Turkish Journal of Chemistry

Volume 30 | Number 3 Article 6

1-1-2006

Effect of Surfactants on Response of Promethazine PVC-Membranes

MOHSEN M. ZAREH

RAGA E. SHOHIAB

MOSTAFA ABD-EL-FATAH

Turk J Chem
30 (2006) , 307 – 323.

Effect of Surfactants on Response of Promethazine PVC-Membranes

Mohsen M. ZAREH*, Raga E. SHOHIAB and Mostafa ABD-EL-FATAH
Chemistry Department, Faculty of Science, Zagazig University, Zagazig, EGYPT
e-mail: mohsenzareh@hotmail.com

Received 03.08.2005

The effect of surfactants (cationic, anionic and non-ionic) on the performance of plastic membrane promethazine electrodes was studied. Three electrodes with membranes containing either sodium tetraphenylborate, sodium tetraphenylborate + 18-crown-6, or 18-crown-6 were prepared. The cationic and the anionic surfactants exhibited potential shifts and a super-Nernstian slope of the calibration graphs. The non-ionic surfactant did not cause alterations in the calibration graphs. The effect of surfactants' concentrations was investigated. The performance characteristics of these electrodes were studied. The slopes of the calibration graphs of the 3 electrodes were 54.4, 54.9 and 48.4 mV/decade. The rectilinear ranges were 2 x 10^{-5}-10^{-2}, 1.0 x 10^{-5}-10^{-2} and 3.2 x 10^{-5}-10^{-2} M corresponding to the 3 electrodes. The optimum pH range was 2-7. The selectivity coefficient values were calculated for different inorganic cations, amino acids and pharmaceutical amines. Direct potentiometry and potentiometric titration were applied for the determination of promethazine in its pure form or in its pharmaceutical preparation. The recovery range and the relative standard deviation values for potentiometric titration were 98.6% -100.1% and 0.79% -1.96% (4 determinations), respectively. For direct potentiometry, the corresponding recovery values were 98.6% and 99.5%, and the relative standard deviation values were 1.49% and 1.02% (4 determinations).

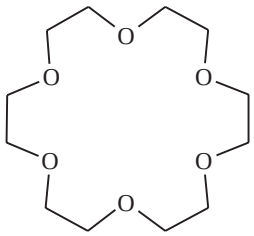
Key Words: Effect of surfactant on PVC-membranes, promethazine determination, promethazine-selective electrode.

Introduction

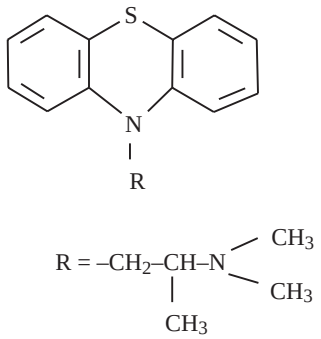
Promethazine (PM) is an antihistamine used for the symptomatic relief of hypersensitivity reactions, for the control of nausea, vomiting and vertigo of various causes, as a sedative and hypnotic, and as a common ingredient of cough and cold preparations. Promethazine and its salts are given by mouth, by the parenteral or rectal route, or applied topically. It has adverse effects, sedation and antimuscarinic effects[1]. As for antihistamines in general, cardiovascular side-effects are more commonly seen after injection, and bradycardia, tachycardia, transient minor increases in blood pressure and occasional hypotension have been reported with promethazine hydrochloride. Jaundice and blood dyscrasias have been observed, and extrapyramidal effects

*Corresponding author

may occur at high doses. Promethazine has pronounced antimuscarinic and antiemetic properties and causes sedation and photosensitivity reactions. The possible association between phenothiazines and sudden infant death is due to toxic neurological syndrome. The structural formula of promethazine hydrochloride is shown below:



18-crown-6



Promethazine

Several methods were utilized for the analysis of phenthazines. Spectrometry is one of the widely known procedures for the determination of these drugs. Saif et al.[2] determined promethazine by the selective reaction with potassium persulfate at 515 nm. Beer's law was obeyed at 0.001-0.1 mg/mL. Sultan et al.[3] assayed promethazine hydrochloride by flow injection chemilumencence after oxidation with acidic permanganate. It was applicable at 1.55 x 10^{-5} and 1.8697 x 10^{-3} mol L^{-1}. Farhadi and Shamsiper[4] employed a method that depends on potentiometric and spectrophotometric titration of promethazine and dichlorodicyanobenzoquinine. After extraction in chloroform or *p*-toluene sulfonate, it was either measured spectrophotometrically or titrated against dichlorobenzoquinine. The spectrometric determination of the colored promethazine cationic radical released from electrooxidation at a gold electrode was applied[5]. The procedure was based on in situ detection of the formed colored cationic radical. Basavaiah and Krishnamurthy[6] assumed an indirect spectrophotometric method based on the determination of residual potassium ferrocyanide in acidic medium. Beer's law was obeyed for 0-115 μg/mL of promethazine. An indirect AAS[7] for promethazine determination was realized by analyzing the remaining potassium ferricyanide at 448 nm. The calibration graph was linear in the range 4.87- 48.5 mg/mL.

An electrometric determination for promethazine, promazine, and other phenazines was recorded in the literature. One of these methods was the application of a modified carbon paste electrode in linear sweep voltametric studies[8]. The measurements were carried for 25-500 μM promazine maleate and 25-250 μM promethazine maleate. Furthermore, Uslu et al.[9] and Biryol et al.[10] used glassy carbon electrodes for the determination of promethazine and phenothiazines by cyclic voltametry. Conductometric titrations against ferrocyanide and tetraphenylborate were employed for phenazine analysis by Issa et al.[11]. The molar combining ratio, effects of dilution titrant, temperature and solvent were involved.

Chromatography is an important method of drug analysis and separation. Rapid micellar liquid chromatographic analytical procedures for promethazine and other antihistaminic drugs were proposed[12]. Au et al.[13] screened promethazine among other Chinese drugs and chemicals by GC-MS. The basic drugs were extracted in ammonium hydroxide and chloroform. Then the extract was filtered through a fused-silica column. Promazine, other drugs, and their metabolities in extracts of horse urine were detected by GC-MS method[14].

Selective electrodes were applied for promethazine determination. Tetraphenylborate was the main ionophore of them. Ayad et al. [15] constructed a PVC-electrode based on promethazinium-tetraphenylborate ion-associate for promazine determination. It showed a linear range of 10^{-2}-10^{-5} M. The workable pH range was 2-6. The same ionophore (tetraphenylborate) was used for preparing a PVC-membrane for promethazine in nitrophenyl octyl ether[16]. The linear range was 5 x 10^{-5}-1 x 10^{-2} M. The electrode was used in presence of phosphate buffer at pH 6. In an earlier work, Cosofert and Buck[17] found the TPB-phenothiazinium and dinonylnaphthalene sulfonate-phenthiazonium ion-associates for promethazine, perphenazine and chlorpromazine ISEs. The usable linear range was 10^{-2}-10^{-5}M. The workable pH range for promethazine was up to 7.8. All of them were based on precipitation of the ion pairs.

