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Disopyramide ion-selective plastic membrane sensors and their pharmaceutical applications

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Disopyramide ion-selective poly(vinyl chloride) membrane electrodes contain an ion-pair complex of disopyramide – tetrakis (4-chlorophenyl)borate as the electroactive material with 2-nitrophenyl octyl ether (electrode I) or bis(2-ethylhexyl)sebacate (electrode II) as the solvent mediators. The electrodes (I and II) show a linear response for the disopyramide concentration range 3.0×10^{-4}–10^{-2} and 8.5×10^{-5}–10^{-2} mol · l^{-1} over a pH range of 3.75–8.30 with a cationic slope of 57.3 and 58.5 mV decade^{-1}, respectively. The response time varied from 20 s to 1 min depending on the disopyramide concentration. Electrode II was used for the potentiometric determination of the disopyramide phosphate substance and the content of capsules with average recovery and mean standard deviation (± SD) of 100.8 ± 0.34 and 100.1 ± 0.68 of the nominal values, which are comparable with those obtained by the U.S. Pharmacopoeia method.

1. Introduction

Disopyramide, (*RS*)4-di-isopropylamino-2-phenyl-2(2-pyridil)butyramide suppresses artial and ventricular arrhythmias and has a longer duration of action than other antiarrhythmics. Disopyramide has anticholinergic properties and resembles quinidine in many of its direct electrophysiological actions [1].

The official pharmacopoeias recomended a non-aqueous titration for the determination of disopyramide phosphate [2, 3]. Many organic substances interfere significantly, thus the results obtained do not correlate well with the drug content. This fact justified the development of other methods, for example UV spectrophotometry [1], or colorimetry with Folin-Ciocalteu reagent [4].

HPLC is the most often applied method for assaying disopyramide [5–7], disopyramide and its main metabolite mono-*N*-dealkylated disopyramide [8–13] in biological samples. Horiuchi et al. [14] determined free disopyramide concentration using a fluorescence polarization immunoassay.

The present work describes sensitive and reasonably selective poly (vinyl chloride) membrane electrodes based on the use of disopyramide-tetrakis-(4-chlorophenyl) borate as a novel electroactive material. These electrodes are satisfactorily used for the determination of disopyramide as a substance and in pharmaceutical forms with good precision and accuracy.

2. Investigations, results and discussion

Disopyramide reacts with potassium tetrakis-(4-chlorophenyl)borate to form a stable ion-pair complex which is water insoluble but readily soluble in an organic solvent such as tetrahydrofuran, chloroform and nitrobenzene. The complex was prepared and tested as an active material with two solvent mediators in a poly(vinyl chloride) membrane response for disopyramide. The critical response characteristics of disopyramide-tetrakis(4-chlorophenyl)borate PVC membrane electrodes with 2-nitrophenyl octyl ether (electrode I) and bis(-ethylhexyl)sebacate (electrode II) were determined and the results are given in Table 1.

The electrodes I and II exhibit a near-Nernstian response over the concentration range from 3.0×10^{-4} to 10^{-2} and 8.5×10^{-5} to 10^{-2} mol · l^{-1} disopyramide phosphate with a cationic slope of 57.3 and 58.5 mV/decade and the lower detection limits of 2.5×10^{-5} mol · l^{-1} and 9.5×10^{-6} mol · l^{-1}, respectively. A comparison of the response parameters of the electrodes I and II showed that the electrode II with bis (2-ethylhexyl) sebacate as the membrane solvent was the best in term of slope and linear range.

The choice of membrane solvent to achieve the required selectivity is based on its electric permittivity and it immiscibility with aqueous phase, high viscosity, low solubility of the matrix in the membrane and its ability to dissolve the ion-pair complex.

The response time of the electrodes was tested for 10^{-5}–10^{-2} mol · l^{-1} disopyramide phosphate solutions. The sequence of measurements was from low to high concentrations. These electrodes exhibit a fast dynamic response of about 20 s although at the lower concentration, below 10^{-4} mol · l^{-1}, the response time is expectedly sluggish about 50–60 s. The electrode I was used for a period of 9 weeks and the electrode II for 12 weeks without significant changes in the electrodes parameters.

