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ORIGINAL ARTICLE

A new ion selective electrode method for determination of oseltamivir phosphate (Tamiflu) and its pharmaceutical applications

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Phosphomolbdate;
Phosphotungestate

Abstract Oseltamivir phosphate (OP) is an antiviral drug that is used in the treatment and prophylaxis of both influenza A and influenza B. It is effective against all known influenza viruses that can infect humans, including pandemic influenza viruses and may be the most appropriate antiviral option against avian influenza caused by H5N1 virus. Tamiflu, the registered trademark used under exclusive license by Roche laboratories with OP as active pharmaceutical ingredient, is considered the best treatment for the bird flu disease.

The construction and electrochemical response characteristics of poly vinyl chloride (PVC) membrane sensors for the determination of (OP) were described. The sensors are based on the use of the ion association complexes of (OP) cation with sodium tetraphenylborate–oseltamivir phosphate (NaTPB–OP), tungestosilisate–oseltamivir phosphate (TS–OP), phosphomolbdate–oseltamivir phosphate (PM–OP) and phosphotungestate–oseltamivir phosphate (PT–OP) as ion exchange sites in the PVC matrix. The performance characteristics of these sensors, which were evaluated according to IUPAC recommendations, reveal a fast, stable and linear response for (OP) over the concentration range from 10^{-5} to 10^{-2} mol L^{-1} with cationic slopes of 51.5 ± 0.3, 50 ± 0.5, 55 ± 0.2 and 50 ± 0.4 mV per decade across an extended OP concentration range from 1.0×10^{-6} to 1.0×10^{-2} mol L^{-1} for NaTPB–OP, TS–OP, PM–OP and PT–OP, respectively. The direct potentiometric determination of (OP) using the proposed sensors gave average recoveries of 99.9, 99.8, 99.9 and 99.7 for NaTPB–OP, TS–OP, PM–OP and PT–OP, respectively. The sensors are used for determination of (OP) in tablets. The method was successfully applied to commercial pharmaceuticals, Tamiflu. Validation of the method shows suitability of the proposed sensors for use in the quality

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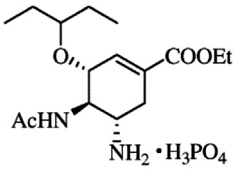
control assessment of (OP). The developed method was found to be simple, accurate and precise when compared with a reported HPLC method.

1. Introduction

Oseltamivir is an antiviral drug that slows the spread of influenza (flu) virus between cells in the body by stopping the virus from chemically cutting ties with its host cell—median time to symptom alleviation is reduced by 0.5–1 day. The drug is sold under the trade name Tamiflu and is taken orally in capsules or as a suspension. It has been used to treat and prevent influenza virus A and influenza virus B. Systematic (IUPAC) name: Ethyl (3R, 4R, 5S)-5-amino-4-acetamido-3- (pentan-3-yloxy) cyclohex-1-ene-1-carboxylate phosphoric acid and the structure is: $C_{16}H_{31}N_2O_8P$ (Burch et al., 2009).



Oseltamivir phosphate (Tamiflu)

Oseltamivir is administered by oral inhalation for the treatment of influenza infection. It is a neuraminidase inhibitor. When started within 36 h of symptom onset, oseltamivir can decrease the severity and duration of symptoms caused by either influenza A or B (Mondel, 2008). The antiviral drug oseltamivir (Tamiflu) has received recent attention due to the potential use as a first-line defense against H5N1 and H1N1 influenza viruses. Oseltamivir is not removed during conventional wastewater treatments, thus having the potential to enter surface water bodies (Accinelli et al., 2010). Oseltamivir is it not virally effective; however, once in the liver, it is converted by natural chemical processes, hydrolyzed hepatically to its active metabolite, the free carboxylate of OP.

