

Short Communication

Potentiometric determination of iodipamide using an iodipamide ion-selective electrode

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Introduction

Drug anion-selective electrodes are mostly based on Aliquat 336S [1, 2] and Fe(Bphen)₃ [3, 4]. Other quaternary ammonium compounds have also been suggested as exchange sites for the electrode, such as trioctylmethylammonium [5-7], tetraheptylammonium [8], cetylpyridinium [9] and cetyltrimethylammonium [10]. However, the linear response ranges of the electrodes are rather narrow, the lower limit of the linearity range being usually only 10⁻³-10⁻⁴ M [1, 2, 4, 8-10]. It has been found [11] that quaternary ammonium compounds with a long carbon chain in the alkyl groups can give better electrode performances than those with a short carbon chain; the electrode performance improves with an increasing number of carbon atoms in the quaternary ammonium compound, due to the additional molecular weight. It is also of interest to make a comparative study of performances of electrodes based on ion-association complexes of quaternary ammonium and quaternary phosphonium compounds.

Iodipamide, *N,N'*-di(3-carboxy-2,4,6-triiodophenyl)adipamide or 3,3'-adipoylidi-aminobis(2,4,6-triiodobenzoic acid), is a contrast medium which is used for the examination of the biliary tract. Most pharmacopoeias [12, 13] recommend determination of this substance by decomposition with powdered zinc in a sodium hydroxide solution followed by titration with silver nitrate [12] or potassium iodate [13]. The method is tedious and in-

accurate. Other methods for the assay of iodipamide include spectrophotometry [14] and acidometry [15]. Ion-selective electrode methods have also been proposed to determine iodipamide; combustion of the drug in an oxygen flask to form iodine is followed by reduction of the iodine to iodide which is then determined potentiometrically using an iodide electrode [16, 17]. But these methods are complex and time-consuming. Recently, the authors of the present paper have proposed an all-purpose indicator electrode for the potentiometric titration of drugs including iodipamide [18]. Such an electrode has poor selectivity, however, and cannot be used for the direct potentiometry of iodipamide. Therefore, it is of interest to develop a new electrode that is selective to iodipamide.

Materials and Methods

Apparatus and reagents

Potentiometric measurements were made with: a model UJ-25 precision DC potentiometer (Shanghai Electronic Instruments) and a model PHS-2 precision pH-meter (Shanghai Analytical Instruments) connected in series; an iodipamide ion-selective electrode; and a saturated calomel electrode connected to the magnetically stirred sample solution by a 1 M sodium nitrate bridge. The purity of the iodipamide was >98.0%. The synthesis of cetyltrioctylammonium iodide has been described previously [11] and comprises reaction of cetyl iodide with trioctylamine in ethanol followed

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by recrystallization from ethyl acetate. Cetyltriphenylphosphonium iodide was synthesized [19] by the reaction of cetyl iodide with triphenyl phosphine in dimethylformamide under nitrogen, followed by recrystallization from ethyl acetate. Other chemicals used were of analytical reagent grade. Double-distilled water was used.

Sodium iodipamide (0.01 M) was prepared by dissolving 0.5699 g of iodipamide in a minimum amount of a dilute solution of sodium hydroxide, adjusting to pH 10 and diluting to 50 ml with a dilute solution of sodium hydroxide (pH 10) or 0.05 M sodium fluoride (pH 10) in an amber-coloured volumetric flask. Standard series of sodium iodipamide were prepared by serial dilution with a diluted solution of sodium hydroxide (pH 10) or a 0.05 M sodium fluoride (pH 10), respectively. Care was taken to avoid absorption of carbon dioxide from air by the sodium iodipamide solution.

Synthesis of ion-association complexes

Cetyltriocetylammmonium iodipamide was synthesized by shaking 2 mM cetyltriocetylammmonium iodide in chloroform with an equal volume of 2 mM sodium iodipamide in a separating funnel for 15 min. After separation, the organic phase was treated repeatedly with the sodium iodipamide solution until no iodide was detected in the aqueous phase, dried with anhydrous sodium sulphate and filtered through dry filter paper. The chloroform was then evaporated on a water bath at 65°C. Other ion-association complexes of iodipamide were prepared in a similar way.

Electrode construction

The preparation of the membrane electrode of all-solid-state construction has been described previously [20] and comprises spreading 5–6 drops (24 drops = 1 ml) of a mixed solution [0.34 ml of 5 mM ion-association complex in dibutyl phthalate mixed with 2.4 ml of a 5% solution of poly(vinylchloride) in tetrahydrofuran] on the outer surface of the gold-plated copper disc; this disc is 10 mm dia and is firmly fixed by adhesive to one end of the poly(vinylchloride) tube (12 mm o.d., 8 mm i.d., 75 mm long, with a shallow cavity of 1.5 mm depth and 10 mm dia on the same end); an outlet wire is soldered on the inner surface of the metallic disc. The poly(vinylchloride) membrane electrode was prepared as

previously [21]. A silver/silver chloride electrode with 0.01 M sodium chloride as the reference solution was used as the internal reference electrode.

