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Ion Selective Electrodes For Potentiometric Determination of Promethazine In Its Pharmaceutical Dosage Form

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I. INDRODUCTION

Promethazine or N,N-dimethyl-1-phenothiazin-10-ylpropan-2-amine (Fig.1), is an antihistamine drug Promethazine is in a group of drugs called phenothiazines (FEEN-oh-THYE-a-zeens). It works by changing the actions of chemicals in our brain. Promethazine also acts as an antihistamine. It blocks the effects of the naturally occurring chemical histamine in our body.Promethazine is used to treat allergy symptoms such as itching, runny nose, sneezing, itchy or watery eyes, hives, and itchy skin rashes. It also prevents motion sickness and treats nausea and vomiting or pain after surgery. It is also used as a sedative or sleep aid. Promethazine is not for use in treating symptoms of asthma, pneumonia, or other lower respiratory tract infections. Get emergency medical help if you have any signs of an allergic reaction: hives; difficult breathing; swelling of your face, lips, tongue, or throat.

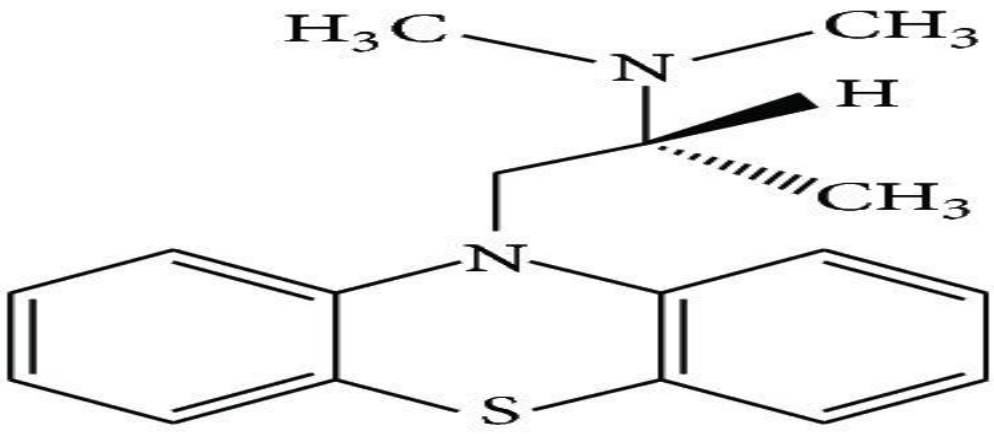

Figure-1

Is a first-generation H1 receptor antagonist, antihistamine and antiemetic medication. It can also have strong sedative effects although it is rarely used specifically for this. It is a prescription drug in the United States, but is available over the counter in the United Kingdom, Switzerland, and many other countries[1].

Chemically, promethazine hydrochloride appears as a white to faint yellow crystalline powder which is practically odourless. Slow oxidation may occur upon prolonged exposure to air usually causing blue discoloration. Promethazine as the hydrochloride salt is freely soluble in water and somewhat soluble in alcohol [1].

Chemical structure of promethazine (PM) Different methods have been reported for the determination of promethazine in products and biological samples such as high performance liquid chromatography (HPLC)[2],the UV spectrophotometry [3,4], capillary electrophoresis [5], voltammetric method [6]. Potentiometric membrane sensors are playing an important role in pharmaceutical analysis[7-10] because of their simplicity, rapidity and accuracy over some other analytical methods like spectrophotometry and HPLC. Also, other mentioned methods are elaborate , time consuming methods and involve sophisticated equipment that might not be available in most analytical laboratories. In present paper, interaction of promethazine with some ion-pair reagents was studied by theoretical and calculation methods and according to the obtained results a promethazine ion-selective potentiometric membrane electrode is developed based on ion-pair compound of promethazine-tetraphenylbroate (PM-TPB) as the electroactive substance. The proposed electrode was successfully applied for the determination of promethazine hydrochloride in the pharmaceutical Tablets formulations samples.

The present work shows the development of selective, inexpensive diagnostic tool for the determination of the Promethazine. To the best of our knowledge, only one study of polymeric membrane electrodes selective to Promethazine.The electrode is based on the ion-exchange mechanism of ion pair complex of Promethazine and sodium tetraphenyl borate as electroactive material. The electrode has narrow concentration range, high detection limit and limited selectivity of the drug over various ions. The present study has wide concentration range, long life high selectivity and sensitivity towards drug over various organic and inorganic ions.

