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ION SELECTIVE ELECTRODES FOR POTENTIOMETRIC DETERMINATION OF CYCLIZINE IN ITS PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

The two ion-pair complex of Cyclizine (Cy) with sodium tetraphenyl borate (TPB) and Phosphotungstic acid (PT) was prepared and used for the construction of Cy-selective electrode. The electrode based on the Cy-PT ion-pair complex has a lower detection limit of 1.5×10^{-7} M in a linear concentration range of $3.5 \times 10^{-7} - 1.0 \times 10^{-2}$ M with a slope of calibration curve of 50.5 mV/decay. The selectivity coefficient was calculated with separate solution method dictates the high selectivity of the electrode over other tested ions.

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INTRODUCTION

Cyclizine or 1-(diphenylmethyl)-4-methylpiperazine (Fig.1), is an antihistamine drug. It is among the list of most essential medicines characterized by world health organizations (WHO). It is used to treat nausea, vomiting and dizziness associated with motion sickness (Campbell, 1980; Vasile, 2013; Clubley, 1979). Several analytical methods such as spectrophotometry (Devarajan, 2006; Walash *et al*., 2011; Sankar, 2007; Dumasia, 2002), spectrofluorimetry (Ulu, 2012), voltammetry (Kauffmann, 1992), high performance thin layer chromatographic (HPTLC) (Jonczyk, 1999; Kuntzman, 1967), high performance liquid chromatography (HPLC) (Ravisankar, 2013; Somasekhar, 2011; Gandhimathi, 2005), and HPLC- mass spectrometry (MS) (Qi, 2003) have been reported for the determination of the drug. However, these methods are either time consuming, required large infrastructure back up and involved sample manipulations. The present work shows the development of selective, inexpensive diagnostic tool for the determination of the Cyclizine. To the best of our knowledge, only one study of polymeric membrane electrodes selective to Cyclizine was reported (Ganjali, 2013).

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The electrode is based on the ion-exchange mechanism of ion-pair complex of Cyclizine and sodium tetraphenyl borate as electroactive material. The electrode has narrow concentration range, high detection limit and limited selectivity of the droug over various ions. The present study has wide concentration range, long life high selectivity and sensitivity towards drug over various organic and inorganic ions.

MATERIALS AND METHODS

Apparatus

All potentiometric measurements were made at 25 ± 1 °C unless otherwise stated using pH/mV meter using Cyclizine membrane electrode in conjunction with saturated silver reference electrode containing 10% (w/v) potassium nitrate in the outer compartment.

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 Aldrich Chemical

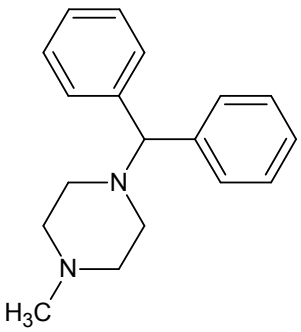

Figure 1. Structure of Cyclizine

Company and Cyclizine hydrochloride was obtained from Sigma Chemical Company, Switzerland. Phosphotungstic acid (PT), was obtained from BDH, Chemical Ltd. The stock solution of 1×10^{-2} M drug was prepared by dissolving the appropriate amount of drug in 100 ml of water. The standard Cyclizine solution were prepared 1×10^{-2} - 1×10^{-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 NaH_2PO_4 and Na_2HPO_4.

Preparation of Cyclizine (Cy) selective membrane electrode

The ion-pairs of Cy-PT was prepared upon addition of 15 ml of 1×10^{-2} M of Cyclizine solution to 15 ml of phosphotungstic acid . The resulting mixtures were stirred for 5 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 24h at 25°C, then ground to a fine powder in mortar, forming ion-pairs complex. The elemental analysis confirmed the formation of 2:1 complex of Cy: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 (Hassan, 1994; Carggs, 1974). 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 Cy 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	Cyclizine Selective Membrane	Test solution	1 M KCl, Ag / AgCl

The Cyclizine PVC membrane electrodes were immersed in conjunction with the reference electrode in a 50 ml beaker containing 9.0 ml of phosphate buffer of pH 7.0.

Then 1.0 ml aliquot of Cy solution was added with continuous stirring, to give final Cyclizine 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 $-log a_{Cyclizine}$. The resulting graphs were used for subsequent determination of unknown Cyclizine concentration or/ and the regression equations of the linear part are used to calculate the unknown solution.

