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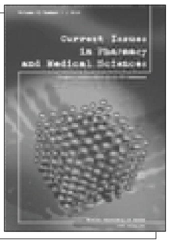

Meclophenoxate ion-selective plastic membrane sensors and their pharmaceutical applications

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ABSTRACT

The present work describes the construction and general characteristics of meclophenoxate ion-selective plastic membrane sensors, based on the use of a meclophenoxate–tetrakis(4-chlorophenyl)borate ion-pair complex as electroactive material, with 1-isopropyl-4-nitrobenzene (electrode A), 2-nitrophenyloctyl ether (electrode B), 2-nitrodiphenyl ether (electrode C) or bis(2-ethylhexyl) sebacate (electrode D) as solvent mediators. The electrodes show a linear response to the meclophenoxate concentration ranges of $10^{-4,1}$ – 10^{-2} $moll^{-1}$ (electrode A), $10^{-5,1}$ – 10^{-2} $moll^{-1}$ (electrode B), 10^{-4} – 10^{-2} $moll^{-1}$ (electrode C), $10^{-4,9}$ – 10^{-2} $moll^{-1}$ (electrode D), over the pH range of 4.12–6.18 with a cationic slope of 61.7; 64.7; 63,33; 64,41 mV $decade^{-1}$, respectively. The response time varied from 5 to 20 s, depending on the meclophenoxate concentration. Electrode B was used for the potentiometric determination of the content of meclophenoxate hydrochloride in pure form, dragees and dragee dissolution test, with average recovery and mean standard deviation (±SD) of 101.79±1.57, 102.72±0.91 and 101.32±0.84 of nominal values respectively.

Keywords: ion-selective electrode, potentiometric titration, drug analysis, meclophenoxate hydrochloride, meclophenoxate determination

INTRODUCTION

Meclophenoxate hydrochloride (2-(dimethylamino)ethyl 2-(4-chlorophenoxy)acetate hydrochloride) is an anti-aging drug widely used by humans to increase brain energy, since it stimulates the chemical activity of the brain [25, 26].

Methods available in literature for the quantification of meclophenoxate including spectrophotometry [1, 14] chromatography TLC [9, 17, 18, 19], gas chromatography [11, 21], high performance liquid chromatography HPLC [8, 13, 20], micellar liquid chromatography [4], capillary electrophoresis [10] or proton magnetic resonance (PMR) spectroscopy [23], give good results, but require sophisticated expensive equipment controlled by highly skilled personnel. Using a Pt electrode with non–aqueous titration for the determination of meclophenoxate [2] has been recommended for monitoring low levels of the substance.

Potentiometric methods using ion-selective electrodes have found wide applications [3, 5, 12], as they tend to be simple, economical, precise, accurate, applicable in different areas, and selective in turbid and coloured solutions.

The present work describes novel sensitive and reasonably selective poly(vinyl chloride) membrane electrodes using water insoluble ion-pairs of meclophenoxate – tetrakis(4-chlorophenyl)borate as electroactive material. These electrodes are satisfactorily used for the determination of meclophenoxate in substance and in pharmaceutical forms by a potentiometric technique with good precision and accuracy.

MATERIALS AND METHODS

Reagents and materials: The Meclophenoxate hydrochloride *MEX HCl* substance and dragees *Lucidril* containing 0,1 g *MEX HCl* were produced by *Jelfa S.A.* (Poland). In addition, the potassium tetrakis(4-chlorophenyl)borate (ClTPB), sodium tetraphenylborate (TPB) and 1-isopropyl-4-nitrobenzene (IpNB), 2-nitrophenyloctyl ether (NPhOE), 2-nitrodiphenyl ether (NdPhE) and bis-(2-ethylhexyl) sebacate (DOS) as solvent mediators, were obtained from *Fluka* (Switzerland). Moreover, the poly(vinyl chloride) (PVC) of high molecular mass was from *Aldrich* (USA), and the tetrahydro2uran (THF) used in this research was produced by *Romil Chemicals LTD* (England). Furthermore, the majority of the reagents were produced by *POCh* (Gliwice, Poland), and all of these were of analytical – reagents grade.

