Construction of Ion-selective Electrodes for Chlorpromazine, Amitriptyline, Propantheline and Meperidine: Analytical Study and Application to Pharmaceutical Analysis

Anastasid Mitsana-Papazoglou, Theodore K. Christopoulos, Eleftherios P. Diamandis and Themistocles P. Hadjiioannou*

Laboratory of Analytical Chemistry, University of Athens, 104 Solonos Street, Athens 106 80, Greece

Liquid-membrane ion-selective electrodes that respond to the cationic forms of chlorpromazine, amitriptyline and meperidine and to the quaternary ammonium compound propantheline are described. The liquid ion exchangers used were the salts of chlorpromazine or amitriptyline with eosin and tetraphenylborate in *p*-nitrocumene, propantheline with tetraphenylborate in 2-nitrotoluene and meperidine with tetrakis(*m*-chlorophenyl)borate in *p*-nitrocumene. The electrodes exhibited near-Nernstian response in the range 6×10^{-3}–4×10^{-5} M, working pH range 1–6 (chlorpromazine); 6×10^{-3}–6×10^{-5} M, pH 1–6 (amitriptyline); 6×10^{-3}–3×10^{-6} M, pH 1–9 (propantheline); and 10^{-2}–7×10^{-6} M, pH 1–7 (meperidine). The interferences from the alkali and alkaline earth metals were negligible but cationic molecules of similar structure interfered strongly. The electrodes were applied successfully to the assay of active compounds in pharmaceutical preparations. The major advantages of the proposed methods are their simplicity and speed.

Keywords: *Ion-selective electrodes; chlorpromazine; amitriptyline; propantheline; meperidine*

Ion-selective electrodes (ISEs) have found many successful applications in pharmaceutical analysis,[1–7] mainly because of their low cost, ease of use and maintenance and the simplicity and speed of the assay procedures. It is usually possible to develop procedures for the determination of drugs in pharmaceutical preparations that need only a pre-dilution step with a suitable buffer (*e.g.*, injection preparations) or dissolution of tablets in the measuring solvent. Turbidity due to the tablet matrix is not usually a problem, so that even the filtration step can be avoided.

The most important limitation of ISEs is their poor selectivity, especially for compounds of similar structure. With multi-component drugs, it is sometimes possible to measure specifically a single compound by optimisation of the analytical parameters.

In this paper, the construction of four liquid-membrane ISEs that respond to the cationic forms of the drugs chlorpromazine, amitriptyline, propantheline and meperidine is described. Chlorpromazine is the most widely used major tranquilliser, amitriptyline is a major tricyclic antidepressant, propantheline is an anticholinergic drug used extensively for the treatment of peptic ulcers and meperidine is a potent analgesic. An analytical study of the electrodes showed that they exhibit satisfactory sensitivity and selectivity and a broad working pH range. Titrimetric and direct potentiometric procedures have been developed for the rapid and simple assay of the active compounds present in various pharmaceutical formulations.

Experimental

Apparatus

All electrodes were used with a single-junction Ag - AgCl electrode as the reference (Orion Model 90-01-00). Potential readings were obtained with a Corning Research pH/mV meter (Model 12), and recorded simultaneously on a strip-chart recorder. All titrations were carried out with a Radiometer system consisting of a multi-speed constant-rate burette (Model ABU 12) and a recorder (REC 61) equipped with an REA 112 high-sensitivity unit. All measurements were carried out at room temperature with constant magnetic stirring.

* To whom correspondence should be addressed.

Reagents

All solutions were prepared in de-ionised, distilled water from analytical-reagent grade materials. Stock solutions (0.1000 M) of chlorpromazine hydrochloride, amitriptyline hydrochloride, propantheline bromide and meperidine hydrochloride were prepared in water. The pure substances used were of the highest quality available, and were gifts from various pharmaceutical companies. All solutions were stored at room temperature except for chlorpromazine, which was stored in amber bottles at 4 °C to avoid photochemical oxidation.[8] Pharmaceutical preparations were obtained from local pharmacies.