II. MATERIALS AND METHODS

2.1 Apparatus

All potentiometry measurements were made at 25°C unless otherwise stated using pH/mV meter using Promethazine membrane electrode in conjunction with saturated silver reference electrode containing 10% (w/v) potassium nitrate in the outer compartment.

2.2 Reagents and materials

All chemicals used were of analytical reagent grade unless otherwise stated and doubly distilled water was used throughout the investigations. Polyvinyl chloride powder (PVC) high molecular weight, dibutyl phthalate (DBP), dioctyl phthalate (DOP), o-nitrophenyl octylether (NPOE),tetrahydrofurane (THF) were obtained from Merk Chemical Company and Promethazine hydrochloride was obtained from Lobachemie Chemical Company, Switzerland. Phosphotungstic acid (PT) was obtained from BDH, Chemical Ltd. The stock solution of 1x10-2 M drug was prepared by dissolving the appropriate amount of drug in 100 ml of water. The standard Promethazine solution were prepared 1x10-2 to 1x10-7 M by diluting the appropriate amount of the stock solution in double distilled water. Phosphate buffer solution of pH 7.0 was prepared by mixing appropriate amount of 0.05M of NaH2PO4 and Na2HPO4.

2.3 Preparation of Promethazine (Pr) selective membrane electrode :

The ion-pairs of Pr-PT was prepared upon addition of 12 ml of 1x10-2 M of Promethazine solution to 16 ml of phosphotungstic acid . The resulting mixtures were stirred for 10 min. The precipitate obtained was filtered off, washed with cold deionized water until no chloride ion was detected into the washing solution. The precipitate was dried for 20h at 25°C then round to a fine powder in mortar, forming ion-pairs complex. The elemental analysis confirmed the formation of 2:1 complex of Pr:PT. In glass Petri dishes (5 cm diameter) a, portions of 10 mg the prepared ion -pairs were thoroughly mixed with PVC powder, plasticizers (DBP or DOP or o-NPOE) and dissolved in 5ml THF. The solvent has been allowed to evaporate overnight while the sensing membranes have been formed. A master membrane with a thickness of 0.10 mm was obtained. A disk of an appropriate diameter (about 5.00 mm) was cut from the master membrane and glued at the one end of a Pyrex glass tube with the help of araldite.A saturated silver electrode was inserted in the tube for electrical contact and another saturated silver electrode was used as an external reference electrode. The ionic strength of various solutions was maintained with the help of saturated solution of KCl. The electrodes were conditioned by soaking for 4h in a 0.01 M aqueous Pr solution and were kept in the same solution when not in use.The Emf measurements were carried out with the cell assembly given below:

Ag / AgCl, 0.1M KCl)	Internal reference Solution	Promethazine Selectivity Membrane	Test solution	1 M KCl Ag/AgCl

The Promethazine PVC membrane electrodes were immersed in conjunction with the reference electrode in a 50 ml beaker containing 10.0 ml of phosphate buffer of pH 7.0. Then 1.0 ml aliquot of Promethazine solution was added with continuous stirring, to give final Promethazine concentration (10-2 to 10-7 M) and the potential was recorded after stabilization to ± 1.0 mV.A calibration graphs were then constructed by plotting the recorded potentials as a function of -logaPromethazine. The resulting graphs were used for subsequent determination of unknown Promethazine concentration or/ and the regression equations of the linear part are used to calculate the unknown solution.

2.4 Determination of Promethazine in the pharmaceutical dosage form :

Ten tablets of Phenergan (Sanofi Pharmaceuticals,) 25 mg each were accurately weighed crushed and mixed in a mortar. An appropriate amount of tablets powder was weighed transferred to a 100 ml beaker. 5.0 ml aliquots of this solution was transferred to 50 ml standard measuring flask and 10 ml of phosphate buffer of pH 7.0 was added and filled up to the mark with water. The potential of the solution was measured using Pr-selective electrode in

conjunction with saturated silver reference electrode. The potential of the stirred solution was recorded after the signal stabilization (± 1 mV/min) and the concentration was calculated from the calibration graph under identical experimental conditions from standard solutions of Pr .A Laboratory made powder containing fixed amount of Pr powdered (5 mg) and other components such as starch, lactose and magnesium stearate (complete table composition) was prepared and used to investigate the accuracy and precision of the potentiometric determination of Pr-selective electrode.