OP is a neuraminidase inhibitor, serving as a competitive inhibitor toward sialic acid, found on the surface proteins of normal host cells. By blocking the activity of the viral neuraminidase enzyme, oseltamivir prevents new viral particles from being released by infected cells (R. Laboratories, 2008). The most common side effects are mild to moderate nausea and vomiting (Rossi, 2006). Clinical practices showed that oseltamivir was effective to treat the 2009-H1N1 influenza but failed to the 2006-H5N1 avian influenza (Wang et al., 2009). A number of studies have been reported for the determination of OP by chromatographic methods (Lindegårdh et al., 2007; Fuke et al., 2008; Charles et al., 2007; Lindegardh et al., 2008, 2006; Bahrami et al., 2008; Yamazaki et al., 2008; Heinig and Bucheli, 2008). OP has been predicted to reach high concentrations in surface waters and sewage works (Straub, 2009; Bartels and Tümpling, 2008). OP is the first orally administered neuraminidase (NA) inhibitor approved for use in treatment and prevention of influenza virus infection in man (Carr et al., 2002). OP resistance among influenza A (H1N1) viruses rapidly emerged and spread globally during the 2007–2008 and 2008–2009 influenza seasons (Adhiambo et al., 2010). Several neuraminidase (NA) assays are available for the evaluation of neuraminidase inhibitors (NAIs) (Su et al., 2008). Electrophoresis method was developed and validated for the assay of OP in capsules (Kummer et al., 2009). We present a sensitive and specific approach for detection of pandemic influenza A/H1N1 2009 and a rapid RT-PCR assay detecting a primary oseltamivir resistance mutation which can be incorporated easily into clinical virology algorithms (Vries et al., 2010). OP is converted in the human body into the pharmacologically active metabolite, oseltamivir acid, with a yield of 75%. Oseltamivir acid is indirectly photodegradable and slowly biodegradable in sewage works and sediment/water systems (Escher et al., 2010). There are many conserved residues in the Neuraminidase (NA) active site that are involved in NA inhibitor binding; only a few have been demonstrated to confer resistance (Ho et al., 2007). A resin linked with the Tamiflu core was synthesized by modifying our original synthetic route of OP (Kimura et al., 2009). Oseltamivir Carboxylate (OC), the active metabolite of the prod rug (OP), has the potential to be released into water bodies (Saccà et al., 2009). The neuraminidase inhibitors (NAIs) are an effective class of antiviral drugs for the treatment of influenza A and B infections. Until recently, only a low prevalence of NAI resistance (< 1%) had been detected in circulating viruses (Hurt et al., 2009). In this work the determination of OP was done by the ion-selective electrode method, some Voltammetric and Electroanalytical methods were used in the literature (Gupta et al., 2006, 2008, 2010a,b, 2011a,b, 1997; Singh et al., 2007; Srivastava et al., 1995; Jain et al., 1995a,b, 2005, 1997; Srivastava et al., 1996; Prasad et al., 2004; Gupta and Kumar, 1999; Goyal et al., 2009a,b, 2008, 2007a,b,c, 2005a,b; Goal et al., 2008; Bachheti et al., 2006; Goyal and Gupta, 2011a; Goyal and Gupta, 2011b; Gupta, 2011; Dwivedi et al., 2011; Gupta and Jain, 2010).

2. Experimental

2.1. Apparatus

All Potentiometric measurements were made at 25 ± 1 °C with an Orion (Model 720) pH/mV meter. Double junction Ag/AgCl reference electrode was used. An Orion electrode (Model 90–02) filled with 10% (w/v) potassium chloride was used in the outer compartment. Combination glass (Ross pH) electrode (Orion Model 81–02) was used for all pH measurements.

2.2. Reagents and materials

All chemicals were of analytical reagent grade unless otherwise stated and doubly distilled water was used throughout. Oseltamivir Phosphate (OP), Poly (vinyl chloride) powder (PVC), Tetrahydrofuran, butylatedhydroxytoluene, and o-Nitrophe-

nyloctylether (o-NPOE), were obtained from Aldrich Chem. Co. (Milwaukee, WI, USA. OP (10^{-2} M) stock solution was prepared by dissolving 0.1025 g of OP in 25 ml of (0.05 M) phosphate buffer solution (pH 7). OP (10^{-2}–10^{-6} M) standard solutions were prepared by appropriate dilution of the stock OP solution with 0.05 M phosphate buffer solution of pH 7.

The following cations and compound solutions were prepared and standardized using the standard methods. Dilute solutions (10^{-2}–10^{-6} mol L^{-1}) of these cations and compounds were prepared by a 10-fold dilution of the stock solutions with 0.05 M phosphate buffer solution of pH 7. Sodium tetraphenylborate (NaTPB), tungestosilisate (TS), phosphomolbdate (PM) and phosphotungestate (PT) as ion-exchangers ion pair (electroactive material) were used.

