Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Pharmaceutical and Biomedical Analysis 41 (2006) 1280–1286
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Flow injection potentiometric determination of chlorpromazine

M. Goreti F. Sales *, José F.C. Tomás, Sandra R. Lavandeira

CEQUP, Instituto Superior de Engenharia do Porto, Department of Chemical Engineering, Porto, Portugal

Received 19 January 2006; received in revised form 20 March 2006; accepted 23 March 2006
Available online 2 May 2006

Abstract

New chlorpromazine selective electrodes with a tubular arrangement and no internal reference solution are proposed. Selective membranes are of poly(vinyl chloride) (PVC) with the tetraphenylborate·chlorpromazine (TPB·CPZ) ion-exchanger dissolved in *o*-nitrophenyl octyl ether (*o*NPOE). Analytical features of the electrodes were evaluated on a single-channel flow assembly having 500 μl injection volumes and flow-rates of 4.5 ml min^{-1}. For a carrier solution of 3.3×10^{-3} M in sodium sulphate, Nernstian response was observed over the concentration range 1.0×10^{-5} to 1.0×10^{-2} M. Average slopes were about 59 mV $decade^{-1}$ and squared correlation coefficients were >0.9984. Slight *hiper*-Nernstian behaviour was observed in buffer solutions of 4.4 pH; average slopes were of 62.06 mV $decade^{-1}$. The electrode displayed a good selectivity for CPZ, with respect to, several foreign inorganic and organic species.

The selective electrodes were successfully applied to the analysis of pure solutions and pharmaceutical preparations. Proposed method allows the analysis of 84 samples h^{-1}, producing wastewaters of low toxicity. The proposed method offers the advantage of simplicity, accuracy, applicability to coloured and turbid samples, and automation feasibility.

Keywords: Chlorpromazine; Ion-selective electrodes; Flow injection analysis; Potentiometry; Pharmaceuticals

1. Introduction

Chlorpromazine (CPZ) is a phenothiazine drug with an aliphatic side chain, used in the management of psychotic conditions [1]. It controls excitement, agitation and other psychomotor disturbances in schizophrenic patients and reduces the manic phase of manic-depressive conditions. It is used to control hyperkinetic states and aggression and is sometimes given in other psychiatric conditions for the control of anxiety and tension. CPZ is also used in palliative care to act as an anti-emetic.

Several methods have been reported for the quantitative determination of CPZ in pure solution and/or in pharmaceutical preparations. Most of them imply optical-based methods, namely spectrophotometric [2–15] and fluorimetric [16–19] procedures that regard several chemical transformations of CPZ. In this context, the oxidation of CPZ has been extensively explored, using as oxidising reagents V(V) [2,3], Cr(VI) [4], Fe(III) [5,6] and Ce(IV) [7–9,16]. High performance liquid chromatography (HPLC) [20–26], voltametric [27–30] and polarographic [31] procedures have been reported as well. Globally, all these methods involve several time-consuming manipulation steps and require sophisticated equipment, being also a source of wastewaters of considerable high toxicity.

Ion-selective electrodes (ISEs) have found vast applications in diverse fields of analysis [32–34], due to their high precision, low cost of analysis, selectivity and sensitivity over a wide range of concentrations [35]. In addition, they are easy to construct and manipulate and no sample pre-treatment is needed before analysis itself. However, no work has been done on the development of ISEs for the determination of CPZ which has considerable application in the laboratory of drug control and in many other biological and chemical research areas, especially when applied in the flow injection analysis (FIA) mode, providing high sampling through outputs. Politou et al. reported a poly(vinyl chloride) (PVC) membrane sensor for CPZ control in charcoal studies that are performed in steady state [36,37]. Their analytical features were, however, unsatisfactory with regard to linear ranges (mainly along the 10^{-4} M decade) and sub-Nernstian behaviour (−54 to −56 for 37 °C). Indirect potentiometric CPZ readings in flow media were also reported [38]. They regard the potentiometric determination of Pb^{2+} after its consumption by redox reaction with CPZ.

* Corresponding author. Tel.: +351 2 28340500; fax: +351 2 28321159.
E-mail address: mgf@isep.ipp.pt (M.G.F. Sales).

0731-7085/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2006.03.027

In the present work, ISEs based on incorporation of different levels of tetraphenylborate·chlorpromazine (TPB·CPZ) ion-exchanger in plasticized PVC membranes are proposed. The electrodes are evaluated in FIA mode, which provides several analytical advantages such as low cost, simple instrumentation, rapid response, high reproducibility, high selectivity, and high sensitivity. Preliminary flow studies select the membrane composition and the analytical features of the selected sensing device are described. Application of proposed potentiometric procedure is also established.