The standard solutions of 10^{-2}–10^{-7} $moll^{-1}$ *MEX HCl* were prepared in water and in 10^{-3} $moll^{-1}$ NaCl. The standard solution of TPB of 10^{-2} $moll^{-1}$ was prepared by dissolving the compound in water, diluting to 250 ml, and standardizing as previously described [24]. The solutions were prepared using bi-distilled deionized water throughout.

Apparatus and electrodes: A multifunctional apparatus, Elmetron CX (Poland), was used for measuring the electrode potentials and pH. Furthermore, all the potentiometric measurements were made using saturated calomel electrodes (SCE) and Ag/AgCl membrane electrodes. What is

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more, pH adjustment was made with a combination glass electrode. All the measurements were carried out at room temperature (21° ± 2°C). A magnetic stirrer was used; however, the readings of the potential value were taken after the stirrer had been switched off. In this work, the SCE was used as the reference electrode connected with the sample solution by a sodium nitrate bridge. Finally, the Evolution 6100-Distek Bathless Dissolution (USA) paddle apparatus with embedded temperature sensor in each shaft, with media heating to 37°C and rotation of 75 rpm was used for the dissolution test.

Preparation of meclophenoxate ion – pair complex: To 10 ml of well-shaken 10^{-2} moll^{-1} *MEX HCl* aqueous solution, 10 ml of 10^{-2} moll^{-1} ClTPB in 50° ethyl alcohol solution was added. The precipitate resulted after cooling and evaporation of the ethyl alcohol. The precipitate was filtered using a (G4) sintered glass crucible, washed with water to remove any non– complexed material. This was then dried at room temperature and ground to a fine powder. The melting point of obtained ion–pair complexes was determined at 148–150°C. The results of the elemental analysis agree well with the molar ratio 1 : 1 of the reacting substances.

Preparation of the membranes: 20 mg of the ion–pair complexes was added to a solution of 170 mg PVC in 6 ml THF and 360 mg of IpNB or NPhOE or NdPHE or DOS as plasticising solvent mediators. The homogeneous mixtures were poured into a glass ring (diameter 3.1 cm) and covered with a sheet of filter paper, and a glass plate cover was placed over it. The membrane formed as the THF was evaporated slowly at room temperature.

Construction of electrode: To prepare an electrode (according to Craggs et al. [22]), a membrane disc of 8 mm diameter was cut from the obtained film and glued onto the front and body of PVC electrode containing an inner Ag/AgCl junction. A 10^{-3} moll^{-1} *MEX HCl* in 10^{-3} moll^{-1} NaCl solution was used as the inner electrolyte. The membrane electrodes were conditioned overnight in a solution of the same composition as the internal filling solution and stored in the same solution before use. Electromotive force (e.m.f) measurements were performed using the cell assembly: Ag/AgCl 10^{-3} moll^{-1} *MEX HCl* in 10^{-3} moll^{-1} NaCl solution PVC membrane test solution |SCE.

Electrode characteristics: The performance of the obtained electrodes A, B, C and D was investigated by measuring e.m.f. values of 10^{-2} – 10^{-7} moll^{-1} of *MEX HCl* in water solution and in 10^{-3} moll^{-1} NaCl solution. The potential was recorded when stable readings were obtained. A calibration graph was made by plotting the observed potential as a function of logarithm of *MEX HCl* concentration.

Potentiometric titration of meclophenoxate hydrochloride (in substance, dragees and after dissolution test): Samples of solution containing 2.35–7.35 ppm of substance *MEX HCl* in 10^{-3}moll^{-1} sodium chloride were titrated with 10^{-2} moll^{-1} of TPB standard solution using the electrode with membrane containing *MEX* – ClTPB and NPhOE (electrode B). The dragees of *Lucidril* (a mean mass of each dragee was 0.5159 g) were finely powdered and an accurately weighed portion of the powder equivalent to about 3.53 ppm of *MEX HCl* was transferred into the beaker and then 5 ml of 10^{-2}moll^{-1} NaCl solution and about 35 ml of water were added. The samples were extracted for 15 min and titrated as above. The dragees of *Lucidril* were transferred into vessels with 900 ml of acetate buffer pH 4.5. The dissolution test was developed for 30 min. and after this, the samples were titrated as above.

