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PVC Membrane Sensor for Potentiometric Determination of Dicyclomine in Pharmaceutical Formulation

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A simple, rapid and low-cost potentiometric method for determination of dicyclomine, anticholinergic compound, in pharmaceutical formulations is introduced. Dicyclomine-tetraphenyl borate ion-pair compound was first synthesized and then applied as a sensing element in preparation of the PVC membrane sensor. The best PVC membrane sensor response was obtained by a membrane composition of 30% PVC, 63% DBP, and 7% ion-pair. The detection limit of the sensor was obtained 1×10^{-5} M. The proposed sensor has a fast response time of less than 15 s. The proposed method was successfully applied in determination of dicyclomine in some pharmaceutical formulations.

Keywords: Dicyclomine, Ion-Pair, Potentiometric Sensor, PVC membrane

1. INTRODUCTION

Dicyclomine, also known as Dicycloverine (2-(diethylamino) ethylbicyclo-hexyl-1-carboxylate hydrochloride, DCM) (Figure 1), is an anticholinergic chemical compound and one of the most important antispasmodic drugs. Dicyclomine is used to treat intestinal hypermotility and the symptoms of Irritable Bowel Syndrome (IBS) which also known as spastic colon. It relieves muscle spasms and cramping in the gastrointestinal tract by blocking the activity of acetylcholine on cholinergic receptors on the surface of muscle cells. It is a smooth muscle relaxant [1,2]. It decreases spasms of the gastrointestinal tract, biliary tract, ureter, and uterus without producing characteristic atropinic effects on the salivary, sweat, or gastrointestinal glands, the eye, or the cardiovascular system except in the large doses [3].

The reported methods for determination of the Dicyclomine in pharmaceutical preparations, including microcrystallography [4], nuclear magnetic resonance techniques [5], gas-liquid chromatography [6,7], spectrophotometry [8,9] and thin-layer chromatography (TLC) [10].

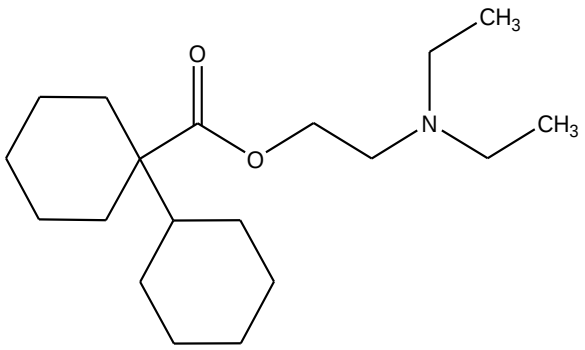

Figure 1. Chemical structure of Dicyclomine

Potentiometric using indicator electrodes have advantages of rapid and ease of preparation and procedures, fast response time, reasonable selectivity, wide linear dynamic range, and low cost. These characteristics have certainly led to the preparation of many sensors for several ionic species, and the list of available electrodes has grown largely over the past years [11-20]. PVC membrane electrodes are one of the subdivisions of potentiometric sensors which are widely used and have different application in analysis of ionic species [21-29].

In this work, the electrode works based on ion-pair which was made from the interaction between Dicyclomine and sodium tetraphenyl borate and they respond according to the ion-exchange mechanism. PVC membrane electrode was made after series of experiments.

2. EXPERIMENTAL SECTION

2.1. Apparatus

The glass cell where the DCM indicator electrode (PVC membrane) was placed; consisted of two Ag/AgCl double junction reference electrodes (Azar-Elelectrode Co., Iran) as internal and external reference electrodes. Both electrodes were connected to a Corning ion analyzer with a 250 pH/mV meter with ±0.1 mV precision.

2.2. Materials and Reagents

Chemicals (of analytical reagent grade) were: high-molecular weight polyvinylchloride (PVC) (Fluka Co., USA), sodium tetraphenyl borate (NaTPB), dibutyl phthalate (DBP), nitrobenzene (NB), benzyl acetate (BA) and tetrahydrofuran (THF) (Merck Co., Germany). All materials were of the

highest available purity without further modification. Dicyclomine hydrochloride and its pharmaceutical formulations were obtained from a local pharmaceutical manufacturer (Tehran, Iran) as gift samples.

2.3. Standard DCM solution preparation

The solubility of DCM-HCl is as follow: soluble 1 in 20 of water, 1 in 5 of ethanol, and 1 in 2 of chloroform, very slightly soluble in ether. A stock solution of 0.01 M DCM-HCl solution was prepared by dissolving the solid of DCM-HCl in distilled water. The working standard solutions (1×10^{-7} to 1×10^{-2} M) were then prepared by appropriately dilution of the stock solution with distilled water.