2. Experimental

2.1. Instrument

The flow injection setup was composed by a four-channel peristaltic pump Gilson® Minipuls 3 fitted with Tygon® tubing (2.00 mm i.d.) and a four-way Rheodyne 5020 injection valve of exchangeable sample loop. All components were gathered by PTFE tubing (Omnifit, Teflon, 0.8 mm i.d.), Gilson® end-fittings and connectors. The support devices for tubular and reference electrodes [39] were made in Perspex®.

The electrodes were connected to a Crison® μpH 2002 decimilivoltammeter (±0.1 mV sensitivity) interfaced to a Kipp & Zonnen strip chart recorder, model BD 111. The reference electrode was an Orion, 90-02-00, of double junction, and the selective electrode had a solid contact made of graphite (epoxy resin was used to bind graphite powder) arranged with a tubular configuration [40]. If adjusted to steady state, the electrochemical system would be composed as follows: graphite contact|membrane|test solution||Na_2SO_4 salt bridge||Ag/AgCl (3 M KCl). When necessary, pH values were controlled by means of a Crison® CWL/S7 combined glass electrode connected to a decimilivoltammeter Crison®, pH meter, GLP 22.

2.2. Reagents and solutions

Deionised water of conductivity <0.1 $\mu S\,cm^{-1}$ was used throughout. All chemicals were of analytical grade or similar—CPZ hydrochloride (CPZ·HCl, Fluka), barium chloride (Merck), hydrochloric acid (37%, Merck), nitric acid (65%, Merck), fructose (Merck), glucose (Merck), sacarose (Merck), sodium hydroxide (Merck), sodium sulphate (Merck), potassium chloride (Merck), magnesium chloride (Riedel-deHaën), *o*-phosphoric acid (85%, Merck), calcium nitrate (Merck), and dihydrogenphosphate sodium (Riedel-deHaën) were used. For the selective membrane preparation sodium TPB (Aldrich), *o*NPOE (Fluka), PVC of high molecular weight (Fluka) and tetrahydrofuran (THF, Riedel-deHaën) were used.

Ionic strength (IS) of solutions was adjusted to 1.0×10^{-2} M by means of a 3.3×10^{-3} M Na_2SO_4 solution. Simultaneous pH and IS adjustments were attained with a H_3PO_4/NaH_2PO_4 buffer of 4.4 pH and 1×10^{-2} M IS. Standard solutions ranged 5.0×10^{-6} to 1.0×10^{-2} M. These were prepared by accurate dilution of a stock CPZ·HCl solution of 1.0×10^{-1} M with an IS and/or pH adjuster solution. Solutions of 1.0×10^{-4}, 2.0×10^{-4}, 4.0×10^{-4} and 6.0×10^{-4} M of potassium chloride, magnesium chloride, barium chloride, calcium chloride, sucrose, glucose or fructose were prepared in IS adjuster solution and used at selectivity studies.

Pharmaceutical preparations analysed were purchased from local drug stores.

Table 1
Overall composition (%, w/w) of CPZ selective membranes

	Components		
	I	II	III
TPB·CPZ	0.7	2.0	3.2
*o*NPOE	69.4	68.7	67.9
PVC	29.9	29.3	28.9

2.3. Preparation of ISEs

The selective electrodes were obtained after applying membrane solutions in a tubular shape support, constructed as described elsewhere [40]. This support may be reused after suitable removal of the old membranes and convenient cleaning of the hole with THF.

Preparation of the PVC membranes started with the synthesis of the ion-exchanger. It was carried out by precipitation of TPB·CPZ after mixing 50 ml of a 1.0×10^{-2} M CPZ·HCl solution with 50 ml of a 1.0×10^{-2} M sodium TPB solution. Resulting solid was isolated by filtration, thoroughly washing with water, and kept in a dark flask inside a dessicator in order to prevent alterations caused by light and humidity. Sensor solutions were prepared by dissolving an appropriate amount of sensor in about 0.2000 g of *o*NPOE. These were added of 0.09 g of PVC formerly dissolved in 2 ml of THF. Composition of the resulting membranes is presented in Table 1.

After application in the tubular support, each membrane was let dry for 24 h. The resulting electrodes were first preconditioned by soaking for about 3 h in a 1×10^{-3} M CPZ·HCl solution prepared in water, and making use of a closed loop circuit device.