RESULTS AND DISCUSSION

Ion-pair complex of the meclophenoxate cation with tetrakis(4-chlorotetraphenyl)borate anion was obtained and tested as ion-exchangers in PVC membrane electrodes. The composition of the ion-pair complex was verified by data gained by way of elementary analysis and by IR. The suggested structural formula is shown in Fig 1. This ion-pair complex is readily soluble in an organic solvent such as tetrahydrofuran, chloroform or nitrobenzene. The obtained compound was incorporated into a PVC membrane with the following solvent mediators: IpNB (electrode A), NPhOE (electrode B), NdPhE (electrode C), DOS (electrode D).

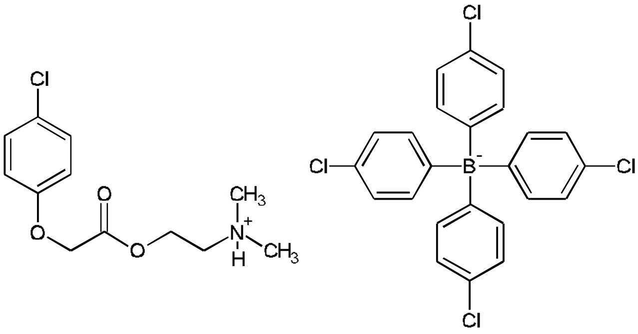

Fig. 1. Suggested structural formula of the ion-pair complex of the meclophenoxate cation with tetrakis(4-chlorotetraphenyl)borate anion

The working characteristics for the investigated A, B, C and D electrodes were assessed on the basis of calibration curves. These were obtained by measuring the e.m.f. values of the set of *MEX HCl* solutions in intervals of 10^{-2}–10^{-7} moll^{-1} concentrations in water and in an ionic strength adjusted to 10^{-3} moll^{-1} NaCl. The E(mV) vs. log (c) graph obtained for A, B, C, D electrodes in aqueous solution are presented in Fig. 2. The derived results indicate that the tested electrodes have a sub-Nernstian cationic response to *MEX* activity in different concentration ranges, depending on the properties of the solvent mediator. Slopes of electrodes A, B, C, D per decade in an aqueous solution are 61.7; 64.7; 63.35; 64.41 mV decade^{-1}, respectively. Table 1 shows the values obtained for the general operating characteristics of *MEX* electrodes. It can be seen from this table that a general increase in the lower limit of the linear response range was obtained for electrode A containing IpNB and electrode B containing NPhOE as solvent mediators. These results show that using ClTPB counter-anion as ion-exchange sites in PVC matrix with IpNB, NPhOE, NdPhE, or DOS as plasticizers, gives better parameters than using sodium tetraphenylborate, ammonium reineckate, or betacyclodextrin as ion-exchange [7] – near-Nernstian response – slopes (52.73; 51.64 and 54.05 per concentration decade, respectively, over the concentration range of 10^{-5}– 10^{-2} $moll^{-1}$ *MEX HCl*).

Table 1. Effect of plasticizer on response of meclophenoxate sensitive electrode (3.(63)% content ion-pair) (average of six measurements)

Parameter	Electrode A	Electrode B	Electrode C	Electrode D
Slope* (mv/decade)	61.70/60.0	64.69/61.15	63.33/63.11	64.41/62.75
Intercept (mv)	154.12±1.54	156.78±0.44	180.70±1.72	167.05±0.83
Correlation coefficient (r)	0.9999	0.9999	0.9993	0.9999
Usable concentration range* ($moll^{-1}$)	10^{-2}–$10^{-4.1}$ / 10^{-2}–$10^{-4.1}$	10^{-2}–$10^{-5.1}$ / 10^{-2}–$10^{-5.1}$	10^{-2}–$10^{-4.0}$ / 10^{-2}–$10^{-4.4}$	10^{-2}–$10^{-4.9}$ / 10^{-2}–$10^{-4.8}$
Lower limit detection* ($moll^{-1}$)	$10^{-4.77}/10^{-5.1}$	$10^{-5.3}/10^{-5.3}$	$10^{-4.55}/10^{-5.0}$	$10^{-5.1}/10^{-4.9}$
Potential drift mv/day^{-1}	4–7	2–3	3–5	3–5
Working ph range	4.12–6.18	4.12–6.18	4.12–6.18	4.12–6.18
Recovery time (s)	10	5	10	7
Life span (week)	8	9	9	9
Repeatability cv_w	0.80	0.99	0.94	0.94
Between day variability cv_b	0.6	0.2	0.4	0.4

