ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Conductimetric and potintiometric Determination of Oxomemazine Hydrochlorides in solution pharmaceutical formulation

M S Abd-Elmonem* and Shaban A Abdulla.

[1*] National Organization for Drug Control and Research(NODCAR), P.O. Box. 29, Giza, Egypt.

ABSTRACT

The construction and performance characteristics of PVC electrodes for Oxomemazine Hydrochloride (OXCl) are described. Different methods for electrode fabrication (modified with the ion-pair, ion pairing agent or soaking the plain electrode in the ion-pair suspension) have been used. Matrix compositions were optimized on the basis of effects of type and content of the modifier as well as influence of the plasticizers. The fabricated electrodes worked satisfactorily in the concentration range from 1×10^{-6} to 0.001 M with Nernstian cationic slopes, depending on the method of electrode fabrication. The ion-pair modified electrode showed the best performance (slope 57.45 ± 2.1 mV decade^{-1}) compared with the plain electrodes or modified with sodium tetraphenylborate (NaTPB) and fast response time of about 9 sec and adequate lifetime (4 weeks). The developed electrodes have been successfully applied as well as end point indicator electrode for the potentiometric titration of OXCl with high accuracy and precision. The solubility products of different OXCl ion-pair were determined conductometrically.

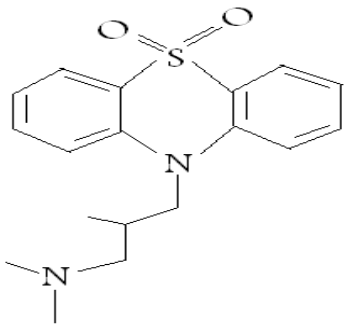
Keywords: Oxomemazin HCl, pharmaceutical analysis, ion-selective electrodes; potentiometry and conductimetric titration; solubility products.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Oxomemazine, a phenothiazine derivative, is an antihistamine used for the symptomatic relief of hypersensitivity reaction. It is also an ingredient of compound preparations for the symptomatic treatment of couhs and the common cold. It is given orally in doses equivalent to 10 to 40 mg of oxomemazine daily. Oxomemazine may also be administered rectally in form of suppositories. Oxomemazine hydrochloride (OXCl) has been used similarly by mouth. It is chemically known as [3-(5, 5 – dioxodo-10 *H* – phenothiazin – 10- yl)-N,N,2-trimethylpropan-1-amine] (Scheme 1) [1]. The assay of the drug in pure and dosage forms is, as far as we know, not official in any pharmacopoeia, and therefore requires much more investigation. The different analytical techniques that have been reported for its determination including spectrophotometry [2, 3], and HPLC [4].Regarding the quality control, it is used in pharmaceutical industry to analyze starting materials, intermediates, and finished products.



Scheme 1. the chemical structure of Oxomemazine
[$C_{18}H_{22}N_2O_2S$] = 330.444 g/mol

Electrolytes are substances that produce free ions when they are placed into solvent such as water. Their molecules split up into individual atomic components, which form ions, in a process called dissociation. Positively charged ions are cations and those with a negative charge are anions. Due to the presence of free ions, electrolyte solutions behave as an electrically conductive medium. Ion-selective electrode (ISE_s) are electrochemical sensors based on a thin selective membrane or a film, allowing us the potintiometric determination of the activity of certain ions in the presence of others ions in the sample solution. In recent years, ISE_s have also been used for the determination of solubility products of different sparingly soluble salts. In spite of the successful progress in the design of highly selective electrodes for various ions, there has not been any report on the development of selective and sensitive sensors for Oxomemazine.

The present study is concerned with preparation, characterization and application of simple potentiometric sensors for rapid determination of OX. Electrodes were fabricated in plain and modified forms and then subjected to a series to tests to elect sensor possessing the most facorable analytical characteristics. The developed sensors were also applied as indicator electrode in the potentiometric titration of OX.

ISSN: 0975-8585

EXPERIMENTAL

Chemical and Reagents

All reagents were of the analytical grade and double distalled water was used throughout the experiments. Oxomemazine hydrochloride (OXCl: 3-(5,5 – dioxodo-10 *H* – phenothiazin – 10- yl)-N,N,2-trimethylpropan-1-amine, Merck) was used without further purification. O-Nitrophenyloctylether (o-NPOE) from Sigma was used for preparation of the sensors. Other types of plasticizer, namely dibutylphthalate (DBH), dioctylphthalate (COP), dioctylsebacate (DOS) and tricresylphosphate (TCP) were purchased from BDH, Sigma and AVOCADO, respectively.