In addition, many selective electrodes were reported for the determination of some surfactants[18−21]. None of the aforementioned work[15−17] deal the surfactant effect on the response of ion-selective electrodes for drugs. It was found that the surfactant has an effect on the dissociation of phenthiazines[22]. Therefore, it is important to decide if the addition of a surfactant to the drug solutions will improve the electrode performance (increase sensitivity, improve slope value, etc.). Here, promethazine is chosen as an example of phenthiazines to perform this study. Anionic surfactant SDS, cationic surfactant and neutral surfactant Triton-X were chosen as examples of the different surfactant ionic-categories. These promethazine membranes were prepared by the simple doping technique. They contained NaTPB, 18-crown-6 + NaTPB, or 18-crown-6. The ether was introduced here to compare between the different membrane structures. This is because it improved the performance of a previously prepared drug electrode[23]. Their properties were studied and compared to each other. It is important to have complete information about their properties before studying the effect of the surfactants. Although tetraphenylborate is a common factor between previous and present studies, the themes of this work were not investigated in any past research.

Experimental

Reagents and material

The following materials were the main components for the membrane preparation: pre-distilled tetrahydrofuran (THF) [Fluka, USA], tetraphenylborate sodium salt (NaTPB) [Prolabo, France], 18-crown-6 (CE) [Fluka, Germany], polyvinyl chloride (PVC) high molecular weight [Fluka, USA] and dioctylsebacate (DOS) [Fluka, USA].

Promethazine HCl (PMHCl) [Aldrich, USA], strychnine HCl [Sigma, USA], ephedrine HCl [Sigma, USA] and diphenhydramine HCl [Sigma, USA] were used. Three examples of surfactants were applied: Triton X-100 (poly (ethylene glycol) p-isooctylphenyl ether) with an average of 10 ethylene oxide units [Sigma, USA], sodium dodecylsulfate [Prolabo, France] as anionic surfactant and the cationic surfactant CH_3-$(CH_2)_9$-NH-$(CH_2CH_2O)_{21}$ [provided by Local Institute of Mineral Research, Academy of Science] with an average of 21 ethylene oxide units. All of the amino acids and common cation salts used were of the highest analytical grade. Bidistilled water was used for preparing all solutions.

Membrane preparation

The membranes were prepared by dissolving 33% (wt/wt) PVC, 66% (wt/wt) DOS and 1% (wt/wt) of the ionophore in about 2 mL of THF. They were based on either NaTPB (type-I), both NaTPB and 18-crown-6 in a ratio of 1:1 (type-II), or 18-crown-6 (type-III). Then the solution obtained was poured into a glass ring (2.5 cm) resting on a clean glass plate. The solvent was allowed to evaporate at room temperature while covered with a piece of glass. Then it was left for 1-2 days to dry in air.

Electrode assembly and potential measurements

For preparing the electrode, disks (7-mm diameter) were punched from membranes and fixed to an electrode body (type IS 561, Phillips, Eindhoven, the Netherlands). The inner filling solution was composed of 10^{-3} M PMH^+ and 10^{-1} M KCl. The electrodes were doped for 24 h in 10^{-2} M PMH^+ solution before use. The following represents the cell assembly:

Ag-AgCl / Aqueous inner filling solution //Membrane// Sample / AgCl-Ag Double junction reference electrode.

The potential measurements were carried with a pH/mV-meter (Chemcadet-Cole Parmer Series 5986) (sensitivity ± 0.1 mV) coupled with a channel selector of the same make. The potential values were recorded versus the double-junction reference electrode (Orion model 900200) with its outer compartment filled with 10% KNO_3 solution. For constructing calibration graphs, the cell potentials were plotted against PMHCl concentrations. The pH adjustment was operated by an Orion Ionalyzer (model 407) fitted with a combined glass electrode.

The potentiometric selectivity coefficient, log $K^{pot}{}_{PMH^+,J^{z+}}$ was obtained by the separate solution method[24]. The following equation was used for calculating the selectivity coefficient values:

$$\log K^{pot}{}_{PMH^+,J^{z+}} = (E_j - E_{PMH^+})/S$$

where E represents the emf readings for the primary ion $PMH^+$and the interfering ion (J^{z+}), and (S) is the observed slope for the primary ion.

The effect of the presence of a large number of interfering cations (Na^+, K^+, NH_4^+, Ca^{2+}, Ba^{2+}, Zn^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+} and Al^{3+}) in the same solution was studied by adding volumes of 10^{-1} M of the interference to 25 mL of 10^{-2}-10^{-7} M PMH^+ solutions. The calibration graphs were constructed after each addition using the proposed electrodes.

Furthermore, calibration curves for the electrodes were prepared in the presence of 1.82 x 10^{-4}, 6.88 x 10^{-4}, 1.55 x 10^{-3} and 2.1 x 10^{-3} M concentrations of Triton X-100 solution, 1.63 x 10^{-4}, 4.7 x 10^{-4}, 7.55 x 10^{-4} and 1.9 x 10^{-3} of the cationic surfactant solution and 2.08 x 10^{-4}, 4.08 x 10^{-4}, 8.16 x 10^{-4} and 1.77 x 10^{-3}M of sodium dodecyl sulfate solution. The effect of higher concentrations of cationic surfactant was studied by constructing calibration graphs for the PMH^+-electrode in the presence of 1.6 x 10^{-3}, 3.2 x 10^{-3}, 6.2 x 10^{-3}, 1.2 x 10^{-2} and 2.0 x 10^{-2} M of the surfactant solutions.

Analytical application

1-Potentiometric titration

1, 2 and 5 mL PMHCl either 10^{-2} or 10^{-3} M aliquots were transferred to the potentiometric cell. The double-junction reference electrode and PMH^+-selective electrode with membrane type-I were immersed into the above solutions, after dilution with bidistilled water to about 20 mL. Dropwise addition of standard 9.6 x 10^{-4} M $AgNO_3$ solution from a microburette was applied until potential became steady after the end point.

2-Determination of promethazine by direct potentiometry

Samples of Phenergan (expectorant) [containing: promethazine HCl 5 mg, thiocol 45 mg, ipecacuanha extract 3 mg per 5 mL] and Expectyl (syrup) [containing 20 mg promethazine HCl, sodium benzoate 1 g, ammonium chloride 2 g, tincture squill 2 mL, liq. ext. senega 2 mL per 100 mL] were analyzed. Both drug samples were purchased from local drug stores.

A calibration graph was constructed for the drug in the presence of 5 x 10^{-3} M sucrose using electrode type-I. Diluted samples (to contain 1.25 and 1.14 mg PMHCl for first drug; 0.45 and 0.57 mg PMHCl for the second drug) were transferred to the potentiometric cell. Potential measurements were performed and then were referred to a previously prepared calibration graph for promethazine.

Results and Discussion

Ionophore effect

Different studies were recorded for many ion-selective electrodes for different drugs and alkaloids[25–27]. Most of them were based on preparing an ion pair for the appropriate compound. Some papers applied the doped membrane type using the lipophilic ionophores and ionic sites[28]. In this work, the use of 18-crown-6 plus TPB was compared to other membrane types (containing either TPB or crown alone). After studying the properties of the membranes, the effect of different kinds of surfactants was investigated.

