# Reineckate based PVC Membrane Electrode for the Selective Determination of Diphenylpyraline in Aqueous Solutions

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**Summary-**The construction of PVC matrix type diphenylpyraline ion-selective electrode and its use for potentiometric determination of diphenylpyraline hydrochloride (DpCl) are described. The membrane of this electrode consists of diphenylpyralinium reineckate ion-exchanger (Dp-REN) dispersed in PVC matrix with dibutylphthalate (DBP) plasticizer. The electrode exhibits a linear response over the concentration range $3.16 \times 10^{-5}$-$5.0 \times 10^{-3}$ M DpCl. The working pH range of the electrode was 2.2-8.0 and its thermal coefficient was 0.0007 V/$^o$C. The electrode showed good selectivity to DpCl with respect to many inorganic cations, sugars, amino acids and urea. The results obtained for the determination of 0.96-47.68 mg of DpCl in the pure form or in pharmaceutical preparations with the proposed electrode show average recoveries of 99.5 to 100.9% and relative standard deviation of 0.42-0.85%. The data agree well with those obtained by the application of the standard official method.

## Introduction

The wide spread adulteration and/or dilution of commercially available pharmaceutical preparations demand reliable methods for drug determination that are preferably selective, rapid and can be undertaken with simple equipment. Diphenylpyraline (4-benzhydroxy-1-methyle-piperidine) hydrochloride (DpCl) is used clinically as an antihistaminic drug, but its neurobiological effects are not completely understood[1]. The drug causes mild sedation and used in the treatment of cold and cough associated with nasal allergy, rhinitis, influenza, sinusitis and bronchitis[2]. Official methods used for the determination of DpCl are based on its titration in non-aqueous medium[3]. Other reported methods for

determination of DpCl include liquid chromatography[4], gas chromatography[5-7], HPLC[8,9] and fluorometry[10]. Many of these methods, however, require several time-consuming manipulation steps, sophisticated instruments and special training.

Potentiometry with ion-selective electrodes is now a well-established method that, when applied to the analysis of pharmaceutical products can be considered to be an advantageous alternative to others normally used, owing to its selectivity, reduced implementation costs and versatility of application. In spite of successful progress in the design of highly selective electrodes for various ions, there has not been any report on the development of selective and sensitive diphenylpyraline sensors.

The present work, thus, describes the construction and performance characteristics of a PVC membrane selective electrode for the determination of diphenylpyraline in pure solutions and in pharmaceutical preparations

## Experimental

### *Reagents and materials*

Pure DpCl was kindly provided from the Saudi Pharmaceutical Industries & Medical Appliances Corporation (SPIMACO). The pharmaceutical preparations containing DpCl (Eskornade, syrup and tablets, smith Kline & French Labs, Ltd, England) were obtained from local drug stores. Dilute solutions of DpCl were freshly prepared by accurate dilution of a 0.1 M stock solution and were kept in brown bottles. The exact concentration of DpCl stock solution was determined by the pharmacopoial method[3]. Ammonium reineckate (amm.REN), poly (vinyl chloride) powder, dibutylphthalate, and tetrahydrofuran were used as received from Aldrich. The ion-exchanger, diphenylpyralinium reineckate (Dp-REN), was prepared by adding slowly a three-fold molar excess of ammonium reineckate dissolved in the minimum volume of doubly distilled water to 25 ml of $10^{-2}$ M

aqueous DpCl solution. The mixture was stirred for 10 min and the resulting pink precipitate was filtered using a sintered glass crucible (porosity G3), washed thoroughly with distilled water and dried at room temperature. The chemical composition and stoichiometry of the diphenylpyralinium-reineckate precipitate was found to be $(C_{19}H_{24}NO)[Cr(NH_3)_2(SCN)_4]$ as confirmed by (C, H, N and Cr) elemental and atomic absorption analyses at King Abdulaziz City for Science and Technology (KACST), Riyadh, Saudi Arabia and the Microanalytical Center, Cairo University, Giza, Egypt.

