Preparation and Potentiometric Study of Promethazine Hydrochloride Selective Electrodes and Their Use in Determining Some Drugs

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Promethazine hydrochloride selective electrodes were constructed based on promethazine-phosphotungstic acid ion pair in PVC matrix membrane. The plasticizers used were di-butyl phosphate (DBP), tri-n-butyl phosphate (TBP), o-nitro phenyl octyl ether (ONPOE), and di-n-butyl phthalate (DBPH). The electrodes based on DBP, TBP, and ONPOE gave the same linear range between 1×10^{-4} and 1×10^{-1} M, while the one based on DBPH ranged between 5×10^{-4} and 1×10^{-1}M. The slopes for linear range ranged from 40 to 56 mV/decade with correlation coefficients lying between 0.9984 and 0.9993. The best detection limit was 2×10^{-5}M for the electrode based on DBPH. The standard deviation of potential drift ranged from ± 1 to ± 9 mV. The measurement interferences in the presence of Li$^+$, Na$^+$, K$^+$, Mg^{2+}, Ca^{2+}, Zn^{2+}, Fe^{3+}, Cr^{3+}, and Al^{3+} were studied using separate and match methods for selectivity coefficient determination. The pH and life time of the electrodes were also studied.

Key Words: Promathazine-HCl selective electrodes, phosphotungstic acid, promethazine determination.

Introduction

The determination of bulk drugs has become increasingly important in the pharmaceutical industry. Ion selective membranes have been widely used for drug analysis with the advantage of determining the sample directly, rapidly, and more easily. Promethazine is commonly used to relieve itchy, irritated, and watery eyes, runny nose, sneezing, and itchy skin.[1] A simple spectrophotometric method for the determination of promethazine hydrochloride in bulk powders and its dosage forms was studied by Devani et al.[2] in the concentration range of 10-80 μg/mL. Potentiometric titration and spectrophotometric techniques were described by Ramakrishna et al.[3] for the determination of promethazine in pure and dosage forms. The titration procedure (1:1 stoichiometry) was applicable over the 1-10 mg range. The spectrophotometric measurement works for the 10-120 μg/mL concentration range. These methods were used for the determination of promethazine hydrochloride in tablets, injections, and elixir formulations. Francisco et al.[4] have developed a capillary zone

electrophoresis method for quantitative analysis of thiazinamium methylsulfate and promethazine-HCl in pharmaceutical formulations with a detection limit of 0.074 μg for all enantiomers.[5] Nassory et al.[6] prepared amines and amiloride ion selective electrodes using phosphotungstic acid ionophore with various plasticizers. The response characteristics, effect of pH, and selectivity were studied and used for the determination of amiloride in tablets. Atenolol selective electrodes were prepared by Nassory et al.[7] based on atenolol-phosphotungstate complex as an active material. The experimental results showed that the best electrode was the one when DOP was used as the plasticizer. The slope was 55.91 mV/decade with a correlation coefficient of 0.9995 and a detection limit of 5.0×10^{-5}M. The electrode was successfully applied for the determination of atenolol in tablets and the recovery was 98.5% with a standard deviation of $\pm$ 0.1. Yang et al.[8] studied the voltammetric behaviors of promethazine hydrochloride on a DNA-modified glassy carbon electrode. The method was used to determine promethazine in human blood samples. New chloridiazoxide hydrochloride ion selective electrodes based on phosphomolybdic and phosphotungstic acids were prepared by Issa et al.[9] These electrodes were utilized for the potentiometric determination of chlordiazoxide ions in pharmaceutical preparations.

In this work, several promethazine hydrochloride electrodes were constructed based on phosphotungstic acid as ionophore with different plasticizers. The properties of the prepared electrodes, pH effect, and selectivity coefficient measurements were evaluated.

Experimental Part

Equipment

An expandable ion analyzer (Orion model EA-940, USA), a pH meter (WTW model pH 522, Germany), and a saturated calomel electrode (Gallenkamp, USA) were used in this work.

Reagents and solutions

Promethazine hydrochloride standard was a gift from the State Company of Drug Industries and Medical Appliances (Samara IRAQ-SDI).

Phenergan tablets (25 mg promethazine-HCl) (Bristol-Myers Squibb Company, USA) were purchased locally.

Di-n-butyl phosphate 98.9% (DBP), tri-n-butyl phosphate 97% (TBP), o-nitrio phenyloctyl ether 98% (ONPOE), and di-n-butyl phthalate 99% (DBPH) were obtained from Fluka AG, Switzerland.