The effect of pH on the potential readings of the disopyramide electrodes was checked by the recording of the e.m.f. of 10^{-3} mol · l^{-1} disopyramide phosphate in 10^{-3} mol · l^{-1} sodium chloride solution with various pH values, which were obtained by the addition of volumes of hydrochloric acid and/or sodium hydroxide solution. The pH profiles obtained for both electrodes are shown in the Fig. The potential did not fluctuate by more than about ±1 mV in the pH range 3.75–8.30 for both electrodes. Higher pH values were hindered due to the formation of unprotonated disopyramide (pK_a value for disopyramide is 8.40) [15] or may be due to decomposition of the disopyramide ion-pair complex at the membrane surface.

Table 1: Response characteristics of disopyramide PVC membrane electrodes I and II

Parameter	Electrode I	Electrode II
Slope/(mV/decade)	57.3	58.0
Usable concentration range (mol · l^{-1})	$10^{-2} - 3.0 \times 10^{-4}$	$10^{-2} - 8.5 \times 10^{-4}$
Lower limit detection (mol · l^{-1})	2.5×10^{-5}	9.5×10^{-5}
Working pH range	3.75 – 8.30	3.75 – 8.30
Recovery time(s)	20	20
Life time (weeks)	about 9	about 12

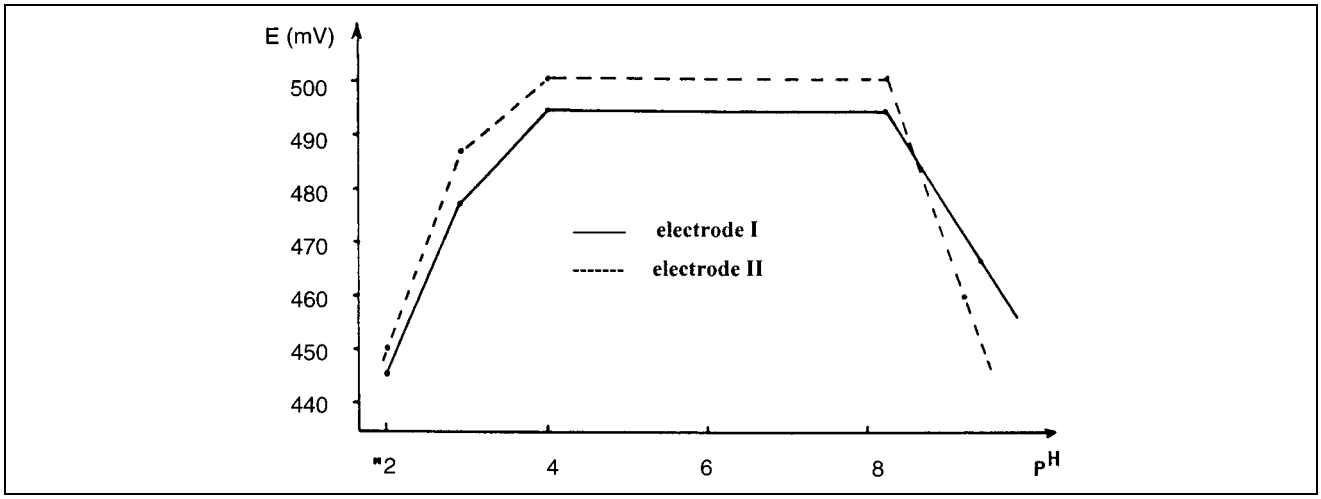

Fig.: Effect of variation of pH electrodes I and II for 10^{-3} mol · l^{-1} disopyramide phosphate solution

The influence of potentially interfering drugs on the response characteristics of both electrodes was investigated. Potentiometric selectivity coefficients were performed by the standard separate solution method [16] and calculated from the equation

$$\log K_{ij}^{pot} = (E_j - E_i)/S$$

where E represents the e.m.f. measured for the primary ion (i) and the interfering ion (j) respectively and S is the slope of the corresponding disopyramide electrodes.