### *Preparation of membrane and electrode*

The required amounts of PVC, DBP and ion-exchanger (Table 1), of total weight 0.35 g were dissolved in a 7.5 cm diameter Petri-dish containing 10.0 mL tetrahydrofuran (THF). To obtain uniform thickness, the amount of THF was kept constant and the membranes were left to dry very slowly in air (not less than 24 h). Average thickness (150 μm) has been calculated for the membrane[11]. The electrode was constructed as previously described[12]. A 12 mm diameter disk was cut out from the prepared membrane and glued to the polished end of plastic cap attached to a glass tube. An internal solution consisting of equal volumes of $10^{-3}$ M DpCl and $10^{-3}$M NaCl was used to fill the electrode.

### *Electrochemical system*

The potentiometric measurements were carried out with a Jenway 3101/3015 pH-ion meter. An Accumett packed saturated calomel electrode (SCE) was used as a reference electrode. A Memmret circulator thermostat IP-120 was used to control the temperature of the test solution throughout the work. The electrochemical system is represented as follows:

Ag / AgCl / filling solution / PVC membrane / test solution // SCE

*Potentiometric determination of DpCl*

The standard additions method[13] was applied for the potentiometric determination of DpCl samples. In this method, small increments (50–100 µL) of standard 0.1 M DpCl were added to 50 mL aliquot samples containing 1-47 mg of DpCl or its equivalent from the pharmaceutical preparations. The change in mV-reading was recorded after each addition and used to calculate the concentration of DpCl sample solution. For the analysis of Eskornade syrup, the content of 5 bottles (100 ml each) was mixed and used to apply the standard additions method in a similar way as described above. For Eskornade tablets, the contents of 25 tablets were mixed and pulverized. Weights how much to 0.1g of the DpCl were dissolved in water, shaken for 24 h, filtered and the filtrate made up to 25 ml, and the DpCl content of the sample solution was determined applying the standard additions method.

## Results and Discussion

*Composition of the membrane*

The ion-exchanger used to construct the present membrane for the potentiometric measurements should be selective for the diphenylpyralinium ion ($Dp^+$) over other ions, should show rapid exchange kinetics, and should be sufficiently lipophilic to prevent leaching into the solution surrounding the membrane electrode. The diphenylpyralinium reineckate (Dp-REN) that we used has a good behavior for $Dp^+$ ion and satisfies the previously stated requirements. The suitability of reineckate as a counter anion for the preparation of PVC membrane electrodes that are sensitive and selective for some pharmaceutical compounds have been reported[14-17].The successful use of Dp-REN as sensory element for DpCl is associated with the higher insolubility of this ion-associate, which offers sensitive and selective ion-exchange with diphenylpyralinium cation.

In preliminary experiments, membranes with and without ion-exchanger were prepared. The membrane with no exchanger displayed no measurable response toward $Dp^+$ ions, whereas, in the presence of the proposed ion-exchanger, the optimized sensor demonstrated an appreciable response and remarkable selectivity for $Dp^+$ over several inorganic catios and some common excipients. It is well known that the selectivity, linear dynamic range and sensitivity obtained for a given PVC electrode depend significantly on the composition of the membrane and the nature of the solution (e.g. ionic strength, pH, …etc) to which the electrode is exposed[18,19]. Thus several membranes of varying nature and ratios of plasticizer/PVC/ion-exchanger were prepared for the systematic investigation of the membrane composition, and the results are summarized in Table 1. As expected, the amount of ion-exchanger Dp-REN was found to affect membrane sensitivity (Nos. 1-4). The calibration slope increased with increasing Dp-REN content until a value of 7% was reached (No. 4).

