Journal of Pharmaceutical & Biomedical Analysis
Vol. 4, No. 1, pp. 45–51, 1986
Printed in Great Britain

0731–7085/86 $3.00 + 0.00
Pergamon Press Ltd.

A poly(vinylchloride) membrane electrode for determination of phenytoin in pharmaceutical formulations

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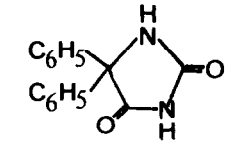
Abstract: The construction and general performance characteristics of an ion-selective membrane electrode sensitive to the drug phenytoin, based on its ion-pair complex with the quaternary ammonium cation, tricaprylmethylammonium, in a PVC matrix are described. The electrode shows near-Nernstian response over a 10^{-1}–10^{-4} mol l^{-1} range and a detection limit of 1.5×10^{-5} mol l^{-1}. The selectivity of the electrode to a number of inorganic and organic anions is reported. OH^- interference, in the linear range of the calibration curve, is negligible up to pH 11.0. The standard addition method is used to determine phenytoin in pharmaceutical formulations, such as tablets and capsules, with good results. The method is rapid and simple, and does not require prior sample pretreatment.

Keywords: *Phenytoin determination; phenytoin-membrane electrode; standard addition method; pharmaceutical formulations.*

Introduction

Recent developments in pharmaceutical analysis with membrane electrodes [1–4] enable us to measure the activities of various drugs directly and selectively and, in most cases, without prior separation of the drug of interest from the formulation matrix. The present paper reports the use of the water-insoluble ion-pair phenytoin–tricaprylmethylammonium as the electroactive material for a phenytoin-sensitive membrane electrode, which has proved useful in pharmaceutical analysis. It is possible that this system can be applied to the analysis of phenytoin in biological samples after simple, sample preconcentration.

Phenytoin (5,5-diphenylhydantoin, **I**), after more than three decades of clinical application, remains one of the most effective antiepileptic drugs, with minimal sedative–hypnotic side effects [5].

(I) 

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The official standard method for phenytoin assay in pharmaceutical preparations is based on its extraction and spectrophotometric quantitation at 258 nm [6]. Many other recent analytical methods based on gas chromatography [7], liquid chromatography [8, 9], fluoroimmunoassay [10–13], nephelometry [14] and enzyme-multiplied immunoassay technique [15] have been developed for phenytoin assay in clinical samples.

The electrode method proposed in this paper for assaying phenytoin in tablet and capsule dosage forms has the advantage of simplicity, reduced analysis time and economy.

Experimental

Reagents and materials

All reagents were of analytical reagent grade. Phenytoin (sodium salt) and decanol were supplied by Sigma (St Louis, MO); other materials were tricaprylmethylammonium chloride or Aliquat 336S (General Mills Chemicals, Inc., Kankakee, IL), 2-nitrophenyl-octyl ether (Fluka, Hauppauge, NY) and poly(vinylchloride) (PVC) of high molecular mass (Aldrich, Milwaukee, WI). Pharmaceutical preparations were purchased locally and were of USP quality. Solutions of sodium phenytoin were prepared by serial dilution while keeping both pH and ionic strength constant. The selectivity coefficients were determined at pH 10.0 and 0.1 mol l^{-1} ionic strength, both being adjusted with borax–NaOH buffer solution of pH 10.0.

Apparatus

An Orion digital pH/mV-meter, Model 701A, was used for all potentiometric measurements. The phenytoin-membrane electrode was used in conjunction with an Orion 91-01 double junction reference electrode with saturated $Na_2B_4O_7$ solution in the outer compartment. pH measurements were performed with an Orion 91-02 combination glass electrode.

Electroactive material

Five grams of Aliquat 336S was mixed with 5.0 g of decanol and equilibrated with ten separate 15 ml aliquots of 0.1 mol l^{-1} sodium phenytoin solution in 20%, v/v, methanol. The organic phase was washed twice with distilled water and then centrifuged until a clear solution was obtained.