Measuring cell

Saturated calomel electrode–1 M sodium nitrate-sample solution (pH 10)-iodipamide ion-selective electrode.

Assay of iodipamide meglumine injection

One millilitre of the injection was diluted and adjusted to pH 10, transferred to a 250-ml flask and diluted to volume with a sodium hydroxide solution (pH 10). Potentiometric measurements were made in replicate on the sample solution and on a standard solution containing approximately the same concentration of iodipamide until reproducible (± 0.1 mV) values were obtained using four cells connected in series.

Results and Discussion

Effects of electroactive material and electrode construction

Conventional poly(vinylchloride) membrane electrodes and membrane electrodes of all-solid-state construction were prepared with different ion-association complexes as the electroactive material and their electrode performances were investigated to study the effect of electroactive material and electrode construction on electrode function. Results for cetyltriocetylammmonium iodipamide electrodes and cetyltriphenylphosphonium iodipamide electrodes are shown in Table 1. Both the long-carbon-chain quaternary ammonium and quaternary phosphonium compounds yield good electrode performances. The linear response ranges extend down to an iodipamide anion concentration of about 10^{-5} M, the response slopes being nearly Nernstian. Preliminary tests with membrane electrodes based on ion-association complexes of iodipamide with quaternary ammonium compounds with a shorter carbon chain in the alkyl group showed that the electrode performances (linear response range and response slope) decrease with decreasing molecular weight of the electroactive material studied in the order of cetyltriocetylammmonium > cetyltributylammmonium > cetyltrimethylammmonium. A favourable effect of the additional molecular weight of the electroactive material on elec-

Table 1
Characteristics of iodipamide ion-selective electrodes

Electroactive material	Electrode type	Slope (mV/log C)	Linearity range (M)	Detection limit (M)
Cetyltriocetylammmonium iodipamide	PVC membrane	-29.3 ± 0.2	1 × 10 ⁻² -2 × 10 ⁻⁵	4 × 10 ⁻⁶
	All-solid state	-29.8 ± 0.2	1 × 10 ⁻² -1 × 10 ⁻⁵	3 × 10 ⁻⁶
Cetyltriphenylphosphonium iodipamide	PVC membrane	-29.7 ± 0.2	1 × 10 ⁻² -5 × 10 ⁻⁵	1 × 10 ⁻⁵
	All-solid state	-29.3 ± 0.3	1 × 10 ⁻² -5 × 10 ⁻⁵	1 × 10 ⁻⁵

Measurements were made in 0.05 M sodium fluoride. Slopes are mean values of five successive measurements and their standard deviations.

trode performance was also observed in previous studies on sulphonamide ion-selective electrodes [20] and phenytoin ion-selective electrodes [11].

It is of interest that the response function of the cetyltriphenylphosphonium iodipamide electrode is less satisfactory than that of the cetyltriocetylammmonium iodipamide electrode. The linear response range of the former electrode extends down to 1 × 10⁻⁵ M iodipamide, whereas the latter electrode exhibits a linear response down to only 5 × 10⁻⁵ M, although both electrodes give nearly Nernstian anionic slopes.

No significant differences were found between the performances of the conventional poly(vinylchloride) membrane electrode and that of the membrane electrode of all-solid-state construction made with the same electroactive material. Since the membrane electrode of all-solid-state construction eliminates the use of the internal reference electrode and the internal reference solution, it can be used for determining µg-amounts of iodipamide in micro-volume samples with the inverted electrode.

Selectivity

The effect of other substances on the response of the iodipamide ion-selective electrode was examined by measuring the selectivity coefficients using the mixed-solution method. The selectivity coefficients obtained with more than 20 substances are presented in Table 2. No significant interference was caused by most of the substances tested including benzoate, glutamate, diatrizoate and nicotinate. On the contrary, such anionic species can also be detected and titrated together with iodipamide and cause significant interference in the determination of iodipamide when the general-purpose electrode [18] is used to indicate the end-point in the potentiometric titration of iodipamide.

The order of selectivity of the iodipamide selective electrode for halides is iodide > bromide > chloride > fluoride. Hence, in this work, 0.05 M sodium fluoride was used to adjust the ionic strength.

pH effect

The effect of pH on the potential readings of the iodipamide ion-selective electrode was

Table 2
Selectivity coefficients obtained with other substances*

Substance	K _{ij}	Substance	K _{ij}
Sodium fluoride	2.2 × 10 ⁻⁴	Sodium benzoate	3.3 × 10 ⁻³
Sodium chloride	1.1 × 10 ⁻³	Sodium citrate	3.3 × 10 ⁻⁴
Potassium bromide	1.1 × 10 ⁻²	Sodium aminoacetate	7.5 × 10 ⁻⁵
Potassium iodide	12.5	Sodium aminopropionate	8.0 × 10 ⁻⁵
Sodium carbonate	2.0 × 10 ⁻⁴	Sodium aspartate	1.7 × 10 ⁻⁴
Sodium sulphate	1.8 × 10 ⁻⁴	Sodium glutamate	3.2 × 10 ⁻⁴
Glucose (1%)	No interference		
Sodium acetate	3.7 × 10 ⁻⁴	Sodium sulphamate	1.7 × 10 ⁻⁴
Potassium oxalate	4.7 × 10 ⁻⁴	Sodium succinate	3.3 × 10 ⁻⁵
Urea	2.6 × 10 ⁻⁴	Sodium mandelate	4.8 × 10 ⁻⁶
Starch (1%)	No interference		
Sodium diatrizoate	2.0 × 10 ⁻²	Sodium nicotinate	2.2 × 10 ⁻²