2.4. Preparation of the ion-pair compound

Sensing element used in the proposed sensor was an ion-pair compound made from the interaction of Dicyclomine hydrochloride and sodium tetraphenyl borate. It was prepared by mixing about 20 mL of 0.01 M acidic solution of DCM with 20 mL tetraphenyl borate solution. The resulting precipitate was then filtered, washed with distilled water and dried in room temperature [12,14].

2.5. Preparation of PVC membrane Electrodes

General procedure to prepare PVC membrane was as follow: different amounts of ion-pair along with appropriate amounts of PVC, plasticizer and additive were dissolved in tetrahydrofuran (THF), and the solution was mixed well into a glass dish of 2 cm diameter. Then, THF was evaporated slowly until an oily concentrated mixture was obtained. A plastic tube (about 3 mm o.d.) was dipped into the mixture for about 10 s so a transparent membrane of about 0.3 mm in thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for about 5 h. Afterwards, the tube was filled with an internal filling solution (1.0×10^{-3} M of DCM-HCl solution). The electrode was finally conditioned for about 20 h by soaking in the same solution [10-12].

2.6. The emf Measurements

Following cell assembly were used for emf (electromotive force) measurements:

Ag-AgCl || internal solution, 1×10^{-3} M DCM-HCl solution | PVC membrane | sample solution || Ag-AgCl, KC1 (satd.)

These measurements were done using calibration of the PVC membrane electrodes with several standard solutions of DCM-HCl.

3. RESULTS AND DISCUSSION

3.1. PVC Membrane Composition Selection

The composition of the membrane affects on the sensor characterization and response [19-29]. Membrane composition effect on the potential responses of the electrode was tested. The operating characteristics of PVC membrane sensor can be significantly modified by changing the relative amount of the membrane components of the electrode. The main components of a membrane are PVC matrix, plasticizer and the ion-pair as a sensing material. Each membrane component plays a special role in the sensor response. Previous studies shows that the membrane prepared with a plasticizer/PVC ratio about 2.2 can show the best performance [30-35]. According to the previous studies, the optimum amount of PVC was selected 30 mg.

Table 1. Optimization of the PVC membrane ingredients

No.	Composition (%)			Slope (mV per decade)	LR (M)	DL (M)	R^2	Response time
	PVC	Plasticizer	DCM-TPB					
1	30	DBP, 67	3	20.2±1.1	1.0×10^{-4}-5.0×10^{-3}	5.0×10^{-5}	0.933	1.5 min
2	30	DBP, 65	5	42.8±0.8	5.0×10^{-5}-5.0×10^{-2}	3.0×10^{-5}	0.965	42 s
3	30	DBP, 63	7	58.5±0.5	1.0×10^{-5}-1.0×10^{-2}	1.0×10^{-5}	0.997	15 s
4	30	DBP, 61	9	54.9±0.7	1.0×10^{-5}-1.0×10^{-2}	1.0×10^{-5}	0.988	34 s
5	30	NB, 63	7	13.2±1.1	1.0×10^{-4}-1.0×10^{-3}	1.0×10^{-4}	0.942	2 min
6	30	BA, 63	7	22.3±0.6	1.0×10^{-4}-1.0×10^{-2}	1.0×10^{-4}	0.971	1 min
7	30	DOP, 63	7	51.3±0.5	5.0×10^{-5}-1.0×10^{-2}	5.0×10^{-5}	0.975	38 s
8	30	NPOE, 63	7	19.3±0.6	1.0×10^{-4}-5.0×10^{-2}	1.0×10^{-4}	0.966	1.8 min
9	30	DBP, 70	0	4.0±1.1	5.0×10^{-4}-5.0×10^{-3}	-	-	3 min

The most important ingredient of the membrane which has the main and most effect on the selectivity of the sensor is sensing element. In this work, an ion-pair of DCM-TPB was synthesized and then applied for sensing element. 3, 5, 7 and 9 mg of DCM-TPB was tested. According to the results, 7 mg is a suitable amount.

Plasticizer which mainly acts as a membrane solvent causes homogeneous dissolution and diffusional mobility of the ion-pair complex inside the membrane [26-31]. The plasticizer is a water-immiscible liquid with low vapor-pressure, compatible with PVC, no functional groups which can undergo protonation reactions. The selectivity of such electrode can be drastically influenced by the choice of the membrane solvent [24-34]. Nature of the plasticizer has also important effect on analytical responses of the membrane. Five plasticizers with different polarity (dielectric constant) were tested, dibutyl phthalate (DBP with DC of 6.4), dioctyl phthalate (DOP with DC of 5.1), nitrobenzene (NB with DC of 35.7), *o*-Nitrophenyl octyl ether (NPOE with DC of 24) and benzylacetate (BA with DC of about 5.7), as listed in Table 1. The electrode responses showed that

membrane had DBP better respond. DBP among the used plasticizers provided an effective linear range and a lower detection limit due to the better extraction of DCM with Log $P_{(octanol/water)}$ about 3.98 (for hydrochloride form), which is a almost hydrophobic organic cation, from aqueous phase into the organic layer of the membrane. As it can be seen from Table 1, absence of ion-pair in the membrane causes a very poor response (membrane no. 9), which confirm significance of the ion-pair. The electrodes behavior show that the best Nernstian slope is 58.5±0.5 mV per decade. Finally, membrane no. 3 with the composition of 30% PVC, 7% ion-pair, and 63% DBP was the optimum one for the sensor design.