Sodium tetraphenylborate (Na-TPB) solution (ca 0.01M) was prepared by dissolving a weighed amount of the substance (Fluka) in worm water, then adjusted to pH 9 by adding sodium hydroxide and competed to the desired volume with water. The resulting solution was standardized potentiometrically against standard 0.01 M HNO_3 solutions [5] . Reineckate ammonium salt (RAS, Fluka). Phosphotungestic acid (PTA, BDH) and phosphomolybdic acid (PMA, Fluka) were used for precipitation of different OX ion pairs.

Apparatus and Other Instrumentation

All potential measurements were performed using a 3510 Jenway pH meter with PC interface, equipped with silver-silver chloride double junction reference electrode in conjugation with the sensing drug ISE. A combined pH glass electrode was used for all pH measurements. Conductance was measured using 4310 Jenway Conductivity meter.

Construction of the Electrode

Ion-pair preparation. Ion-pairs synthesis protocol included drop wise addition of 10^{-2} M aqueous solution of ion pairing agents (NaTPB, RN, PTA or PMA) to 50 mL 10^{-2} M drug solution with continuous stirring. The mixture was left to react for 5 min under stirring at room temperature. The resulting precipitates were then filtered off on Whatman filter paper and washed several times with double distilled water. The compound was left to dry for 24h at 60°C, washed with petroleum ether to remove any residual moisture, and then grinded to fine powder. Small sample portions were sent for elemental analysis.

Determination of the stoichiometric ratios of complexes

A definite volume (5 ml) of 10^{-2} M Drug was transferred to a 50 ml volumetric flask and made up to the mark with bidistilled water. The drug solution was placed in a suitable titrating vessel and the conductivity cell was immersed, then 10^{-2} M TPB, RN, PMA or PTA was added from a digital burette. After each addition (0.2 ml), the solution was stirred for 1-2 min and allowed to attain equilibrium [6, 7]; the conductance was measured using Conductivity meter 4310 Jenway. To eliminate the effect of dilution on the increase in conductance, the measured values were corrected for volume change.

$$K = K_{obs}[(v_0+v_{added})/v_0]$$

Where, K_{obs}, the observed specific conductivity, v_0, the initial volume, and v_{added}, the added volume.

The corrected conductivity was then plotted against the volume added of titrant and the end point was determined as shown from Fig.

Determination of the solubility products of the ion exchangers

Conductometric method was applied for the solubility products determination, where a series of solutions of different concentrations (C = 10^{-4}- 10^{-2} M) were prepared for Drug, TPB, RN, PMA and PTA. The conductivities of these solutions were measured at 25 ^{o}C and the specific conductivities (K), corrected for the effect of dilution were calculated and used to obtain the equivalent conductivities (λ) of the solutions.

$$\lambda = 1000\ K/$$

Straight line plots of λ versus $C^{1/2}$, were constructed and the equivalent conductance values at infinite dilution ($\lambda_{\circ Drug}$, $\lambda_{\circ TPB}$, $\lambda_{\circ RN}$, $\lambda_{\circ PMA}$ and $\lambda_{\circ PTA}$) were determined from the intercept of the respective line with the λ axis. The activity coefficients were taken as unity since the solutions were sufficiently dilute and the equivalent conductance values of the IPs under complete dissociation condition ($\lambda_{\circ IP}$) were calculated from Kohlrausch's law of independent migration of the ions [8]. The solubility (S) and the solubility product (K_{sp}) of a particular ion associate were calculated using the following equations:

$$S = K_s \times 1000/\ \lambda_{\circ IP}$$

$K_{sp} = S^2$ for 1: 1 ion associate
$K_{sp} = 4S^3$ for 1: 2 ion associate
$K_{sp} = 27S^4$ for 1: 3 ion associate
$K_{sp} = 256S^5$ for 1: 4 ion associate

Where K_s, is the specific conductivity of a saturated solution of IP determined at 25^{o}C. The saturated IP solutions were prepared by stirring a suspension of the precipitate in distilled water for 3 h. The conductivities were measured using Conductivity meter 4310 Jenway.

PVC Electrode construction. Matrices compositions composed of 10 mg of OX-TPB or 20 mg of Na-TPB were mixed with 240 mg o-NPOE, 6 mL THF And 240 mg PVC for electrode fabricated by different methods were described elsewhere [9,10]. The internal filling solution (10^{-3} M OX and 10^{-2} M KCl) and Ag/AgCl internal reference electrode were used. The fabricated sensors were conditioned for 24h in 10^{-3} M OX before use and soaked in the same solution. Plain electrode was prepared in the same manner using the plain PVC membrane and presoaked in freshly prepared OX-IPs suspension for 24h.