2.3. Preparation of NaTPB–OP, TS–OP, PM–OP and PT–OP, the ion exchangers

The ion exchangers, (NaTPB–OP), (TS–OP), (PM–OP) and (PT–OP) were prepared by mixing 25 ml of 1.0×10^{-2} mol L^{-1} OP with 20 ml of 1.0×10^{-2} mol L^{-1} NaTPB, TS, PM and PT, respectively. The white, the white, the yellow and the yellowish white, respectively, precipitates formed, after digestion overnight, were filtered, and washed by double distilled water until dried at room temperature.

2.4. Electrodes preparation

Master PVC membrane of approximately 0.1 mm thick was optimized and prepared as described elsewhere (Elsaid et al., 2010). By mixing a 10 mg (NaTPB–OP), (TS–OP), (PM–OP) and (PT–OP) based ion pair complexes with 200 mg of o-NPOE plasticizer, 100 mg of PVC matrix, and 6 mL THF. The viscous solution thus obtained was poured in a glass Petri dish (5 cm diameter) and the solvent was allowed to evaporate for about 24 h at room temperature. The master PVC membranes were sectioned with a cork borer (8 mm diameter) and attached to a polyethylene tubing (3 cm length and 5 mm i.d.) using THF. A home made electrodes body was used which consists of a glass tube, to one end of which the polyethylene tubing was tightly inserted and filled with an equimolar mixture of 10^{-2} mol L^{-1} KCl and OP as an internal reference solution. An Ag/AgCl internal reference wire electrode was immersed in the internal reference solution. This assembly was used as a sensitive electrode in the potentiometric measurements of OP. The electrode was conditioned by soaking in 10^{-2} mol L^{-1} OP solution for 4 h before use and stored in the same solution when not in use.

2.5. Analytical characterization of OP electrodes

The proposed electrode was calibrated by measuring the emf values after stabilization to ±0.5 mV in a series of OP solutions covering the concentration range from 1.0×10^{-6} to 1.0×10^{-2} mol L^{-1} OP. The emf values were plotted on a semi logarithmic paper as a function of OP concentration. The obtained calibration curve was used for subsequent determination of the unknown OP samples. The selectivity coefficients for foreign ions were determined by the separate solution method (SSM) Umezaw et al., 2000 in which the potential readings (mV) of the two separate solutions one containing only the OP ion at the concentration level of 10^{-3} mol L^{-1} and the other containing the interferent ions at the same concentration level were measured. The selectivity coefficients K_{OP}^{Pot} were calculated using the experimentally obtained slope. The response time (t 95%) of the proposed electrode was also, tested by measuring the time required to achieve a 95% steady potential for the test solutions, when the OP ion concentration was rapidly increased by one decade from 1.0×10^{-6} to 1.0×10^{-2} mol L^{-1}. The potential readings were recorded against time (sec). The lifetime of the investigated OP electrodes was measured from the response potential to the varying OP concentration 2 days a week for more than one month.

3. Results and discussion

3.1. The Calibration curve and statistical data

The optimum responses of the NaTPB–OP, TS–OP, PM–OP and PT–OP sensors were evaluated, after conditioning the membranes with the same composition for different time periods in a 1.0×10^{-2} mol L^{-1} OP solution. The slope, obtained after a 12 h conditioning, was closer to the theoretically expected slopes, considering the Nernstian equation as a basis. Longer conditioning times produced no further improvement in the response. The optimum conditioning solution was found to have a concentration of about 10^{-2} mol L^{-1} for four membranes. The critical response characteristics of the recommended sensor were assessed according to the IUPAC recommendations (IUPAC, 1976). The emf response of the polymeric membrane indicated Nernstian slopes of 51.5 ± 0.3 mV, 50 ± 0.5, 55 ± 0.2 and 50 ± 0.4 per decade across an extended OP concentration range from 1.0×10^{-6} to 1.0×10^{-2} mol L^{-1} for NaTPB–OP, TS–OP, PM–OP and PT–OP, respectively. The detection limits, defined as OP concentration obtained when extrapolating the linear region of the calibration graph to the base line potential, were 1.5×10^{-5} to 1.0×10^{-2} mol L^{-1}, 2.0×10^{-5} to 1.0×10^{-2} mol L^{-1}, 2.5×10^{-5} to1.0×10^{-2} mol L^{-1}, 3.5×10^{-5} to 1.0×10^{-2} mol L^{-1}, respectively. The results observed are presented in Fig. 1.