3.2. Calibration Graph and Statistical Data

The measuring range of a potentiometric sensor is the linear part of the calibration graph as shown in Figure 2.

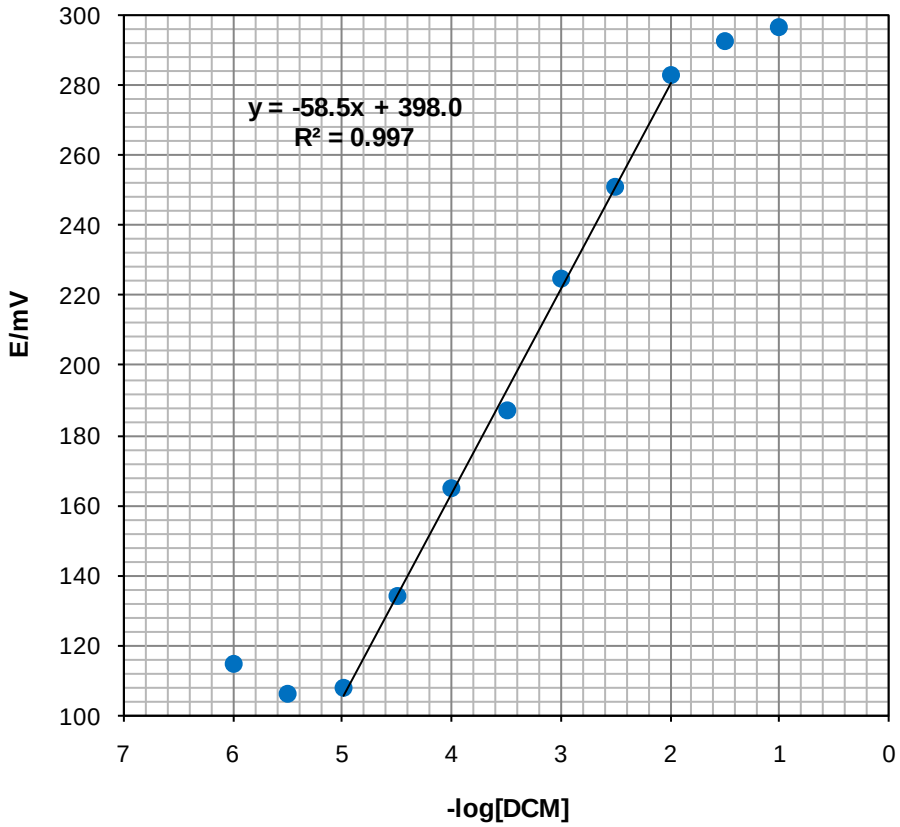

Figure 2. Calibration curve of PVC membrane electrode, the results are based on 5 replicate measurements.

One of the advantages of potentiometric sensors are their wide linear range. For many electrodes the measuring range can extend from 1 molar to 10^{-6} or even 10^{-7} molar concentrations [19-24]. However, it should be noted that more closely spaced calibration points are required for

more precise determinations. Calibration graph slope for PVC membrane electrode is 58.5 mV per decade of the DCM-HCl concentration and a standard deviation of ±0.5 mV after five replicate measurements. A linear response towards the DCM concentration was from 1.0×10^{-5}-1.0×10^{-2} M. In this work, detection limit of the PVC membrane sensor was 1.0×10^{-5} M which was calculated by extrapolating the two segments of the calibration curves.

3.3. pH Effect on the Sensor

To examine the effect of pH on the electrode responses, the potential was measured at specific concentration of the Dicyclomine solution (1.0×10^{-4} M) from the pH value of 1.0 up to 10.0 (concentrated NaOH or HCl solutions were employed for the pH adjustment) by PVC membrane electrode. The results showed that the potential remained constant despite the pH change in the range of 3.0 to 6.5 which indicates the applicability of this electrode in the specified pH range.

Relatively noteworthy fluctuations in the potential *vs.* pH behavior took place below and above the formerly stated pH limits. In detail, the fluctuations above the pH value of 6.5 might be justified by removing the positive charge on the drug molecule. Fluctuations below the pH value of 3 were caused by removal of the membrane ingredients or analyte in the solution.