Membrane material

The quaternary ammonium cation, tricaprylmethylammonium, is a well known ion-pairing extracting agent and was used to obtain the ion-pair association complex with the 5,5-diphenylhydantoinate anion. The ion-pair complex was embedded in a PVC matrix, containing 2-nitro-phenyl-octyl ether as plasticizer. The membrane composition was 7.7% m/m electroactive material, 61.5% m/m 2-NPOE and 30.8% m/m PVC.

Construction of the electrode

The basic principle of the electrode construction has been described elsewhere [16]. The electroactive material (50 mg) was well mixed with 400 mg plasticizer (2-nitro-phenyl-octyl ether) and later with 200 mg PVC powder dissolved in 6 ml of tetrahydrofuran. The clear liquid was poured into a 28 mm i.d. glass ring on a sheet of plate glass. A pad of filter paper placed on top of the ring was kept in place by a heavy

metallic weight and the assembly left for 48 h to allow slow solvent evaporation. A disc (0.9 cm diameter) was cut from the membrane and fixed to the end of a 10 mm Tygon tube using a PVC–tetrahydrofuran solution as adhesive. The other end of the Tygon tube was fitted on to a glass tube to form the electrode body. A silver/silver chloride wire was then inserted and the electrode body was filled with 10^{-3} mol l^{-1} sodium phenytoin solution of pH 10.0 (borax–NaOH buffer). The electrode was preconditioned for 1 h by soaking it in a 10^{-2} mol l^{-1} sodium phenytoin solution of pH 10.0, and stored in 10^{-3} mol l^{-1} sodium phenytoin solution of pH 10.0 between use.

Electrode characteristics

The performance of the electrode was investigated by measuring the e.m.f. values of 10^{-1}–10^{-6} mol l^{-1} sodium phenytoin solutions. In most of the further studies with the phenytoin-membrane electrode, the highest concentration of sodium phenytoin used was 10^{-2} mol l^{-1}; it was not considered necessary to use the electrode with 10^{-1} mol l^{-1} solution. Potentials were recorded when stable readings were obtained.

Potentiometric assay of phenytoin tablets

Phenytoin tablets were analysed by finely powdering five tablets from the same lot. A portion of the powder equivalent to about 50 mg of phenytoin was transferred to a 500-ml volumetric flask; 3.0 ml of 0.1 mol l^{-1} NaOH solution and 50.0 ml of borax–NaOH buffer solution of pH 10.0 were added and the solution was made up to volume with distilled water (solution A). An aliquot of 20-ml solution A was pipetted into a 100-ml volumetric flask; 10.0 ml of borax–NaOH buffer solution (pH 10.0) was added and the solutions made up with distilled water (solution B). An aliquot of 25.0-ml solution B was pipetted into a 100-ml beaker in which both the indicator and reference electrodes were immersed. After electrode equilibration by stirring and recording the e.m.f., 1.0 ml of 10^{-2} mol/l sodium phenytoin standard solution (pH 10.0) was added and the change in e.m.f. recorded and used to calculate the phenytoin content of the tablets.

Potentiometric assay of phenytoin capsules

The content of five capsules from the same lot was well mixed. A portion of the powder equivalent to about 50 mg of sodium phenytoin was used for the phenytoin assay following the procedure described above with the exception that no sodium hydroxide solution was added to prepare solution A.

Results and Discussion

Electrode response

Typical calibration curves for the phenytoin-membrane electrode in sodium phenytoin solutions of different pH values (Fig. 1) show that the electrode response is linear down to 10^{-4} mol l^{-1}, with a near-Nernstian slope, when pH is not higher than 11.0. The critical response characteristics of the electrode are summarized in Table 1.

The calibration curves at pH 10.0 (borax–NaOH buffer) for a set of four phenytoin-membrane electrodes were found to be similar and reasonably reproducible from day to day.