Analytical Procedure

Calibration of Sensors. Sensors were calibrated by transferring 25 ml aliquots of 10^{-7}-10^{-3} M OX solutions into 50 mL double jacket thermostated glass cell at 25 ^{o} C followed by immersing the sensor in conjugation with Ag/AgCl double junction reference electrode in the solution. The potential reading were recorded after stabilization and plotted against drug concentration in logarithmic scale (-log [OX]). The sensors performances were evaluated according to IUPAC recommendation [11].

Electrode Response Time

The dynamic response time of the electrode was tested by measuring the time required to achieve a steady state potintal (within ±1mV) after sudden 10-fold increase in OX concentration from 10^{-6} to 10^{-3}M.

Effect of pH

The influence pH on the response of PVC was checked by recording the potential reading of the cell for solutions containing 10^{-3}M OX at different pH values (pH3-11). Variation of pH value was done by adding very small volumes of HCl and/or NaOH solution (0.1-1M of each)to the drug solution.

Potentiometric Titration

An aliquot of the sample solution containing 0.33 -23.1 mg OX was titrated with standardized NaTPB. The titration process was monitored using OX sensor in conjugation with Ag/AgCl reference electrode where the emf values plotted against the ml added from the titrant to estimate the end point. Result and Discussin

Preliminary IP Identfication studies

OX forms water insoluble ion-pair complexes with the oppositely charged anions such as TPB, RAS, PTA or PMA [12, 14]. the resulting IPs can be used as ion exchangers for OX potentiometric sensors. From this point of view, different types of OX-IPs were prepared and their stoichiometric ratios were estimated from elemental analysis and conductometric titration data. The elemental analysis data (see Table 1) revealed that OX forms 1:1 IPs with both TPB and RAS. Complexes of OX with PTA and PMA showed ratio 1:3.

ISSN: 0975-8585

Table 1: Characterization of different OX-IPs

IP	MW_{cal}	C%		H%		N%		S%		Tentative Formula	K_{sp}
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found		
OX-TPB	649	77.6	76.8	6.5	6.52	4.3	4.45	4.9	4.88	$[C_{18}H_{22}N_2O_2S][C_{24}H_{20}B]$	2.75×10^{-7}
OX-RAS	648	40.7	40.3	4.3	4.25	17.3	17.29	24.7	24.3	$[C_{18}H_{22}N_2O_2S][C_4H_6CrN_6S_4]$	1.28×10^{-8}
OX-PMA	2813	23.04	22.38	2.35	2.25	2.98	3.02	3.41	3.24	$[C_{18}H_{22}N_2O_2S]_3[PMo_{12}O_{40}]$	1.01×10^{-10}
OX-PTA	3869	16.75	16.71	1.71	1.54	2.17	2.18	2.48	2.51	$[C_{18}H_{22}N_2O_2S]_3[PW_{12}O_{40}]$	4.33×10^{-11}

ISSN: 0975-8585

The stoichiometric ratios of the IPs formed can be estimated from the conductometric titration curve, obtained by plotting the change in conductance versus volume of titrant added (see Fig. 1). By ddition of the titrant to OX solution, the system showed a regular rise in conductance up to the equivalence point where a sudden change in the conductance observed. Intersect of the two straight lines determine the stouchiometric ratio of the complexes formed. The obtained results sustained the elemental analysis data for the complex formation ratios.