Three compositions of the ionophores were utilized. The first membrane (I) contained sodium tetraphenylborate (NaTPB) (2 mg) as a lipophillic ionophore. The second membrane (II) was immobilized by NaTPB as an ionophore and the 18-crown-6 (CE) as a neutral carrier. The third membrane (III) was like a blank to check the sensitivity of the 18-crown-6 towards promethazine. Figure 1 shows the calibration graphs of electrodes fitted with the 3 membrane versions. The Nernstian slopes of membranes I and II were 54.4 and 54.9 mV/decade, while for membrane III, a poor Nernstian slope was obtained, 48.4 mV/decade. This is explained as a reason for the absence of the charged component in membrane III. The rectilinear concentration ranges for the electrodes with membranes I, II and III were 2 x 10^{-5}-10^{-2}, 1.0 x 10^{-5}-10^{-2} and 3.2 x 10^{-5}-10^{-2} M PMH^+.

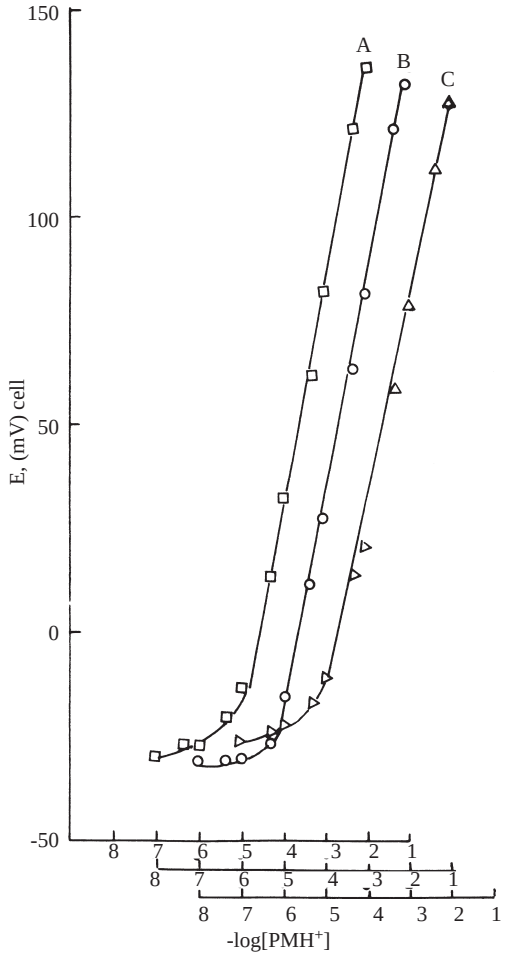


Figure 1. Calibration graphs for PMHCl electrodes with membranes type I (A), type II (B) and type III (C) after 24 h soaking in 10^{-2} M PMHCl solution.

pH effect

The effect of changing the pH on the potential of electrodes comprising the 3 types of membranes (I, II and III) was examined. For electrodes with membrane types I and II, the pH profiles are the same (Figure 2 shows the EMF changes with different pH values for membrane II). A steady potential plateau is observed for pH range 2-7 for 10^{-3} and 10^{-2}M promethazine concentrations. For $10^{-4}$and 10^{-5} M, the peaks appear at pH 4 due to the formation of the diprotonated species. The similar behavior of membranes I and II is ascribed to the presence of NaTPB. In the absence of NaTPB (membrane III), the pH picture is different, especially in the acidic part of the curve (Figure 3). In this case, there is a break up in the acidic part of the curve and it is based on the concentration of promethazine. For 10^{-2}, 10^{-3} and 10^{-4}M the corresponding acidic pH breaks were at 3, 4 and 5, while for 10^{-5} M PMH^+ there was a gradual increase in the potential as pH increased. This behavior may be due to the sensitivity of the 18-crown-6 towards H^+-ion, which increases at lower drug concentrations.

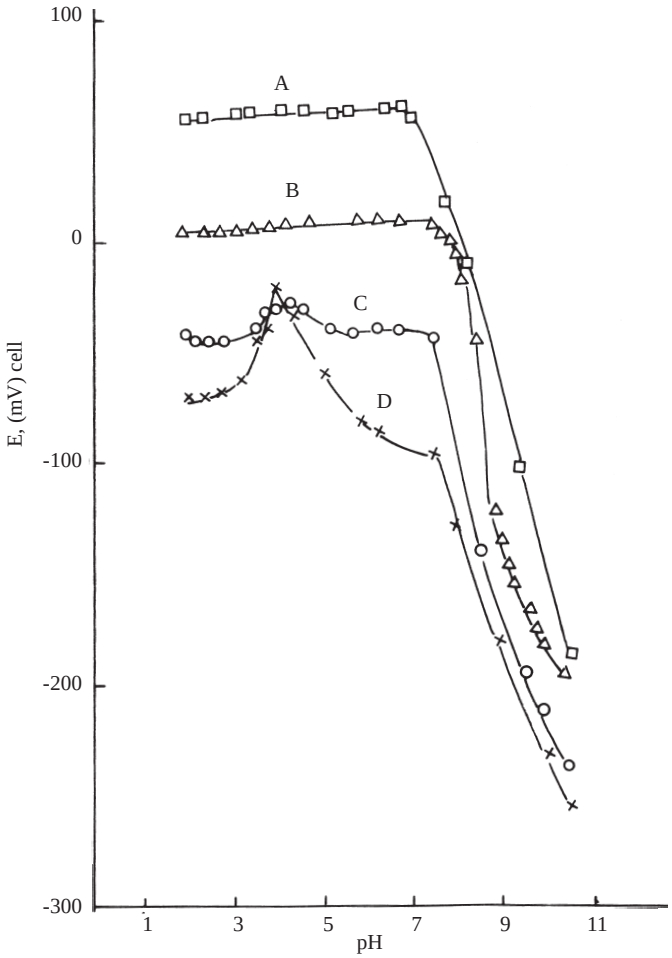


Figure 2. pH potential curves of membrane electrode of type II ionophore for PMHCl 10^{-2} (A), 10^{-3} (B), 10^{-4} (C) and 10^{-5} M (D) solutions.

Selectivity evaluation

The selectivity of the electrodes composed of the 3 membrane types was determined by the separate solution method[24]. The 3 electrodes show suitable selectivity towards different inorganic and organic cations. The presence of the 18-crown-6 does not improve the selectivity properties of the electrode. This is shown for all the selectivity coefficient values (Table 1) of membrane II for monovalent cations. The presence of CE either alone or with TPB gave values of the selectivity coefficient higher than for electrodes with membranes comprising only TPB (membrane I). The same behavior was found for amino acids. Slightly higher values of the selectivity coefficient for electrode types II and III are predictable. This is due to the ability of this crown to coordinate the cationic species (inorganic cations and amino acids). For more complicated organic molecules (thiamphenicol glycinate, strychnine and ephedrine), the selectivity coefficient values did not change largely for the 3 membrane types. In the case of anthranilic acid, diphenhydramine and pyridoxine, the presence of TPB gave better selectivity properties. This is because the 18-crown-6 has no tendency towards promethazine relative to the interference compounds. Thus, it is concluded that to obtain a change in the electrode selectivity by the addition of a carrier, it must have some negative discrimination towards the tested interference compared to promethazine.