* Using the mixed-solution method.

examined by measuring the e.m.f. of the cell in aqueous sodium iodipamide solutions of different basicity. The pH was varied by adding the appropriate amounts of sodium hydroxide and/or hydrochloric acid solutions. At pH 9.4–12.0, no significant change of the membrane potential was observed. At lower pH values, the potential shifts to less negative values due to the formation of free iodipamide acid.

Response time and reproducibility

Iodipamide ion-selective electrodes of both the conventional poly(vinylchloride) type and the all-solid-state construction type exhibit fast response. The response time ranges from 12–35 s in 10^{-2} – 10^{-4} M solutions to about 1 min in $\leq 10^{-5}$ M solutions.

The reproducibility of the potential measurements in a 10^{-3} M standard solution of sodium iodipamide was checked periodically. A shift of <0.5 mV/day in the absolute millivolt values was observed. The electrode potential was repeatedly measured in 10^{-4} – 10^{-2} M standard solutions of sodium iodipamide; a standard deviation of <0.5 mV was obtained for eight measurement cycles. No significant change in the response slope was observed during 2 months.

Performance of cells connected in series

Iodipamide has two identical carboxylic

groups in its molecule, yielding a nearly Nernstian anionic slope of only about -29 mV/log C . It was found that, when two or more cells were connected in series, the respective response slope could be increased n times, where n was the number of cells (Table 3), but the linearity range and detection limit remained unchanged. When more than six cells were used, the potential reading became less stable.

Iodipamide assay

Results for the direct potentiometric assay of iodipamide using a calibration curve are reported in Table 4. The mean recoveries were 98.9% ($n = 1$) and 99.8% ($n = 5$); the corresponding standard deviations were 3.3 and 0.9%. The accuracy of the method increased when the cells were connected in series. Results for the potentiometric titration of iodipamide with sulphuric acid yielded a mean recovery of 99.7% and a standard deviation of 1.4%. These results were in agreement with those by the argentometric titration method [12]. Both the conventional poly(vinylchloride) membrane electrode and the electrode of all-solid-state construction can be used in the potentiometric determination of iodipamide, but the latter electrode is preferred because it eliminates the use of the internal reference electrode and is more convenient to handle.

Table 3
Characteristics of cells connected in series

Number of cells	Slope (mV/log C)	Linearity range (M)	Detection limit (M)
1	-29.4 ± 0.2	1×10^{-2} – 2×10^{-5}	4×10^{-6}
2	-58.8 ± 0.4	1×10^{-2} – 2×10^{-5}	4×10^{-6}
3	-87.6 ± 0.2	1×10^{-2} – 2×10^{-5}	4×10^{-6}
4	-118.5 ± 0.15	1×10^{-2} – 2×10^{-5}	4×10^{-6}
5	-148.8 ± 0.8	1×10^{-2} – 2×10^{-5}	4×10^{-6}

Table 4
Assay of iodipamide*

Direct potentiometry			Cells connected in series			Potentiometric titration		
Taken (mg ml $^{-1}$)	Found (mg ml $^{-1}$)	Recovery (%)	Taken (mg ml $^{-1}$)	Found (mg ml $^{-1}$)	Recovery (%)	Taken (mg ml $^{-1}$)	Found (mg ml $^{-1}$)	Recovery (%)
0.0730	0.0753	103.2	0.0830	0.0838	101.0	1.18	1.19	100.8
0.216	0.207	96.0	0.316	0.313	98.9	1.05	1.07	101.9
0.355	0.369	102.4	0.410	0.410	100.0	0.426	0.419	98.4
0.558	0.538	98.4	0.568	0.571	100.5	0.941	0.935	99.4
0.688	0.668	97.1	0.708	0.701	99.0	1.37	1.36	99.3
0.816	0.788	96.6	0.926	0.921	99.5	0.873	0.869	99.5

*The recovery by the pharmacopoeial method [12] was $99.4 \pm 1.0\%$.

Assay of iodipamide meglumine injection

Iodipamide meglumine injections were analysed using a method similar to that reported previously [22]. The mean result of the potentiometric analysis of iodipamide meglumine injection with a nominal concentration of 0.3 g ml^{-1} using the cetyltrioctylammonium iodipamide electrode was 0.293 g ml^{-1} and the standard deviation for six determinations was 0.004 g ml^{-1} . The corresponding mean result (\pm standard deviation) by the pharmacopoeial method [12] was $0.290 \pm 0.004 \text{ g ml}^{-1}$.

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