2.4. Potentiometric measurements

All potentiometric measurements were carried out at room temperature. Solution had an IS of at least 1.0×10^{-2} M and concentrations were used instead of activities. General working characteristics of the CPZ selective electrodes were evaluated after calibration procedures carried out in a single-channel manifold (Fig. 1). The setup had as carrier a solution enabling the IS adjustment of test solutions or a suitable buffer that allowed fixed pH and IS at test solutions. The injection volume was of 500 μl and the flow-rate was 6.5 ml min^{-1}. Each calibration was attained by injecting to the flow stream a series of freshly prepared solutions of CPZ·HCl covering the range of 5.0×10^{-6}–1.0×10^{-2} M. The corresponding peak heights were converted to potentials and used to plot calibration graphs.

The effect of pH of a test solution (5.0×10^{-4} M) on the electrode response was investigated by following the variation

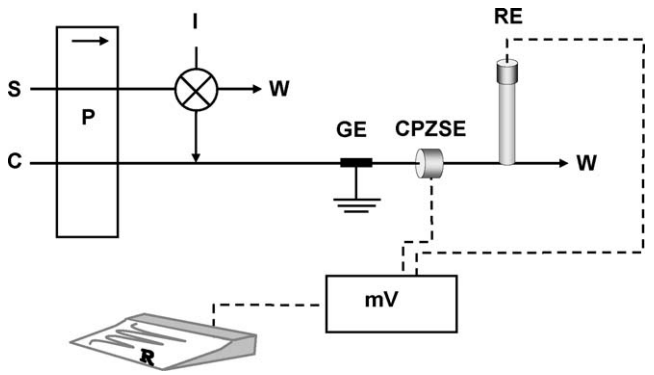

Fig. 1. Schematic diagram of the flow injection system P: peristaltic pump; S: sample; C: IS and/or pH adjuster solutions; I: injection valve; GE: grounding electrode; CPZSE: CPZ selective electrode; RE: reference electrode; w: waste; mV: decimilivoltammeter; R: recorder.

in potential with change in pH by addition of very small amounts of concentrated hydrochloric acid or saturated sodium hydroxide solution. A high volume of test solution was used (200 ml) to ensure a constant chlorpromazinium ion concentration. The sampling line of the flow setup was dipped in solution and formed a closed circuit by dipping its exit in the same solution. For each pH value – measured by a combined glass electrode dipped as well in the test solution – an aliquot of 500 μl of test solution was injected in the flow stream.

Selectivity evaluations required the injection of pure CPZ or interfering compound solutions of 1.0×10^{-4}, 2.0×10^{-4}, 4.0×10^{-4} and 6.0×10^{-4} M, into an IS adjuster carrier.

2.5. Samples analysis

For analysis of pharmaceutical preparations, appropriate weights of grounded tablets (Largactil® 100 and Largactex® 25) or volumes of oral solutions (Largactil® or Largactex®) or injection (Largactil®), containing an amount of 16 mg of CPZ were taken for dissolution or dilution up to a final volume of 50.00 ml in suitable buffer. A concentration of about 1.0×10^{-3} M in CPZ was expected for this solution. It was diluted after with the same buffer in order to obtain sample solutions of 2.5×10^{-5} M in CPZ. The latter was injected directly into the flow system for its potentiometric analysis. The same samples were analysed by the official method described elsewhere [41].

3. Results and discussion

3.1. Membrane composition

Three membrane compositions were prepared by varying the percentage of ion-exchanger while keeping the amounts of PVC and plasticizer. A borate derivative was used as ion-exchanger. Ion-exchangers of this kind are widely used in potentiometric analysis because they provide selective readings for a wide range of organic molecules [33], and represent low cost and low environmental impact. *o*NPOE was used as plasticizer. It is characterised by a high dielectric constant [42] and was selected after our previous studies pointing out that this feature enhanced sensitivity and selectivity [43,44]. A tubular arrangement was always present as it decreases dead volume and the response time of the detector.

Main analytical features of the selective electrodes were evaluated in a single-line FIA setup; the sample was injected in a carrier stream of IS adjuster solution (Fig. 1). Flow measurements were carried out at this stage with 500 μl injection volumes and 4.6 ml min^{-1} flow-rates. These conditions ensured dispersion values close to those of steady state.

The results showed that electrodes gave Nernstian responses, with slopes ranging 59.6–58.5 mV $decade^{-1}$, over a wide concentration range. Detection limits were found to be about 8×10^{-6} M. The analytical signal drifted about ± 0.4 mV for consecutive injections of a 1.0×10^{-4} M CPZ solution.

Response time of the potentiometric devices was evaluated in terms of analytical frequency as this feature was conditioned by the flow-rate. Average analytical frequencies ranged 75–80 injections h^{-1}. Standard solutions within 2.0×10^{-5}–4.0×10^{-4} M of CPZ were considered for this calculation.

Since the prepared sensors behaved similarly, the one presenting a medium amount of ion-exchanger was selected. Higher concentrations could have favoured an extended life span of the potentiometric sensor, but a significant increase of it could contribute as well to an increase at the lower limit of linear range within time.