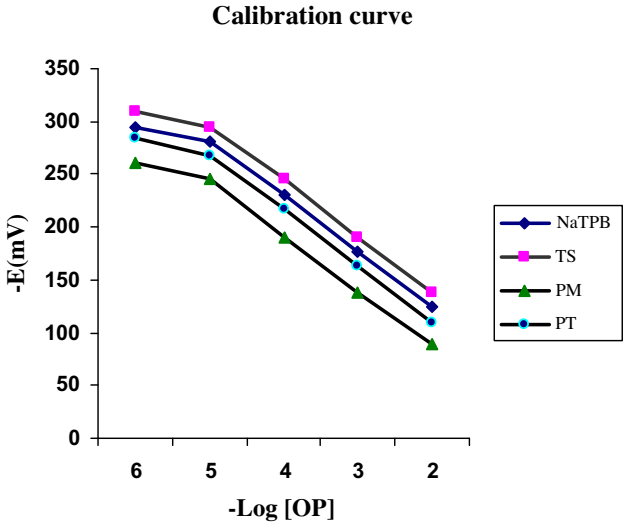


Figure 1 Calibration curves and the optimum responses of the NaTPB–OP, TS–OP, PM–OP and PT–OP sensors.

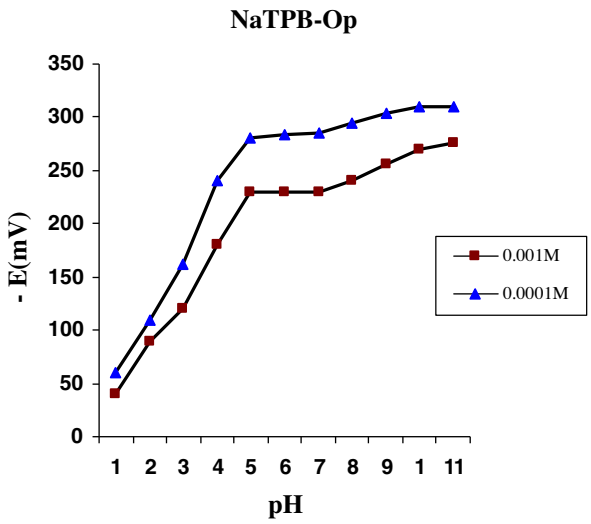


Figure 2 Effect of pH of the test solution on the potential reading: 1.0×10^{-4} and 1.0×10^{-3} mol L^{-1} OP solution at 25 °C using NaTPB–OP electrode.

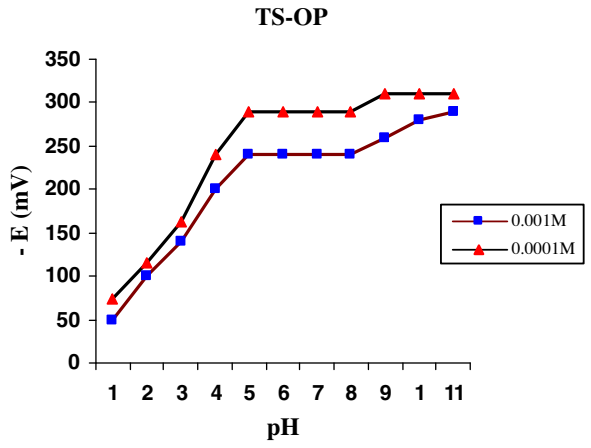


Figure 3 Effect of pH of the test solution on the potential reading: 1.0×10^{-4} and 1.0×10^{-3} mol L^{-1} OP solution at 25 °C using TS–OP electrode.

3.2. Influences of pH on the potentiometric response of OP electrodes

The influences of the pH of a test solution on the proposed OP electrodes potentiometric response were studied at two OP concentrations (1.0×10^{-3} and 1.0×10^{-4} mol L^{-1}), where the pH was adjusted from 1 to 10 with H_3PO_4 or NaOH solutions. The results observed are presented in Figs. 2–5.