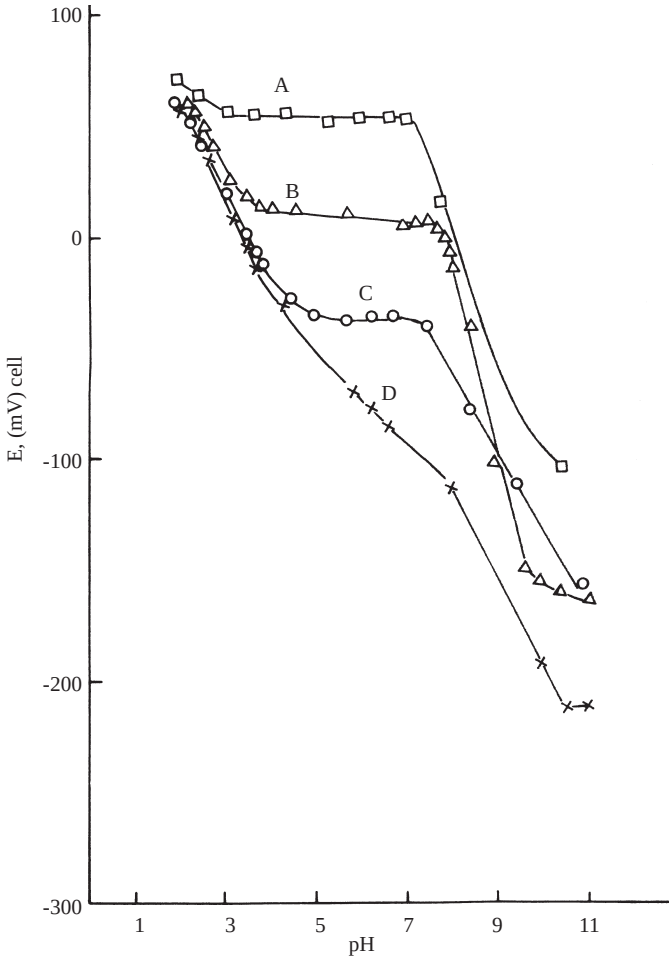


Figure 3. pH potential curves of membrane electrode of type III ionophore for PMHCl 10^{-2} (A), 10^{-3} (B), 10^{-4} (C) and 10^{-5} M (D) solutions.

Selected sugars (maltose and glucose) were tested as interference for the 3 electrodes with membranes I–III. None of these compounds interfered with the measurements, because of the neutral nature of these molecules.

The effect of presence of several selected monovalent and divalent cations in the same solution on the calibration graphs of the 3 electrode types were examined. Tables 2-4 show the variation obtained after the addition of each cation on PMH^+-solution using electrodes with membrane types I, II and III. Table 2 shows that the slope of the calibration graph of type I has almost the same value, 54.3 or 53.3 mV/decade, in the presence of Na^+, K^+ and NH_4^+ (at concentrations $\leq 9.1 \times 10^{-3}$ M). The lower limit of the linear range does not change largely. It varies from 1×10^{-5} to 5.6×10^{-5} M. It is improved in the case of K^+ and Na^+, while it shows the highest value in the case of NH_4^+. When Ca^{2+}, Ba^{2+}, Zn^{2+}, Cu^{2+}, Ni^{2+} and Co^{2+} were added (with concentrations $\leq 7.1 \times 10^{-3}$ M), the slope values varied a little in the range of 47.2-50.1 mV/decade. The lower limit of linear range has the same value 5×10^{-5} M, but for Zn^{2+}it is 2.5×10^{-5} M and for Cu^{2+} it is 4.5×10^{-5}M. When Al^{3+} was added, the slope value became 45.2 mV/decade, but the lower value of the linearity curve did not vary from 5×10^{-5} M.

Table 1. Selectivity coefficient values ($K^{pot}{}_{PMH^+,J^{Z+}}$) for electrodes with membranes I, II and III.

Interference	log $K^{pot}{}_{PMH^+,J^{Z+}}$		
	(I) TPB	(II) TPB + CE	(III) CE
Na^+	-2.16 ± 0.04	-1.43± 0.02	-2.07 ± 0.03
K^+	-2.17± 0.05	-1.55± 0.02	-2.17± 0.43
NH_4^+	-2.20± 0.01	-1.57± 0.02	-0.92± 0.03
Ca^{2+}	-3.34± 0.01	-3.12± 0.01	-3.64± 0.03
Ba^{2+}	-3.21± 0.01	-2.80± 0.04	-2.77± 0.02
Ni^{2+}	-3.96± 0.027	-2.83± 0.04	-2.68± 0.03
Zn^{2+}	-3.25± 0.01	-2.83 ± 0.02	-2.70± 0.03
Cu^{2+}	-3.26 ± 0.01	-2.83± 0.04	-2.92± 0.03
Pb^{2+}	-3.00± 0.03	-2.48 ± 0.02	-2.64± 0.01
L-Cystine	-2.10 ± 0.01	-0.75± 0.03	-0.96± 0.03
Lysine	-1.89 ± 0.023	-0.86± 0.04	-1.26± 0.01
Tryptophan	-1.09± 0.01	-0.65± 0.03	-0.68± 0.03
Glycine	-1.14± 0.01	-1.34± 0.01	-1.57± 0.02
Arginine	-4.57± 0.01	-1.52± 0.02	-
Thiamphenicol glycinate	-1.54± 0.01	-1.39± 0.01	-1.43± 0.02
Anthranilic acid	-1.68± 0.014	-0.60± 0.01	-0.92± 0.03
Strychnine	-1.42± 0.01	-1.15± 0.01	-1.16± 0.01
Ephedrine	-2.00 ± 0.03	-1.88± 0.06	-1.86± 0.04
Diphenhydramine	-0.77± 0.02	-0.72± 0.03	-0.076± 0.02
Pyridoxine	-2.14± 0.03	-0.95± 0.04	-1.32± 0.01

(Average of 4 determinations)

Table 2. Effect of addition of different cations on the performance of promethazine selective electrode comprising membrane type I.