Table 1. Optimization of Membrane Ingredients

| No. | Composition (w/w)% | | | Slope mV/decade | RSD*% | Linear concentration range (M) |
|---|---|---|---|---|---|---|
| | Ion-Pair | DBP | PVC | | | |
| 1 | 1 | 49.5 | 49.5 | 48.3 | 0.98 | $2.10 \times 10^{-4} – 5.00 \times 10^{-3}$ |
| 2 | 3 | 48.5 | 48.5 | 52.7 | 0.65 | $2.10 \times 10^{-4} – 5.00 \times 10^{-3}$ |
| 3 | 5 | 47.5 | 47.5 | 55.2 | 0.47 | $6.30 \times 10^{-5} – 5.00 \times 10^{-3}$ |
| 4 | 7 | 46.5 | 46.5 | 58.0 | 0.53 | $3.16 \times 10^{-5} – 5.00 \times 10^{-3}$ |
| 5 | 10 | 45.0 | 45.0 | 54.7 | 0.45 | $6.30 \times 10^{-5} – 5.00 \times 10^{-3}$ |
| 6 | 13 | 43.5 | 43.5 | 53.6 | 0.49 | $6.30 \times 10^{-5} – 5.00 \times 10^{-3}$ |
| 7 | 15 | 42.5 | 42.5 | 53.3 | 0.34 | $7.90 \times 10^{-5} – 5.00 \times 10^{-3}$ |
| 8 | 20 | 40.0 | 40.0 | 47.4 | 0.56 | $7.90 \times 10^{-5} – 5.00 \times 10^{-3}$ |

Relative standard deviation (five preparations)

However, further addition of Dp-REN resulted in diminished response slope of electrode (Nos. 5-8), most probably due to some inhomogenities and possible saturation of the membrane[20]. Results in Table 1, show that the use of

membrane No. 4 (7% of the ion-exchanger, 46.5% DBP and 46.5% PVC) resulted in improved response characteristics and selectivity of the resulting Dp-ion selective electrode. The performance characteristics of this electrode were systematically evaluated according to IUPAC recommendations[21], and summarized in Table 2. The lower limit of detection (LOD) of the electrode, defined as the concentration range of DpCl corresponding to the intersection of the two extrapolated linear segments of the calibration graph, equals to $3.16(\pm0.1)\times10^{-5}$ M.

Table 2. Response characteristics of Dp-electrode

| Parameter | Values |
|---|---|
| Electrode composition | 7% Dp-REN, 46.5% PVC, and 46.5% DBP |
| Slope (mV/decade) | $58.0\pm0.6$ |
| Concentration range, M | $3.16\times10^{-5} – 5.00\times10^{-3}$ |
| Lower detection limit (LOD), M | $1.0\times10^{-5}$ |
| Limit of quantification (LOQ), M | $3.16\times10^{-5}$ |
| RSD (%) of intercepts | 0.850 |
| Working pH range | 2.2-8.0 |
| Response time (s.) | $\leq 15$ |

### Effect of soaking

Freshly prepared electrodes must be soaked to activate the membrane surface to form a thin gel layer at which the exchange occurs. This preconditioning process depends on diffusion and equilibrium at the membrane/ test solution interface. Fast establishment of equilibrium is certainly a sufficient condition for fast potential response[22]. For Dp-REN electrode, the presoaking time was $1\frac{1}{2}$ h. The response time of the electrode was nearly instantaneous ($\leq$ 15 sec). As is quite obvious from Fig. (1), the slope of the calibration graphs obtained by the pre-conditioned electrode was nearly constant for 18 days and then started to decrease gradually to approximately 53 mV/decade after 28 days and reaching about 45 mV/decade after 30 days. However, it was noted that the electrodes that had been stored dry in a closed vessel in a refrigerator and preconditioned for $1\frac{1}{2}$ h before use showed good preservation of the slope values