The values given were evaluated from the e.m.f. readings obtained from 10^{-3} mol · l^{-1} disopyramide phosphate and the interfering ion at the same concentration in 10^{-3} mol · l^{-1} sodium chloride. The selectivity coefficients values are summarized in Table 2. The results obtained show that disopyramide electrodes do not exhibit a high selectivity for the investigated drugs. This behaviour is expected from electrodes based on ion-pairing agents where larger lipophilic species will also be efficiently extracted into the membranes [17].

The disopyramide electrode II with bis(2-ethylhexyl)sebacate could be successfully applied in the potentiometric determination of disopyramide phosphate in the pure form and in the content of capsules (100 mg) without any prior sample preparation, which is necessary for most other analytical methods. Sodium tetraphenylborate of 10^{-2} mol · l^{-1} standard solution turned out to be the most suitable titration reagent. Typical titration curves with potential breaks of about 90 mV at the points corresponding to 1 : 1 disopyramide/tetraphenylborate reaction were obtained. Gran's method [18] was used to determine the equivalence points. The ingredients in capsules did not interfere. Table 3 shows the results obtained from the determination of disopyramide in pure form and in capsules by means of the proposed procedure and the reference method. The analysis of pure disopyramide phosphate and the content of capsules provided an average recovery and mean standard deviation (± SD) of 100.8 ± 0.34 and 100.1 ± 0.68 with a relative standard deviation of 0.72% and 1.82% respectively. These results correlate with those obtained by the USP method [2].

Table 2: Potentiometric selectivity coefficients of disopyramide PVC membrane electrodes

	$\log K_{i,j}^{pot}$	
Interferent, j	Electrode I	Electrode II
Quinine	−0.88	−0.11
Procainamide	+0.69	+0.62
Amidopyrine	−0.14	−0.08
Cordarone	−0.88	−1.07

Table 3: Results of disopyramide phosphate determinations with statistical evaluation

			*USP Pharmacopoeia	
Product	Recovery ± SD (%)	RSD (%)	Recovery ± SD (%)	RSD (%)
Disopyramide phosphate substance	100.8 ± 0.34	0.74	99.7 ± 0.41	0.89
Disocor (capsules 100 mg)	100.1 ± 0.68	1.82	101.2 ± 0.73	1.95

Mean standard deviation ± SD (%) of seven determination
* UV Spectrophotometric method at 268 nm in the medium of sulfuric acid in methyl alcohol

3. Experimental

3.1. Reagents and materials

Disopyramide phosphate (D) was produced by Pol-Pharm (Poland) and Disocor capsules (100 mg) were purchased from the local pharmacy.

Sodium tetraphenylborate (Na-TPB), potassium tetrakis (4-chlorophenyl)borate (KTClPB), bis (2-ethylhexyl)sebacate (BEHS) and 2-nitrophenyl octyl ether (NPOE) were obtained from Fluka (Switzerland). Powdered poly(vinyl chloride) (PVC) of high molecular mass and tetrahydrofuran were obtained from Aldrich (USA).

All other reagents: quinidine sulphate (Polfa-Warszawa), procainamide (Polfa-Pabianice), cordarone (Krka), sodium chloride, sodium nitrate POCH (Poland) were also used.

The standard solutions 10^{-2}–10^{-6} mol · l^{-1} of disopyramide phosphate were prepared in a 10^{-3} mol · l^{-1} sodium chloride solution. A standard solution of NaTPB of 10^{-2} mol · l^{-1} was prepared and standardized as previously described [19]. All the solutions were prepared in double distilled water from the analytical reagent grade materials.