Cations	Cation concentration, (M)	Linear range, (M)	Detection limit, (M)	Slope*, (mV/decade)
Promethazine	1 x 10^{-2}	2 x 10^{-5}-10^{-2}	7.1 x 10^{-6}	54.4 ± 0.3
+Na^+	9.1 x 10^{-3}	1.3 x 10^{-5}-10^{-2}	5.6 x 10^{-6}	54.2 ± 0.4
+K^+	8.3 x 10^{-3}	1.0 x 10^{-5}-10^{-2}	4.5 x 10^{-6}	54.3 ± 0.7
+NH_4^+	7.7 x 10^{-3}	5.6 x 10^{-5}-10^{-2}	1.3 x 10^{-5}	53.3 ± 0.5
+Ca^{2+}	7.1 x 10^{-3}	5 x 10^{-5}-10^{-2}	7.1 x 10^{-6}	47.2 ± 0.4
+Ba^{2+}	6.7 x 10^{-3}	5 x 10^{-5}-10^{-2}	2.2 x 10^{-5}	50.1 ± 0.6
+Zn^{2+}	6.3 x 10^{-3}	2.5 x 10^{-5}-10^{-2}	1.0 x 10^{-6}	49.9 ± 0.3
+Cu^{2+}	5.9 x 10^{-3}	4.5 x 10^{-5}-10^{-2}	7.1 x 10^{-6}	48.5 ± 0.5
+Ni^{2+}	5.6 x 10^{-3}	5 x 10^{-5}-10^{-2}	1.3 x 10^{-5}	49.8 ± 0.6
+Co^{2+}	5.3 x 10^{-3}	5 x 10^{-5}-10^{-2}	1.0 x 10^{-5}	48.0 ± 0.2
+Al^{3+}	5.0 x 10^{-3}	5 x 10^{-5}-10^{-2}	1.6 x 10^{-5}	45.2 ± 0.5

*Average of 4 calibration graphs carried out over 2 weeks of 2 electrodes

Table 3. Effect of addition of different cations on the performance of promethazine selective electrode made of membrane type II.

Cations	Cation concentration, (M)	Linear range, (M)	Detection limit, (M)	Slope*, (mV/decade)
Promethazine	1×10^{-2}	1.0×10^{-5}-10^{-2}	5.6×10^{-6}	54.9 ± 0.4
$+Na^{+}$	9.1×10^{-3}	1.0×10^{-5}-10^{-2}	4.0×10^{-6}	55.6 ± 0.4
$+K^{+}$	8.3×10^{-3}	1.8×10^{-5}-10^{-2}	5.6×10^{-6}	57.9 ± 0.5
$+NH_4^{+}$	7.7×10^{-3}	5.6×10^{-5}-10^{-2}	1.3×10^{-5}	54.3 ± 0.7
$+Ca^{2+}$	7.1×10^{-3}	5.6×10^{-5}-10^{-2}	1.3×10^{-6}	52.4 ± 0.6
$+Ba^{2+}$	6.7×10^{-3}	5.6×10^{-5}-10^{-2}	1.3×10^{-5}	51.4 ± 0.7
$+Zn^{2+}$	6.3×10^{-3}	5.6×10^{-5}-10^{-2}	1.8×10^{-6}	51.4 ± 0.3
$+Cu^{2+}$	5.9×10^{-3}	5.6×10^{-5}-10^{-2}	1.4×10^{-6}	51.2 ± 0.5
$+Ni^{2+}$	5.6×10^{-3}	5.6×10^{-5}-10^{-2}	1.0×10^{-5}	49.1 ± 0.6
$+Co^{2+}$	5.3×10^{-3}	5.6×10^{-5}-10^{-2}	1.8×10^{-5}	50.4 ± 0.6
$+Al^{3+}$	5.0×10^{-3}	1.0×10^{-4}-10^{-2}	3.2×10^{-5}	45.3 ± 0.6

*Average of 4 calibration graphs carried out over 2 weeks of 2 electrodes

Table 4. Effect of addition of different cations in the same solution on the performance of promethazine selective electrode made of membrane type III.

Cations	Cation concentration, (M)	Linear range, (M)	Detection limit, (M)	Slope*, (mV/decade)
Promethazine	1×10^{-2}	3.2×10^{-5}-10^{-2}	5.6×10^{-6}	48.4 ± 0.7
$+Na^{+}$	9.1×10^{-3}	1.0×10^{-5}-10^{-2}	1.6×10^{-5}	50.3 ± 0.5
$+K^{+}$	8.3×10^{-3}	3.2×10^{-5}-10^{-2}	5.6×10^{-5}	48.2 ± 0.5
$+NH_4^{+}$	7.7×10^{-3}	5.6×10^{-5}-10^{-2}	1.3×10^{-5}	46.2 ± 0.7
$+Ca^{2+}$	7.1×10^{-3}	1.0×10^{-4}-10^{-2}	2.8×10^{-5}	49.9 ± 0.5
$+Ba^{2+}$	6.7×10^{-3}	5.6×10^{-5}-10^{-2}	3.2×10^{-5}	47.2 ± 0.5
$+Zn^{2+}$	6.3×10^{-3}	5.6×10^{-5}-10^{-2}	1.6×10^{-5}	46.3 ± 0.7
$+Cu^{2+}$	5.9×10^{-3}	5.6×10^{-5}-10^{-2}	5.0×10^{-4}	39.8 ± 0.4
$+Ni^{2+}$	5.6×10^{-3}	5.6×10^{-4}-10^{-2}	5.0×10^{-5}	47.4 ± 0.5
$+Co^{2+}$	5.3×10^{-3}	5.0×10^{-4}-10^{-2}	3.2×10^{-5}	42.3 ± 0.5
$+Al^{3+}$	5.0×10^{-3}	5.6×10^{-4}-10^{-2}	5.6×10^{-5}	35.4 ± 0.7

*Average of 4 calibration graphs carried out over 2 weeks of 2 electrodes

By observing the changes for the electrode with membrane type II (Table 3), it is shown that the linearity range does not change after the addition of Na^{+}, although the slope value is better. After the addition of potassium, NH_4^{+} or any of the tested divalent or trivalent cations, the linearity range becomes shorter. It is 1.8×10^{-5}-10^{-2}M for K^{+}, and 5.6×10^{-5}-10^{-2}M for NH_4^{+} and most of the tested divalent cations. In addition, a different range is found for Al^{3+} (1×10^{-4}-10^{-2}M). The slope of the calibration graph was improved after the addition of Na^{+} or K^{+} (55.6 and 57.9 mV/decade) due to their ability to adjust the ionic strength. After the addition of NH_4^{+}, the slope value decreases to 54.3 mV/decade. Then another decrease occurs whenever divalent cations (Ca^{2+}, Ba^{2+}, Zn^{2+}, Cu^{2+}, Ni^{2+} and Co^{2+}) were added at concentrations $\leq 7.1 \times 10^{-3}$M. The slope ranges between 52.4 and 49.1 mV/decade. Al^{3+} was chosen as a trivalent cation to study its effect on the electrode behavior. When it was added to the PMH^{+}-solution,

it gave rise to a bad effect (like type I) either in the slope (45.3 mV/decade) of the calibration graph, or in its lower limit of linearity (1.0 x 10^{-4} M). The similarity in behavior between electrode types I and II is attributed to the presence of sodium tetraphenylborate salt.

The picture of the changes is different in case of the last electrode, type III. Although Na^+ improved the slope of the calibration graph (50.3 mV/decade), K^+ did not show a significant effect (48.2 mV/decade). Like the other two types (I and II), NH_4^+ ion shows an increase in the lower limit of the linear range of the calibration graph (5.6 x 10^{-5} M) and a negative effect on its slope (46.2 mV/decade). This is because of the expected competition with the promethazine cationic species at lower concentrations (¡5.6 x 10^{-5} M). The divalent Cu^{2+}, Co^{2+} and trivalent Al^{3+} cations produce a significant decrease in the slope of the calibration graph (39.8, 42.3 and 35.4 mV/decade). This effect is because of the available complexing interaction of those cations with CE. The results are shown in Table 4.