and response properties extending to several months. So it is recommended to store the unused electrodes dry in closed vessels in a refrigerator.
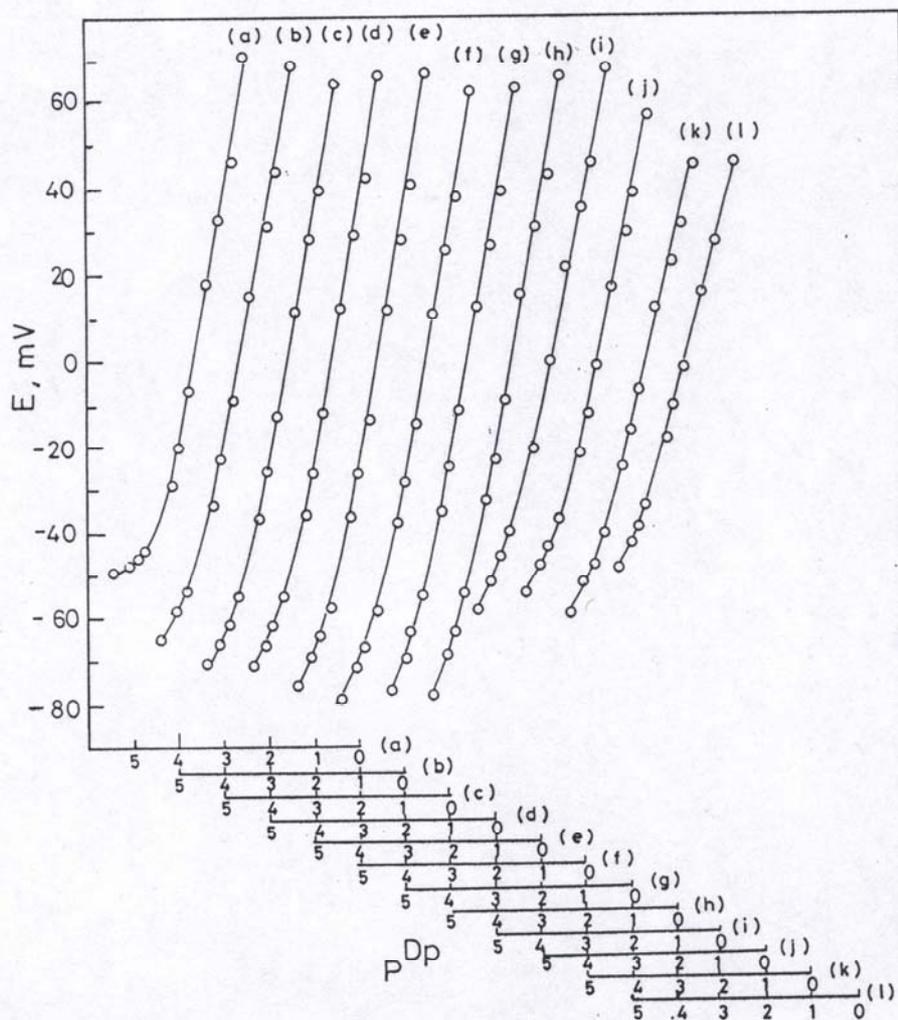


Fig. 1: Calibration curves obtained at 25°C, after soaking the Dp-electrode for 1(a), 2(b), 8(c) and 24 hours (d), 2(e), 4(f), 8(g), 12(h), 18(i), 28(j), 29(k) and 30 days (l).

## Thermal stability of the electrode

To study the thermal stability of the electrode, calibration plots [electrode potential ($E_{elect.}$) vs pDpCl] were constructed at different test solution temperatures covering the range 25-60°C. The standard cell potentials ($E°_{cell}$)

were determined at different temperatures from the respective calibration plots as the intercepts of these plots at pDp = 0, and used to determine the isothermal temperature coefficient $(dE°/dt)_{cell}$ of the cell with the aid of the following equation[23]:

$$E°_{cell} = E°_{cell\ (25°C)} + (dE°/dt)_{cell}\ (t\text{-}25)$$

Plot of $E°_{cell}$ versus (t-25) produced a straight line. The slope of this line was taken as the isothermal temperature coefficient of the cell. It amounts to 0.0009 V/°C.

Plot of $E°_{electrode}$ versus (t-25) gave a straight line, its slope was taken as the isothermal temperature coefficient of the electrode $(dE°/dt)_{electrode}$. It amounts to 0.0007 V/°C. The small values of $(dE°/dt)_{cell}$ and $(dE°/dt)_{electrode}$ reveal the high thermal stability of the electrode within the investigated temperature range.

### Effect of pH

The effect of pH of the test solution (9 x $10^{-5}$, 1.7 x $10^{-4}$ and 7.7 x $10^{-4}$ M DpCl) on the electrode potential was investigated by the addition of small volumes of hydrochloric acid and/or sodium hydroxide (0.1-1.0 M) to the test solution. Figure 2 shows the variation in the potential of the electrode with pH. It is evident that the potential variation due to pH change is considered acceptable in the pH range 2.2-8.0. Nevertheless, at pH values lower than 2.2, the potential slightly decreases, which may be attributed to penetration of $Cl^-$ ions. At pH values more than 8.0, the decrease in the potential readings is attributed to the formation of the free diphenylphraline base as a white precipitate in solution, consequently, the decrease in the concentration of diphenylpyraline cation.