3.4. Life-time Study

Electrode lifetime was estimated by the calibration curve, periodical test of a standard solution and calculation of its response slope.

Table 3. Lifetime of PVC membrane electrode

Week	Slope (mV per decade)	DL (M)
First	58.5	1.0×10^{-5}
Second	58.2	1.5×10^{-5}
Third	58.0	3.5×10^{-5}
Fourth	57.1	5.0×10^{-5}
Fifth	56.7	8.0×10^{-5}
Sixth	55.3	1.0×10^{-4}
Seventh	51.3	5.0×10^{-4}
Eighth	47.4	7.0×10^{-4}
Ninth	39.2	1.0×10^{-3}
Tenth	30.3	3.0×10^{-3}

For this estimation, three electrodes were employed 1 hour per day for 10 weeks. After 6

weeks utilization of PVC membrane electrode, two changes were observed: a slight gradual decrease in the slope and an increase in the detection limit. In PVC membrane electrodes after several time of usage, the membrane ingredients leak from the organic layer and affect the membrane response.

3.5. Response Time

Dynamic response time is the required time for the electrode to achieve values within ±1 mV of the final equilibrium potential, after successive immersions in the sample solutions [25-37]. Its calculation involved the variation and the recording of the DCM concentration in a series of solutions from 1.0×10^{-5} to 1.0×10^{-2} M. Sensor was able to quickly reach its equilibrium response in the whole concentration range. This time for PVC membrane electrode was less than 15 s in the solutions.

3.6. Analytical Applications

Linearity, limit of detection, recovery test, selectivity, precision, accuracy, and ruggedness/robustness were the parameters used for the method validation.

3.6.1. Selectivity study

Selectivity, which describes an ion-selective electrode's specificity toward the target ion in the presence of interfering ions, is the most important characteristic of these devices. The potentiometric selectivity coefficients of the Dicyclomine sensor were evaluated by the matched potential method (MPM) [38-41].

Table 4. Selectivity coefficients of various interfering compounds for Dicyclomine sensor

Interfering ion	Log (K_{MPM})
Na^+	-3.3
K^+	-3.4
NH_4^+	-3.2
Ca^{2+}	-3.3
Mg^{2+}	-3.7
Cl^-	-3.7
NO_3^-	-3.6
Lactose	-4.1
Glucose	-4.0

The resulting values of the selectivity coefficients are shown in Table 4. The selectivity

coefficients show that the interferences have negligible effect on the performance of the electrode in an assay.

3.6.2. Recovery Test from Pharmaceutical formulations

The proposed sensor was evaluated by measuring the drug concentration in some pharmaceutical formulations (Dicyclomine amount of some tablets) (Table 5). The drug concentration was determined using calibration method and the proposed sensor with membrane no. 3. The results are in satisfactory agreement with the labeled amounts.

Table 5. Potentiometric determination of Dicyclomine in pharmaceutical formulations

Sample	Labeled amount	Found by electrode*
DICYCLOMINE HCL TAB Sample 1	10 mg/tab.	11.2±0.9
Sample 2		9.9±0.7
Sample 3		10.3±0.6
DICYCLOMINE HCL ELIXIR Sample 1	10 mg/5 ml	9.8±0.8
Sample 2		11.5±0.6
Sample 3		12.0±0.5
DICYCLOMINE HCL AMP Sample 1	20 mg/2 ml	21.8±0.7
Sample 2		18.9±0.5
Sample 3		22.1±0.8

* The results are based on five replicate measurements.

3.6.3. Precision and accuracy

For repeatability monitoring, 3 standard samples were measured. The RSD values by PVC membrane were not exceeding 3.7%.

3.6.4. Ruggedness/Robustness

For ruggedness of the methods a comparison was performed between the intra- and inter-day assay results for Dicyclomine obtained by two analysts. The RSD values for the intra- and inter-

day assays in the cited formulations performed in the same laboratory by the two analysts did not exceed 4.2%. On the other hand, the robustness was examined while the parameter values (pH of the solution and the laboratory temperature) changed slightly. Dicyclomine recovery percentages were good under most conditions, and not showing any significant change when the critical parameters were modified.

4. CONCLUSIONS

In the present work, potentiometric electrode was constructed for determination of Dicyclomine. Sensor respond based on ion-exchange mechanism. DCM-TPB was synthesized and used as sensing element in the PVC membrane. The best PVC membrane electrode performance was achieved by a membrane composition of 30% PVC, 63% DBP, and 7% DCM-TPB. The sensor showed advanced performance with a fast response time, a lower detection limit of 1.0×10^{-5} M for PVC membrane electrode and potential responses across the range of 1.0×10^{-5}-1.0×10^{-2} M. The sensor can determine Dicyclomine content of some pharmaceutical formulations.

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