Stock solutions of 0.1 M for each of LiCl, NaCl, KCl, $CaCl_2$, $MgCl_2$, $ZnCl_2$, $FeCl_3$, $AlCl_3$, and $CrCl_3$ were prepared. More diluted solutions were prepared by subsequent dilution of the stock solutions.

A solution of 0.1 M promethazine-HCl was prepared by dissolving 0.8023 g of standard and making the solution up to 25 mL with deionized water. A 0.05 M potassium hydrogenphthalate buffer solution (pH 4.01) was prepared by dissolving 10.21 g of solid potassium hydrogen phthalate in 1 L of water after adjusting the pH.

Procedure

Preparation of ion-pair compound

PMH-PT ion-pair was prepared by mixing 50 mL of 0.01 M promethazine-HCl with 50 mL of 0.01 M phosphotungstic acid while stirring. The resultant precipitate was filtered, washed with water, and dried at 60 °C.

Assembly of ion-selective electrodes

The construction of the electrode body and the immobilization were done as described by Craggs et al.[10] The glass tube was 3/4 filled with 0.1 M promethazine-HCl solution as an internal filling solution. The membrane was conditioned by immersing in a standard solution of 0.1 M for at least 2 h before measurements. Calibration curves were prepared by plotting the potential versus the concentration of promethazine-HCl. The pH of 10^{-3} and 10^{-2}M promethazine-HCl was adjusted with dilute solutions of sodium hydroxide and hydrochloric acid.

Selectivity measurements

A separate solution method was used for the selectivity coefficient measurement, and was calculated according to the equation[11]

$$\log K_{pot} = [(E_B - E_A)/(2.303RT/zF)] + (1 - z_A/z_B) \log a_A \tag{1}$$

E_A, E_B; z_A, z_B; and a_A, a_B are the potentials, charge numbers, and activities for the primary A and interfering B ions, respectively, at $a_A = a_B$.

The selectivity coefficients were also measured by the match method according to the equation[12]

$$K_{pot} = \Delta a_A/a_B, \Delta a_A = a'_A - a_A \tag{2}$$

Results and Discussion

Promethazine hydrochloride-phosphotungstate was a stable water insoluble ion-pair complex though readily soluble in organic solvents such as tetrahydrofuran. The complex was incorporated into a PVC membrane with the following plasticizers: di-n-butyl phosphate (membrane I), tri-n-butyl phosphate (membrane II), o-nitro phenyl octyl ether (membrane III), and di-n-butyl phthalate (membrane IV). The working characteristics for the electrodes were assessed on the basis of their calibration curves. The physical properties of these membranes were as follows: white, flexible, clear, and transparent (non-crystalline). Non-Nernstian slopes were obtained for electrodes based on DBP and TBP (membranes I and II). The slopes are 40.58 and 39.83 mV/decade with correlation coefficients of 0.9984 and 0.9988, respectively. The linear range for both electrodes was 1×10^{-4}-1×10^{-1}M with detection limits of 3.5×10^{-5} and 5×10^{-5}M, respectively. The non-Nernstian slope behaviors could be attributed to the high viscosity of DBP (112.89 cST), which may slow down the ion exchange process between ion pair complex in membrane with the external solution of promethazine hydrochloride. Moreover, the steric effect of the alkyl group on the DBP may decrease the bond strength of the ion pair complex. The TBP, which has a low viscosity (3.11 cSt), leads to leaching of the complex from the membrane or may have a high steric effect on methyl groups. Near Nernstian slopes

were obtained for the electrodes based on ONPOE and DBPH (membranes III and IV). The electrode based on ONPOE gave a slope of 51.52 mV/decade with a correlation coefficient of 0.9991, a linear concentration range 1×10^{-4}-1×10^{-1}M, and a detection limit of 5.5×10^{-5}M. However, the DBPH electrode gave a slope of 56.17 mV/decade with a correlation coefficient of 0.9993, a linear concentration range of 1×10^{-4}-5×10^{-1}M, and a detection limit of 2×10^{-4}M. The life time of electrode III was around 2 days. This short time may be due to the low viscosity of ONPOE (11.44 cSt) or incompatibility of the plasticizer with the complex in PVC. The life time of the DBPH electrode was around 72 days. A typical calibration plot for electrodes I and IV is shown in Figure 1.
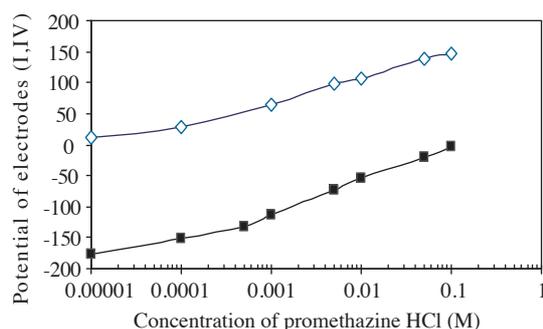

