the aqueous analyte solution, by orienting themselves based on the Hardy-Harkins rule of the least abrupt change, i.e., the least abrupt transition to the neighbouring phase possible, so that the polar groups are directed towards the aqueous bulk phase. The coverage of the electrode membrane surface with surfactant molecules would prevent the diffusion of PRO ions across the membrane. Thus, the results obtained with PRO-surfactant system could be explained on the bases of electrostatic and hydrophobic adsorptive forces between the PRO-sensitive membrane surface of the electrode and the surfactant molecules. Non-ionic surfactants Tween-20 and Tween-80 were partially adsorbed at this surface by hydrophobic adsorptive forces and reduced the diffused PRO ions across the membrane surface, yielding lower concentration readouts. Furthermore, increasing the concentration of negatively charged sodium dodecyl sulphate caused lower cell potential. This was consistent with the anionic nature of surfactant. The larger slopes of the anionic surfactant were likely due to the fact that the preconditioning with

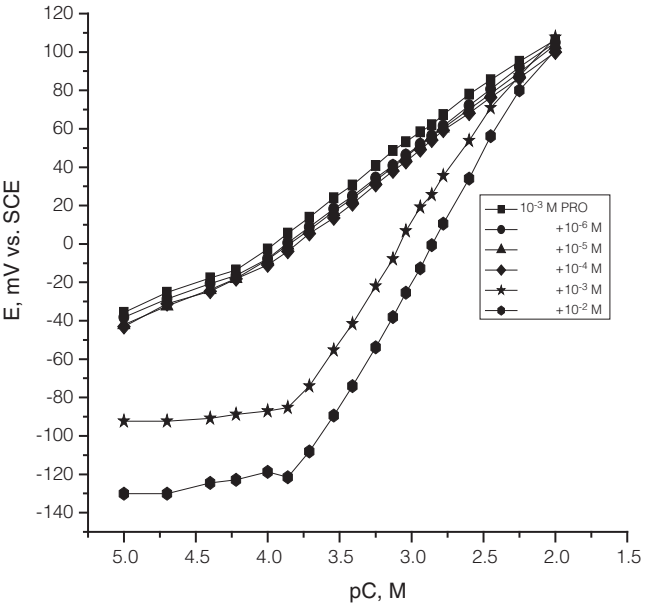

Figure 6. Effect of different concentrations of sodium dodecyl sulphate on the calibration curve of electrode containing 5% (w/w) ion pair.

Table 3. Effect of inorganic cations on the selectivity of propranolol electrode in absence and presence of the organized media at 25°C

Interferant	M .WT	$\log K^{pot}_{PRO}$					
		Free	SDS	CET	Tween-20	Tween-80	β-cyclodextrin
NH_4^+	18.00	-1.62	-1.53	-1.57	-1.61	-1.62	-1.52
Na^+	23.00	-1.69	-1.54	-1.62	-1.67	-1.69	-1.53
Mg^{2+}	24.30	-2.97	-2.86	-2.90	-2.93	-2.94	-2.84
Al^{3+}	26.98	-3.34	-3.25	-3.31	-3.30	-3.32	-3.24
K^+	39.00	-1.66	-1.51	-1.61	-1.66	-1.66	-1.50
Ca^{2+}	40.08	-3.05	-2.98	-3.01	-3.03	-3.05	-2.92
Mn^{2+}	54.09	-3.08	-2.89	-3.00	-3.05	-3.08	-2.92
Co^{2+}	58.93	-2.92	-2.81	-2.84	-2.90	-2.91	-2.81
Ni^{2+}	58.69	-2.95	-2.84	-2.86	-2.93	-2.94	-2.86
Cu^{2+}	63.55	-2.30	-2.28	-2.29	-2.30	-2.30	-2.27
Sr^{2+}	87.62	-1.29	-1.18	-1.22	-1.27	-1.29	-1.18
Cd^{2+}	112.41	-2.72	-2.60	-2.68	-2.71	-2.74	-2.59
Cs^+	132.00	-1.19	-1.08	-1.16	-1.19	-1.20	-1.07
Ba^{2+}	137.33	-2.93	-2.84	-2.89	-2.92	-2.94	-2.81
Hg^{2+}	200.59	-1.75	-1.66	-1.70	-1.75	-1.74	-1.65

Table 4. Effect of different organic compounds on the selectivity of propranolol electrode in absence and presence of the organized media at 25°C.

Interferant	M.WT	$\log K_{PRO}^{pot}$					
		Free	SDS	CET	Tween-20	Tween-80	β-cyclodextrin
Urea	60.06	-1.63	-1.52	-1.56	-1.59	-1.61	-1.48
Glycine	75.07	-1.56	-1.42	-1.48	-1.54	-1.55	-1.36
Fructose	180.16	-1.61	-1.47	-1.53	-1.62	-1.65	-1.46
Glucose	180.16	-1.65	-1.36	-1.53	-1.62	-1.65	-1.27
Atenolol	266.34	-1.74	-1.64	-1.68	-1.72	-1.75	-1.62
Nadolol	309.40	-1.97	-1.80	-1.84	-1.93	-1.97	-1.75
Timolol	432.49	-1.00	-0.88	-0.94	-0.99	-1.00	-0.67

this surfactant greatly increased the R-sites in the organic membrane. Upon addition of PRO, the non-equilibrium Hulanciki-type effect yielded very large slopes. Positively charged cetrimide was adsorbed on the electrode surface more effectively by the additional electrostatic attraction forces. The repelled positively charged PRO ions led to larger decrement in the concentrations readout.

