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*Short Communication*

# Amantadine ion-selective membrane electrodes and their use in pharmaceutical analysis

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## Introduction

Many ion-selective membrane electrodes for organic cations or anions of pharmaceutical interest have been described [1–3]. However, some do not provide sufficient sensitivity and selectivity for the respective ions. This paper describes the preparation and the characterization of two types of amantadine-ion selective membrane electrodes. One of them uses dipicrylamine as the counter-ion in the electroactive material of the membrane and the other electrode uses dinonylnaphthalene sulphonic acid. Both electrodes have been used successfully for the assay of 1-adamantanamine hydrochloride in amantadine hydrochloride tablets by potentiometric titration with a solution of sodium tetraphenylboron.

Amantadine (1-adamantanamine) is a well known antiviral and anti-Parkinsonian drug, in therapeutic use since 1966 [4]. Analytical methods for the assay of amantadine are based on non-aqueous titration [5], potentiometry using a tetraphenylborate electrode [6], gas-chromatography [7–9], reversed-phase high-performance liquid chromatography [10], and spectrophotometry [11]. The present procedure allows the determination of 4 mg of amantadine in the drug substance or in tablets without any prior separation, with an average error of less than 2.0%.

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## Experimental

*Reagents and materials*

All reagents except amantadine were of analytical reagent grade. 1-Adamantanamine hydrochloride was synthetized in this laboratory. Amantadine hydrochloride tablets (100 mg) were also prepared in this laboratory.

All solutions were prepared with distilled water. Solutions of 1-adamantanamine hydrochloride were prepared by serial dilution while keeping both pH and ionic strength at constant values.

*Standard solution of 1-adamantanamine hydrochloride (0.1 mol $l^{-1}$)* — A 18.770 g sample of 1-adamantanamine hydrochloride was dissolved in, and diluted to 1 l with, acetate buffer (pH 4.6).

*Standard solution of sodium tetraphenylboron ($5 \times 10^{-2}$ mol $l^{-1}$)* — A 17.112 g sample of sodium tetraphenylboron was dissolved in distilled water and diluted to 1 l.

*Apparatus*

A Präcitronic digital pH/mV-meter, Model 870 MV was used for all direct potentiometric measurements.

The potentiometric titration curves were obtained using an automatic titration assembly consisting of ABU-12 Autoburette, TTT2 Titrator and SBR 2c Recorder (Radiometer). pH measurements were performed with a Radiometer G202B glass electrode in combination with a Radiometer K401 calomel electrode.

The amantadine-selective membrane electrode, based on a 1-adamantanamine–dipicrylamine ion-pair complex (Electrode A), was prepared by impregnating the support material (a graphite rod, 15 mm long, 6.5 mm diameter, made water-repellent) attached to the end of a Teflon tube, with a solution of 1-adamantanamine–dipicrylamine ion-pair complex ($5 \times 10^{-3}$ mol $l^{-1}$) in nitrobenzene. The internal reference element was made by using a stainless steel wire introduced into the graphite rod. The electrode was stored in the organic electroactive material (ion-pair complex).

The basic principle of the amantadine-selective membrane electrode construction based on 1-adamantanamine–dinonylnaphthalene sulphonic acid ion-pair complex (Electrode B) has been described elsewhere [12–14] and the PVC-membrane composition was 4.0% w/w dinonylnaphthalene sulphonic acid, 64.0% w/w 2-nitrophenyloctyl ether and 32.0% w/w PVC. The internal filling solution was $10^{-3}$ mol $l^{-1}$ 1-adamantanamine hydrochloride of pH 4.6 (acetate buffer solution). The dinonylnaphthalene sulphonic acid in the PVC membrane was converted to the ion-pair complex by soaking the electrode in 1-adamantanamine hydrochloride solution ($10^{-2}$ mol $l^{-1}$) for 24 h. When not in use, the electrode was stored in the internal filling solution.