Table 5. Potentiometric titration of promethazine HCl using PMH^+-selective electrode based on membrane type I.

Sample no.	Found, (M)	Recovery, (%)	RSD, (%)*
1	1.5 x 10^{-3}	97.9	1.05
2	2.3 x 10^{-3}	96.8	1.65
3	4.8 x 10^{-3}	98.9	0.79
4	1.1 x 10^{-2}	99.4	1.44
5	2.1 x 10^{-2}	99.7	1.96
6	5.2 x 10^{-2}	100.1	1.76

(*)Relative standard deviation (4 determinations)

Effect of surfactants

Since the presence of surfactants shows an effect on the dissociation constants of the phenthiazines[22], they will affect the performance of promethazine electrode. Moreover, it is known that phenthiazines can form mixed micelles with the surfactants[29]. These are 2 reasons for studying the effect of surfactant on a promethazine electrode.

The effect of surfactants on the calibration graphs of electrodes comprising membranes I, II and III was studied. Three types of surfactants, representing the 3 ionic categories (cationic, anionic and neutral), were applied in this work. In the case of the non-ionic surfactant Triton X-100, no significant changes were noted on the calibration graphs after the addition of different concentrations (1.82 x 10^{-4}-2.1 x 10^{-3} M). This is attributed to the non-ionic nature of Triton X-100. Figure 4 shows the calibration graphs for the electrode with membrane type II as an example. The slope of the calibration graph changed within a very small range (1-3 mV/decade) for both membrane types I and II. Higher slope differences were recorded for membrane type III (5-9 mV/decade). It can be stated that there is no experiential effect of the non-ionic surfactant on high primary cation activity. This is because the surfactant molecules are not able to compete with the carrier that forms stable complexes with the primary ion.

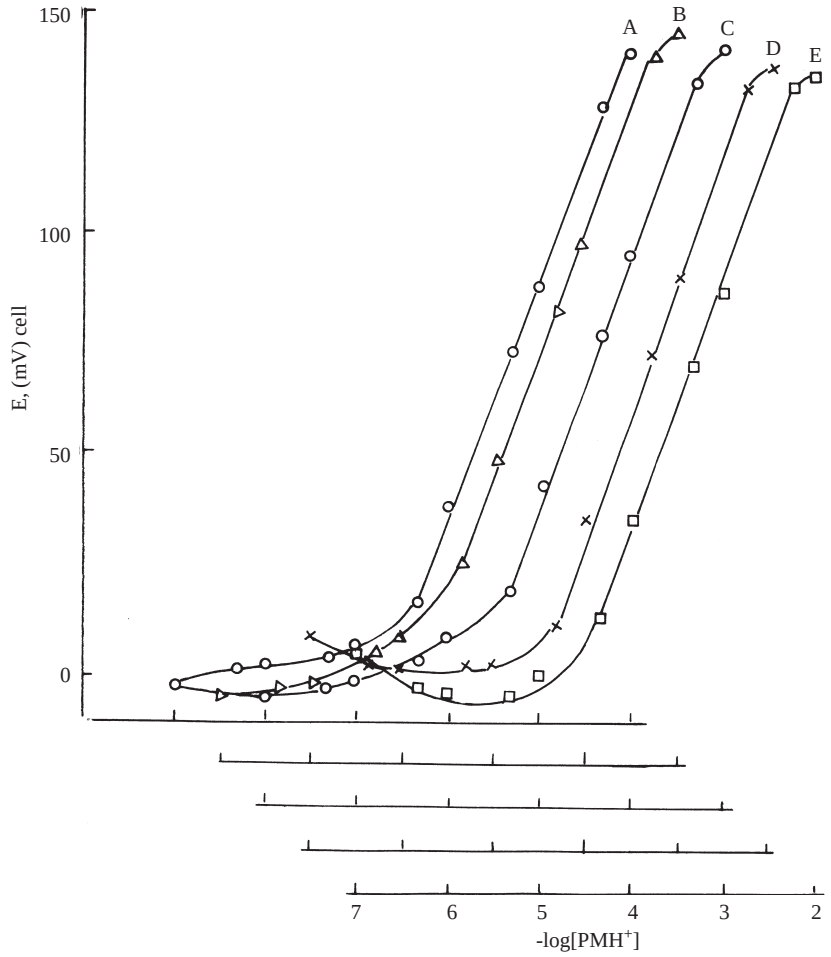


Figure 4. Calibration graphs for PMH^+ electrode with membrane type II when measurements are carried out for PMHCl only (A) and in presence of 1.82 x 10^{-4} (B), 6.88 x 10^{-4} (C), 1.55 x 10^{-3} (D) and 2.1 x 10^{-3}M (E) of Triton X-100.

The presence of cationic surfactant ($CH_3 - (CH_2)_9 - NH - (CH_2CH_2O)_{21}$ with concentrations 1.63 x 10^{-4}-1.9 x 10^{-3} M) shows a super-Nernstian response of 105-118 mV/decade for type I, 97-129 mV/decade for type II and 100-164 mV/decade for type III membranes. The lower limit of the linearity range of the calibration graph was shifted up with increasing amount of surfactant. For the type II membrane electrode the lower limit of the linearity range was 5 x 10^{-5} M and 6.3 x 10^{-4} M in presence of 1.63 x 10^{-3} M and 1.9 x 10^{-3} M of the cationic surfactant. The same changes were found for the type III electrode, but the values of the lower limit of linearity were 6.3 x 10^{-5} M in the presence of 1.63 x 10^{-3} M, and 1.2 x 10^{-3} M in the presence of 1.9 x 10^{-3} M surfactant solution. Types I and II membrane electrodes show similar variation patterns. Figure 5 shows the calibration graphs after each addition of surfactant for type II. The potential values of the lower part of the calibration graphs were raised with increasing concentration of added surfactant. At higher concentrations (1.6 x 10^{-3}-2 x 10^{-2}) M of the cationic surfactant, the slopes of the calibration graphs were 123, 113, 192, 60 and 76 mV/decade for type I. In the second case (membrane type II), these slopes were 136, 140, 120, 53 and 54 mV/decade. Figure 6 shows the changes on the calibration graph in the presence of different amounts of the cationic surfactant for the promethazine selective electrode

with membrane type I. The interference of cationic surfactant is due to strong competition with primary cations for exchange sites within the membranes of these sensors[30,31]. In addition, the presence of cationic surfactant enhances the dissociation of phenthiazines[22].