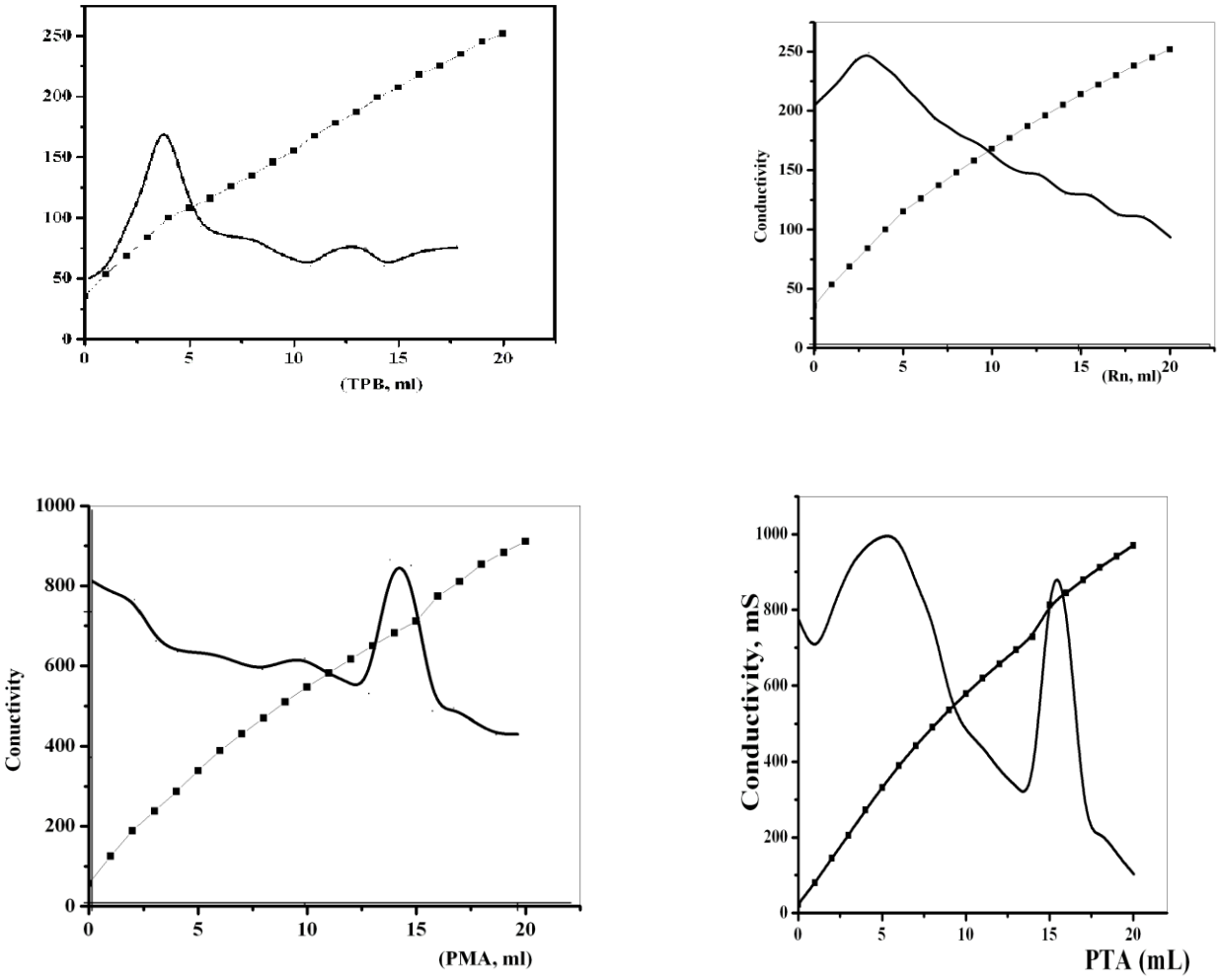


Figure 1: Conductivity measurements of different OX-ion pairs

Solubility product of the IPs is important since its reciprocal is approximately equal to its formation constant, which in turns is tightly related to the degree of hydrophobicity of the ion exchanger and its solubility in the electrode matrix. The solubility products of the ion associates were determined conductimetrically, and found to be 2.75×10^{-7}, 1.28×10^{-8}, 1.01×10^{-10} and 4.33×10^{-11}, for OX-TPB, OX-RAS, OX-PMA and OX-PTA, respectively.

Optimization of the electrode Performance

For quantitative composition optimization of the developed PVC sensors, an election scheme was followed. Both unmodified (plain) and modified electrodes (either with the OX-IPs, or the ion pairing agents) electrodes were prepared and tested for nature and content of modifier, type of plasticizer, pH effect, response time and applications.

Electrodes Modified with OX-Ion Pairs

The customary of ion selective electrode is one in which the membrane is composed of a water-immiscible organic solvent containing the ion in question, usually in the form of an ion-pair with some anionic ion pairing agents such as NaTPB, PTA, TSA, RAS and PMA in the electrode matrixes. Different OX-IPs were incorporated in the PVC matrix, and the fabricated electrodes were conditioned in 10^{-3} M of OX solution for 24 h. preliminary experiment declared that PVC electrodes that contain no electroactive material, and plasticized with o-NPOE showed no response towards the OX; while those modified with different ion pairs gave Nernstian responses with different slopes, and sensitivities depend on the nature of the ion pair used. Electrode incorporated with OX-TPB showed the best performance slope (56.7 ±3.1 mV decade^{-1} in the concentration range 3×10^{-7} – 0.001M) compared to those modified with other OX ion pairs.