Liquid Ion Exchangers

The cationic forms of chlorpromazine, amitriptyline, propantheline and meperidine were precipitated from aqueous solutions with bulky anions. The resulting insoluble compounds were extracted into organic solvents and the extracts were dried with anhydrous sodium sulphate and used to fill the electrodes. The best liquid ion exchanger for each compound was prepared as described below. Less satisfactory liquid ion exchangers were prepared in a similar way and are described later.

Chlorpromazine. Chlorpromazine was precipitated by mixing 1 ml of sodium tetraphenylborate solution (5×10^{-2} M), 1 ml of sodium eosin solution (5×10^{-2} M) and 1.5 ml of chlorpromazine hydrochloride solution (0.10 M). The precipitate was extracted with 5 ml of *p*-nitrocumene (4-isopropylnitrobenzene) (Fluka) and the organic phase was washed three times with water. The organic solution was dried by adding 0.5 g of sodium sulphate, which was then removed by centrifugation.

Amitriptyline. The same procedure as for chlorpromazine was used, but amitriptyline hydrochloride was used instead of chlorpromazine hydrochloride.

Propantheline. Propantheline was precipitated by mixing 2 ml of sodium tetraphenylborate solution (5×10^{-2} M) and 2 ml of propantheline bromide solution (0.10 M). The precipitate was extracted with 5 ml of 2-nitrotoluene and the liquid ion exchanger was dried as above.

Meperidine. The same procedure as for chlorpromazine was used, but meperidine was precipitated by mixing 2 ml of sodium tetrakis(*m*-chlorophenyl)borate solution (5×10^{-2} M) and 2 ml of meperidine hydrochloride solution (0.10 M).

Procedures

Construction of the electrodes

An Orion liquid membrane electrode body (Model 92) was used as the electrode assembly with a Millipore LCWPO 1300 PTFE membrane; the PTFE membranes were cut to the appropriate size and a stack of four was used to avoid any leakage of the liquid ion exchanger. All the internal aqueous reference solutions were 0.010 M with respect to the cation measured and 0.10 M in NaCl. They were saturated with AgCl. The operating life of the electrodes used was about 2 months.

Preparation of calibration graphs

A 20.00-ml volume of water was pipetted into a 50-ml beaker, the electrodes were immersed in it and, after the potential had stabilised, various increments of a 0.10 M solution of the cation of interest were added. The e.m.f. readings were recorded after stabilisation following each addition, and the *E versus* log[cation] plot was constructed. The slope of the electrodes was found by regression analysis of the linear part of the graph.

Direct potentiometric assay of pharmaceutical preparations (standard additions method)

Drugs for injection. The commercial product was diluted with water so as to obtain a solution with a final concentration with respect to the active drug in the range 3×10^{-3}–3×10^{-4} M. A 20.00-ml volume of this solution was used for analysis. A potential reading was first recorded for this solution. Subsequently, a second potential reading was obtained after the addition of a small volume of a concentrated standard drug solution. The initial concentration of the sample was calculated from the change in potential.[9]

Tablets. At least five tablets were powdered and dissolved by stirring for 15 min in water. The final volume was adjusted so as to obtain a final solution concentration for the active compound in the range 3×10^{-3}–3×10^{-4} M. The resulting solution was analysed as described above by the standard additions method.

An alternative procedure was used for propantheline bromide tablets, as follows (see Results and Discussion). The powdered tablets were mixed with 25 ml of dichloromethane and stirred for 30 min at room temperature. The mixture was filtered through a sintered-glass funnel and the solid residue was washed with 10 ml of dichloromethane. The combined filtrate was evaporated to dryness by gentle heating under a stream of air. The residue was dissolved in 20 ml of water and the resulting solution was analysed as described above by the standard additions method.

Potentiometric titrations

Drugs for injection and tablets were treated as described under *Drugs for injection* and *Tablets* in order to prepare sample solutions. An 18.00-ml aliquot of the sample and 2.00 ml of buffer solution (1.00 M) were pipetted into the beaker, the electrodes were immersed in it and the titration was performed with constant stirring with either 0.01000 M tetraphenylborate or picrate solution, at a flow-rate of 0.36 ml min^{-1}. The buffers tested (0.10 M) were acetate (pH 3.3 and 5) and phosphate (pH 6). Titration curves were recorded.