III. RESULTS AND DISCUSSION:

The ion-selective electrode offer a selectivity and sensitivity in drug analysis because the calculated the activity of ion instead of concentration. The response characters of the electrode are highly dependents in the presence of membrane components. In the present study an ionic pair of sodium tetraphenyl borate (TBP) and phosphotungstic acid (PT) were used the preparation of an electroactive ion association complexes for Pr. Plasticized polymeric membranes were prepared by using membrane cocktails with compositions 2% of the corresponding ion-associate (Pr-TBP or Pr- PT), 35. 54% of poly vinyl chloride (PVC) and 63% of the specific plasticizer (DBP, DOP and 0-NPOE).

3.1 Effect of plasticizer type on the characteristic performance of the sensors:

Promethazine ion-selective membrane electrodes with different compositions were prepared in order to get the optimum composition of membrane components. The two ion-pairs Pr-TPB and Pr-PT gives the linear response and wide concentration range with low detection limit. It is well known fact that the construction of PVC based ISEs required the use of a plasticizer which acts as a fluidizer allowing homogenous dissolution and diffusion mobility of the ion-pair inside the membrane. Therefore the effect of various plasticizers (DOP,DBP and o-NPOE) on the potential response of the electrodes were investigated. The response characters of membranes of various plasticizers are summarized in table 1 and table 2. The data presented in table 1 indicates that the electrode assembly based on Pr – PT ionic pair with the composition of ionic pair: plasticizer: PVC of the 2%: 63%: 35% (w/w) shows the best possible response in terms of linear working concentration range, detection limit and slope of calibration curves. The membrane electrode no. 1 based on DOP as plasticizer works satisfactorily in the linear concentration range of 3.2 x 10-7 –1.0 x 10-2 (M) with a detection limit of 1.5 x 10-7 and has a slope of 50.5 ± 1.0 (mV/decay). The amount of ion pair more than or less than 2% (electrode no. 2 and 3) as membrane component does not improve the response characters of the membrane electrode.

On comparing the data presented in table 1 and 2 we found that the electrode based on ion-pair Pr-PT and DOP as plasticizer exhibit the best possible response among all the tested electrodes. This is probably due to the fact that the DOP ($\varepsilon = 5.1$) provides the best possible environment for the response of the electrode due to its low polarity as compared to other plasticizers DBP ($\varepsilon = 6.4$) and o-NPOE ($\varepsilon = 23.6$). Thus the electrode no. 1 based on Pr-PT ion-pair as electro active material and DOP as plasticizer was selected as the most

Table – 1.

Electrode No.	Ion-pairs Pr-PT(%)	Plasticizers (%)	PVC (%)	Working Concentration range (M)	Slope (mV/decay) (mV/decay)
1	2	63 (DOP)	35	3.2 x 10-7 – 1.0 x 10-2	50.5 ± 1.0
2	1.2	65 (DOP)	33	8 8.6 x 10-7 – 1.0 x 10-2	43.3 ± 1.0
3	2.5	60.5 (DOP)	37	4.8 x 10-7 – 1.0 x 10-2	51.4 ± 1.0
4	2	63 (DBP)	35	8.5 x 10-6 – 1.0 x 10-2	40.5 ± 1.0
5	2	63 (o-NPOE)	35	1.0 x 10-5 – 1.0 x 10-2	38.6 ± 1.0

Table – 2. Optimization of components of membrane of Pr – TBP ionic pair

Electrode No.	Ion-pairs Pr-TBP (%)	Plasticizers (%)	PVC (%)	Working concentration range (M)	Slope (mV/decay)
6	2	63 (DOP)	35	1. x 10-6 – 1.0 x 10-2	46.8 ± 1.0
7	1.5	65 (DOP)	33.5	8.2 x 10-6 – 1.0 x 10-2	45.3 ± 1.0
8	2.5	60.5 (DOP)	37	4.5 x 10-6 – 1.0 x 10-2	44.6 ± 1.0
9	2	63 (DBP)	35	1.3 x 10-5 – 1.0 x 10-2	42.5 ± 1.0
10	2	63 (O-NPOE)	35	3.6 x 10-5 – 1.0 x 10-2	40.4 ± 1.0