3.2. Optimisation of flow conditions

Important variables of a single-line flow setup are confined to sampling volumes and flow-rates. The length of the tubing from injection valve port to electrochemical cell was made as small as possible to minimize dispersion and dilution. The optimisation was carried out in a multivariate mode, by checking the analytical signals produced after injecting 200, 500 and 1000 μl sampling volumes, in carrier streams of 2.6, 4.6, 6.5, 8.5 and 10.5 ml min^{-1} flow-rates. Each condition was set for tracing calibration curves with five standard solutions ranging 5.0×10^{-5}–1.0×10^{-2} M and prepared in IS adjuster.

Recordings attained were evaluated in terms of dispersion, signal percentage to steady state, and sampling-rates. Important analytical features such as slope, linear concentration ranges and sampling-rates were also considered. Transversal comparison within these features pointed out a 500 μl loop and a 6.5 ml min^{-1} flow-rate.

Peaks heights increased with increasing sampling volumes. Concomitantly, a decrease in both dispersion and sampling-rates could be observed (Fig. 2). A slight improvement at sensitivity that was coupled to extended linearity ranges was also recorded. Selection of the highest injection volume would, however, decrease sampling-rates and increase both toxicity of wastewaters produced after this work and consumption of reagents. Thus, a global perspective of the results suggested the selection of 500 μl injection volumes.

Increase of flow-rates reduces the residence time of the sample. Thus, increase in the flow-rate augmented both dispersion and sampling-rates of the potentiometric response

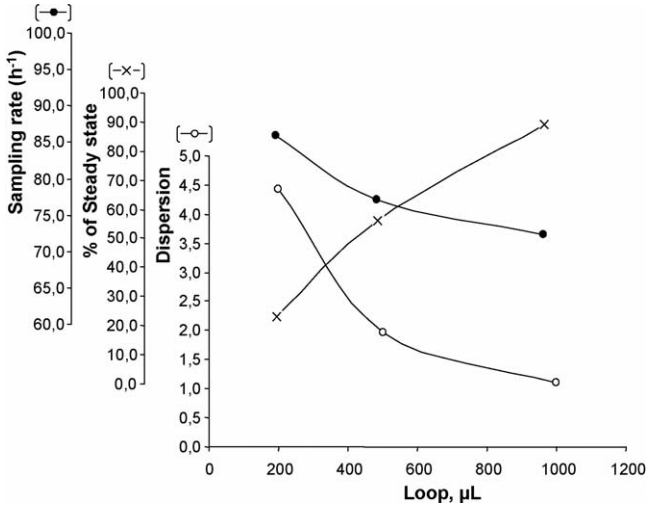

Fig. 2. Effect of loop at relevant flow parameters.

(Fig. 3). In addition, peaks became narrower taking less time to recover the baseline. As a compromise, a 6.5 ml min^{-1} flow-rate was selected, providing suitable analytical features and high sampling-rates with low consumption of carrier solution/reagents.

3.3. Effect of pH

Potentials of a standard solution of constant CPZ concentration and variable pHs were plotted. The results indicated that the electrode did not respond to the pH change in the range 4–9. Lower pHs rendered an increase of the analytical signal. Since the CPZ selective electrode responds to a cationic species, this increase in potential was correlated to an interference of H^+. Above pH 9, potentials started decreasing. This behaviour was attributed to the formation of the free CPZ base in the solution, leading to a decrease in the concentration of chlorpromazinium ion. This was confirmed by a perceptible precipitation occurring at higher pH values. Facing the wide operational pH range, a pH of 4.4 was selected because solubility and ionisation of CPZ were both promoted by acidic solutions.

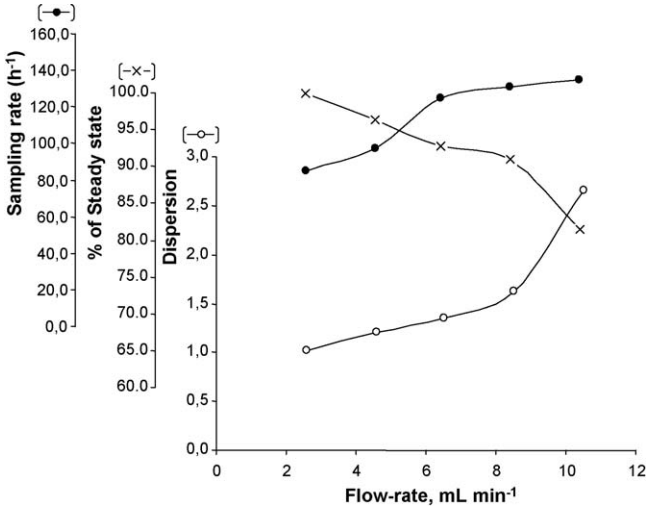

Fig. 3. Effect of flow-rate at relevant flow parameters.