Results and Discussion

Choice of Optimum Liquid Ion Exchanger

The water-insoluble salts of the cations of interest with various bulky anionic compounds dissolved in organic solvents were used as possible liquid ion exchangers for electrode construction. The slopes of the calibration graphs and the linear response ranges of various chlorpromazine electrodes are given in Table 1. It can be seen that in general the lower limit of the linear response range is smaller for electrodes containing eosin in the liquid ion exchanger. Therefore, we selected the mixture of chlorpromazine eosin with chlorpromazine tetraphenylborate dissolved in *p*-nitrocumene for further studies with the chlorpromazine electrode.

A chlorpromazine electrode has recently been reported[10] in which the membrane consists of chlorpromazine tetraphenylborate or chlorpromazine dinonylnaphthalenesulphonate in a poly(vinyl chloride) (PVC) matrix. The characteristics of these electrodes were similar to those described here. We have also constructed PVC electrodes for chlorpromazine by use of the liquid ion exchanger that contains eosin and tetraphenylborate but we did not use them routinely because of their short operating life (*ca.* 1 week) compared with 2 months or more when the liquid ion exchanger was used.

For the amitriptyline electrode we tested the amitriptyline salts with eosin, alizarin red S, tetraphenylborate, anilinonaphthalenesulphonate, eosin - tetraphenylborate mixture, eosin - tetrakis(imidazolyl)borate (all dissolved in 2-nitrotoluene), and eosin - tetraphenylborate mixture dissolved in *p*-nitrocumene, as possible liquid ion exchangers. All liquid ion exchangers were 10^{-2} M with respect to each of the dissolved salts. On the basis of the same criteria as for the chlorpromazine electrode, we selected the mixture of amitriptyline eosin with amitriptyline tetraphenylborate *m*-*p*-nitrocumene for further study. The slope of the best amitriptyline electrode was 60 mV per decade at 25 °C and the linear working range was 6×10^{-3}–6×10^{-5} M.

No optimisation was necessary for the construction of the

Table 1. Slopes and linear response ranges for various chlorpromazine electrodes

Liquid ion exchanger*	Solvent	Slope/mV	Linear response range/M
Chl tetraphenylborate	2-Nitrotoluene	58	3×10^{-3}–8×10^{-5}
	p-Nitrocumene	60	3×10^{-3}–8×10^{-5}
Chl picrolonate	2-Nitrotoluene	46	
Chl tetrakis(*m*-chlorophenyl)borate	*p*-Nitrocumene	51	3×10^{-3}–2×10^{-4}
Chl tetrakis(imidazolyl)borate	*p*-Nitrocumene	51	4×10^{-3}–3×10^{-4}
Chl bromcresol purple	*p*-Nitrocumene	54	6×10^{-3}–6×10^{-5}
Chl eosin	*p*-Nitrocumene	62	6×10^{-3}–4×10^{-5}
	2-Nitro-*m*-xylene	53	6×10^{-3}–8×10^{-4}
	4-Nitro-*m*-xylene	51	6×10^{-3}–1×10^{-4}
Chl eosin + Chl picrate	*p*-Nitrocumene	58	4×10^{-3}–4×10^{-5}
	Decanol - *p*-nitrocumene (2 + 3)	59	5×10^{-3}–1×10^{-4}
Chl eosin + Chl tetraphenylborate	*p*-Nitrocumene	60	6×10^{-3}–4×10^{-5}

* Chl = chlorpromazine. All liquid ion exchangers were 10^{-2} M with respect to each salt dissolved.

propantheline and meperidine electrodes. Propantheline tetraphenylborate dissolved in 2-nitrotoluene (10^{-2} M) provided a suitable liquid ion exchanger. The electrode constructed had a slope of 58 mV per decade and a linear working range of 6×10^{-3}–3×10^{-6} M. Therefore, this electrode was used for further studies.