Table 2. Response characteristics of Pr-PVC membrane electrode no.1 and 6

Parameter	Pr-PT	Pr-TPB
Slope, (mV/ decade)	50.5 ± 1.0	46.8 ± 1.0
Correlation Coefficient,	(r) 0.998	0.998
Lower limit of quantification,(LOQ), (M)	1.0 x 10-7 (M)	1.2 x 10-6 (M)
Lower limit of detection, (LOD), (M)	1.5 x 10-7	8.0 x 10-6
Response time for1x 10-3 M solution, (s)	8	12
Working pH range	3.0 - 7.0	3.0 -7.0

Optimization of components of membrane of Pr – PT ionic pair The electrodes based on ion pair Pr-PT was found to work in the linear concentration range of 1.0 x 10-6 – 1.0 x 10-2 M with DOP as plasticizer and in the range of 1.3 x 10-5 – 1.0 x 10-2 M for DBP and 3.6 x 10-5 – 1.0 x 10-2 M for o-NPOE

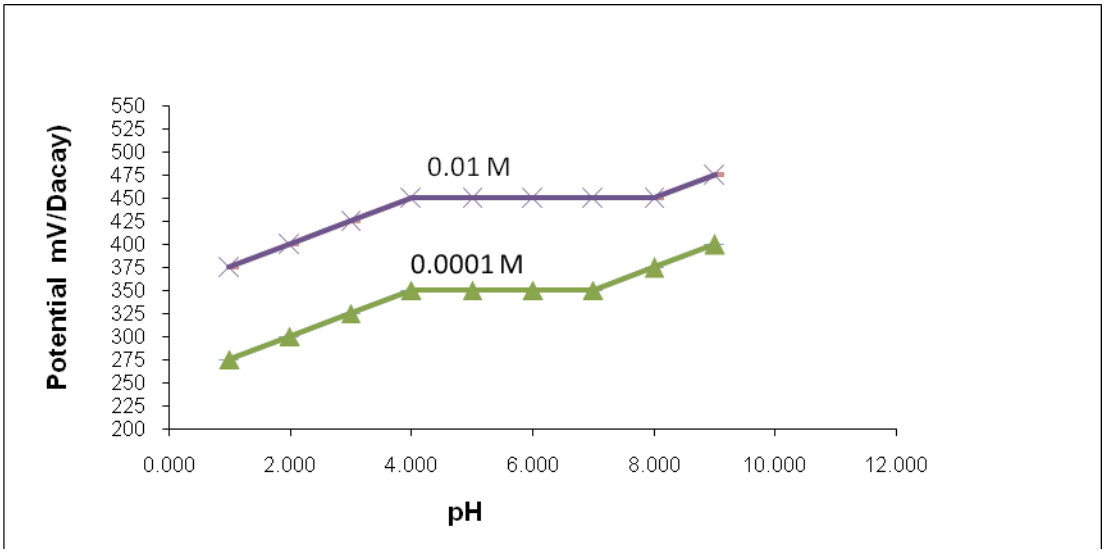

Figure.2 Potential response of electrode no. 1 based on Pr-PT ion pair

Optimized electrode and was used for further investigations. The other response characters of the electrode no. 1 are summarized in table 3. The potential response of the electrode with concentration for electrode no. 1 is shown in figure 2.

3.2 Effect of pH and the response time

The effect of pH on the potential response of the electrode no.1 was recorded in the range of 1.0 – 9.0 for 0.01M and 0.001M solutions of Promethazine. It was observed that the potential response remains almost same in the pH range of 3.0 – 7.0. This pH range was considered as the optimum working pH range for the electrode no. 1. However a significant drift in the potential was observed at pH <3 and at pH > 7 due to interference caused by hydrogen ion and hydroxide ion respectively. The pH being adjusted using standard hydrochloric acid or sodium hydroxide solutions (Fig. 3). The average response time is defined as the time required for the electrode to reach a static potential within ±1 mV of the final equilibrium value, after successive immersion of the electrode in different Promethazine solutions each having a 10-fold change in concentration. It was observed that the electrode no. 1 on Pr-TP ion reached the equilibrium value of potential in a very short time of about 8 sec. Day-to-day reproducibility of the sensor is about ± 0.5 mV/decay for the same solution and the useful lifetime of the sensor is one month, during which the potential slope is reproducible and more accurate. Also after more than one month a new section from the master membrane was found to be very suitable.