*Potentiometric titration of 1-adamantanamine hydrochloride drug substance*

A 10-ml aliquot of the sample (containing 4–20 mg of 1-adamantanamine hydrochloride) was pipetted into the reaction cell. About 20 ml of acetate buffer solution of pH 4.6 was added, and with stirring, the solution was titrated with the standard solution of sodium tetraphenylboron using an amantadine-saturated calomel reference electrode. The inflection point of the titration curve was used to determine the end-point of the titration.

*Potentiometric assay of amantadine tablets*

Amantadine tablets were analysed by finely powdering ten tablets from the same lot. An accurately weighed portion of the powder equivalent to about 25 mg of 1-adamantanamine hydrochloride was transferred to the reaction cell and dissolved in about 10 ml of distilled water. About 20 ml of pH 4.6 acetate buffer solution was added and the potentiometric titration was carried out as described above for the drug substance.

*Content uniformity assay of amantadine tablets*

Ten individual tablets were transferred to separate 100-ml volumetric flasks and dissolved by shaking with acetate buffer solution of pH 4.6. Aliquots (25 ml) (in duplicate) from each volumetric flask were titrated potentiometrically as described above for the drug substance.

## Results and Discussion

*Membrane materials*

1-Adamantanamine, in a protonated form, as well as other amines or quaternary ammonium compounds, reacts with either dipicrylamine or dinonylnaphthalene sulphonic acid to form a stable ion-pair complex.

1-Adamantanamine-dipicrylamine ion-pair complex was dissolved in nitrobenzene and the resultant solution was used as the electroactive material for electrode A. The ion-pair complex with dinonylnaphthalene sulphonic acid was obtained *in situ*, by soaking the dinonylnaphthalene sulphonic acid–PVC membrane in a solution of $10^{-2}$ mol $l^{-1}$ 1-adamantanamine hydrochloride. Of the plasticizers tested, 2-nitrophenyloctyl ether gave the best response time and reproducibility of e.m.f. readings of the electrode. The composition of the membrane in electrode B is given in the Experimental section.

*Electrode responses*

The critical response characteristics for both electrodes are shown in Table 1. The linear range of electrode B, and consequently the usable linear range and the detection limit are superior for electrode B. This is probably because the dinonylnaphthalene sulphonic acid forms a less soluble ion-pair complex with 1-adamantanamine than that between dipicrylamine and 1-adamantanamine.

**Table 1**
Respones characteristics for the amantadine ion-selective membrane electrodes

| Parameter | Electrode A | Electrode B |
|---|---|---|
| Slope (mV/log a) | 50.4 ± 0.9* | 55.6 ± 0.8* |
| Intercept, $E_o$ (mV) | 319 ± 3.7† | 375 ± 2.9† |
| Linear range (mol $l^{-1}$) | $10^{-1}$–5 × $10^{-4}$ | $10^{-1}$–$10^{-5}$ |
| Usable range (mol $l^{-1}$) | $10^{-1}$–$10^{-4}$ | $10^{-1}$–5 × $10^{-6}$ |
| Detection limit (mol $l^{-1}$) | 5.0 × $10^{-5}$ | 4.0 × $10^{-6}$ |

*Standard deviation of average slope values for multiple calibration in $10^{-2}$–$10^{-3}$ mol $l^{-1}$ range.

†Standard deviation of values recorded during one month ($n$ = 65).

The calibration curves for the individual electrodes were found to be reproducible from day to day.

*Effect of pH*

The effect of pH on the potential of the amantadine electrodes was checked by measuring the e.m.f. of solutions of amantadine ($10^{-4}$ mol $l^{-1}$) at different pH values. Variation of pH was carried out by addition of very small volumes of hydrochloric acid or sodium hydroxide solution to aqueous solutions of amantadine hydrochloride. The plots in Fig. 1 show that the linearity of $E$(mV)–pH functions depends on the nature of the ion-pair complex used as electroactive membrane. In acidic medium, only the electrode A is strongly affected by pH. This is due to the conversion of the electroactive membrane to its $H^+$ form at pH values below 4.0. At pH values higher than 8, the potentials of both electrodes decrease because of the decreased concentration of the protonated 1-adamantanamine which is converted to free base.