For the meperidine electrode we selected the meperidine salt of tetrakis(*m*-chlorophenyl)borate (10^{-2} M) dissolved in *p*-nitrocumene for further studies. The meperidine electrode had a slope of 60 mV per decade and a linear working range of 10^{-2}–7×10^{-6} M.

The upper concentration range of all electrodes was established experimentally and it is the point where curvature of the calibration graph begins. This curvature is, presumably, due to micelle formation.

Typical calibration graphs for the electrodes described are shown in Fig. 1.

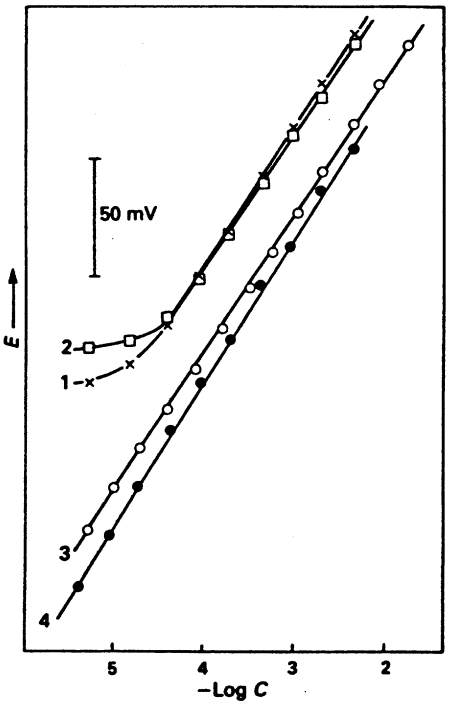

Fig. 1. Calibration graphs for (1) chlorpromazine, (2) amitriptyline, (3) meperidine and (4) propantheline electrodes

Effect of pH

The response of the four electrodes is practically unaffected by changes in pH over the pH ranges 1–6 (chlorpromazine and amitriptyline), 1–9 (propantheline) and 1–7 (meperidine). At lower acidities (higher pH) the potential changes markedly with pH because of the progressive loss of the positive charge of the molecules with increasing pH (except for propantheline, which is a quaternary ammonium compound and not a base). The potential *versus* pH graphs can be used to calculate the dissociation constant, K_a, of the cationic acid, because pK_a is equal to the pH where the initial concentration of the protonated molecule is halved, *i.e.*, when the electrode potential decreases by $0.30S$ mV (S = electrode slope).[11] With this method we calculated the pK_a of meperidine to be 8.57 ± 0.6 (at 20 °C); a value of 8.7 (at 20 °C) has been reported.[8] This graphical technique is not applicable if the unprotonated molecule is insoluble in water and precipitates at pH values lower than the pK_a (as with chlorpromazine and amitriptyline). An alternative procedure that overcomes these limitations is described elsewhere.[12]

Selectivity

The interference of various cations was studied by the mixed solution method.[9] Potentiometric selectivity coefficients are presented in Table 2. There is little interference by many common cations. Cations of similar structure or cations that form water-insoluble eosin or tetraphenylborate salts that are extractable in the organic solvents used for the preparation of liquid ion exchangers interfere seriously.

The potentiometric selectivity coefficients for amitriptyline, promethazine and thioproperazine for the chlorpromazine electrode were 0.2, 0.1 and 0.02, respectively. The K^{pot} values for chlorpromazine and perphenazine for the amitriptyline electrode were 0.4 and 0.02, respectively. Chlordiazepoxide, which is frequently present in amitriptyline and propantheline preparations, does not interfere with the electrodes at pH ≥ 6.