Effect of pH

The effect of pH on the potential readings of the phenytoin-membrane electrode was checked by recording the e.m.f. of the cell of the type:

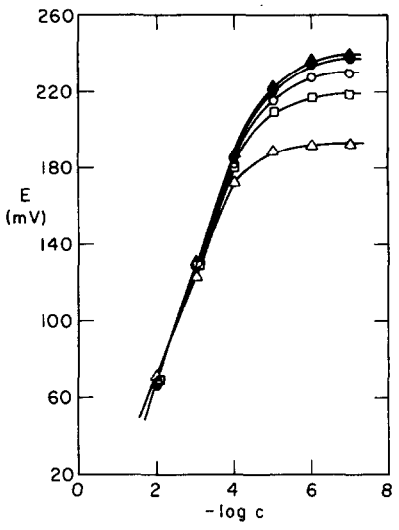

Figure 1
Electrode functions for the phenytoin-membrane electrode in sodium phenytoin solutions of different pH values: ● pH 9.5; ▲ pH 10.0; ○ pH 10.5; □ pH 11.0; △ pH 12.0.

Table 1
Response characteristics for the phenytoin-membrane electrode

Slope (mV log C^{-1})	56.25 ± 0.83*
Intercept (mV)	182 ± 2.1†
Linear range (mol l^{-1})	10^{-1}–10^{-4}
Usable range (mol l^{-1})	10^{-1}–10^{-5}
Detection limit (mol l^{-1})	1.5×10^{-5}
(μg ml^{-1})	4.1

*Standard deviation of average slope value for multiple calibrations in the 10^{-2}–10^{-4} mol l^{-1} range.
†Standard deviation of values recorded during one month.

Ag|AgCl|10^{-3} mol l^{-1} sodium phenytoin (pH 10.0)‖PVC matrix membrane‖10^{-3} or: 10^{-4} mol l^{-1} sodium phenytoin (I = 0.1 mol l^{-1}), adjusted with $Na_2B_4O_7$|Orion double junction electrode with saturated $Na_2B_4O_7$ in the outer compartment.

Varying pH was achieved by addition of very small volumes of sulphuric acid and/or sodium hydroxide solutions to the test solution. The plots presented in Fig. 2 show that between pH 9.2 and 11 the potential is very little affected by pH. At high pH values, the potential decreased slowly because of hydroxide anion interference. This interference was greater at 10^{-4} mol l^{-1} sodium phenytoin solution that with 10^{-3} mol l^{-1}. At lower pH the potential increased sharply because the concentration of dissociated 5,5-diphenylhydantoinate was considerably diminished.

During one month of using the electrode, no change in e.m.f.–pH behaviour was observed.

Selectivity of the electrode

The selectivity of the phenytoin-membrane electrode is related to the free energy of transfer of the 5,5-diphenylhydantoinate anion between aqueous and organic phases.

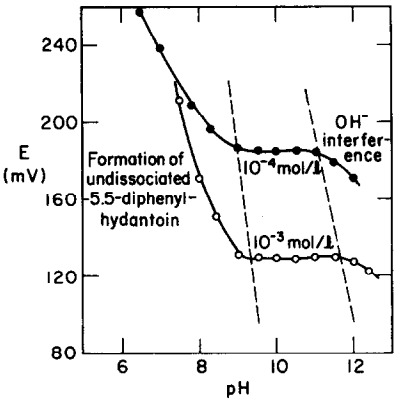

Figure 2
pH-effect on electrode response at two different concentrations of sodium phenytoin solutions.

The response of the electrode towards different inorganic and organic anions was studied by the graphical mixed solution method [17]. The concentration of the anion tested was kept constant, while the sodium phenytoin concentration varied in the range 10^{-2}–10^{-6} mol l^{-1}. Similar graphs to those in Fig. 1 were plotted, the values for selectivity coefficients obtained being given in Table 2.