*Selectivity of the electrodes*

Potentiometric selectivity coefficients for both electrodes were evaluated by the mixed solution method and calculated as previously described [15].

The results presented in Table 2 confirm that the ion-pair complex in electrode B is more stable than that used in electrode A. The data in this table also show high selectivity of the electrode B over all inorganic and organic cations tested. Also, the common tablet excipients, lactose, glucose, cornstarch and gelatin do not show any interference for both electrodes.

*Response times*

The electrode B provides stable e.m.f. readings within 30 s in the linear range of the calibration curve while the response time of the electrode A is longer even in concentration solutions (e.g. it is about 2 min in $10^{-2}$ mol $l^{-1}$ solution).

*Analytical applications*

Both electrodes proved useful in the potentiometric titration of 1-adamantanamine hydrochloride in the drug substance and in tablets. The average recovery of six drug substance samples, each assayed in duplicate and containing between 4 and 10 mg, was 100.3% and the relative standard deviation was 1.3%. The results of the assay of 1-adamantanamine hydrochloride in four samples of amantadine tablets are given in Table 3 and show that good recovery was achieved. Also, the results in Table 3 show that high precision (relative standard deviation $\leq$1.2%) was obtained. In contrast to most of the common methods used for the determination of 1-adamantanamine hydrochloride in pharmaceuticals, which are time-consuming and require sample pretreatment, the electrode method is simple, fast and selective.

The electrode can also be used to determine the content uniformity and dissolution rate of amantadine tablets. In many cases the content uniformity test is preferred to the assay of a composite sample, as both preparation of the sample and measurement can be carried out more rapidly than that of the assay of a composite sample. If the accuracy of the assay is satisfactory, the mean value of the content uniformity test can be used as an assay result. The results obtained for the determination of content uniformity of amantadine tablets indicate the suitability of the electrode method for this purpose.

The dissolution rate is used mainly to check the release of the active ingredients from

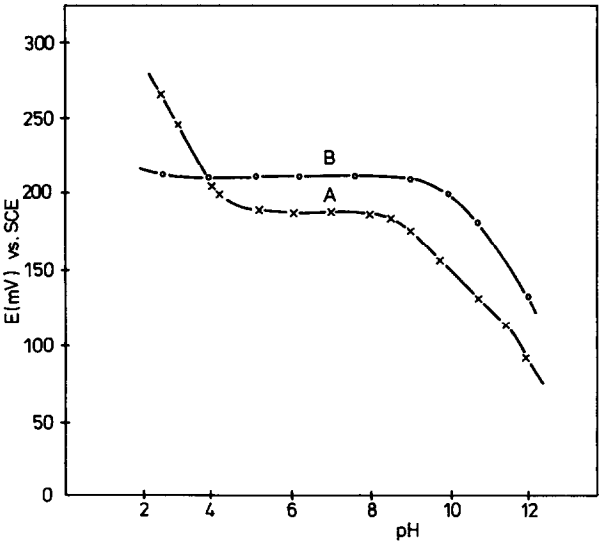


**Figure 1**
Effect of variation of pH on electrode response for $10^{-4}$ mol $l^{-1}$ 1-adamantanamine hydrochloride. (A) Electrode A (1-adamantanamine–dipicrylamine ion-pair complex); (B) electrode B (1-adamantanamine–dinonylnaphthalene sulphonic acid ion-pair complex).

