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A phenobarbital ion-selective electrode without an inner reference solution, and its application to pharmaceutical analysis*

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Abstract: This paper describes the construction and assessment of a phenobarbital ion-selective electrode and a rapid and reliable phenobarbital tablet assay potentiometric method that provides results which are in good agreement with those obtained by the British Pharmacopoeia (BP) method.

Keywords: *Phenobarbital determination; ion-selective electrode; drug analysis.*

Introduction

Many electrodes sensitive to organic species of pharmaceutical interest have been reported in the literature over the past few years [1–3]. Some of these, due to their good operating characteristics, have been suggested as an advantageous alternative to conventional methods for the analytical control of drug-type substances [1, 2].

Today, the use of selective electrodes is not as widespread as one would have expected from the advantages they present. This is a consequence of the fact that these units are not available on the market, their construction is not easily accessible, and their operating characteristics are not the most appropriate for routine work.

The phenobarbital-sensitive electrodes constructed so far [4, 5], present some of the aforementioned disadvantages such as reproducibility [4], thus requiring periodic calibrations or, in the case of chemically-sensitive field effect transistors, there are obvious difficulties inherent to their preparation [5].

This paper refers to the construction, assessment, and analytical application of a phenobarbital ion-selective electrode without an inner reference solution, using the construction procedure presented elsewhere [6], with minor modifications [7], and a sensor system consisting of a solution of phenobarbiturate of tetraoctylammonium in 2-nitrophenyloctylether (2-NPOE) which is a solvent mediator with good plastifying characteristics.

Experimental

Apparatus and reagents

A Crison 517 (sensitivity ±0.1 mV) potentiometer coupled to an Orion 605 electrode switcher was used for measuring the electrode potentials.

All determinations were performed at 25.0 ± 0.02°C, using an Ag/AgCl Orion 900200 double-junction reference electrode with a K_2SO_4 0.033 M solution in the outer compartment, and an Ingold 10/402/3092 electrode for pH measurements.

Analytical reagent grade chemicals were used without additional purification, except for tetraoctylammonium bromide which was always recrystallized from ethyl acetate prior to the preparation of the sensor.

Electrode construction

Chloroform (5 ml) was added to the tetraoctylammonium bromide (0.3 g) in 2-NPOE (2 g) solution which was than shaken with six separate 20-ml aliquots of 0.1 M sodium phenobarbital. After the last extraction process, the organic phase was separated and the

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chloroform evaporated by a current of dry nitrogen. The remaining solution was kept over sodium sulphate as reported elsewhere [7].

The ion-pair association (phenobarbiturate of tetraoctylammonium) in a 2-NPOE as a plasticizer was immobilized in a PVC membrane that was applied drop-wise in a graphite conductor support which consisted of a blend of graphite (1 g) and a non-conductive epoxy resin (Araldite 1.2 g). The final composition of the membrane was 8.6% (w/w) electroactive material, 60.4% (w/w) 2-NPOE, and 31.0% (w/w) PVC after the evaporation of the THF.

Finally, the electrodes were conditioned in a 0.1 M solution of the respective anion and stored in the same solution when not in use.

Potentiometric assay of phenobarbital tablets

For the phenobarbital determination in tablet dosage forms, about 20 tablets from the same lot were finely powdered, and approximately 150 mg placed in a 100-ml volumetric flask to which 5 ml of a 0.1 M NaOH solution was added. The remaining volume of the flask was filled with a 0.1 M borate solution whose pH had been adjusted with NaOH to 9.6.

The potentiometric determinations were performed on samples of this solution after dilution with an equal volume of a 0.066 M K_2SO_4 solution. These measurements were preceded by the calibration of the electrodes with solutions of different sodium phenobarbiturate concentrations in the presence of the same concentration of ionic strength and pH adjuster.

For comparison purposes, and in addition to direct potentiometric assay, determinations were also performed on samples from the same lot of tablets using the potentiometric standard addition method, or the procedure suggested by the British Pharmacopoeia (BP) [8] which is essentially based on a continuous extraction with ethyl ether and a weighing of the residue of the solvent evaporation.

Results and Discussion

Electrode behaviour

The overall electrode working characteristics were assessed on the basis of the calibration curves obtained by measuring the e.m.f. values of a set of sodium 5-ethyl-5-phenylbarbiturate solutions, in the intervals of 10^{-1}–10^{-5} M concentrations with a ionic strength adjusted to 0.1 M with K_2SO_4. The electrodes presented a linear response of between 10^{-1}–2×10^{-4} M with a slope of 59.0 ± 0.2 mV per concentration decade. In this range of concentrations, the electrode potential stabilized (±0.1 mV) after 15 s.

With a view to the future use of the electrodes in the analysis of pharmaceutical preparations, we also studied their behaviour in solutions where the pH and ionic strength had been adjusted with a 0.1 M borate and a 9.6 pH solution. Under these conditions, although the value of the slope was similar to the aforementioned value, the lower limit of linear response increased (10^{-3} M) due to interference by the tetrahydroborate anion.

The reproducibility of the electrode system was assessed on the basis of the values obtained from repeated calibrations in the linear response range. The potential did not differ by ±0.2 mV throughout a working day.