Determination of Cyclizine in the pharmaceutical dosage form

Ten tablets of cyclivert (Laser Pharmaceuticals, USA) 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. A 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 Cy-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 Cy (Ma, 1982).

A Laboratory made powder containing fixed amount of Cy 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 Cy-selective electrode.

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 on 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 Cy. Plasticized polymeric membranes were prepared by using membrane cocktails with compositions 2% of the corresponding ion-associate (Cy-TBP or Cy- PT), 35. 54% of poly vinyl chloride (PVC) and 63% of the specific plasticizer (DBP, DOP and 0-NPOE).

Effect of plasticizer type on the characteristic performance of the sensors

Cyclizine ion-selective membrane electrodes with different compositions were prepared in order to get the optimum composition of membrane components. The two ion-pairs Cy-TPB and Cy-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. There for 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 Cy – 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. Table – 1.

On comparing the data presented in table 1 and 2 we found that the electrode based on ion-pair Cy-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 (ε = 5.1) provides the best possible environment for the response of the electrode due to its low polarity as compared to other plasticizers DBP (ε = 6.4) and o-NPOE (ε = 23.6). Thus the electrode no. 1 based on Cy-PT ion-pair as electro active material and DOP as plasticizer was selected as the most

Electrode No.	Ion-pairs Cy-PT (%)	Plasticizers (%)	PVC (%)	Working concentration range (M)	Slope (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 Cy – TBP ionic pair

Electrode No.	Ion-pairs Cy-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 Cy-PVC membrane electrode no.1 and 6

Parameter	Cy-PT	Cy-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 × 10^{-7} (M)	1.2 × 10^{-6} (M)
Lower limit of detection, (LOD), (M)	1.5 × 10^{-7}	8.0 × 10^{-6}
Response time for1×10^{-3} M solution, (s)	8	12
Working pH range	3.0 - 7.0	3.0 -7.0

Optimization of components of membrane of Cy – PT ionic pair The electrodes (no.6, 7, 8, 9 and 10) based on ion pair Cy-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.

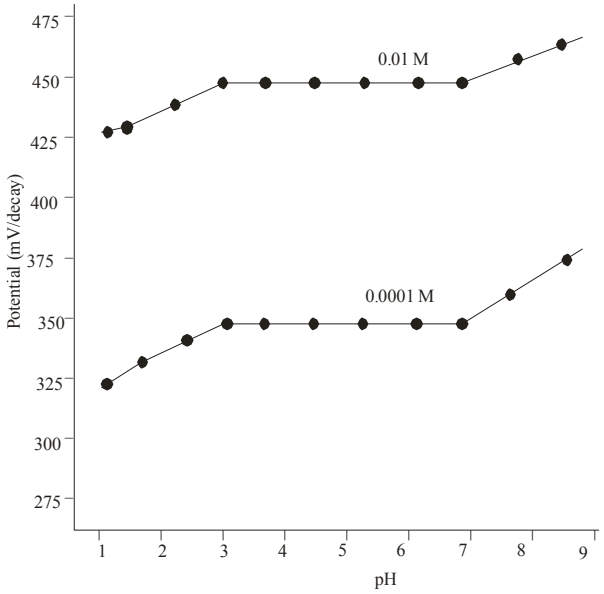

Figure 2. Potential response of electrode no. 1 based on Cy-PT ion pair

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.

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 0.001 M solutions of cyclizine. 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 Cyclizine solutions each having a 10-fold change in concentration. It was observed that the electrode no. 1 baed on Cy-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.