* in aqueous / 10^{-3} $moll^{-1}$ NaCl solution

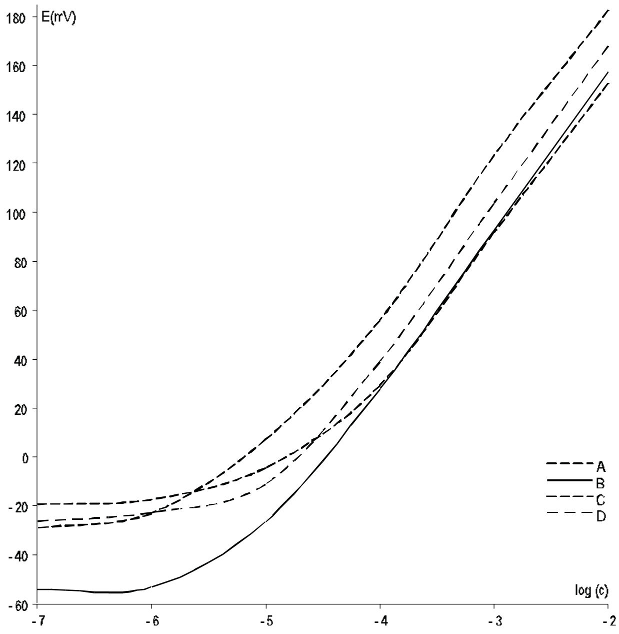

Fig. 2. Potentiometric response of obtained ISEs in aqueous solution

The response times of the electrodes were tested for 10^{-5} – 10^{-2} $moll^{-1}$ *MEX HCl* solutions. The sequence of measurements was low to high concentrations. Those electrodes exhibits a fast dynamic response of about 5 s for the higher concentrations. However, below 10^{-4} $moll^{-1}$, the response time was expectedly sluggish, about 15–20 s, which is typical for ion-selective electrodes containing bulky PVC membranes of similar thickness (about 0.2 mm). The lifetime of the electrodes is about 2 months, after which the electrode membrane should be renewed.

The effect of pH on the potential readings of the *MEX* electrodes A, B, C and D was checked by recording the e.m.f. of 10^{-3} $moll^{-1}$ *MEX HCl* in 10^{-3} $moll^{-1}$ NaCl solution with various pH values. These were obtained by the addition of small volumes of hydrochloric acid and/or sodium hydroxide solution of 10^{-1} or 1 $moll^{-1}$ each. The E(mV) vs. pH graph presented in Fig. 3 shows the pH independence in the range obtained for A, B, C, D electrodes. It should be noted that the potential did not fluctuate by more than about ±1 mV in the pH range 4.12–6.18 for all obtained electrodes. Higher pH values were hindered due to the formation of unprotonated *MEX* or may have been due to decomposition of the *MEX* ion-pair complex of the membrane surface.