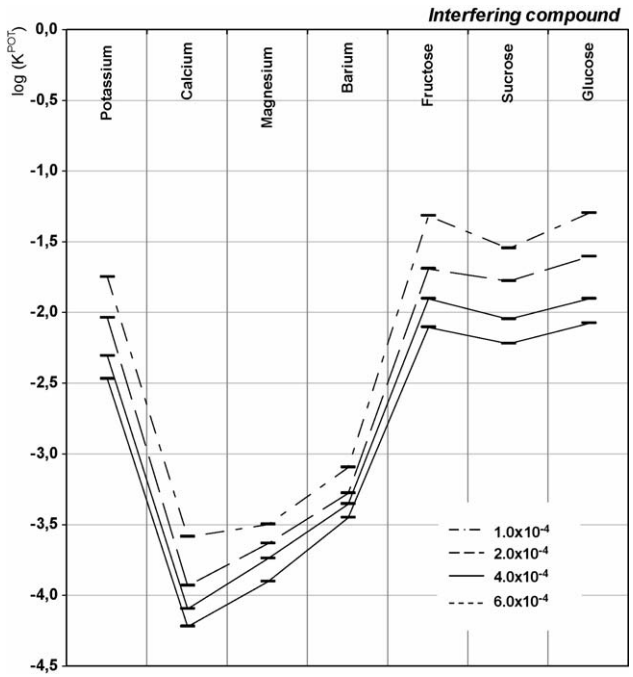

Fig. 4. Selectivity coefficients (in $\log K^{POT}$) of CPZ selective electrodes for several interfering concentrations (in M).

3.4. Selectivity of the electrodes

The influence of some inorganic cations and sugars was investigated in flow conditions. The values of selectivity coefficients were calculated after potential values measured at the top of the peak for the same concentrations of the drug and the interfering species, according to the separated solutions method [45]. The selectivity coefficients, calculated in $\log K^{POT}_{CPZ^+,J^{z+}}$, are indicated in Fig. 3 and were calculated after the equation:

$$\log K^{POT}_{CPZ^+,J^{z+}} = \frac{E_2 - E_1}{S} + \left(1 - \frac{1}{z}\right) \times \log 1.0 \times 10^{-4}$$

E_1 is the electrode potential in a 1.0×10^{-4} M CPZ solution, E_2 the potential of the electrode facing a 1.0×10^{-4} M concentration in interfering species J^{z+}, and S the practical slope calculated after the calibration experiments. The same principle was applied to the concentrations 2.0×10^{-4}, 4.0×10^{-4} and 6.0×10^{-4} M. The relative order of interference was $Ca^{2+} \approx Mg^{2+} < Ba^{2+} < K^+ <$ sucrose $<$ fructose $\leq$ glucose, with lower interference for higher concentrations (Fig. 4).

Among organic compounds, carbohydrates were tested. Because they are molecules, their interference should have been calculated by a different strategy, namely the matched potential [46]. In this method, the potentiometric selectivity coefficient is defined as the activity ratio of the primary and interfering ions that give rise to the same potential change under identical conditions. In practice, several concentration levels of primary ion were tried out, but no potential match was found. Thus,

Table 2
Working characteristics of CPZ selective electrodes

Analytical features	Type II sensor	
	IS (1×10^{-2} M)	IS (1×10^{-2} M) and pH (4.4)
LLLR (M)[a]	1.0×10^{-5}	1.0×10^{-5}
Slope (mV decade^{-1})	59.07 ± 1.42	62.06 ± 0.63
Repeatability ($\pm$mV)[b]	± 0.53[c]	± 0.99[d]
R-squared	>0.9984	>0.9974
Analytical frequency (peaks h^{-1})	74[e]	78[e]
Operational pH[f]	4.1–8.8	–

[a] Lower limit of linear range.
[b] Average of 15 consecutive readings of CPZ standard solutions.
[c] 1.00×10^{-3} M.
[d] 1.00×10^{-4} M.
[e] 5.00×10^{-3} M.
[f] 5.00×10^{-4} M.

and solely for comparison purposes, interference from carbohydrates was tested after the separated potential method; they were assumed as singly charge cations in order to consider their highest possible interference. Results were similar for all carbohydrates, and indicated a negligible interference as well (Fig. 4).