As it can be seen, the potential is independent on the pH changes in the range of 5–8. Thus, this range may be chosen as the working pH for the electrodes assembly. At pH < 5, the OP cation was protonated, whereas, at relatively high pH the potential decreases more significantly probably due to membrane response to OH^-. The observed potential changes at the lower and higher pH values could be caused by the

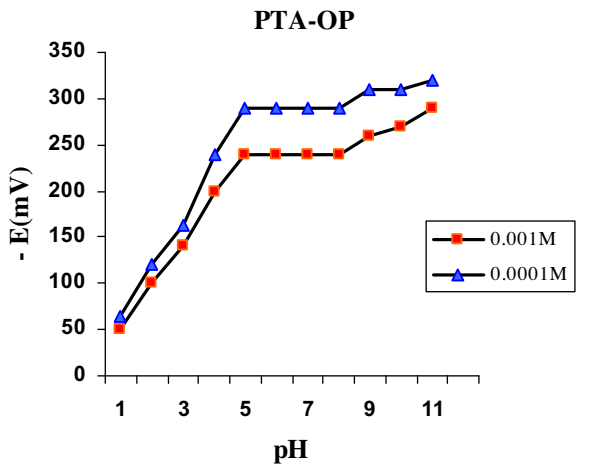


Figure 4 Effect of pH of the test solution on the potential reading: 1.0×10^{-4} and 1.0×10^{-3} mol L^{-1} OP solution at 25 °C using PT–OP electrode.

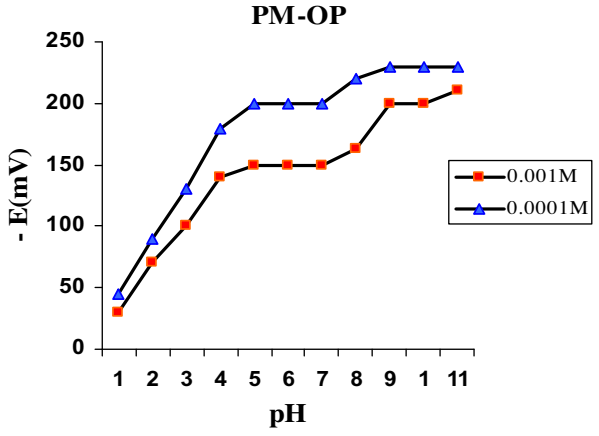


Figure 5 Effect of pH of the test solution on the potential reading: 1.0×10^{-4} and 1.0×10^{-3} mol L^{-1} OP solution at 25 °C using PM–OP electrode.

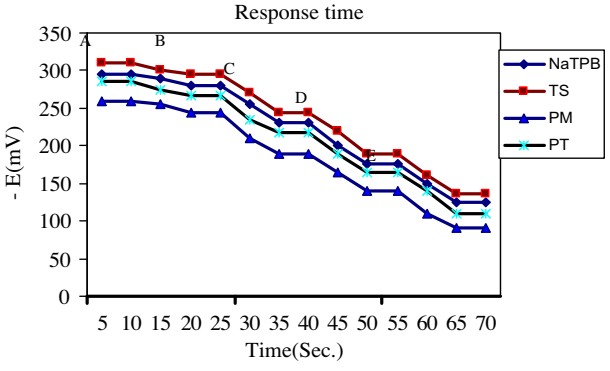


Figure 6 The response time of the membranes NaTPB–OP, TS–OP, PM–OP and PT–OP sensors, A = 10^{-6}, B = 10^{-5}, C = 10^{-4}, D = 10^{-3}, and E = 10^{-2} mol L^{-1}.

Table 1 Potentiometric selectivity coefficients (K_{OP}^{Pot}) for the four proposed electrodes (NaTPB–OP, TS–OP, PM–OP and PT–OP).

Interferents	NaTPB–OP	TS–OP	PM–OP	PT–OP
p-Nitroanaline (pNA)	1.1×10^{-1}	6.5×10^{-2}	6.0×10^{-3}	5.2×10^{-2}
Nicotine amide (NA)	3.2×10^{-1}	4.6×10^{-2}	9.2×10^{-3}	7.6×10^{-2}
Ammonium oxalate (AO)	5.8×10^{-2}	5.1×10^{-1}	1.4×10^{-2}	7.5×10^{-2}
Ammonium citrate (AC)	3.2×10^{-1}	8.5×10^{-1}	3.9×10^{-2}	2.4×10^{-1}
L-Alinine (L-al)	1.6×10^{-1}	1.4×10^{-1}	2.4×10^{-2}	9.2×10^{-2}
Semicarbazide (SC)	8.5×10^{-1}	8.5×10^{-1}	1.9×10^{-1}	3.5×10^{-1}
Glutamine (GLU)	3.2×10^{-1}	8.5×10^{-1}	9.2×10^{-2}	5.8×10^{-1}
Nicotine (Nic)	3.2×10^{-1}	1.3×10^{-1}	1.3×10^{-2}	9.0×10^{-2}
Sodium salicylate (SS)	1.4×10^{-3}	4.6×10^{-3}	6.0×10^{-3}	1.6×10^{-2}
Sodium benzoate (SB)	5.8×10^{-1}	1.5×10^{-2}	1.2×10^{-2}	3.5×10^{-2}