Propantheline is hydrolysed in solutions at pH > 5,[13] the decomposition products being xanthenecarboxylic acid and the quaternary 2-hydroxyethyldiisopropylmethylammonium cation. It was of interest to study the response of the propantheline electrode to the cationic product of hydrolysis. We hydrolysed completely a 0.01 M propantheline solution by heating in 0.1 M NaOH solution, the pH was then adjusted to 4.5 with concentrated HCl and the propantheline concentra-

Table 2. Potentiometric selectivity coefficients for the constructed electrodes

	$K_{i,j}^{pot}$			
Interferent, *j*	Chlorpromazine	Amitriptyline	Propantheline	Meperidine
Na^+	2×10^{-4}	3×10^{-4}	$<10^{-5}$	$<10^{-5}$
K^+	2×10^{-4}	3×10^{-4}	$<10^{-5}$	$<10^{-5}$
Li^+	2×10^{-5}	3×10^{-4}	$<10^{-5}$	$<10^{-5}$
NH_4^+	1×10^{-3}	5×10^{-4}	$<10^{-5}$	$<10^{-5}$
Mg^{2+}	5×10^{-5}	9×10^{-5}	$<10^{-5}$	$<10^{-5}$
Ca^{2+}	6×10^{-5}	1×10^{-4}	$<10^{-5}$	$<10^{-5}$

Table 3. Assay of chlorpromazine in pharmaceutical preparations by direct potentiometry (standard additions method)

	Content*				
Compound	Nominal	Found	CV, %	Reference method†	Recovery, %‡
Zuledin injection	5	5.46	2.0 (n = 10)	5.24	101 ± 3.5 (n = 7)
Largactil tablets	100	106	1.7 (n = 10)	99	100 ± 4.4 (n = 5)
Ancholactil tablets	100	94	4.0 (n = 5)	90	—
Antistress tablets	100	105	1.5 (n = 5)	—	—

* Contents are given as mg ml^{-1} for liquid preparations, otherwise as mg per tablet.

† The reference method was according to the USP.[14]

‡ With respect to amount taken. Additions were made to the drug solution, following the extraction from tablets, or directly to the diluted injection preparation.

Table 4. Assay of amitriptyline in pharmaceutical preparations by direct potentiometry (standard additions method)

Compound	Content/mg per tablet			
	Nominal	Found	CV, % ($n = 5$)	Reference method
Stelminal	25	21.3	2.6	21.1‡
Limbitrol* . .	12.5	11.2	2.0	13.5§
Saroten Retard	75	78.1	1.2	74.5§
Minitran† . .	25	25.5	3.3	30.0¶

* This preparation also contained 5 mg of chlordiazepoxide per tablet.

† This preparation also contained 4 mg of perphenazine per tablet.

‡ The reference method was according to the BP.[15]

§ The reference method was that used by the Greek National Drug Organisation, which utilises a solvent extraction step followed by spectrophotometry.

¶ This assay was based on the measurement of the chloride content by flow injection analysis. This preparation also contained 4 mg of perphenazine per tablet.

tion was determined with the electrode. We found no measurable propantheline, which suggests that the electrode only responds to the non-hydrolysed drug.

Analytical Applications

The drugs present in pharmaceutical preparations can be determined after their dissolution in water or buffer by direct potentiometry (standard additions method) or by potentiometric titration. The results of the assay of chlorpromazine in pharmaceutical preparations by direct potentiometry are given in Table 3. Zuledin injection and Largactil tablets were also analysed by potentiometric titration with sodium picrate at pH 3.3 (acetate buffer). This titrant was found to be more satisfactory than sodium tetraphenylborate because of improved precision. The results of the titrations were 5.10 mg ml^{-1} [coefficient of variation (CV) = 3.6%, $n = 3$] for Zuledin and 115 mg per tablet (CV = 0.8%, $n = 3$) for Largactil. The results suggest that the direct potentiometric methods are to be preferred to the titration methods because the titrations are more time consuming. The results for the determination of amitriptyline in pharmaceutical preparations are given in Table 4. The preparations Stelminal and Saroten Retard were also analysed by potentiometric titration with sodium picrate at pH 3.3 (acetate buffer). The results were 23.4 mg per tablet (CV = 0.6%, $n = 3$) and 73.3 mg per tablet (CV = 2.3%, $n = 3$), respectively. Chlordiazepoxide (a constituent of Limbitrol) and perphenazine (a constituent of Minitran) are weak interferents with the amitriptyline electrode. However, these compounds did not affect the assay results obtained by the electrode procedure because chlordiazepoxide was insoluble at the pH of the assay (*ca.* pH 6) and perphenazine was present at a much lower concentration than amitriptyline.