Figure 1. Calibration curves of promethazine hydrochloride selective electrodes. ◇- DBP, ■- DBPH.

The response characteristics of promethazine-HCl electrodes are listed in Table 1. The stability of the electrodes was monitored continuously at 1×10^{-3}M promethazine hydrochloride solution by measuring the potential drift and evaluated for a period of 6 days. The standard deviations of the potential drift obtained for these 6 days were equal to ± 3, ± 4, ± 9, and ± 1 mV for membranes No. I, II, III, and IV, respectively.

Electrode parameters for DBPH as a plasticizer gave a good response. The electrode had good stability and was used for the quantitative determination of pharmaceutical drugs. The relative standard deviations were obtained from the calibration curves at a concentration of 1×10^{-2}M (n = 5). Electrode IV gave the lowest value (0.287%) among the others, which may mean greater stability and reproducibility. The accuracy of electrodes III and IV was compared by F-test. The calculated value was 0.375 at a confidence limit of 95% (n-1). This indicates that the 2 electrodes were equivalent in accuracy and could be used for measurements.

Three synthetic promethazine hydrochloride solutions at concentrations of 1×10^{-3}, 5×10^{-3}, and 5×10^{-2}M were used for measuring % recovery (R), % relative error (RE), and confidence limit at 95%. The calculated values for electrodes I and IV are listed in Table 2.

Effect of pH

The pH effect on the electrode response was examined by measuring the e.m.f. of the cell for 2 different promathezine-HCl solutions (10^{-3} and 10^{-2}M). A representative plot for the DBPH electrode is shown in Figure 2. The results of the pH ranges of the promethazine hydrochloride selective electrodes are listed in Table 3.

The slope of the calibration curve for DBPH (membrane IV) was changed to non-Nernstian by buffering each solution (10^{-5} to 10^{-1}M promethazine-HCl) at pH 4 (using potassium-hydrogen phthalate buffer). The slope was changed from 56.17 to 27.32 mV/decade with a correlation coefficient of 0.9650. A

drift in the potential was observed at pH 8. This may be caused by poisoning of the electrode by forming a white precipitate of tungsten oxide or sodium phosphotungstate forms.

Table 1. Parameters of promethazine hydrochloride selective electrodes.

Parameters	Electrode number			
	I	II	III	IV
Plasticizer	DBP	TBP	ONPOE	DBPH
Slope mV/decade	40.58	39.82	51.52	56.17
Correlation coefficient	0.9984	0.9988	0.9991	0.9993
Linearity range (M)	1×10^{-4}-1×10^{-1}	1×10^{-4}-1×10^{-1}	1×10^{-4}-1×10^{-1}	1×10^{-4}-5×10^{-1}
Detection limit (M)	3.5×10^{-5}	5.0×10^{-5}	5.5×10^{-5}	2.0×10^{-4}
Potential drift (mV/day)	3	4	9	1
% RSD	0.662	0.802	0.414	0.287
Life time (days)	~ 29	~ 23	~ 2	~ 72
F-test	-	-	0.375	0.375

Table 2. Statistical treatments of promethazine electrodes I and IV.

Parameters	Electrode I			Electrode IV		
Amount of PMH taken (M)	1×10^{-3}	5×10^{-3}	5×10^{-2}	1×10^{-3}	5×10^{-3}	5×10^{-2}
Amount of PMH found (M)	9.94×10^{-4}	5.01×10^{-3}	4.99×10^{-2}	1.01×10^{-3}	4.99×10^{-3}	4.95×10^{-2}
%R	99.4	100.2	99.8	101	99.8	99.0
%RE	-0.6	0.2	-0.2	1.0	-0.2	-1.0
Mean %RE	-0.200	-	-	-0.067	-	-
Regre. Eq. Y = mX + b	$Y = 17.621 \ln(X) + 189.32$			$Y = 24.39 \ln(X) + 54.275$		
Conf. limit for pot. at 95%	136.48 ± 0.4762			75 ± 0.196		