### Selectivity of the electrode

The most important parameter of any potentiometric ion sensor is its response to the primary ion in the presence of other ions in solution, which is

expressed in terms of the potentiometric selectivity ($K_{M, J}$). The selectivity coefficient values, $-\log K_{PD,J^{Z+}}^{Pot}$ of the electrode toward different cationic species
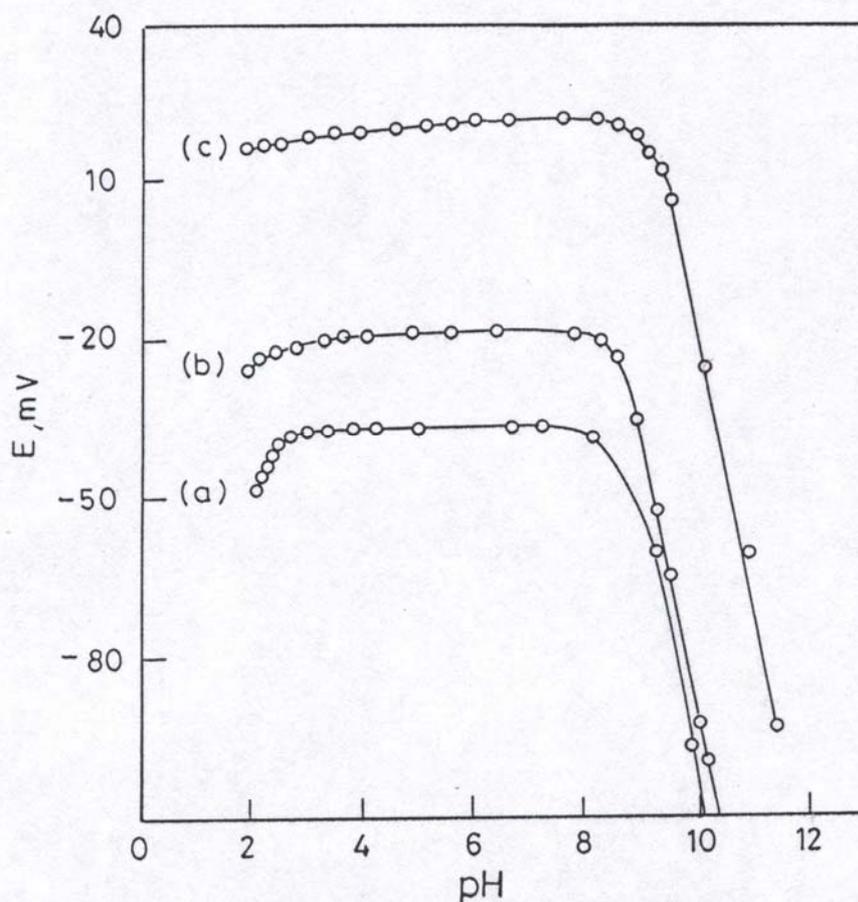


Fig. 2 : Effect of pH of the test solution of concentrations $9\times10^{-5}$ (a), $1.7\times10^{-4}$ (b) and $7.7\times10^{-4}$ M (c) DpCl on the potential response of Dp-: electrode.

($J^{Z+}$) were determined by the separate solutions method[24] in which the following equation is used:

$$-\log K_{PD,J^{Z+}}^{Pot} = [(E_1-E_2)/S] + \log [Dp^+] - \log [J^{Z+}]^{1/Z}$$

Where $E_1$ and $E_2$ are the electrode potentials in $10^{-2}$ M solutions of DpCl and interferent, $J^{z+}$, respectively and S is the slope of the calibration graph in mV.

The influence of some inorganic cations, sugars, amino acids and urea on the Dp-electrode was investigated. The selectivity coefficient values of the electrode (Table 3) reflect a very high selectivity of the investigated electrode for the $Dp^+$ cation. The inorganic cations do not interfere due to the differences in ionic size, mobility and permeability. The electrode exhibits good tolerance towards sugars, amino acids and urea (The tolerance amounts to $10^3$ on the average).