Constructing ion selective electrode, the amount of ion pair in the electrode matrix should be sufficient to obtain reasonable ionic exchange and equilibrium at the membrane gel layer-test solution interface that is responsible for the membrane potential. If such salt is present in excess, over saturation occur in the network of the membrane hindering the ionic exchange process and leading to unsatisfactory result; therefore, the influence of the OX-TPB concentration in the PVC matrix was investigated. For this purpose, 8 electrodes were prepared containing different amount of the ion pair (2.5-20 mg). incorporation of 10 mg in the membrane matrix was sufficient for the ionic exchange at membrane interface, the corresponding slope 57.5 ±4.3 mV/ decade in the tested concentration range, above this value the slope of the electrode decreased to reach 49.8 mV/decade with 20 mg IP>

Electrode Modified with the Ion-Pairing Agents (*In Situ)*

Incorporation of a suitable ion pairing agent in the electrode matrix followed by soaking in the drug solution may led to the formation of an ion exchanger at the electrode surface being subsequently extracted by plasticizer into the electrode bulk. Such an approach will reduce the time required for electrode fabrication as there is no need for IP precipitation.

The effect of the ion pairing agent type was tested with the electrode matrices prepared and incorporated via different ion pairing agents (NaTPB, RAS, PTA or PMA) soaked in 0.001 M OX solution. The results obtained indicated the superiority of the incorporation of NaTPB indicated by the lowest detection limit (4×10^{-7}M). the content of NaTPB in the PVC matrix gave the highest slope (53.4±4mV/decade).

ISSN: 0975-8585

The Plain Electrode

In addition to the aforementioned methods for the electrode fabrication. A simple and reliable suggested procedure could be applied soaking the plain electrodes in the aqueous suspension of the lipophilic IP solutions. The electrode mediator (plasticizer) extracts IPs and becomes gradually saturated with this IP and hence, there is no need to incorporate neither the IPs nor the ion pairing agents into the electrode matrix. The IP concentration in the organic phase increases with increasing both the extractability and the solubility product of the IP formed [15,16].

The plain electrodes were soaked in the aqueous suspensions of different OX-IPs for 24 h before potentiometric measurements. The results obtained showed that the electrodes soaked in the OX-TPB had the best sensitivity indicated by thighst slope (54.5±3.5mV/decade) when compared with other IPs (45.5±8.5, 41.7±1.3 and 42.9±2.5mV/decade for PVC soaked in OX-RAS, OX-PMA and OX-PTA, respectively) which is directly related to the solubility products of these IPs and the extent of their extraction into the electrode matrix.

Sensors Performance

The potentiometric response characteristics of different OX sensors prepared with different methods of preparation (modification with OX-TPB, modification with NaTPB or plain) were evaluated according to IUPAC recmmendations. The data obtained (Figure 2) Indicated that the developed sensors can be successfully applied for the potentiometric determination of OX in concentration range 10^{-6} to 10^{-3}M with Nernstian cationic slopes depend on the method of electrode fabrication. The modified electrode showed the best performance compared with the plain electrodes or modified with the ion pairing agents (slope values were 75.45, 54.35 and 55.7 mV/ decade for the electrodes 7 mV/ decade for the electrodes modified with OX-TPB, NaTPB or plain electrode, respectively) with detection limit about3×10^{-7}M.