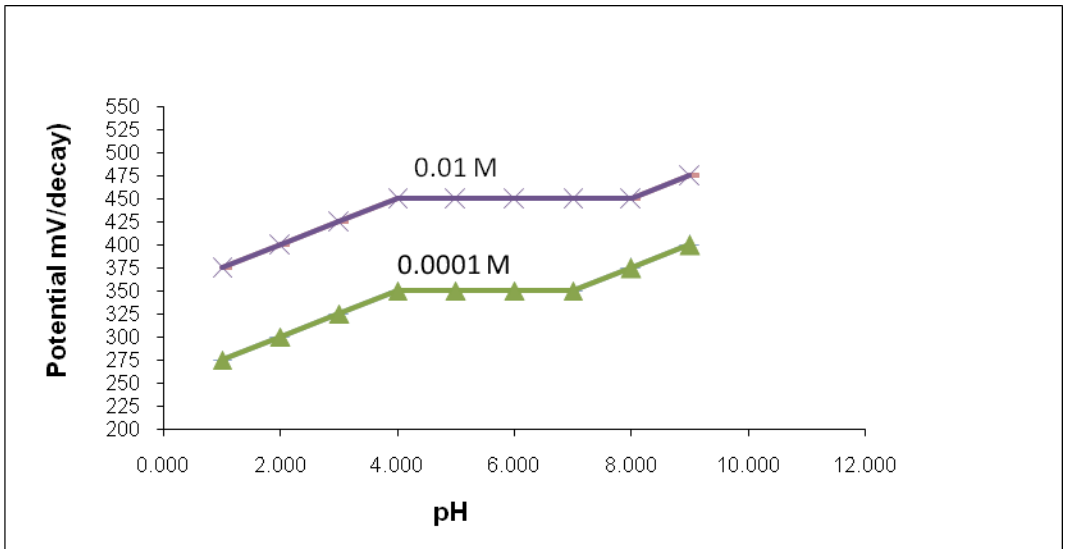

Figure 3. Effect of pH on potential response of electrode no. 1

3.3 Selectivity

The characteristics performances of the sensors influences by different organic and inorganic ions on the response were investigated. The selectivity coefficients K pot A,B were measured
using IUPAC guidelines using the separate solution method (SSM) or mixed solution method (IUPAC, 1994; 2000) in phosphate buffer solution of pH 7.0. The selectivity coefficient K pot
A,B measured by separate solution method using fixed concentration of the drug and interfering species was calculated from the following equation:
log K pot A,B = EB-EA/S + (1- ZA/ZB) log aA
where EA and EB are the potential reading observed after 1 min of inserting the sensor to the same concentration of Pr and interfering species (1x10-3 each) alternatively. The symbol aA
are the activity of Pr ; ZA and ZB are the charges of Pr and interfering species and S is slope of calibration graph (mV/concentration). The selectivity coefficient by mixed solution method was defined as the activity ratio of primary and interfering ions that give the same potential change under identical conditions as given in equation 3.
K pot A,B = (a`A- aA)/aB (2)
Where a'A known activity of primary ion solution added into a reference solution that contains a fixed activity (aA) of primary ions, and the corresponding potential change is recorded.

Table 3. Potentiometric selectivity coefficients of some interfering ions, using Promethazine electrode no. 1

Interfering species	Pot KPr B PR –PT
Magnesium stearate	4.7x 10-3
Acetate	1.0 x 10-3
Citrate	4.7x 10-3
Glucose .	7x 10-3
Lactose monohydrate	4.7x 10-3
Starch	4.7x 10-3
Microcrystalline cellulose	4.7x 10-3

Next, a solution of an interfering ion (aB) is added to the reference solution until the same potential change is recorded. The change in potential produced at the constant background of the primary ion must be the same in both cases. The results are given in Table 3. The results indicting a reasonable level of selectivity of Promethazine in presence of many related substances.

3.4 Recovery

The recoveries (R) of Pr were calculated by comparing the potential of the found concentration to direct added standard in phosphate buffer pH 7.0. The assay of recovery, at each oncentration, was computed using the following equation:

$$\text{Recovery\%} = \frac{[\text{Pr}]\ \text{found}\ \times 100}{[\text{Pr}]\ \text{Added}}$$

The average recovery of the direct determinations of 300 µg/ml of Pr was 97.5 and 98.0% for electrode no. 1 and 6 respectively.