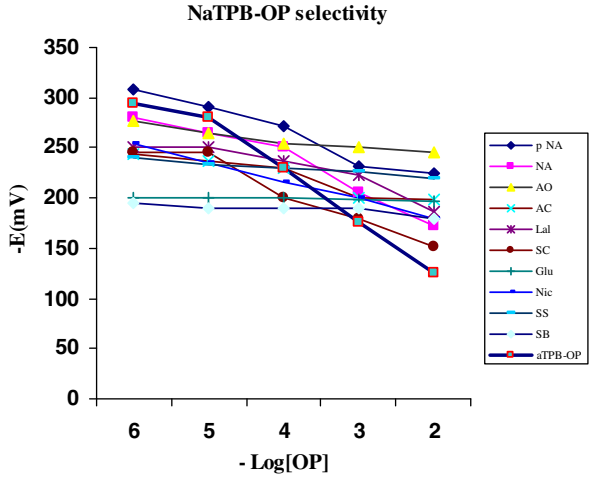


Figure 7 The response of NaTPB electrode against OP and some cations.

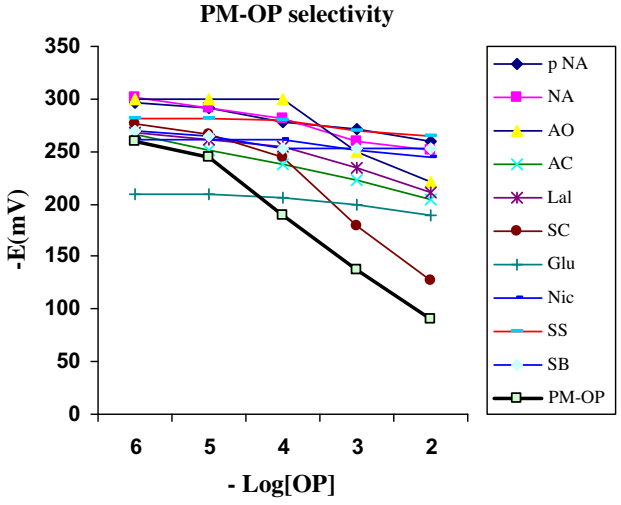


Figure 9 The response of PM electrode against OP and some cations.

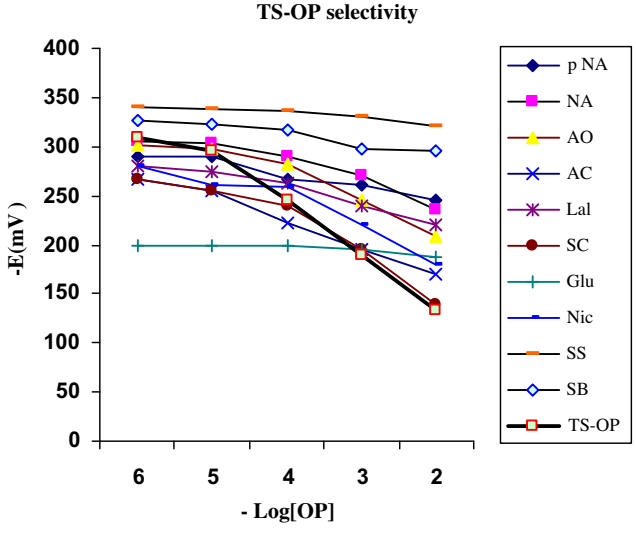


Figure 8 The response of TS electrode against OP and some cations.

ion carrier protonation as well as the formation of some hydroxyl complexes of OP ion in the solution.