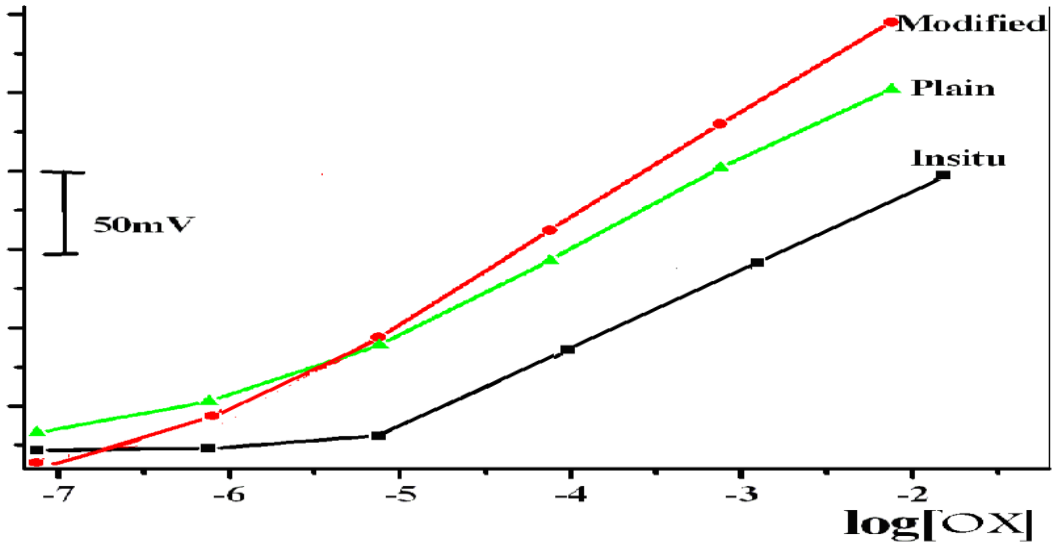


Figure 2: Potentiometric determination of OX using different PVC electrodes

ISSN: 0975-8585

The response times. For analytical applications, the response time of a new fabricated sensor is of critical importance. The response time of the fabricated electrodes was measured by using IUPAC recommendation. The average response time is defined as the time required for the electrode to reach a stable potential (within ±1mV of the final equilibrium value) after sudden 10-fold increase in concentration by addition of small increments of 10^{-2}mol L^{-1} VB solution. For the modified and soaked electrodes, the response time was found to be 8s for concentration of ≥ 1×10^{-4}M and 10s for lower concentrations while the insitu electrode showed longer response time of 12 and 14s respectively (Fig. 3).

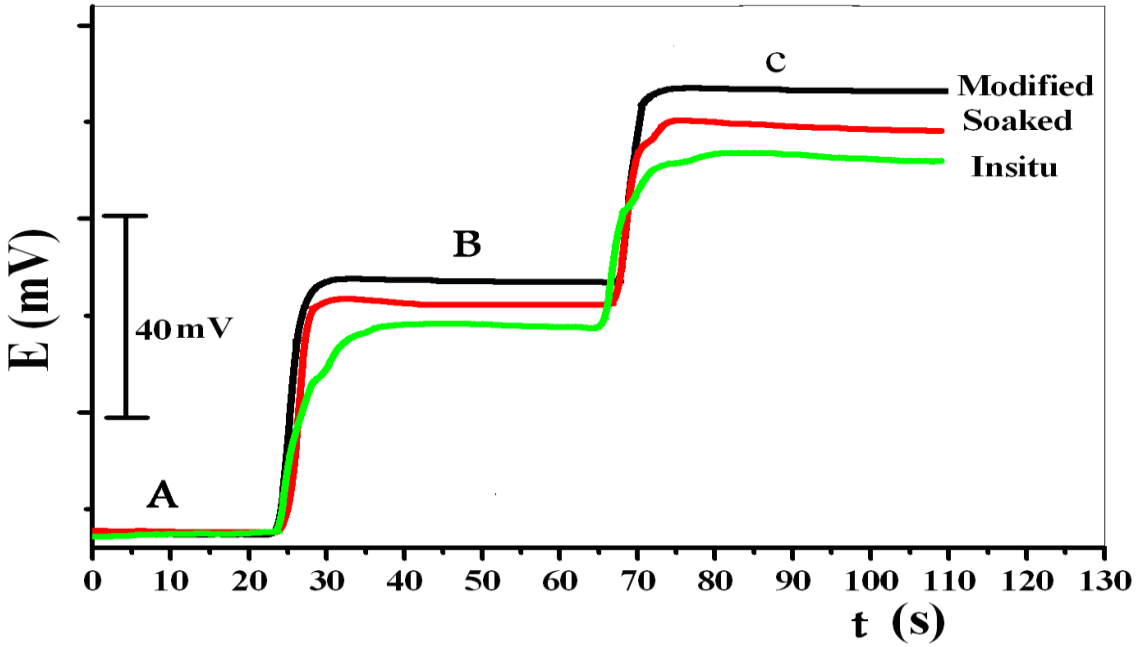


Figure 3: Dynamic response of OX PVC electrodes: (a) 1×10^{-5}, (b) $1\times10^{-4}$and (c) 1×10^{-3}mol L^{-1} OX.

The effect of pH on the OX electrode potential was investigated by observing the changes in the potential with pH of the solution after the addition of small volumes of HCl and/or NaOH (0.1 or 1 M). the investigated electrode gave a useful pH range from 3.0 – 7.0.

Potentiometric Titration

In contrast to direct potentiometric measurements requiring careful calibrations of measuring cells. The potentiometric titration techniques offers the advantage of high accuracy and precision: although the cost of increased time and consumption of reagents used as titrants. Parallel to the studying of the factors affecting the electrodes performance under the batch conditions, the effect of these factors was also investigated under the conditions of potentiometric titration of OX with NaTPB.