**Table 2**
Selectivity coefficients for various cations with amantadine ion-selective membrane electrodes

| Interfering species, $J^{z+}$ | Selectivity coefficient, $K^{Pot}_{Ad^+,J^{z+}}$ Electrode A | Electrode B |
|---|---|---|
| $K^+$,$Na^+$,$Ca^{2+}$,$Mg^{2+}$ | $<10^{-3}$ | $<10^{-3}$ |
| L-Histidine | $5.0 \times 10^{-3}$ | $<10^{-3}$ |
| Methionine | $5.1 \times 10^{-3}$ | $<10^{-3}$ |
| Nicotinamide | $2.0 \times 10^{-2}$ | $1.4 \times 10^{-3}$ |
| Diethylamine | $4.2 \times 10^{-2}$ | $9.6 \times 10^{-3}$ |
| Vitamin $B_1$ | $1.5 \times 10^{-1}$ | $4.9 \times 10^{-2}$ |
| Scopolamine | 2.1 | $3.7 \times 10^{-2}$ |
| Atropine | 13.2 | $3.7 \times 10^{-1}$ |

**Table 3**
Determination of 1-adamantanamine hydrochloride in amantadine tablets* with amantadine ion-selective membrane electrode† by potentiometric titration

| Sample No. | Recovery, % of nominal‡ | Relative standard deviation‡ (%) |
|---|---|---|
| 1 | 98.0 | 0.8 |
| 2 | 101.5 | 1.2 |
| 3 | 99.3 | 1.1 |
| 4 | 98.6 | 0.9 |

*Amantadine tablets contain 100 mg 1-adamantanamine hydrochloride.
†Electrode B was used.
‡Values were calculated from the results of five determinations.

slow release pharmaceutical dosage forms. However, there is a trend towards analysing other dosage forms as well. The advantage of the electrode technique to carry out this test is the fact that the selective electrode can monitor continuously the concentration of the active ingredient in the standardized dissolution cells. Results of investigations using this technique will be published later.

## References

[1] V. V. Coşofreţ, *Ion-Sel. Electrode Rev.* **2**, 159–218 (1980).
[2] V. V. Coşofreţ, *Membrane Electrodes in Drug-Substances Analysis*. Pergamon Press, Oxford (1982).
[3] V. V. Coşofreţ and R. P. Buck, *Ion-Sel. Electrode Rev.* **6**, 59–121 (1984).
[4] M. Sittig, *Pharmaceutical Manufacturing Encyclopedia*, p. 19. NDC, Park Ridge, N.J. (1979).
[5] N. Ozolina and V. Egerts, *Sovrem. Aspecty Issled. v Obl. Farmatsii* 151–152 (1977); *Chem. Abstr.* **88**, 79185 n (1978).
[6] T. K. Christopoulos, E.P. Diamandis and T. P. Hadjiioannou, *Anal. Chim. Acta* **143**, 143–151 (1982).
[7] C. R. Gupta and D. G. Lundberg, *Clin. Toxicol.* **11**, 437–442 (1977).
[8] W. H. Anderson and D. T. Stafford, *J. High Resolut. Chromatogr. Chromatogr. Commun.* **6**, 247–254 (1983).
[9] A. Sioufi and F. Pommier, *J. Chromatogr.* **183**, 33–39 (1980).
[10] T. Daldrup, P. Michalke and W. Boehme, *Chromatogr. Newsl.* **10**, 1–7 (1982).
[11] S. Salman and N. Bayrakdar, *Eczacilik Bul.* **25**, 30–33 (1983).
[12] G. J. Moody, R. B. Oke and J. D. R. Thomas, *Analyst* **95**, 910–918 (1970).
[13] C. R. Martin and H. Freiser, *Anal. Chem.* **52**, 562–564 (1980).
[14] V. V. Coşofreţ and R. P. Buck, *Anal. Chim. Acta* **174**, 299–303 (1985).
[15] V. V. Coşofreţ and R. P. Buck, *Anal. Chim. Acta* **162**, 357–362 (1984).

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