Response time

The response time at t_{95} for all the electrodes at concentrations ranging from 10^{-5} to 10^{-1}M was calculated from the response with time plot and is listed in Table 4.
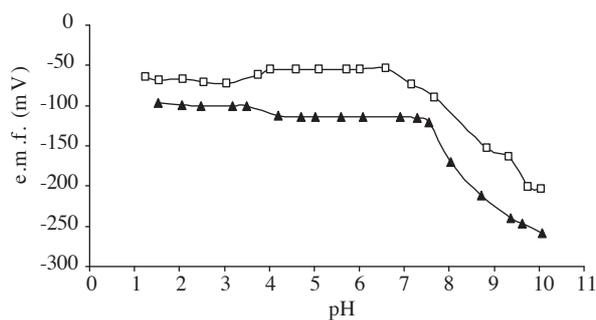
Figure 2. Effect of pH on electrode response using based on DBPH electrode. □- 10^{-2} M, ▲- 10^{-3} M promethazine-HCl.

Table 3. pH range for promethazine electrodes.

Membrane no.	Plasticizers	pH range
I	DBP	2.4-8.4
II	TBP	1.5-6.4
III	ONPOE	3.0-7.3
IV	DBPH	4.1-6.8

Table 4. Response times at t_{95} for promethazine hydrochloride electrodes.

Conc. (M)	Electrode I	Electrode II	Electrode III	Electrode IV
1×10^{-1}	1.5	1.2	1.8	3.9
5×10^{-2}	3.3	3.7	6.6	7.0
1×10^{-2}	6.9	7.2	11.2	8.4
5×10^{-3}	9.5	13.0	12.9	12.4
1×10^{-3}	16.4	15.3	15.9	13.5
1×10^{-4}	18.9	18.9	23.9	23.5
1×10^{-5}	25.4	21.5	25.0	28.0

As shown, the longer response time reached around 30 s at 10^{-5}M. All the electrodes gave the same range of response times. These values indicated the high stability of the electrodes during the measurements. A typical plot for response time is shown in Figure 3 for the electrode based on DBPH as the plasticizer.
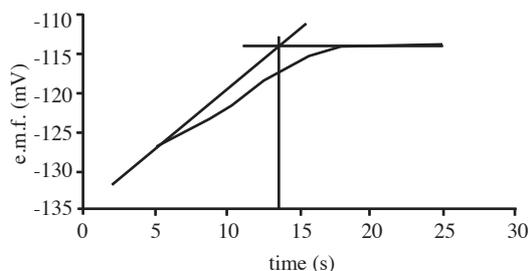

Figure 3. Plot the response time of DBPH electrode using 10^{-3} M promethazine hydrochloride.

Selectivity measurements

The influence of some possible interfering inorganic cations such as Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, Al^{3+}, Fe^{3+}, and Cr^{3+} on the electrode response was also studied. The selectivity of the electrodes based on DBP and DBPH was measured by the separate solution method for a concentration range from 10^{-5} to 10^{-2}M. The potentiometric selectivity coefficients were calculated using equation 1 at cation concentrations ranging between 10^{-5} and 10^{-2}M. A typical plot is shown in Figure 4 for the interference of Cr^{3+} on the DBP electrode. The values of the selectivity coefficients for DBP and DBPH electrodes are listed in Table 5. The selectivity coefficients were very small. This means that there is no interference of these cations with the response of promethazine electrodes. The order of selectivity was: Mono-valent > Di-valent > Tri-valent ions. Selectivity coefficients for TBP as the plasticizer were also calculated by a separate method.
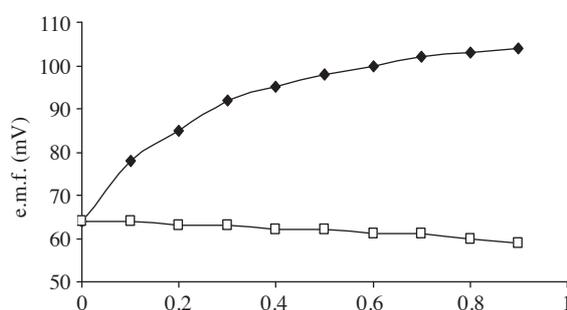

Figure 4. Selectivity of DBPH electrode for interfering Cr^{+3} by separate method, □- promethazine hydrochloride solution, ▲- solutions of Cr^{+3}.