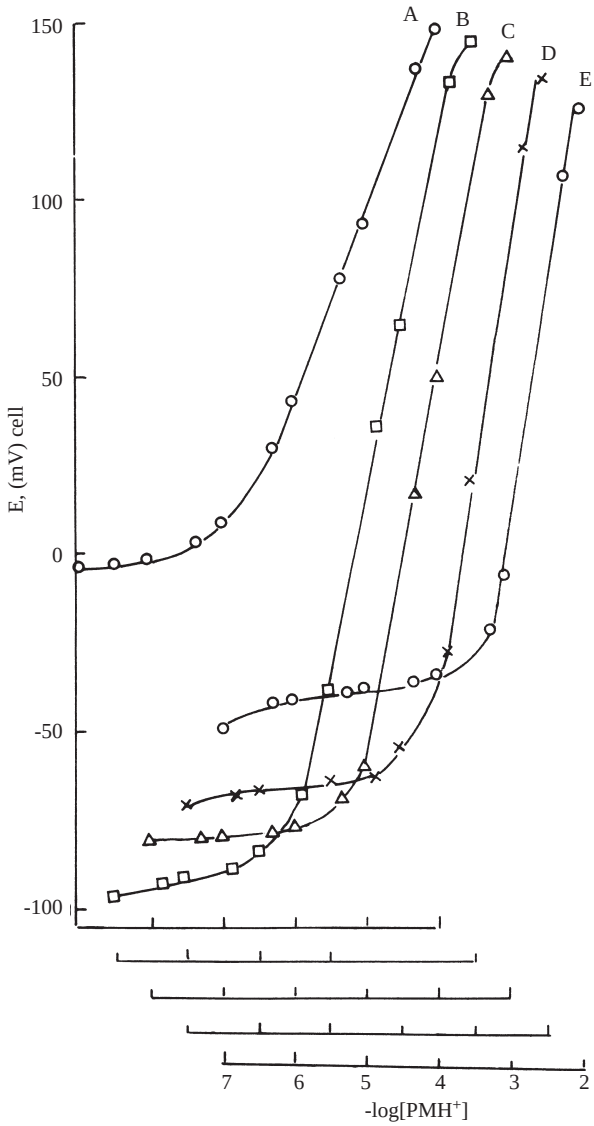


Figure 5. Calibration graphs for PMH^+ electrode with membrane type II when measurements are carried out for PMHCl only (A) and in presence of 1.63 x 10^{-4}(B), 4.7 x 10^{-4} (C), 7.55 x 10^{-4} (D) and 1.9 x 10^{-3} M (E) of cationic surfactant.

Sodium dodecyl sulfate (SDS) was added like an anionic surfactant to the drug solution to study its effect on the calibration graph for the promethazine selective electrode. Figure 7 shows the obtained variation for an electrode comprising membrane type II. The addition of different concentrations (2.08 x 10^{-4}-1.77 x 10^{-3} M) of SDS results in increasing slope values (69-390 mV/decade) of the calibration graph of the type I membrane electrode and 50-440 mV/decade for the type II membrane electrode. The lower limit of the calibration graph moves towards higher values (from 5 x 10^{-5} to 5 x 10^{-3} M) of PMH^+ for type

I and from 1 x 10^{-4} to 5 x 10^{-3} M of PMH^+ for type II, which corresponds to the presence of 2.08 x 10^{-4} to 1.77 x 10^{-3} M SDS. The lower limit of the linear range moved to higher values from 3 x 10^{-4} to 1.5 x 10^{-3} M with increasing amounts of SDS from 5.5 x 10^{-3} to 1 x 10^{-2} M. At the same time the corresponding EMF values decreased. This is opposite to the changes occurring in the case of the cationic surfactant.

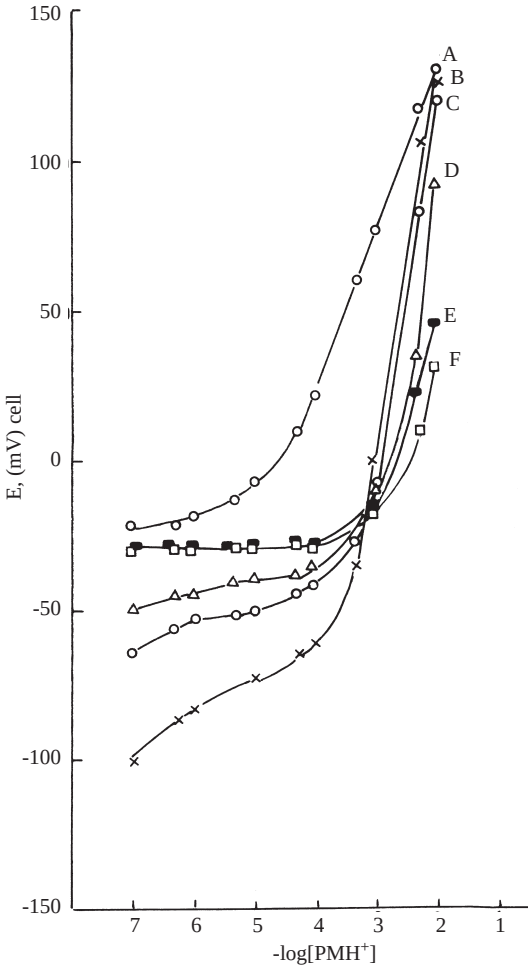


Figure 6. Calibration graphs for PMH^+-electrode with membrane type I when measurements are carried out for PMHCl only (A) and in presence of 1.6 x 10^{-3} (B), 3.2 x 10^{-3} (C), 6.2 x 10^{-3} (D), 1.2 x 10^{-2} (E) and 2 x 10^{-2} M (F) of cationic surfactant.

It is important to note that lowering of the cell-potential value is observed with increasing SDS concentration. This agrees with the anionic nature of the surfactant. The negative shift of EMF is due to the competition of anionic surfactant with the primary ion, especially at lower concentrations of the drug solution. The very large, super-Nernstian slopes for the SDS (anionic) surfactant are likely due to the fact that the preconditioning with this surfactant greatly increased the R-sites in the organic membrane and upon addition of the cationic drug there was a very large non-equilibrium Hulanciki-type effect that gave the very large slopes. Another reason for the changes in the presence of SDS is the decrease in the dissociation constant that was reported for phenthiazine derivatives[22].

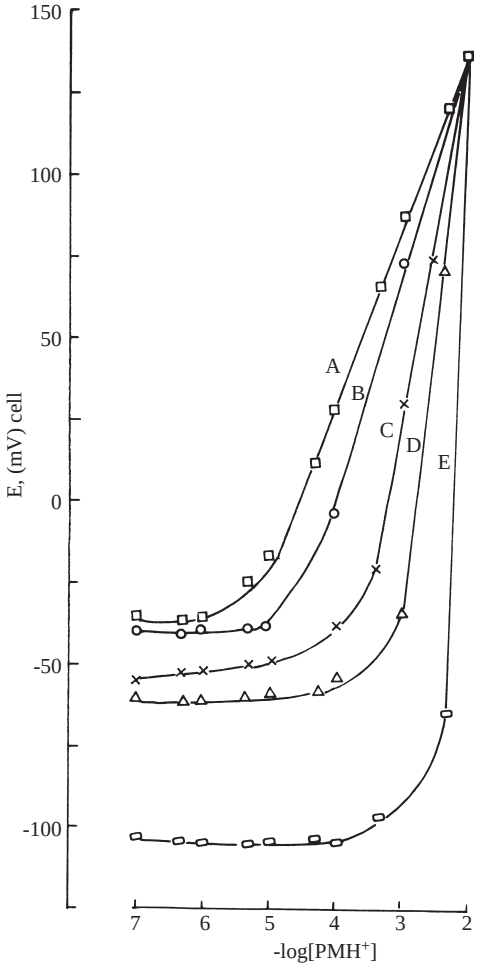


Figure 7. Calibration graphs for PMH^+ electrode with membrane type II when measurements are carried out for PMHCl only (A) and in presence of 2.08 x 10^{-4}(B), 4.08 x 10^{-4} (C), 8.16 x 10^{-4}(D) and 1.77 x 10^{-3}M (E) of anionic surfactant.

