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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 x 10^{-7} M in a linear concentration range of 3.5 x 10^{-7} – 1.0 x 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.

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 [1-3].

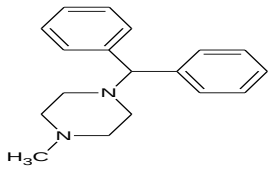

Figure 1. Structure of Cyclizine

Several analytical methods such as spectrophotometry [4-7], spectrofluorimetry [8], voltammetry [9], high performance thin layer chromatographic (HPTLC)[10, 11], high performance liquid chromatography (HPLC)[12-14], and HPLC- mass spectrometry (MS)[15] 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 [16]. 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

2.1. Apparatus: All potentiometric measurements were made at 25 ± 1 ^{o}C unless otherwise stated using pH/mV meter using Cyclizine membrane electrode in conjunction with saturated silver electrode (SSE) 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 Aldrich Chemical 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.

2.3. 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 and washed with double water. The precipitate so obtained was dried for 24h at 25°C and ground to powder form in mortar, forming ion-pairs complex. The ion-pair complex was thoroughly mixed with poly (vinyl chloride) powder and plasticizers (DBP or DOP or o-NPOE). The mixture dissolved in 5 mL THF solution and transferred into a glass dishes (5 cm diameter). The solvent THF was allowed to evaporate overnight to obtain the membrane. A master membrane with a thickness of 0.10 mm was obtained. Membrane of about 5.00 mm diameter was removed from the master membrane and fixed at the one end of the glass tube [18]. To make the electrical contract a saturated reference (SSE) was inserted in the tube and another SSE was used as an external reference electrode. A saturated solution of KCl was used to maintain the ionic strength of solutions. The electrode was kept in 0.01 M solution of Cy when not in use to avoid the damage of the membrane**.**

The potential measurements were carried out with the following cell assembly:

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.

2.4. **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. A Mixture containing fixed amount of Cy powdered (5 mg) 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.

3. RESULTS AND DISCUSSION

The ion-selective electrode offer a high selectivity and sensitivity in the analysis of target species in the solution because work on the activity of the ion instead of concentration. The response mechanism of the ion-selective membrane electrode is highly dependent on the composition and membrane components. In the present study an ion-pair complex of sodium tetraphenyl borate (TBP) and phosphotungstic acid (PT) with Cy were used as electoactive material for the development Cy selective PVC based membrane electrode. Plasticized polymeric membranes were prepared by using membrane components with the compositions of 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).

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

In order to get the most optimized composition the membranes with the different compositions were prepared and their potential responses were investigated. The two ion-pairs Cy-TPB and Cy-PT gives the linear response and wide concentration range and low detection limit. It is well known fact that the response of PVC based ion-selective electrode considerably depends on the presence of plasticizer which acts as a fluidizer allowing homogenous dissolution of membrane components and diffusion mobility of the ion-pair inside the membrane. There for the effect of various plasticizers (i.e. DOP, DBP and o-NPOE) on the potential responses of the electrode were investigated. The response characters of membranes of various plasticizers are summarized in table 1 and table 2. The 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 3.2×10^{-7} – 1.0×10^{-2} (M) with a lower detection limit of 1.5×10^{-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. Optimization of components of membrane of Cy – PT ionic pair

Electrode No.	**Ion-pairs Cy-PT (%)**	**Plasticizers (%)**	**PVC (%)**	**Working concentration range (M)**	**Slope (mV/decay)**
1	2	63 (DOP)	35	$3.2 \times 10^{-7} – 1.0 \times 10^{-2}$	50.5 ± 1.0
2	1.2	65 (DOP)	33.8	$8.6 \times 10^{-7} – 1.0 \times 10^{-2}$	43.3 ± 1.0
3	2.5	60.5 (DOP)	37	$4.8 \times 10^{--7} – 1.0 \times 10^{-2}$	51.4 ± 1.0
4	2	63 (DBP)	35	$8.5 \times 10^{-6} – 1.0 \times 10^{-2}$	40.5 ± 1.0
5	2	63 (o-NPOE)	35	$1.0 \times 10^{-5} – 1.0 \times 10^{-2}$	38.6 ± 1.0

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 $1.0 \times 10^{-6} – 1.0 \times 10^{-2}$ M with DOP as plasticizer and in the range of $1.3 \times 10^{-5} – 1.0 \times 10^{-2}$ M for DBP and $3.6 \times 10^{-5} – 1.0 \times 10^{-2}$ M for o-NPOE as the plasticizer. 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). Due all the response characters and potential response the electrode no. 1 based on Cy-PT ion-pair complex as electroactive material and DOP as plasticizer was considered as most optimized electrode and used for further studies. 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.