The calculated selectivity coefficients reflect a high selectivity of the proposed electrodes. In case of non-ionic species, the high selectivity is mainly attributed to the difference in polarity and to the moderate hydrophobic nature of their molecules relative to CPZ cation. The mechanism of selectivity is mainly based on the electrostatic environment and it is dependent on how good the fit is between the locations of the liphophilicity sites in the two competing species in the test solutions and those present in the receptor of the ion-exchanger [47].

Selectivity evaluation in flow conditions may also have favoured this feature as sample and interfering species remain in contact with the sensing device for a short period of time. The transient nature of the signal in FIA helps to overcome the effect of the interfering ions if the response to these ions is slower than that of the target analyte.

3.5. General analytical features

Working characteristics of the potentiometric units were evaluated with a flow setup with formerly selected conditions and having as carrier an IS adjuster solution. As required for a single-channel FIA system, standard solutions were always prepared in carrier. Nernstian responses were observed again, having calibration plots of 59 mV decade^{-1} slopes over a wide concentration range (Table 2). The analytical signal drifted about ± 0.5 mV for consecutive injections of a 1.0×10^{-4} M CPZ solution. Analytical frequency was about 70 samples h^{-1}.

When carrier solution was a suitable buffer (pH 4.4 and 1.0×10^{-2} M IS), similar behaviour was observed. Only a slight slope increase, of about 5%, that provided slight *hiper*-Nernstian behaviour is of reference (Table 2).

The lifetime of the proposed electrode was calculated after performing periodic calibrations with standard solutions and calculating the response and slope over the range 4.0×10^{-5} to 4.0×10^{-3} M CPZ·HCl solutions. It was found that the electrode showed no significant divergence of slope and sampling-rates over at least 5 months. During this period, electrodes were left soaking while not in use.

4. Analytical applications

CPZ was successfully determined in pure solutions and in commercial pharmaceutical preparations after calibration procedures under constant pH and IS. The calibration curves ranged 1.0×10^{-5} to 6.0×10^{-4} M of CPZ (Fig. 5). The potentiometric results are given in Tables 3 and 4. They represent the mean values and the corresponding standard deviation of five determinations carried in separate runs.

With regard to the analysis of pure solutions, different concentration levels were tried out. Mean recovery values were

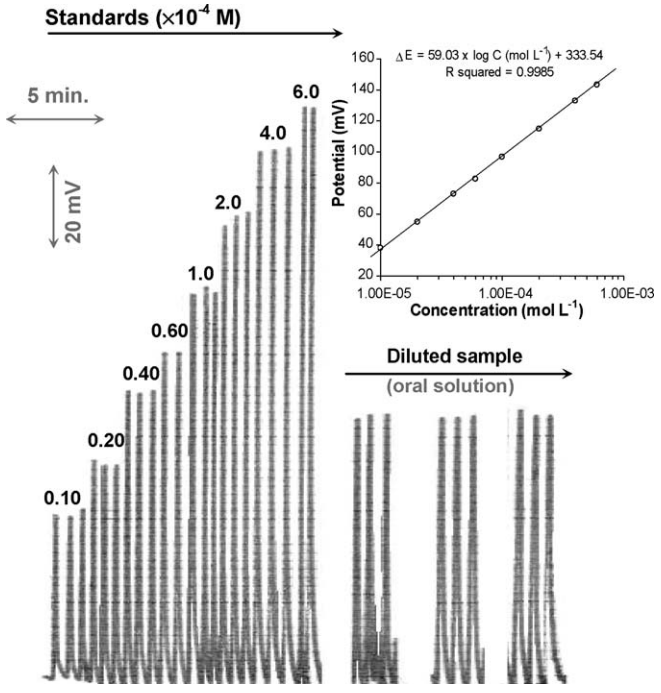

Fig. 5. FIA output for injection of standard and diluted sample solutions. Inset: corresponding calibration curve.

Table 3
Potentiometric determination of CPZ in pure solutions

CPZ concentration (mg l^{-1})		Recovery (%)	R.S.D.[a] (%)	Relative error (%)
Taken	Found			
31.9	32.7 ± 1.2	102.7	3.8	+2.7
63.8	66.8 ± 2.9	104.7	4.3	+4.7
127.3	127.1 ± 2.4	99.5	1.9	−0.5

[a] Relative standard deviation.

