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Pharmaceutical applications of a flurbiprofen sensor

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Abstract

The construction and the performance characteristics of an ion-selective PVC membrane electrode for flurbiprofen are described. The electrode, based on the ion-pair complex with Aliquot 336S (tricaprylmethylammonium chloride) cation shows near-Nernstian response in the concentration range 10^{-2}–7×10^{-5} M. Its selectivity relative to various organic and inorganic anions is reported. Potentiometric methods are used to determine the active component flurbiprofen in pharmaceutical preparations. It was applied to the determination of the dissolution profile of FROBEN® tablets.

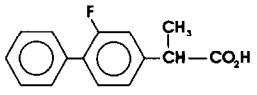
Keywords: Sensors; Flurbiprofen plastic membrane sensor; Drug analysis

1. Introduction

The appearance and large-scale development of ion-selective membrane electrodes (ISMEs) has produced spectacular achievements in the last few years. Drug control is a branch of analytical chemistry that has a wide impact on public health, and so the development of reliable, quick and accurate methods for the active principle determination is welcomed.

In recent years, ISMEs have been used more and more in drug quality control [1–4], but no pharmacopeia has yet introduced their use for assays, though this may occur in the next few years.

Flurbiprofen (**I**, 2-(2-fluoro-4-biphenyl)propionic acid, see Scheme 1) is one of the non-steroidal anti inflammatory drugs (NSAID) which belong to the 2-arylpropionic acid class known as profens. It is recommended in the treatment of rheumatoid disease, osteoarthrosis and ankylosing spondylitis due to its anti-inflammatory, analgesic and antipyretic properties [5].



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Scheme 1.

The official standard methods for flurbiprofen assay in pharmaceutical preparations are based on liquid chromatographic methods [6–9] and a titrimetric method [10].

This paper describes the construction and the characteristics of a new flurbiprofen sensor based on

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the ion pair complex formed between the tricaprylmethylammonium chloride cation and the flurbiprofen anion. The complex is embedded in a PVC matrix. The method proposed is simple, rapid and cheap.

2. Experimental

2.1. Reagents and materials

Flurbiprofen (Batch No. 810878) and the pharmaceutical preparations (FROBEN 50 mg and 100 mg, respectively) were supplied by Boots (Nottingham) while the other materials, i.e., dinonylphthalate (DNP), poly(vinylchloride) (PVC) of relative high molecular mass, tetrahydrofuran (THF) and tricaprylmethylammonium chloride (Aliquot 336S), were of analytical-reagent grade. Solutions of flurbiprofen were prepared by serial dilutions while keeping the pH at a constant value (phosphate buffer, pH 6.8).

2.2. Apparatus

A Pracitronic Digital pH/mV meter (Model MV 87) was used for all direct potentiometric measurements. The 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 a Radiometer G202B glass electrode and a Radiometer K401 calomel electrode. The dissolution test was performed in a ERWEKA DT-D apparatus. The statistical approach and simulation of the experimental data were performed on a 80386 DX (IBM-compatible PC) computer using the ASPRODI 3.0 program [11]. The UV determinations were performed on a LAMBDA 2 UV–visible spectrometer (Perkin Elmer) in 1-cm cells.

2.3. Electroactive material

5 g of Aliquot 336S were mixed with 5.0 g of *n*-dodecanol and then equilibrated with ten separate 10–15 ml aliquots of 0.01 mol flurbiprofen solution. The organic phase was washed with distilled water until the reaction of chloride ion was negative and then centrifuged until a clear solution was obtained.

2.4. 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 2-(2-fluoro-4-biphenyl)-propionate anion. The ion-pair complex was embedded in a PVC matrix containing DNP as plasticizer. The membrane composition was 4.0% (w/w) electroactive material, 64.0% (w/w) DNP and 32.0% (w/w) PVC.

2.5. Construction of the electrode

The basic principle of the electrode construction was described elsewhere [12,13]. The electroactive material (50 mg) was well mixed with 800 mg plasticizer and later with 400 mg PVC powder dissolved in 10 ml THF. The clear liquid was poured into a 28 mm i.d. glass ring on a glass plate. A pad of filter paper placed on the top of the ring was kept in place by a heavy metallic weight and the assembly left for 72 h to allow slow evaporation of the solvent. A disc (9 mm diameter) was cut from the membrane and fixed to the end of a 10 mm Tygon tube using a PVC-THF 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 inserted and the electrode body was filled with 10^{-3} mol flurbiprofen solution. The electrode was preconditioned for 24 h by soaking it into a 10^{-2} mol flurbiprofen solution and then stored in 10^{-3} mol flurbiprofen solution between use.