A study was also made of the influence of pH variation on the potential when the electrode was kept in contact with pure solutions with a constant concentration of the barbiturate anion (10^{-1}, 10^{-2} and 10^{-3} M) or solutions with same barbiturate concentration but in which the ionic strength had been adjusted to 0.1 M with K_2SO_4. Variations in pH were obtained by adding small amounts of concentrated solutions of NaOH (50%, w/w) and H_2SO_4 (8 M) so that it would be legitimate to suppose that the concentration of the main ion would remain unaltered throughout the experiments.

The potential/pH diagram (Fig. 1) show the presence of an operational plateau, depending on the concentration of the main ion, located approximately between 9–11.5 pH units. In the case of high pH values, there is a slight rise in the potential due to hydrolysis of the barbiturate anion [9]. For pH values below 9 units, there is formation of phenylbarbituric acid, a species for which the electrode is not sensitive, and the increase in potential corresponds to a decrease in the concentration of the anion in solution.

The assessment of the interference was performed by determining the potentiometric selectivity coefficients values by using the separated solutions method [10] at several concentration levels (Table 1). The determination was performed for some more frequent ions, such as benzoate, that may be present in pharmaceutical preparations. The bulk of

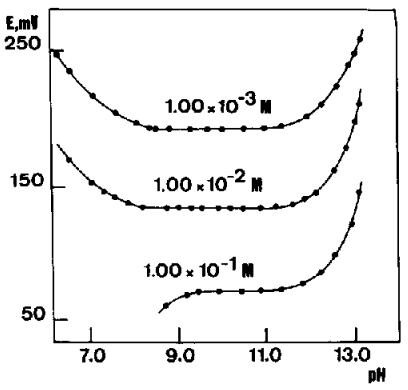

Figure 1
pH profile for responses of a phenobarbital ion-selective electrode in different sodium phenobarbital concentrations.

tablet excipient, usually consisting of a lactose diluent and maize starch binder, as well as caffeine, when present in preparations do not interfere in any manner in the electrode potential.

The study of electrode behaviour was made over a 8-month period during which the working characteristics remained unaltered in four units selected for this evaluation. This long lifetime depends on the type of construction used [11] and on the choice of a plasticizer (2-NPOE) with good mediating characteristics.

The aforementioned working characteristics for the phenobarbital electrode we constructed are, in many ways, similar to those of units previously prepared for the same ion [4, 5], namely regarding the lower limit of linear response, the slope, and the response rate. Nevertheless, other operating aspects are clearly superior, such as the reproducibility of results during a day's work and its lifetime.

Analytical applications

The electrode proved its usefulness for the assay of phenobarbital content in tablet dosage forms, using either direct potentiometry or the potentiometric standard addition method.

Table 2 gives the results obtained by the potentiometric determination (direct and standard addition potentiometry) of phenobarbital and by the British Pharmacopoeia method [8], in certain common pharmaceutical preparations indicated by the trade name in use in Portugal.

The values obtained by these three methods are in good agreement with each other, although, as a whole, there is a better precision in the results obtained by potentiometry as

Table 1
Potentiometric selectivity coefficients (log K^{pot}), of the phenobarbiturate ion-selective electrode determined by the separate solution method*

Interferent	Concentration 10^{-3} M	5×10^{-3} M	10^{-2} M
Nitrate	+0.16 ± 0.02	+0.08 ± 0.01	+0.03 ± 0.01
Chloride	−1.22 ± 0.01	−1.44 ± 0.01	−1.59 ± 0.01
Sulphate	−1.66 ± 0.04	−2.01 ± 0.04	−2.27 ± 0.03
Benzoate	−0.64 ± 0.01	−0.79 ± 0.01	−0.86 ± 0.01

* Averages of two determinations with three electrodes (six values), for all selectivity values listed.

Table 2
Phenobarbital recovery (percentage (w/w) of phenylbarbituric acid) of some commercially available tablet dosage forms*

Brand (claimed content % (w/w) per tablet)	Direct potentiometry	Potentiometric standard addition	BP method
Luminal (39.5)	38.4 ± 0.2	38.4 ± 0.2	39.8 ± 0.5
Luminaletas (21.4)	22.9 ± 0.2	22.5 ± 0.2	21.4 ± 0.9
Bialminal Fortissimo (59.1)	55.4 ± 0.4	56.7 ± 0.1	57.2 ± 0.7
Alepsal Fraco (42.5)	43.9 ± 0.1	43.5 ± 0.1	43.4 ± 0.1
Fenobarbital Unitas (37.7)	35.5 ± 0.2	34.9 ± 0.2	32.9 ± 0.1

* Mean and standard deviation of values obtained in three different samples of the same pharmaceutical preparation.

compared with the BP method [8]. Thus is not surprising as the reference process uses a series of manipulations that contribute to the dispersion of the results.

Conclusions

Our results suggest that the phenobarbiturate ion-selective electrode, without inner reference solution and with a solution of tetraoctylammonium phenobarbiturate in 2-NPOE as sensor, presents good working characteristics, namely potential stability, long lifetime, and ruggedness that recommend its use for routine work. These characteristics which are a consequence of the construction process used, that is accessible to all laboratories, point to the fact that the improvements made earlier on a barium cation-sensitive electrode [11] may well also be applied to organic species of pharmaceutical interest.

The electrode constructed by us for determining phenobarbital in pharmaceutical preparations gives results that are similar to those obtained by the reference method. Furthermore, each analysis with the proposed method takes approximately 15 min which compares favourably with the 60 min that are necessary for the BP test.

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