Table 4
Determination of CPZ by proposed (POT) and comparison (USP) methods, relative errors (RE) and calculated *F*-value

Formulation	CPZ (labelled unit)			RE (%)	*F*-test
	Labelled	POT	USP		
Largactil® (oral solution)	40 (mg ml^{-1})	41.4 ± 1.2	37.9 ± 0.4	+9.5	7.1
Largactex® (oral solution)	40 (mg ml^{-1})	40.8 ± 2.3	42.6 ± 0.2	−4.2	3.9
Largactil® (injection)	50 (mg $injection^{-1}$)	51.9 ± 2.3	49.0 ± 0.9	+5.8	6.5
Largactil® 100 (tablets)	100 (mg $tablet^{-1}$)	97.9 ± 5.4	98.4 ± 2.7	−0.5	1.9
Largactex® 25 (tablets)	25 (mg $tablet^{-1}$)	23.6 ± 0.9	24.4 ± 0.5	−3.1	3.7

close to 100% (Table 3). Results of the commercial formulations were compared to those provided by the official method. The statistical Student's *t*-test and the *F*-tests were selected for this purpose. Considering as null hypothesis that the two methods agree, a paired two-tail test for 5% level of significance gave a calculated *t* (0.632) below the tabulated one ($t_{0.025,4} = 2.160$), therefore accepting the null hypothesis. The comparison of variances attained for each sample was made by the *F*-test using the same assumptions as for the Student's *t*-test, and the calculated values (Table 3) were always below the critical *F*-value ($F_{0.025(5,2)} = 9.60$), thus confirming the null hypothesis. This means that the potentiometric results are of comparable precision to those of the official method and there is no significant difference between the mean values obtained by both methods. In addition, plotting results of official method against proposed one gives a slope close to unit (0.9873), a small origin displacement (1.3103), and a squared correlation coefficient of 0.993.

Regarding reagent consumption, each calibration procedure with eight standard solutions required about 94 ml of phosphate buffer and 1.5 ml of each standard solution (considering three injections per standard). Moreover, several FIA records demonstrated the possibility of analysing at least three diluted samples without requiring re-calibration.

The standard deviation of three consecutive diluted samples injected in triplicate (Fig. 5), was of ±0.7 mV, thus confirming the repeatability of the proposed method. Sampling-rates were about 84 samples h^{-1} when real samples were injected.

The environmental effect of the emitted effluents was considered of small concern. They contain mostly phosphate and a small amount of CPZ. Concerning the analysis of samples, an effluent with 2.2×10^{-6} M in CPZ is expected, while effluents from the calibration may contain 2.3×10^{-5} M. The latter could be decreased to about 3.6×10^{-6} M if calibration would be performed within 1.0×10^{-5} and 6.0×10^{-5} M, including the concentration range of diluted samples. Moreover, the environmental effect of the emitted effluents is connected to the receptor; for instance, phosphate may be of interest to agriculture. An adjustment of pH before discard is most certainly required and CPZ may be decomposed or isolated by precipitation if necessary. The total volume of effluent is also quite low, producing an average of 390 ml h^{-1}.

5. Conclusions

Proposed CPZ potentiometric detectors are simple, of low cost and easy to manipulate. Their inclusion in FIA setups provides an advantageous alternative method for CPZ determinations. The overall procedure is precise, accurate, and inexpensive regarding reagent consumption and equipment involved. Considering its routine application, a main advantage arises from composition and quantity of emitted effluents, with small concern in terms of environmental issues. Aside from dissolution and dilution, no sample pre-treatment or separation steps are required. The proposed method also enables high sampling frequencies with low operator intervention, for which it is suitable for the routine procedures carried out at pharmaceutical industries and analytical laboratories. Lifetime of the detector is estimated in at least 5 months, as longer periods were not tested. Globally, the described method constitutes a good alternative to others previously described in literature, as it offers advantages of fast response, good selectivity, long-term stability, low cost, applicability over a wide pH range with minimal sample pre-treatment and low toxicity wastewaters.

References

[1] T.J.R. Lambert, D.J. Castle, Schizophrenia MJA 178 (2003) S57–S61, accessed on-line at: http://www.mja.com.au/public/issues/178_09_050503/lam10582_fm.pdf.
[2] S.U. Zhang, W.B. Hu, W.W. Li, S.M. Zhang, J. Wuhan Univ. Technol. 13 (1998) 45–49.
[3] S.M. Sultan, Analyst 116 (1991) 177–181.
[4] S.M. Sultan, Talanta 40 (1993) 681–686.