Analytical application

Potentiometric titrations for samples of PMHCl were performed. The results show better end points at higher concentrations than at lower concentrations. Table 5 shows the results of potentiometric titration using the PMH^+-selective electrode (type I membrane). The recovery range was 96.8% -100.1%. The corresponding RSD range was 0.79% -1.76%.

Samples of Phenergan (expectorant) and Expectyl (syrup) were analyzed by direct potentiometry for determination of PMHCl. The results show that the values of recovery for the 2 formulations are 98.6% and 99.5%, and the corresponding RSD values are 1.49% and 1.02%, respectively (Table 6).

Table 6. Direct potentiometric determination for PMHCl using PMH^+-selective electrode based on membrane type I.

Pharmaceutical preparation	**Found, (mg)**	Recovery, (%)	RSD, (%)*
1-Phenergan (expectorant)	4.93	98.6	1.49
2-Expectyl (syrup)	4.98	99.5	1.02

(*)Relative standard deviation (4 determinations)

Conclusion

There are 2 main conclusions of this work. The first is that the performance characteristics of the proposed (I and II) and the previously reported[15−17] electrodes resemble each other. The distinctive point here is the immobilization of 18-crown-6 (CE) into the membrane. The CE-type electrode shows that the linear range values are like those of the TPB-electrodes mentioned before. The pH range of this electrode is 3-7 and 5-7 for promethazine concentrations 10^{-2} and 10^{-5}M; while the TPB-containing electrode has a pH range of 2-7. This is due to the H^+ interference. It is shown that the selectivity coefficient values of the designed 18-crown-6 electrode are in close proximity to those for the electrodes containing TPB (the present electrode type I and the preceding electrodes[15−17]). These values are better than those for the mixed type II electrode, especially for the monovalent interfering cations.

The second but the foremost item in this study is the effect of surfactants (anionic, cationic, or neutral) on the electrode performance. It is concluded that the neutral surfactant has no effect on the calibration graphs (EMF measurements of the tested electrodes). In contrast, the anionic and cationic surfactants have a significant effect on the calibration graphs of the different electrode compositions. There are positive shifts of the EMF values in the presence of the cationic surfactant, while negative shifts are found in the presence of the anionic surfactant. Furthermore, a marked increase in the slope values (super-Nernstian) appears in both cases, accompanied by a higher value of the lower limit of the linear range. It can be concluded that ionic surfactants can work like a magnifying agent for the Nernstian slope. The results also lead to the conclusion that the higher the surfactant concentration, the stronger the deviation from the accustomed performance.

References

1. W. Ford, **"Martindale**, **The extra pharmacopia**", 31st ed. Pharmaceutical Press, 1996.
2. M. Saif and J. Anwar, **Talanta 67**, 869-872 (2005).
3. S. Sultan, Y. Hassan and A. Abulkibash, **Talanta 59**, 1073-1080 (2003).
4. K. Farhadi and M. Shamsipur, **Acta Chim. Solv. 50**, 395-407 (2003).
5. D. Daniel and I.G. Gutz, **Anal. Chim. Acta 494**, 215-224 (2003).
6. K. Basavaiah and G. Krishnamurthy, **Chem. Anal.** (Warsaw) **44**, 67-73 (1999).
7. A. El-Ansary, W. El-Hwary, Y. Issa and A. Ahmed, **Quim.-Anal. 17**, 199-203 (1998).

8. R. Sandulescu, S. Mirel, R. Oprean and S. Lotrean, **Collect. Czech. Chem. Commun. 65**, 1014-1028 (2000).
9. B. Uslu, I. Biryol, S.A. Özkan and Z. Şentürk, **Turk. J. Chem. 20**, 323-328 (1996).
10. I. Biryol, Z. Senturk, S.A. Ozkan, S. Dermis and B. Uslu, **Portugalia Electrochim. Acta 15**, 5-15 (1997).
11. Y. Issa, W. El-Hawary and A. Ahmed, **Microchim. Acta 134**, 9-14 (2000).
12. C. Martinez-Algaba, J.M. Bermudez-Saldana, R.M. Villanueva-Camnanas, S. Sagrado and M.J. Medina-Hernandez**, J. Pharm. Biomed. Anal. (proof online**), 22 Sept. (2005).
13. A. Au, R. Ko, F. Boo, R. Hsu, G. Perez and Z. Yang, **Bull. Environ. Contam. Toxicol. 65**, 112-119 (2000).
14. S.D. Stanley, D. McKemie and W. Skinner, **J. Anal. Toxicol. 27**, 325-331 (2003).
15. M. Ayad, A. Shalaby, H. Abdellatef and H. Elsaid, **Mikrochim. Acta 140**, 93-96 (2002).
16. J. Lima, M. Montegro and M. Sales, **J. Pharm. Sci. 89**, 1234-1238 (1997).
17. V. Cosofret and R. Buck, **Analyst 109**, 1321-1325 (1984).
18. R. Schulz and R. Gerhards, **Am. Lab**. **26**, 40 (1994).
19. W. Szczepaniak and M. Ren, **Electroanalysis 6**, 341-347 (1994).
20. S. Alegret, J. Alonso, J. Bartroli, J. Baro-Roma, J. Sanchez and M. del Valle, **Analyst 119**, 2319-2322 (1994).
21. S. Patil and A. Rakshit, **Anal. Chim. Acta 518**, 87-91 (2004).
22. P. Rychlovsky and I. Nemcova, **Talanta 35**, 211-214 (1988).
23. M.M. Zareh, S.M. Teleb and E.S. Ahmed, **Anal. Lett. 35**, 17-28 (2002).
24. G. Guilbault, R. Drust, M. Frant, H. Freiser, H. Hansen, T. Light, E. Pongor, G. Rechnitz, N. Rice, T. Rhom, W. Simon and J. Thomas, **Pure Appl. Chem. 48**, 127-132 (1976).
25. R. Gilpin and L. Pachla, **Anal. Chem.**, **69**, 145-164 (1997).
26. M. Zareh, **Mikrochim. Acta**, **126**, 271-277 (1997).
27. G. Zhang, T. Imato, Y. Asano, T. Sonoda, H. Kobayashi and N. Ishibashi, **Anal. Chem. 62**, 1644-1648 (1990).
28. M.M. Zareh, E. Malinowska and K. Kasiura, **Anal. Chim. Acta 447**, 55-61 (2001).
29. E. Borrego, D. Sicilia, S. Rubio and D. Perez-Bendito, **Anal. Chim. Acta 362**, 285-297 (1998).
30. R. Llenado, **Anal. Chem. 47**, 2243-2249 (1975).
31. A. Hulanciki, M. Trojanowicj and E. Pobozny, **Analyst 107**, 1356-1362 (1982).