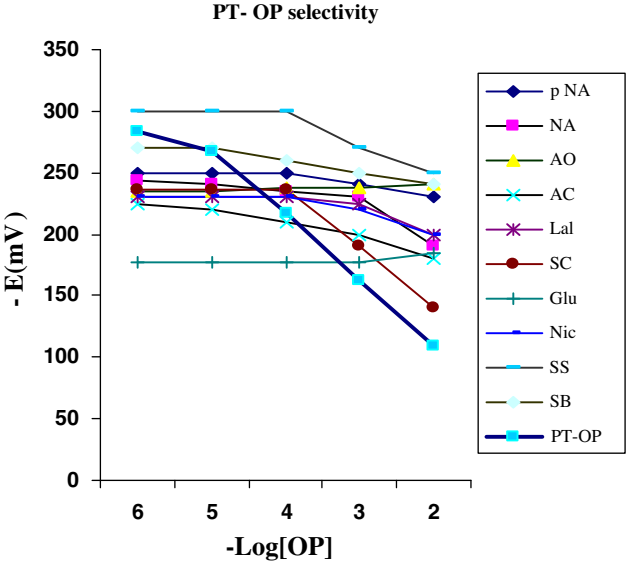


Figure 10 The response of PT electrode against OP and some cations.

Table 2 Response characteristics for NaTPB–OP, TS–OP, PM–OP and PT–OP membranes.

Parameters	NaTPB–OP	TS–OP	PM–OP	PT–OP
Slope (mV/decade)	51.5 ± 0.3	50 ± 0.5	55 ± 0.2	50 ± 0.4
Intercept (mV)	−294	−310	−260	−284
Correlation coefficient	0.9998	0.9999	0.9997	0.99996
Detection limit (M)	1.5×10^{-5}	2.0×10^{-5}	2.5×10^{-5}	3.5×10^{-5}
Quantification limit (M)	1.0×10^{-5}	1.5×10^{-5}	2.0×10^{-5}	2.5×10^{-5}
Response time (s)	30	30	30	30
Working pH range	5–8	5–8	5–8	5–8
Concentration range (M) mol L^{-1}	1.5×10^{-5} to 1.0×10^{-2}	2.0×10^{-5} to 1.0×10^{-2}	2.5×10^{-5} to 1.0×10^{-2}	3.5×10^{-5} to 1.0×10^{-2}
Life span (days)	25	20	20	25
Average recovery [a] (%)	99.9	99.8	99.9	99.7

[a] Average of four determinations.

3.3. The response time and Lifetime study

For analytical applications, the dynamic response time generally consists of a considerable parameter for any sensor (Matysik et al., 1998). The dynamic response time for the OP electrode from lower concentrations (1.0×10^{-6} mol L^{-1}) to higher concentrations (1.0×10^{-2} mol L^{-1}) was recorded. The actual potential versus time tracer is presented in Fig. 6.

The dynamic response time of the membranes was measured at various concentrations (1.0×10^{-6} to 1.0×10^{-2} mol L^{-1}) of the test solutions. The reported results in Fig. 6 illustrate that in the whole concentration range the electrodes reach its equilibrium response very fast (10 s). As it can be seen, the proposed OP electrodes provide fast response time (< 30 s.) to reach 95% of its final steady state potential in the tested concentration range. The electrodes lifetime was also measured by employing one of the electrodes for a 6-week period. In this period, the electrodes were used for 1 h each day and, then, washed and dried. The lifetime measured in this way was found to be two weeks to1 month, during which the electrodes slope displayed only a slight change from 50 to 55 mV per decade.

3.4. Selectivity coefficient of OP

Selectivity is an important characteristic, which defines the nature of the device and the range to which it may be successfully employed. The selectivity of the ion selective electrodes under consideration was also, investigated with respect to some common cations using SSM. The selectivity coefficients of the proposed membrane selective electrode were determined against a number of different cations by using SSM. The data obtained, showed that the selectivity coefficient (K_{OP}^{Pot}) values ranging from 5.8×10^{-2} to 8.5×10^{-1}, 4.6×10^{-3} to 8.5×10^{-1}, 6.0×10^{-3} to 1.99×10^{-1}, 1.6×10^{-2} to 5.8×10^{-1} for NaTPB–OP, TS–OP, PM–OP and PT–OP respectively, for the tested cations. These values clearly indicate that, the proposed electrodes were fairly selective to OP cation over different tested cations. Nevertheless, for all of the diverse ions used, the selectivity coefficients were lower than 8.5×10^{-1}, 8.5×10^{-1}, 1.99×10^{-1}, and 5.8×10^{-1} for NaTPB–OP, TS–OP, PM–OP and PT–OP, respectively, indicating that the studied common cations would not significantly disturb the determination of OP according to the SSM, the potentiometric selectivity coefficients were determined using 1×10^{-3} mol L^{-1} test solution of different cations at pH = 5–8. The resulting selectivity coefficients are summarized in Table 1.