Table 4. Day to day reproducibility of Promethazine using the membrane electrode

Parameter	Promethazine (300µg/ml)* Pr-TPB	within- day Pr-PT
R, %	97.5	98.0
R.S.D, %	1.7	1.5
Slope	50.5 x 1.0	46.8 x 1.0
Response time (s)	8	12

* Average of 5 measurements ± RSD.
*R %, Recovery percentage
-RSD relative standard deviation: Expressed as % RSD = (SD/mean) × 100

3.5 Precision and Accuracy of the method

The intra-day, inter-day accuracy and precision of the electrode assembly was investigated by the analysis of Pr for 300µg/ml solution in five replicate over a period of one day and three days. Calibration curves were prepared and analyzed daily and linear models were used to determine concentrations in the quality control samples. Percent accuracy was determined (using the data from the precision assessment) as the closeness of found concentration to the added standards.

Precision was reported as % RSD. The results obtained (Table 4) are within the acceptance range of less than 2.0 % (precision) and more than 97.0 % for the accuracy.

3.6 Ruggedness

The ruggedness of the potentiometric method was evaluated by carrying out the analysis using two different analyst (operator) and different instruments on different days. The RSD of less than 2.0% were observed for repetitive measurements in on-day and in three different days time periods using two different instruments and operators. The results indicate that the method is capable of producing results with high precision.

Robustness

The robustness of the method was evaluated by the optimized the membrane components and other external factors. Preliminary study of the results under various conditions suggested that the method is fairly robust, but the pH of the measuring solution should be in the range of 3.0 - 7.0. The optimum pH 7.0 was used using phosphate buffer solution.

3.7 Determination of Promethazine

The practical applicability applicability of the Pr membrane electrode was investigated by use of the electrode no. 1 for the determination of drug in various samples. The direct determinations of Promethazine were carried out using the proposed membrane electrode no. 1. The analysis of the

concentration over the calibration graph of 2.0 - 3000.0 µg/ml Promethazine solutions (in five replicate) by direct potentiometry gave an average recovery of 98.85 and 99.0% with a relative

standard deviation of 1.78% and 1.67% were fund (Table 5).

Table 5. Direct determinations of Promethazine using PVC membrane sensors

Added (µg/ml)	Recovery, % * ± RSD PR-PT
2.0	98.0 ± 2.1
5.0	98.3 ± 2.1
10.0	98.7 ± 2.0
50.0	98.5 ± 1.9

100.0	98.6 ± 1.8
150.0	98.5 ± 1.7
600.0	99.5 ± 1.6
900.0	99.6 ± 1.4
1000.0	100.1 ± 1.5
3000.0	100.0 ± 1.4

* Average of 5 measurements % RSD.
*R %, recovery percentage
-RSD relative standard deviation: expressed as % RSD =
(SD/mean) × 100

Table 6. Determination of Promethazine in some pharmaceutical preparations using the membrane sensors

Preparation method*	Promethazine Method	Proposed Method	% RSD
Reconstituted Powder	5mg	97.0	2.3
	25 mg	98.5	1.9
	10 mg	97.5	1.2

The electrode no. 1 was also used for the determination of drug in different dosage samples and the recovery of an accurate amount of pure drug in a reconstituted powder samples (Laboratory made sample) was compared with the standard samples. The recovery obtained for five measurements of solution produced from the sample was found to be 97.0% and 99.0% with a relative standard deviation of 2.5%. On the other hand, the determination of Promethazine in its formulations shows an average recovery of 98.0 to 98.5% with relative standard deviation of 2.05 (Table 5). Results obtained for the analysis of Promethazine in its formulation by direct measurements using the proposed sensors are given in Table 6. The results indicate that proposed method can be used to determine the drug in pure form and in pharmaceutical formulations.

IV. CONCLUSION

The two ion pair Pr-TP and Pr-TPB was prepared and used for the selective determination of Promethazine in different samples. The electrode based on Pr-TP with 2% of ion-pair complex was found best in terms of linear concentration range (3.2 x 10-7 – 1.0 x 10-2M) with lower detection limit of 1.5 x 10-7 M. the electrode has a fast response time of about 8 seconds and could be used in a pH range of 3.0 – 7.0 without and divergence in response characters.

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