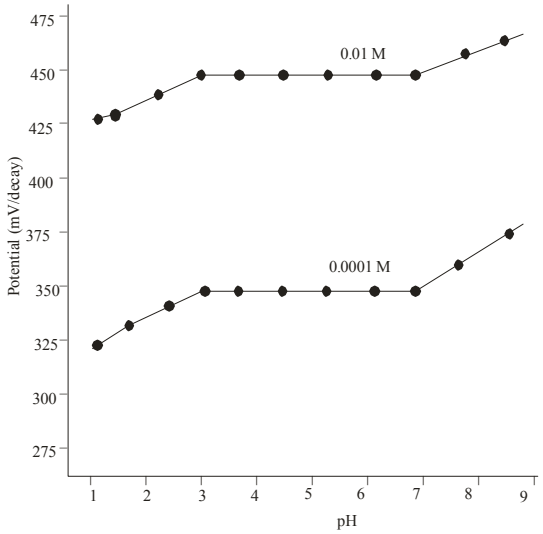

Figure 3. Effect of pH on potential response of electrode no. 1

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:

$$\log K^{pot}_{A,B} = E_B\text{-}E_A/S + (1- Z_A/Z_B) \log a_A \quad (1)$$

where E_A and E_B are the potential reading observed after 1 min of inserting the sensor to the same concentration of Cy and interfering species (1×10^{-3} each) alternatively. The symbol a_A are the activity of Cy ; Z_A and Z_B are the charges of Cy 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.

$$K^{pot}_{A,B} = (a`_A - a_A)/a_B \quad (2)$$

Where a'_A known activity of primary ion solution added into a reference solution that contains a fixed activity (a_A) of primary ions, and the corresponding potential change (ΔE) is recorded.

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

Interfering species	$K^{Pot}_{Cy,B}$ CY –PT
Na^+	4.5×10^{-3}
K^+	4.9×10^{-3}
Ca^{2+}	3.1×10^{-3}
Fe^{2+}	5.2×10^{-3}
Magnesium stearate	4.7×10^{-3}
Acetate	1.0×10^{-3}
Citrate	4.7×10^{-3}
Glucose	4.7×10^{-3}
Lactose monohydrate	4.7×10^{-3}
Starch	4.7×10^{-3}
Microcrystalline cellulose	4.7×10^{-3}

Next, a solution of an interfering ion (a_B) is added to the reference solution until the same potential change (ΔE) 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 Cyclizine in presence of many related substances.

Recovery

The recoveries (R) of Cy 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 concentration, was computed using the following equation:

$$\text{Recovery}(\%) = \frac{[Cy]_{Found}}{[Cy]_{Added}} \times 100$$

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

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

Parameter	Cyclizine (300µg/ml)*		within- day
	Cy-TPB	Tz-PT	
R, %	97.5	98.0	
R.S.D, %	1.7	1.5	
Slope	50.5 ± 1.0	46.8 ± 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

Precision and Accuracy of the method

The intra-day, inter-day accuracy and precision of the electrode assembly was investigated by the analysis of Cy for 300µg/mlsolution 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.

Ruggedness

The ruggedness of the potentiometric method was evaluated (26) 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.

Determination of Cyclizine

The practical applicability applicability of the Cy membrane electrode was investigated by use of the electrode no. 1 for the determination of drug in various samples. The direct determinations of Cyclizine 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 Cyclizine 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 Cyclizine using PVC membrane sensors

Added (µg/ml)	Recovery, % * ± RSD CY-PT
2.0	98.0 ± 2.1
5.0	98.2 ± 2.1
10.0	98.5 ± 2.0
50.0	98.5 ± 1.9
100.0	98.5 ± 1.8
150.0	98.5 ± 1.7
600.0	99.5 ± 1.6
900.0	99.6 ± 1.4
1000.0	100.0 ±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 Cyclizine in some pharmaceutical preparations using the membrane sensors

Preparation	Cyclizine (nominal, value)	Proposed method* (R,%)	(RSD,%)	Spectrophotometric method *(Devarajan, 2006) R, % (RSD, %)	
Reconstituted powder cyclivert	5mg	97.0	2.3	97.0	2.0
	25mg	98.5	1.9	98.0	1.9
	10 mg	97.5	2.0	98.0	1.9

*Average of five determinations.
*R %, Recovery percentage: added concentration
-RSD relative standard deviation: Expressed as % RSD = (SD/mean) × 100

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 Cy 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 Cyclizine in its formulation by direct measurements using the proposed sensors with those of reported spectrophotometric method (Devarajan, 2006) 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.

Conclusion

The two ion pair Cy-TP and Cy-TPB was prepared and used for the selective determination of Cy in different samples. The electrode based on Cy-TP with 2% of ion-pair complex was found best in terms of linear concentration range (3.2×10^{-7} – 1.0×10^{-2}M) with lower detection limit of 1.5×10^{-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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