[5] M.R.M. Santoro, S. Storpirtis, E.R.M. Hackmann, J.F. Magalhães, Anal. Lett. 22 (1989) 929–949.
[6] M.A. Koupparis, A. Burchova, Analyst 111 (1986) 313–318.
[7] Y.M. Huang, Z.H. Chen, Talanta 57 (2002) 953–959.
[8] S.M. Sultan, M.O.H. Al-Turabi, Talanta 51 (2000) 327–331.
[9] F.E.O. Suliman, S.M. Sultan, Talanta 41 (1994) 1865–1871.
[10] B. Starczewska, J. Trace Microprobe Tech. 16 (1998) 151–155.
[11] B. Starczwska, J. Karpinska, Anal. Lett. 29 (1996) 2475–2486.
[12] T. Ghous, A. Townshend, Anal. Chim. Acta 387 (1999) 47–51.
[13] M.I. Albero, M.S. Garcia, C.S. Pedreno, J.A. Canovas, An. Quim. 89 (1993) 611–616.
[14] A.A. Fasanmade, A.F. Fell, Analyst 110 (1985) 1117–1124.
[15] J. Karpinska, Anal. Lett. 33 (2000) 1555–1566.
[16] T. Aman, A. Rashid, I. Khokhar, J. Iqbal, Anal. Lett. 30 (1997) 109–119.
[17] J.M. Calatayud, C.G. Benito, Anal. Chim. Acta 256 (1992) 105–111.
[18] D. Chen, A. Rios, M.D.L. DeCastro, M. Valcarcel, Talanta 38 (1991) 1227–1233.
[19] F.A. Mohamed, Anal. Lett. 58 (1995) 2491–2501.
[20] I.F.S. Chagonda, J.S. Millership, Analyst 113 (1988) 233–237.
[21] D. Stevenson, E. Reid, Anal. Lett. B 14 (1981) 1785–1805.
[22] D.J. Smith, J. Chromatogr. Sci. 19 (1981) 65–71.
[23] D.M. Takahashi, J. Pharm. Sci. 69 (1980) 184–187.
[24] C.M. Davis, C.A. Harrington, J. Chromatogr. Sci. 22 (1984) 71–74.
[25] A.C. Mehta, Analyst 106 (1982) 1119–1122.
[26] K.K. Midha, J.K. McGilveray, A.G. Butterfield, J.W. Hubbard, J. Pharm. Sci. 70 (1981) 1043–1046.
[27] Y.N. Ni, I. Wang, S. Kokot, Anal. Chim. Acta 439 (2001) 159–168.
[28] Z.Q. Zhang, Z.G. Chen, Z.G. Yang, H. Zhan, Microchem. J. 53 (1996) 282–289.
[29] S. Dermis, I. Biryol, Analyst 114 (1989) 525–526.
[30] N. Zimova, I. Nemec, J. Zima, Talanta 33 (1986) 467–470.
[31] F.W. Teare, R.N. Yadav, Can. J. Pharm. Sci. 13 (1978) 69–71.
[32] Z. Zhang, V.V. Cosofret, Sel. Elect. Rev. 12 (1990) 35–135.
[33] V.V. Cosofret, R.P. Buck, Pharmaceutical Applications of Membrane Sensors, CRC Press, Boca Raton, FL, 1992, p. 448.
[34] A.R. Fakhari, M. Alagheman, M. Shamsipur, Anal. Lett. 34 (2001) 1097–1106.
[35] V.V. Cosofret, R.P. Buck, Crit. Rev. Anal. Chem. 24 (1993) 1–58.
[36] J.A. Politou, M. Koupparis, P. Macheras, Eur. J. Pharm. Sci. 4 (1996) 223–230.
[37] J.A. Politou, P.E.O. Macheras, M.A. Koupparis, J. Toxicol.-Clin. Toxicol. 34 (1996) 307–316.
[38] A. Kojlo, Anal. Lett. 30 (1997) 2353–2363.
[39] S. Alegret, J. Alonso, J. Bartroli, J.M. Paulis, J.L.F.C. Lima, A.A.S.C. Machado, Anal. Chim. Acta 164 (1984) 147–152.
[40] S. Alegret, J. Alonso, J. Bartroli, A.A.S.C. Machado, J.L.F.C. Lima, J.M. Paulis, Quim. Anal. 6 (1987) 278–294.
[41] The United States Pharmacopoeia 24, the National Formulary 19, Official monographs for chlorpromazine hydrochloride, 2000, pp. 396–398.
[42] T. Okada, H. Sugihara, K. Hiratani, Analyst 120 (1995) 2381–2386.
[43] M.G.F. Sales, C.E.L. Amaral, C.M.D. Matos, Fresenius J. Anal. Chem. 369 (2001) 446–450.
[44] J.L.F.C. Lima, M.C.B.S.M. Montenegro, M.G.F. Sales, J. Pharm. Biomed. Anal. 14 (1996) 931–938.
[45] R.P. Buck, E. Linder, Pure Appl. Chem. 66 (1994) 2527–2536.
[46] Y. Umezawa, K. Umezawa, H. Sato, Pure Appl. Chem. 67 (1995) 507–518.
[47] N.T. Abdel-Ghani, A.F. Shoukry, R.M. El Nashar, Analyst 126 (2001) 79–85.