3.2. Apparatus and electrodes

The potentials of the electrodes were determined with PHM-22 digital pH/mV-meter with a scale expander type pH-630 (Radiometer, Denmark) equipped with a saturated calomel electrode K-401, a glass electrode G-202 and an Ag/Ag_2S membrane electrode. The disopyramide polymeric membrane electrode was connected to the saturated calomel electrode by a sodium nitrate bridge. The complete cell is represented by the following scheme: Ag/AgCl | 10^{-3} mol · l^{-1} disopyramide phosphate solution, 10^{-3} mol · l^{-1} NaCl | PVC membrane | test solution | SCE. All the measurements were carried out at room temperature of 21 ± 2 °C.

3.3. Preparation of the membrane and construction of the electrode

3.3.1. Disopyramide ion-pair complex

To prepare the membranes, 5 ml of $1.1 \cdot 10^{-2}$ mol · l^{-1} aqueous disopyramide phosphate solution were added to 5 ml of 10^{-2} mol · l^{-1} solution potassium tetrakis-(4-chlorophenyl)borate in ethyl alcohol. The precipitate resulting from the evaporation of ethyl alcohol was filtered and washed with water to remove any non-complexed material and dried at room temperature over the night. Its composition was determined by elemental analysis. A 1 : 1 molar ratio disopyramide to tetrakis (4-chlorophenyl)borate was found. The m.p. of the obtained ion-pair complex was determined to be 158–160 °C.

3.3.2. Preparation of PVC membrane electrode

The membrane electrode was prepared by dissolving 170 mg of PVC and 360 mg of 2-nitrophenyl octyl ether or bis(2-ethylhexyl)sebacate as mediators in 6 ml of tetrahydrofuran and 20.0 mg of D-TClPB ion-pair complex was added to this mixture. The homogeneus cocktails were poured into a 3.1 cm i.d. glass ring on a sheet of the glass plate and were covered with a sheet of filter paper and a cover of a glass plate and then a membrane was formed as the solvent was evaporating at room temperature for 12 h.

3.3.4. Construction of the electrode

Pieces with a diameter of 8 mm were punched out of these membrane sheets and gluted onto the front end of a PVC electrode body containing an inner Ag/AgCl junction. A 10^{-3} mol · l^{-1} disopyramide phosphate in 10^{-3} mol · l^{-1} sodium chloride solution was used as the inner electrolyte. The electrode potential was measured against the SCE as the reference electrode. The basic principle of the selective membrane electrode based on the ion-pair complex was described [20]. The electrodes were preconditioned for 12 h by soaking in a 10^{-3} mol · l^{-1} disopyramide phosphate solution. All the disopyramide membrane electrodes were stored in the same solution between the uses.

3.3.5. Electrode characteristics

Aliquots of 50 ml 10^{-2} to 10^{-6} mol · l^{-1} standard disopyramide phosphate in 10^{-3} mol · l^{-1} natrium chloride solution were transferred into 100 ml beakers. The disopyramide PVC membrane electrodes I or II were connected to the SCE as reference electrode, these were immersed in the solutions. The solutions were stirred and the potential of the electrode of each solution was recorded after stabilization and plotted as a function of the logarithm of disopyramide phosphate concentration.

3.3.6. Potentiometric determination of disopyramide phosphate in the pure form and in capsules

Ten ml of the disopyramide phosphate solution (2.5–10.0 mg) were transferred into a 100 ml beaker, 5 ml of 10^{-2} mol · l^{-1} sodium chloride and about 35 ml of water were added. The solution was titrated with a 10^{-2} mol · l^{-1} standard solution of sodium tetraphenylborate using the electrode II and a SCE as the reference electrode.

One ml of 10^{-2} mol · l^{-1} NaTPB is equivalent to 4.38 mg of disopyramide phosphate. Disocor® capsules (100 mg) were analysed by finely powdering the content of five capsules. An accurately weighed portion of the powder equivalent to about 100.0 mg of disopyramide phosphate was extracted with 80 ml of water in a 100 ml volumetric flask, shaken for about 15 min and the solution was diluted to the mark. An aliquot (10.0 ml) of the solution was used for the determination of disopyramide as described above.

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