Table 5. Selectivity coefficient values for electrodes I and IV at different concentration of promethazine and some cations.

$K_{pot.}$ for electrode IV				$K_{pot.}$ for electrode I				
Concentrations of promethazine hydrochloride								
10^{-5}	10^{-4}	10^{-3}	10^{-2}	10^{-5}	10^{-4}	10^{-3}	10^{-2}	Ion
0.109	5.0×10^{-2}	2.5×10^{-2}	9.0×10^{-3}	4.4×10^{-2}	3.9×10^{-2}	4.7×10^{-2}	5.9×10^{-2}	Li^+
0.179	8.9×10^{-2}	6.4×10^{-2}	1.5×10^{-2}	3.9×10^{-2}	9.2×10^{-2}	3.5×10^{-2}	4.7×10^{-2}	Na^+
5.9×10^{-2}	7.6×10^{-2}	5.7×10^{-2}	1.9×10^{-2}	3.1×10^{-2}	2.6×10^{-2}	3.5×10^{-2}	3.1×10^{-2}	K^+
2.3×10^{-3}	1.1×10^{-2}	1.1×10^{-2}	5.7×10^{-3}	2.3×10^{-5}	1.2×10^{-4}	7.0×10^{-4}	9.0×10^{-3}	Mg^{2+}
3.4×10^{-3}	4.6×10^{-3}	3.8×10^{-3}	1.7×10^{-3}	7.9×10^{-5}	4.4×10^{-4}	1.7×10^{-3}	1.7×10^{-2}	Ca^{2+}
1.9×10^{-3}	1.0×10^{-2}	9.2×10^{-3}	1.3×10^{-2}	5.0×10^{-5}	5.5×10^{-4}	2.1×10^{-3}	1.1×10^{-2}	Zn^{2+}
2.8×10^{-4}	2.1×10^{-3}	1.0×10^{-2}	2.6×10^{-2}	2.8×10^{-6}	2.4×10^{-5}	2.5×10^{-4}	3.0×10^{-3}	Al^{3+}
2.5×10^{-4}	2.2×10^{-3}	8.2×10^{-3}	1.6×10^{-2}	1.2×10^{-5}	8.5×10^{-5}	1.2×10^{-3}	5.0×10^{-3}	Fe^{3+}
2.2×10^{-4}	1.9×10^{-3}	6.1×10^{-3}	1.1×10^{-2}	3.0×10^{-6}	2.0×10^{-5}	2.0×10^{-4}	3.0×10^{-3}	Cr^{3+}

The match method for selectivity coefficients was used for non-Nernstian slopes for electrodes I and II. In this work a plot for the match method was created using 10 mL of 10^{-3}M promethazine and a standard promethazine solution 0.1 M was added step by step (0.1 mL each time); the potential change was measured and plotted against a_A. Another curve was plotted from the potential change by step-wise adding the interfering ion (0.1 mL of 10^{-3}M). From the plots the selectivity can be calculated using equation 2. A typical plot for the match method is shown in Figure 5 for Fe^{3+}. The experiments and the figures showed no interference of cations with respect to promethazine response for electrodes I and II.
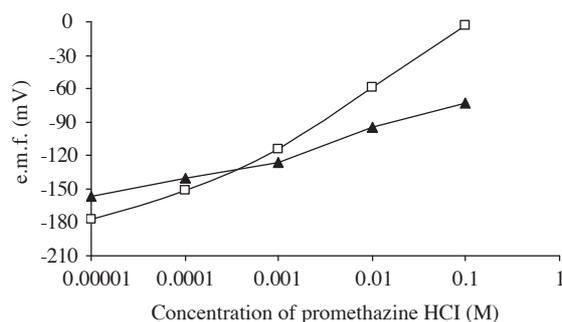
Figure 5. Selectivity of DBP electrode at 10^{-3} M promethazine-HCl in the presence of Fe^{+3} using the match method. ▲- promethazine hydrochloride solutions, □- solutions of Fe^{+3} ion.

Sample analysis

Potentiometric techniques were used for the determination of promethazine hydrochloride, these included direct, standard addition (SA), Gran plot, and titration method. Synthetic solutions of promethazine at concentrations between 10^{-5} and 10^{-3}M were used for the standard addition method[13] using ONPOE and DBPH electrodes. The %R, %RSD, and %RE were calculated and are listed in Table 6.