Table 3. Selectivity coefficients for the Dp-electrode

| Interferent (J) | $K_{Dp,J^{z+}}^{Pot}$ | Interferent (J) | $K_{Dp,J^{z+}}^{Pot}$ |
|---|---|---|---|
| $Li^+$ | $8.2 \times 10^{-3}$ | $Fe^{2+}$ | $8.0 \times 10^{-5}$ |
| $Na^+$ | $5.8 \times 10^{-3}$ | $Co^{2+}$ | $1.6 \times 10^{-4}$ |
| $K^+$ | $4.9 \times 10^{-3}$ | $Ni^{2+}$ | $1.2 \times 10^{-4}$ |
| $NH_4^+$ | $4.2 \times 10^{-3}$ | $Cu^{2+}$ | $6.8 \times 10^{-5}$ |
| $Mg^{2+}$ | $1.2 \times 10^{-4}$ | $Zn^{2+}$ | $7.1 \times 10^{-5}$ |
| $Ca^{2+}$ | $9.4 \times 10^{-5}$ | $Pb^{2+}$ | $5.1 \times 10^{-5}$ |
| $Sr^{2+}$ | $8.1 \times 10^{-5}$ | $Fe^{3+}$ | $2.4 \times 10^{-5}$ |
| $Ba^{2+}$ | $8.0 \times 10^{-5}$ | $Cr^{3+}$ | $1.8 \times 10^{-5}$ |
| $Cd^{2+}$ | $7.1 \times 10^{-5}$ | $Al^{3+}$ | $2.0 \times 10^{-5}$ |
| $Mn^{2+}$ | $7.1 \times 10^{-5}$ | | |

*Analytical applications*

The proposed Dp-electrode was successfully used for determination of $Dp^+$ ions in pure form and in pharmaceutical preparations (Eskornade, tablets and syrup) applying the standard additions method. The results indicated no interference from the coating materials, excipients or additives. The results of analysis (Table 4) are in good agreement with the claimed values and the data obtained by the application of the official method[3]. The mean recoveries of the amounts taken (0.96-47.68 mg DpCl) ranging from 99.5 to 100.9% with relative

standard deviation 0.42-0.85% reflect the accuracy and precision of the proposed method.

Table 4. Determination of diphenylpyraline hydrochroide

| Sample | Taken (mg) | Present Method | | Official Method[2] | |
|---|---|---|---|---|---|
| | | Mean Recovery (%) | RSD* (%) | Mean Recovery (%) | RSD* (%) |
| Pure solution | 0.96 | 100.0 | 0.69 | 100.2 | 0.52 |
| | 3.18 | 100.7 | 0.67 | 100.2 | 0.36 |
| | 5.09 | 99.5 | 0.85 | 99.8 | 0.23 |
| | 22.25 | 100.1 | 0.44 | 100.6 | 0.53 |
| | 28.61 | 100.2 | 0.83 | 98.9 | 0.87 |
| | 47.68 | 100.3 | 0.42 | 100.8 | 0.83 |
| Eskornade syrup | 0.95 | 100.6 | 0.83 | 99.6 | 0.82 |
| | 3.00 | 99.8 | 0.73 | 99.8 | 0.51 |
| | 11.10 | 99.8 | 0.39 | 100.8 | 0.87 |
| | 22.20 | 100.9 | 0.81 | 100.2 | 0.68 |
| | 28.80 | 100.5 | 0.82 | 99.6 | 0.76 |
| Eskornade tablets | 0.955 | 99.7 | 0.77 | 100.5 | 0.86 |
| | 3.11 | 99.6 | 0.78 | 100.7 | 0.90 |
| | 11.75 | 100.5 | 0.54 | 100.9 | 0.89 |
| | 22.76 | 100.3 | 0.69 | 101.3 | 0.78 |

The results obtained from the potentiometric determination of the drug were subjected to linear regression analysis, in order to establish whether the investigated electrode exhibits any fixed or proportional bias. On plotting the amounts of DpCl taken versus the amounts recovered a regression line was obtained in each case with a slope of 0.940±0.005, an intercept of near zero (0.081±0.031%) and a correlation coefficient near unity (0.996). These values revealing the absence of any systematic error during the measurements within the investigated concentration range.

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