The data in Table 2 show high selectivity of the phenytoin-membrane electrode over a number of potentially interfering ionic species present in pharmaceutical preparations or biological samples. Furthermore, the bulk of the excipient in pharmaceutical tablets or capsules, usually consisting of lactose or glucose diluent and cornstarch or gelatin binders, do not show any interference, nor do maltose, mannitol or sugar.

Response time

The response time of the electrode was tested for 10^{-2}–10^{-6} mol l^{-1} sodium phenytoin solutions; the sequence of measurements was from high concentrations to low concentration and back. In the second case a shorter response time was recorded. In both cases response times were relatively fast, and were nearly instantaneous at higher concentrations. Only 1 min was required for solutions of 10^{-4}–10^{-6} mol l^{-1}.

Table 2
Selectivity coefficients for various anions with phenytoin-membrane electrodes*

Interfering species (J^{n-})	Concentration (mol l^{-1})	Selectivity coefficient ($K^{pot}_{Ph^-,J^{n-}}$)
Chloride	10^{-2}	3.2×10^{-3}
Nitrate	10^{-2}	6.3×10^{-1}
Sulphate	10^{-2}	$<10^{-5}$
Phosphate	10^{-2}	$<10^{-5}$
Acetate	10^{-2}	$<10^{-5}$
Oxalate	10^{-2}	$<10^{-5}$
Lactate	10^{-2}	$<10^{-5}$
Tartrate	10^{-2}	$<10^{-5}$
Citrate	10^{-2}	$<10^{-5}$
Benzoate	10^{-2}	5.0×10^{-2}
α-α-Diphenylglycinate†	5×10^{-3}	6.3×10^{-2}

* In all cases pH = 10.0 and I = 0.1 mol l^{-1} (both adjusted with borax–NaOH buffer solution).

† One of the phenytoin-drug metabolites.

Analytical Applications

The electrode proved useful for the assay of phenytoin content both in pure sodium phenytoin solutions and in pharmaceutical formulations using the potentiometric standard addition method. The average recovery of six pure samples, each in triplicate and containing 27–77 $\mu g\ ml^{-1}$, was 100.2%, and the relative standard deviation was 1.8%. The results of the phenytoin assay applied to two pharmaceutical formulations are given in Table 3.

Table 3
Determination of phenytoin in pharmaceutical formulations* with phenytoin-membrane electrode by potentiometric standard addition method†

Product	Sample No.	Recovery (% of nominal)‡	Standard deviation (%)
Dilantin® 50-mg tablets	1	101.5	1.6
(Chevable/infantab)	2	100.7	1.6
Parke Davis	3	102.7	1.9
	4	99.7	1.4
Dilantin® 100-mg capsules	1	99.3	1.2
(extended phenytoin sodium)	2	100.4	2.0
Parke Davis	3	99.5	1.7
	4	100.7	1.9

*Dilantin-tablets contain phenytoin as 5,5-dephenyhydantoin.
†V_x = 25.0 ml (I = 0.1 mol l^{-1}, adjusted with borax–NaOH buffer solution of pH 10.0); V_s = 1.0 ml; C_s = 10^{-2} mol l^{-1} sodium phenytoin.
‡All values are average of eight determinations.

As can be seen in Table 3, a high precision (relative standard deviation $\leq$2.0%) was obtainable. Usually the potentiometric assay could be accomplished within 15 min in contrast to the 5 h required for assay by the official standard method [6]. The present procedure involved fewer manipulation steps and offered the advantages of higher selectivity and greater precision.

Other immediate fields of application of the electrode would seem to be in dissolution profile studies for sodium phenytoin from various pharmaceuticals, tablet content uniformity determinations and for the analysis of sodium phenytoin in clinical samples after a simple, sample preconcentration.

Acknowledgements: Special thanks to Dr D. T. Woodley, University of North Carolina School of Medicine, for his encouraging discussion in performing this work. This work was supported, in part, by International Research Exchanges (IREX) and N.S.F. Grant No. CHE 8103334.

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[*Received for review 3 April 1984*]