Table 6. Analysis of promethazine-HCl samples by potentiometric techniques.

Titration	MSA	SA	Direct	Sample	Elect. No.
Titration	MSA	SA	Direct	Sample	Elect. No.
1.03×10^{-3}	0.99×10^{-3}	1.002×10^{-3}	1.014×10^{-3}	1×10^{-3}	
-	-	1.8042	0.197	%RSD*	
100.3	99	100.2	101.4	%RC	
3.0	-1.0	0.2	1.4	%RE	(III)
0.97×10^{-4}	0.98×10^{-4}	1.004×10^{-4}	1.021×10^{-4}	1×10^{-4}	
-	-	2.036	0.294	%RSD*	
97	98	100.4	102.1	%RC	
-3.0	-2.0	0.4	2.1	%RE	
1.01×10^{-3}	0.99×10^{-3}	1.005×10^{-3}	1.008×10^{-3}	1×10^{-3}	
-	-	0.186	0.099	%RSD*	
99	99	100.5	100.8	%RC	
-1.0	-1.0	0.5	0.8	%RE	(IV)
5.02×10^{-4}	5.01×10^{-4}	5.006×10^{-4}	4.99×10^{-4}	5×10^{-4}	
-	-	0.451	0.810	%RSD*	
100.3	100.2	100.12	99.8	%RC	
0.4	0.2	0.12	-0.2	%RE	

*Each value represents an average of 3 measurements.

The relative recovery was calculated for 5 additions of 0.1 M standard promethazine solution. A typical plot of antilog (E/S) versus the volume of promethazine standards for DBPH electrode together with the concentration of synthetic 10^{-3}M promathezine is shown in Figure 6. Gran plot paper with 10% volume

correction was used. The results in Table 6 showed that the electrode based on DBPH as a plasticizer was the best electrode. For potentiometric titration of promethazine-HCl solution 10^{-2} and 10^{-3}M of phosphotungstaic acid were used as a titrant. A typical titration plot of 1×10^{-3}M of promethazine with 10^{-3}M phosphotugstic acid is shown in Figure 6. The DBPH electrode was used for the determination of promethazine-HCl in phenergan tablets using potentiometric techniques. The results are listed in Table 7.
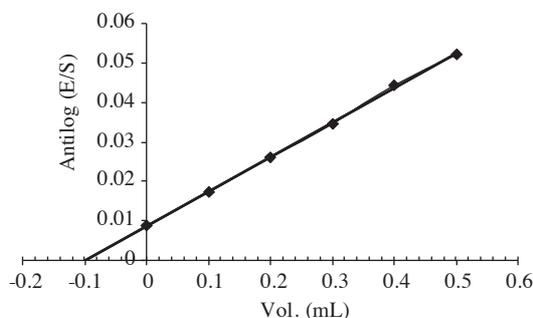

Figure 6. Plot of antilog (E/S) versus the volume of 0.1 M standard promethazine by MSA using DBPH electrode.

Table 7. Determination of promethazine hydrochloride in tablets using potentiometric methods for electrode based on DBPB.

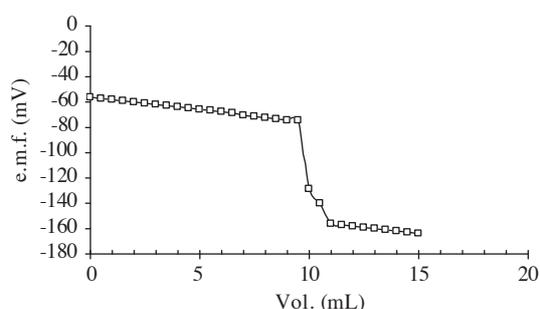| Measured by potentiometric methods			Sample
Titration	MSA	SA	
1.01×10^{-3}	0.99×10^{-3}	1.003×10^{-3}	1×10^{-3}M
101	99	100.3	%R
2.683	-	0.315	%RSD
1.0	-1.0	0.3	%RE

Figure 7. Titration curve of DBPH electrode for 10^{-3} M promethazine titrated with 10^{-3}M phosphotungstic acid.

Conclusion

Promethazine hydrochloride selective electrodes based on ion pair complex of PMH-PT and with different plasticizers were constructed. The best promethazine electrode was based on DBPH. This electrode was used for drug determination in pharmaceutical preparations. The electrode based on DBPH gave excellent electrode parameters and no interference with several cations. The proposed analytical method is proved to be simple and rapid, with good accuracy.

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