When ISEs are used to monitor the titration based on IP formation, the magnitude of both potential break and sharpness at the inflexion point of the titration curve is predetermined by the solubility of the corresponding IP in membrane plasticizer and also related to the extractability of the IP into the membrane mediator. The influence of the membrane plasticizer on the titration performance was investigated by performing the titration of OX with NaTPB using electrodes plasticized with different plasticizer namely *o*-NPOE, TCP, DOP or DOS. Generally, the electrodes plasticized with *o*-NPOE gave the highest

ISSN: 0975-8585

total potential change (ΔE=358 mV) compared with those plasticized with TCP, DOS or DOP (ΔE were 250, 240 and 228 mV for the plasticizers in the same order) which can be explained by higher extractability of the OX-TPB ion pairs into the membrane plasticizer due to the relative higher dielectric constant of *o*-NPOE (see Fig. 4) .

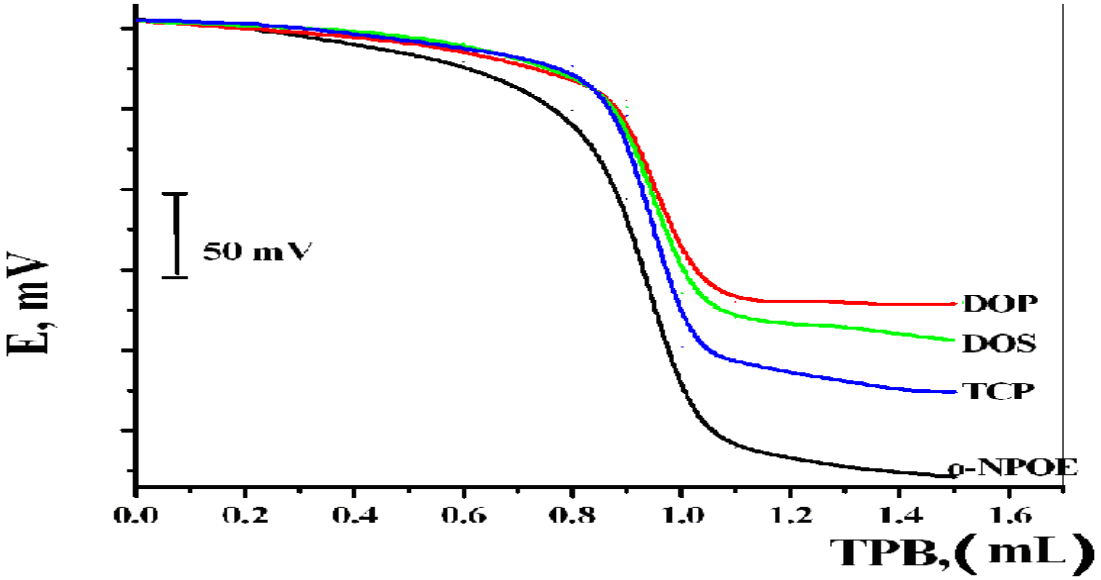


Figure 4: Effect of the electrode plasticizer on the potentiometric titration of OX with NaTPB

The effect of electrode fabrication techniques on the titration process was investigated. The plain electrodes showed the best titration curve compared with the modified with either the OX-TPB ion pair or with the ion pairing agent regarding the total potential charge or the potential break at the end point.