The selectivity coefficient is an important measure on the selectivity of an ion. For the determination of selectivity coefficients mixed solution method was preferred as it usually corresponds more closely to the situation in the sample. For this purpose solutions were prepared with a constant activity of the main ion (10^{-2} mol L^{-1}OP) and varying activity of interfering ion (10^{-2} to 10^{-5}). The change of potential for each addition of interfering ion is recorded. The potentials obtained at different concentrations of OP and interfering ions are plotted against concentrations as shown in Figs. 7–10. In these work possible interferences of p-Nitroanaline (pNA), Nicotine Amide (NA), Ammonium Oxalate (AO), Ammonium Citrate (AC) L-Alinine (L-al), Semicarbazide (SC), Glutamine (GLU), Nicotine (Nic), Sodium Salicylate (SS), and Sodium Benzoate (SB) were studied. Selectivity coefficients ($k_{A,B}^{pot}$) were calculated using the equation given below (Srinivasan and Rechnitz, 1969). $k_{A,B}^{pot} = \text{antilog}E1 - E2/S$ where, $S = 2.303\,RT/nF$ (the slope of OP electrodes), $E1$ the potential measured when only A is present, $E2$ the potential responsive to the primary ion in the presence of interfering ion, $k_{A,B}$ the selectivity coefficient. The results are summarized in Table 1 and as can be observed from Figs. 7–10. No significant interference is caused by the examined ions except semicarbazide (Sc) that explain the monovalent of OP ($n = 1$) response due to –NH group which connected with CO and no effect of $-NH_2$ group (free amino group).

3.5. OP electrodes response characteristics

The proposed (NaTPB–OP), (TS–OP), (PM–OP)and (PT–OP)-based ion pair complexes were prepared, identified and examined as electroactive sensing material in PVC membrane based electrode responsive for OP cation. The electrochemical performance characteristics of the electrodes were systematically evaluated according to IUPAC recommendations (Buck and Lindner, 1994), and the results obtained are given in Table 2.

4. Analytical applications

In order to test the analytical validity of this approach, the method has been applied for the determination of OP in pharmaceutical preparations by direct potentiometry using the

Table 3 Determination of salicylate in different OP tablet samples ($n = 10$): Comparison of potentiometric results with an independent HLPC method.

OP samples mg/tablet	NaTPB–OP	TS–OP	PM–OP	PT–OP	HLPC
75	70 ± 0.5	72 ± 0.6	71 ± 0.8	70 ± 0.6	74 ± 0.5
150	142 ± 0.4	144 ± 0.2	140 ± 0.6	143 ± 0.5	145 ± 0.4

calibration graph and standard additions technique (HPLC method) Charles et al., 2007. Tamiflu, the registered trademark used under exclusive license by Roche laboratories (Swiss made) with OP as active pharmaceutical ingredient, is considered the best drug for treatment of the bird flu disease, one Tamiflu capsule containing 75 mg of OP.

The high degree of OP selectivity exhibited by the electrodes based on the NaTPB–OP, TS–OP, PM–OP and PT–OP makes it potentially useful for monitoring concentration levels of OP in real samples. To assess the applicability of the membrane electrodes in real samples, an attempt was made to determine OP in pharmaceutical preparations. The proposed electrodes were applied to determine OP in pharmaceutical samples using the standard addition method. The solutions were prepared by the method described in reagents and materials and were filtered if necessary. The results are presented in Table 3 and indicate good agreement between the potentiometric and HPLC method.

5. Conclusion

In the present study, we report our observation of new four constructed sensors for OP detection over a wide range of concentrations from 1.0×10^{-5} to 10^{-2} mol L^{-1}. Three are based on the use of NaTPB–OP, TS–OP, PM–OP and PT–OP, ion pair complexes as electroactive compounds dispersed in plasticized poly (vinyl chloride). The fourth sensor is based on plasticized o-NPOE, PVC without ion pair complex. The concentration levels of OP are in the range of these in pharmaceuticals and this is an important consideration. We have developed quicker and more feasible methodologies of analysis based on novel sensors with high selectivity and sensitivity and are very reproducible; they also displayed faster response time, high stability, and suitable life time, low cost and simple design.

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