The results for the determination of propantheline in pharmaceutical preparations are given in Table 5. It was found that propantheline was not released quantitatively from the tablets by simple extraction with water or any buffer in the pH range 1–8. Therefore, we applied the extraction procedure proposed by Chatten and Okamura,[16] which yielded quantitative recoveries.

Table 5. Assay of propantheline in pharmaceutical preparations

	Content/mg per tablet			
	Nominal	Found	CV, %	Reference method*
Pro-banthine . .	15	15.9	2.1 ($n = 5$)	15.0
Flogonevrine . .	15	15.0	5.4 ($n = 4$)	19.3
Proalusin-L . .	20	21.6	2.2 ($n = 4$)	23.6

* As a reference we used a titrimetric method for halides with $AgNO_3$. The end-point was determined potentiometrically with a silver wire as indicator electrode and a double-junction Ag - AgCl reference electrode (external solution 10% NH_4NO_3). The preparations Flogonevrine and Proalusin-L also contained 2.5 and 3 mg of chlordiazepoxide hydrochloride per tablet, respectively. The higher results for these preparations obtained with the reference method are due to coprecipitation of AgCl with AgBr.

We determined meperidine by direct potentiometry in an injection preparation (0.100 g per 2 ml) and found 0.100 g per 2 ml with CV 2.3% ($n = 4$). The reference method (see Table 5) gave 0.103 g per 2 ml.

The authors thank Dr. M. A. Koupparis for the assay of the chloride content by flow injection analysis and Dr. C. Moore for providing tetrakis(*m*-chlorophenyl)borate and tetrakis-(imidazolyl)borate.

References

1. Diamandis, E. P., Athanasiou-Malaki, E., Papastathopoulos, D. S., and Hadjiioannou, T. P., *Anal. Chim. Acta*, 1981, **128**, 239.
2. Christopoulos, T. K., Diamandis, E. P., and Hadjiioannou, T. P., *Anal. Chim. Acta*, 1982, **143**, 143.
3. Diamandis, E. P., and Christopoulos, T. K., *Anal. Chim. Acta*, 1983, **152**, 281.
4. Mitsana-Papazoglou, A., Diamandis, E. P., and Hadjiioannou, T. P., *Anal. Chim. Acta*, 1984, **159**, 393.
5. Coşofreţ, V. V., *Ion-Select. Electrode Rev.*, 1980, **2**, 159.
6. Coşofreţ, V. V., and Buck, R. P., *Ion-Select. Electrode Rev.*, 1984, **6**, 59.
7. Coşofreţ, V. V., "Membrane Electrodes in Drug-substances Analysis," Pergamon Press, Oxford, New York, 1982.
8. "The Pharmaceutical Codex," Eleventh Edition, Pharmaceutical Press, London, 1979.
9. Cammann, K., "Working with Ion-selective Electrodes," Springer-Verlag, Berlin, 1979.
10. Coşofreţ, V. V., and Buck, R. P., *Analyst*, 1984, **109**, 1321.
11. Diamandis, E. P., and Hadjiioannou, T. P., *Anal. Lett.*, 1980, **13**, 1317.
12. Christopoulos, T. K., Diamandis, E. P., and Mitsana-Papazoglou, A., *Analyst*, in the press.
13. Beermann, B., Mellström, K., and Rosen, A., *Clin. Pharmacol. Ther.*, 1971, **13**, 212.
14. "United States Pharmacopeia, Twentieth Revision," US Pharmacopeial Convention Inc., Rockville, MD, 1980, p. 143.
15. "The British Pharmacopoeia 1980," HM Stationery Office, London, 1980, p. 732.
16. Chatten, L. G., and Okamura, K. O., *J. Pharm. Sci.*, 1973, **62**, 1329.

Paper A5/38
Received February 4th, 1985
Accepted March 21st, 1985