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	$1. \times 10^{-6} – 1.0 \times 10^{-2}$	46.8 ± 1.0
7	1.5	65 (DOP)	33.5	$8.2 \times 10^{-6} – 1.0 \times 10^{-2}$	45.3 ± 1.0
8	2.5	60.5 (DOP)	37	$4.5 \times 10^{--6} – 1.0 \times 10^{-2}$	44.6 ± 1.0
9	2	63 (DBP)	35	$1.3 \times 10^{-5} – 1.0 \times 10^{-2}$	42.5 ± 1.0
10	2	63 (O-NPOE)	35	$3.6 \times 10^{-5} – 1.0 \times 10^{-2}$	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

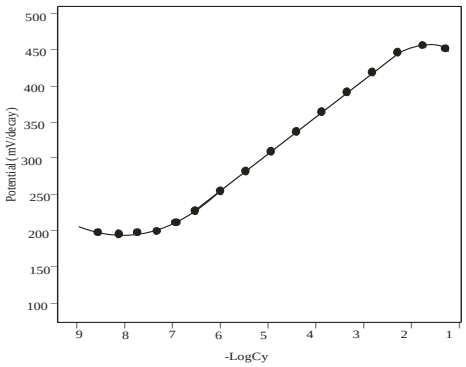

Figure 2. Potential response of electrode no. 1 based on Cy-PT ion pair

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 0.001 M solutions of cyclizine. It was observed that the potential response of electrode no. 1 reached to a stable value in a pH range of 3.0 – 7.0. Thus the hydrogen ion in this pH range does not cause any interference during the complexation kinetics of ionophore and target species. However a significant potential drift 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).

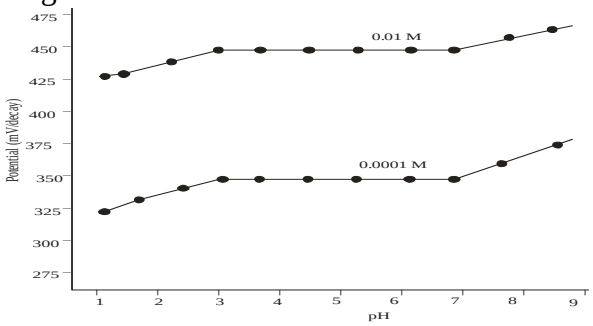

Figure 3. Effect of pH on potential response of electrode no. 1.

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. The reproducibility of the electrode no. 1 is about ± 0.5 mV/decay for the same solution. The life time of the electrode is about 1 month, which was calculated in terms of lower detection limit and slope of calibration curve. However this time period significant change in the potential response was observed.

3.3. Selectivity: The ion-pair complex used as electroactive material may be responsive to a variety of ions in the solution. So the selectivity of the electrode was calculated in terms of selectivity coefficient ($K_{A,B}^{pot}$). The selectivity coefficients $K_{A,B}^{pot}$ (table 3) were measured as per IUPAC recommendations by separate solution method (SSM) [20, 21] in H_3PO_4 + NaH_2PO_4 buffer solution of pH 7.0. The selectivity coefficient $K_{A,B}^{pot}$ measured by separate solution method

using fixed concentration of the drug and interfering species was calculated from the following equation:

$$\log K_{A,B}^{pot} = E_B - E_A/S + [1 - Z_A/Z_B] \log a_A \text{ ----------(i)}$$

Where E_A and E_B are the potential observed after 1 min of inserting the electrode 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 ions and *S* is slope of calibration graph (mV/concentration) [19].

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

Interfering species	$K_{Cy,B}^{Pot}$ 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}

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

3.4. Recovery: The recoveries (R) of Cy were calculated by comparing the potential of the obtained concentration of solution to the direct added standard solution. The percentage of recovery was calculated by equation (ii).

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

The average recovery of the direct determinations of 85 µg/ml of Cy was 97.5 and 98.0% for electrode no. 1 and 6 respectively (table 4).

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 Cy for 85µg/ml solution in five replicate over a period of one day and two days.

Calibration curves were prepared and analyzed; a linear model was used to determine concentrations in the quality control samples. Percent accuracy was determined (using the data from the precision assessment) the obtained values are found to be very close to the values of standard solution.

3.6. Determination of Cyclizine: The practical 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 (□□g/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 *[4] 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 synthetic samples was compared with the standard samples. The recovery obtained for five measurements of solution 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 electrode with those of reported spectrophotometric method [4] 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.

4. CONCLUSION: The two ion pair Cy-TP and Cy-TPB complexes were 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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