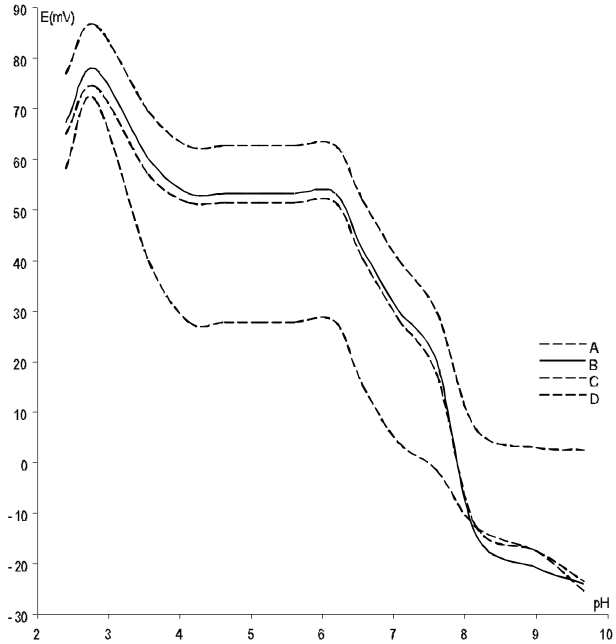

Fig. 3. The effect of variation of pH on electrodes response for 10^{-3} $moll^{-1}$ meclophenoxate hydrochloride solution

The influence of potential drugs on the response characteristics of the four development electrodes was investigated. Potentiometric selectivity coefficients were performed by standard separate solution method [22] 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 *MEX* electrode.

The values given were evaluated from the e.m.f. readings obtained from 10^{-3} $moll^{-1}$ sodium chloride. The selectivity coefficients values are summarized in Table 2. These indicate how the response of the investigated membrane electrodes was affected by the presence of chloropromazine and amitryptyline for all electrodes, and by the presence of promazine and promethazine for electrodes A, C, D. It should be noted that Electrode C was not selective for doxepin or imipramine, and electrode B for opipramol. This behaviour is expected from electrodes based on an ion-paring agent where lager lipophilic species will also be efficiently extracted into the membranes [16].

Table 2. Potentiometric selectivity coefficients of meclophenoxate PVC membrane electrodes

Iinterferent (*j*)	$\log K_{ij}^{pot}$			
	electrode A	electrode B	electrode C	electrode D
Doxepin	−0.0423	−0.2151	+0.1039	−0.8065
Imipramine	−0.2705	−0.1035	+0.1738	−1.1574
Opipramol	−0.9220	+0.7466	−0.2993	−0.6979
Promazine	+0.0309	−0.0334	+0.1984	+0.0868
Promethazine	+0.0207	−0.0221	+0.1679	+1.2850
Chlorpromazine	+0.1299	+0.1464	+0.3160	+0.2137
Amitryptyline	+0.1272	+0.1137	+0.2649	+0.2008

The obtained electrode B (*MEX* – ClTPB – NPhOE) was shown to be useful in the potentiometric determination of *MEX* in the bulk substance, dragees 0.1 g and in the dissolution test. It must be noted that dissolution testing is used in pharmaceutical analysis for optimization of formulation and quality control. In this regard, in vitro dissolution tests are established to ensure batch-to-batch consistency and to signal potential problems with in vivo bioavailability.

In our research, the potentiometric titrations with standard solution of 10^{-2} moll^{-1} of sodium tetraphenylborate were carried out using electrode B as an indicator electrode, and potential breaks of about 52 mV at the points corresponding to 1:1, *MEX* – TPB reaction were obtained. Gran's method was then used to determine the equivalence points [15]. Collective results are given in Table 3. The results reveal that the proposed method shows a high degree of accuracy. An average recovery and a mean standard deviation obtained were 101.79   1.57 for *MEX HCl* substance, 102.72 ± 0.91 for *MEX HCl* dragees and 101.32 ± 0.84 for determining after-dissolution test, with relative standard deviations of 1.55, 0.89, 0.80% respectively.

Table 3. Results of meclophenoxate hydrochloride determination with statistical evaluation for n = 6

Product	$\bar{x}$ [%]	*s*	$\bar{s}$	μ95%	RSD
Meclophenoxate hydrochloride – substance	101.79	1.64	1.57	98.36–105.22	1.611
Lucidril 0.1 dragees	102.72	1.00	0.91	100.37–105.07	0.973
Lucidril 0.1 dragees dissolution	101.32	1.22	0.84	98.42–103.12	1.204

CONCLUSION

The proposed membrane electrode system based on tetrakis(4-chlorophenyl)borate as cation exchanger, offers a simple, rapid, high-degree-of-precision and accurate technique for the determination of meclophenoxate in pure substance, as well as in dosage forms.

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