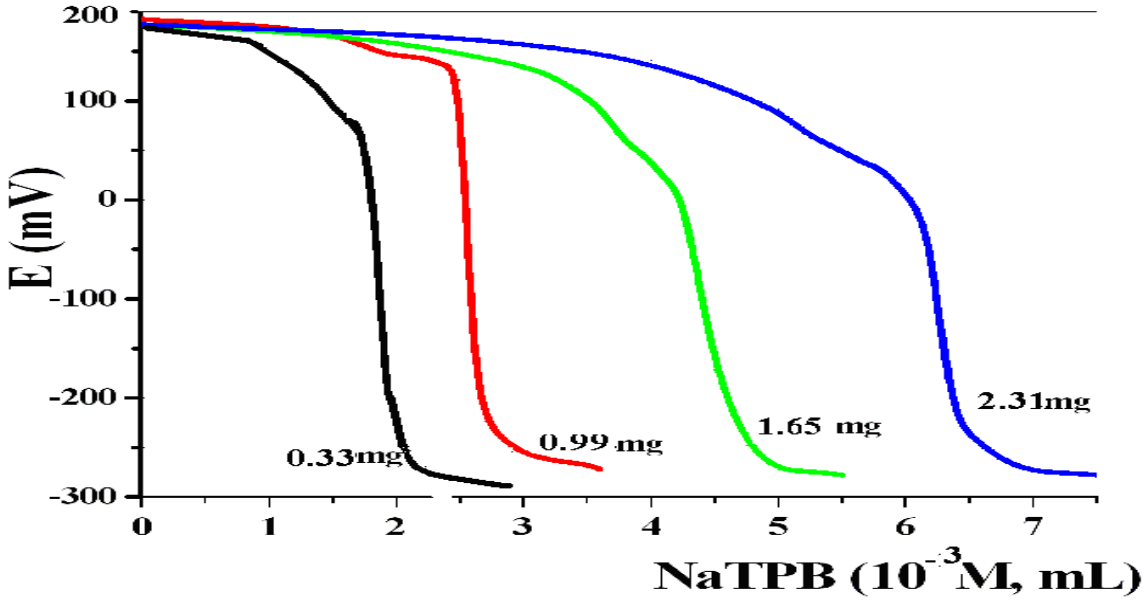


Figure 5: Potentiometric titration of OX with NaTPB using OX PVC electrode

Under the optimum conditions, the titration curves were symmetrical with a very well defined potential jump indicating the high sensitivity of the electrode. Concerning the titration process, the total potential changes and the potential breaks at the end point were large (ΔE=360 mV) allowing the application of the electrode to determine OX reaching down to 0.33 mg (Fig. 5). The titration process was highly reproducible, when the average recovery was 83.2 ±1.5%.

Analytical Applications

The proposed electrode was successfully employed for the assay of OX in their authentic samples applying potentiometric titration method. The data given in table II clearly indicate satisfactory agreement between the OX content in different samples determined by the proposed sensor and elemental analysis as there is no official method.

Table 2: Potentiometric titration of Oxomemazine HCl with NaTPB using OX-PVC electrode as indicator electrode

Taken, mg	Found mg	Recovery%	SD*
0.33	0.26	85.42	2.10
0.99	0.80	86.81	2.10
1.65	1.25	83.33	1.90
2.31	1.67	81.09	1.90
3.3	2.5	83.33	1.20
9.9	7.6	84.16	1.75
16.5	12.2	83.83	1.30
23.1	18.25	84.46	1.20
Average recovery		84.4±1.6	

*Average of five titration process

CONCLUSION

The present work has successfully demonstrated the fabrication of novel OX-PVC electrode utilizing different preparation methods. The fabricated electrodes showed Nernstian slopes in the concentration range 10^{-6}-10^{-3} mol L^{-1} with fast response time (8s), and long operational lifetime. The fabricated electrodes were successfully applied as end point indicator electrode for potentiometric titration of OX with NaTPB in the concentration range 0.33-23.1 mg with good accuracy and sensitivity.the fabricated electrode possessed shorter response time compared with drug electrode.

REFERENCES

[1] RM Jacob, JG Robert, US Patent, assigned to Societe des Usines Chimiques Rhone-Poulenc (France), 2,), 972 (1961, 612.
[2] D Zivanov-Stakic, L Deric. Arch Farm 1979;29:21-24.
[3] Akram M. El-Didamony. Arch Pharm Chem Life Sci 2005;338:190-197.
[4] G Hoogewijs, DL Massart. J Pharm Biomed Anal 1984;2:449-463.
[5] K Vytras. Electrode Rev 1985;7:77.

[6] Issa YM, Shoukry AF, and El-Nashar RM. J Pharm Biomed Anal 2001;26:379-386.
[7] Shoukry AF, Abdel-Ghani NT, Issa YM, and Ahmed HM. Electroanalysis 1999;11(6): 443- 446.
[8] Antropov LL. Theoretical Electrochemistry, Mir, Mosco, 1977.
[9] Nour T Abdel-Ghani, Adel F Shoukry, and Salwa H Hussein. J Parm Biomed Anal 2002;30:601-611.
[10] E Khaled, HNA Hassan, MS Kamel, BN Barssoum. Curr Pharm Anal 2007;3:262.
[11] RP Buck, E Lindner. Pure Appl Chem 1994;66:2527.
[12] Y Tamari. Bunseki Kagaku 2001;50:731.
[13] J isoe, E kaneko, S hoshi, K Akatsuka. Bunseki Kagaku 2002;51:657.
[14] X. –Z. Ding, Lihua Jianyan, Huaxue Fence 1995;31:93.
[15] K Vytras, et al. Czech Chem Commun 1990;55:941.
[16] K Vytras, J Kalous, J Jezkova. Egypt J Anal Chem 1997;6:107.