IV. *Selectivity of the Electrode*

The influence of 22 different inorganic and organic compounds, including inorganic cations, sugars, amino acids and some β-blockers, was investigated in absence and presence of OM. The selectivity coefficients $\log K_{PRO}^{pot}$ were evaluated by the separate solution method[23] using the following equation:

$$\log K_{PRO}^{pot} + J^{z+} = (E_2 - E_1)/s + \log\left[PRO^{+}\right] - \log\left[J^{z+}\right]^{\frac{1}{z}}$$

Table 5. Results of determination and the recovery analysis of PRO in pharmaceutical dosage forms

sample	Taken concentration*(M)	Actual concentration (M)	Recovery (%)	RSD (%)
Inderal 40 mg	2.70×10^{-3}	2.70×10^{-3}	100.00	0.62
	1.35×10^{-3}	1.36×10^{-3}	100.74	0.77
	5.41×10^{-4}	5.39×10^{-4}	99.63	0.64
	2.70×10^{-4}	2.68×10^{-4}	99.26	0.84
Inderal 10 mg	6.76×10^{-4}	6.74×10^{-4}	99.70	0.63
	3.38×10^{-4}	3.37×10^{-4}	99.70	0.56
	6.76×10^{-5}	6.69×10^{-5}	98.96	0.97
	1.35×10^{-5}	1.34×10^{-5}	99.34	0.75

*Each value is the mean of five experiments

Table 6. Comparison of ion selective method with spectrophotometric method for the determination of propranolol in pharmaceutical formulation

Concentration mol/L (Inderal 40 mg)	Ion selective method			Spectrophotometric method*			F test	±t test
	Mean found concentration**	Recovery (%)	RSD (%)	Mean found concentration	Recovery (%)	RSD (%)		
10^{-4}	9.94×10^{-5}	99.40	0.89	9.96×10^{-5}	99.60	0.61	2.120	0.42
5×10^{-4}	4.98×10^{-4}	99.60	0.86	4.94×10^{-4}	98.80	0.54	2.578	1.77
10^{-3}	9.97×10^{-4}	99.70	0.73	9.98×10^{-4}	99.80	0.65	1.259	0.23
5×10^{-3}	4.99×10^{-3}	99.80	0.64	5.00×10^{-3}	100.00	0.41	2.427	0.59
$F_{tabulated}$=5.050 / $t_{tabulated}$=2.31	For P = 0.05							

*Each value is the mean of five experiments

**Data obtained according to reported method[24]

where E_1 is the electrode potential in 10^{-3} M PRO and E_2 is the potential of the electrode in10^{-3} M solution of the interfering J^{z+}.

The obtained values are shown in Tables 3 and 4 as $\log K_{PRO}^{pot}$. The concentration of the OM was chosen where the calibration graph is still in the Nernestian range. Our results reveal that the presence of different OM does not interfere with many foreign basic compounds, and the electrode display reasonable selectivity for propranolol.

V. *Application to Drug Analysis*

Applicability of the proposed method was tested by determination of PRO in its dosage forms Inderal tablets. Excellent recoveries and RSD values were obtained (Table 5). Common tablet excipients, such as lactose, starch, talc, starch, avisil, gelatin, and magnesium stearate, did not interfere with the assay. A previously reported spectrophotometric method[24] was used for comparison using Student's *t*-test and the variance ratio *F*-test. As illustrate in Table 6, the calculated values did not exceed the reference figures indicating lack of significant difference in the performance of the compared methods regarding accuracy and precision[25].

The proposed method was validated based on sensitivity, linearity, intraday and interday precision, accuracy, specificity, and robustness. Sensitivity of the method was evaluated by determining the limit of detection (LOD) and limit of quantitation (LOQ) according to the ICH guide lines. LOD was defined as: 3.3 × σ/S and LOQ was: 10 × σ/S, where σ is the standard deviation of the y-intercept of the regression lines (the standard deviation of the response) and S is the slope of the calibration curve.

Linearity was evaluated by calculation of the regression equations over the ranges given in Table 7. The table also shows the detection limits, slopes, intercepts, and correlation coefficients obtained by linear least squares treatment of the results.

The intra-day and inter-day accuracy and precision for the proposed method were examined by analysis of PRO samples in its dosage forms in two different concentrations. Intra-day precision was assessed by five determinations for each concentration in one day. Inter-day precision was assessed by determination of each concentration on three separate days. Repeatability and reproducibility in the three proposed methods were fairly good, as indicated by the small values of relative standard deviation (RSD), and error (% Er) (Table 8). Specificity of the method was proven by the negligible effect of the presence foreign matters and different surfactants on the potentials.

Table 7. Quantitative parameters for PRO-TPB PVC membrane base sensors

parameter		PRO-TPB PVC membrane base sensors
linear regression y = a + bx	slope(mV per decade)	57.53
	intercept(mv)	220.80
	correlation coefficient (r)	0.9993
LOD(M)		1.53×10^{-5}
LQD(M)		4.64×10^{-5}
RSD%		1.36
working range(M)		3.4×10^{-5}-1.0×10^{-2}

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Table 8. Intra-and inter-day accuracy and precision of propranolol electrode

concentration (M)	intra-day*			inter-day**		
	mean found concentration (M)	RSD (%)	Er (%)	mean found concentration (mol/L)	RSD (%)	Er (%)
10^{-4}	9.94×10^{-5}	0.89	6.00×10^{-5}	9.93×10^{-5}	0.99	7.00×10^{-5}
5×10^{-4}	4.98×10^{-4}	0.86	2.00×10^{-4}	4.96×10^{-4}	0.81	4.00×10^{-4}
10^{-3}	9.97×10^{-4}	0.73	3.00×10^{-4}	$9.99E \times 10^{-4}$	0.93	1.00×10^{-4}

*Intra-day accuracy and precision assessed by five determinations for each concentration in one day.
**Inter-day accuracy and precision was assessed by determination of each concentration on three separate days.

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