2.6. Recommended procedures

Dissolution test

The test is carried out according to the USP XXII method [14] with the equipment described elsewhere [15]. One sugar-coated tablet (FROBEN 50 or FROBEN 100) is placed in the basket and the dissolution medium (900 ml phosphate buffer pH 6.8 for UV determination and 500 ml phosphate buffer pH 6.8 for potentiometric determination) is maintained at 37 ± 0.5°C. The basket is rotated at 100 rpm. For the potentiometric determination, after an appropriate time interval (1.5 min), the potential values are recorded and the amount of flurbiprofen is calculated from a calibration graph obtained by the recalibra-

tion of the electrode in the range 10^{-3}–10^{-5} M. For the UV determination, after an appropriate time interval (3 min), 5 ml aliquots were withdrawn, filtered and the absorbance of the solutions at 247 nm is measured against the dissolution medium as blank in 1-cm cells. In order to investigate all the important physical processes during the dissolution period, the release profiles are numerically simulated by typical equations [11], and the most probably model is chosen.

2.7. Standard addition method

For analyte addition (sample addition to a standard), FROBEN 50 and FROBEN 100 tablets were analysed by finely powdering five tablets from the same batch. For FROBEN 50, a portion of the powder equivalent to about 50 mg of flurbiprofen was transferred into a 50 ml volumetric flask, 25 ml phosphate buffer (pH 6.8) was added and the solution was made up to volume with distilled water (solution A). For FROBEN 100, a portion of the powder equivalents to 100 mg flurbiprofen was transferred into a 100 ml volumetric flask, 50 ml phosphate buffer, pH 6.8, was added and the solution was made up to volume with distilled water (solution B). The e.m.f. is measured for the electrochemical cell containing 25 ml of standard at 10^{-3} mol flurbiprofen. A volume of 2 ml of solution A or 2 ml solution B is added and the new e.m.f. is measured. The changes in e.m.f. recorded are used to calculate the flurbiprofen content of the tablets.

3. Results and discussion

3.1. Electrode response

A typical calibration curve for the flurbiprofen membrane sensor performed with solutions in the range 10^{-2}–10^{-6} M shows that the electrode response is linear in the range 10^{-2}–7×10^{-5} mol. The calibration curve is presented in Fig. 1.

The critical response characteristics of the electrode in a phosphate buffer solution of pH 6.8, calculated with the SERECHAR 1.0 program [16], are summarized in Table 1.

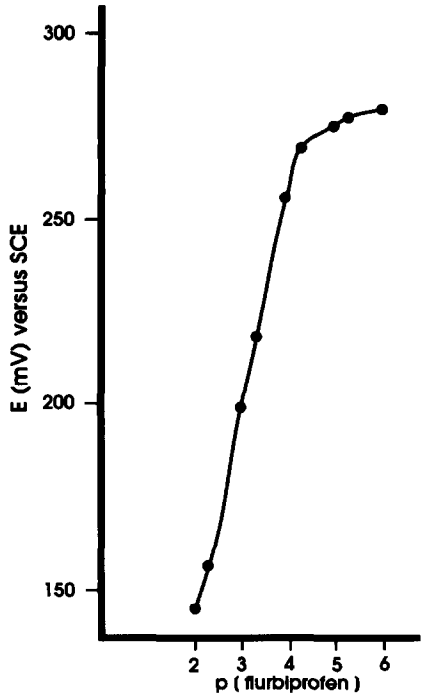

Fig. 1. Typical calibration graph for the flurbiprofen plastic membrane sensor.

3.2. Effect of pH

The effect of pH on the potential readings of the flurbiprofen sensor was checked by recording the e.m.f. of a standard cell Ag–AgCl||10^{-3} M flurbiprofen solution (inner solution)||plastic membrane||10^{-3} mol flurbiprofen solution (outer solution)||SCE and varying the acidity by the addition

Table 1
Response characteristics for flurbiprofen sensor

Parameter	Results
Slope (mV per decay) [a]	55.4 ± 0.7
Intercept, E (mV) [b]	34.4 ± 1.1
Linear range (mol)	10^{-2}–7×10^{-5}
Detection limit (mol)	4.1×10^{-5}

[a] Standard deviation of average slope values for multiple calibrations.
[b] Standard deviation of values recorded over a period of two months ($n = 45$).

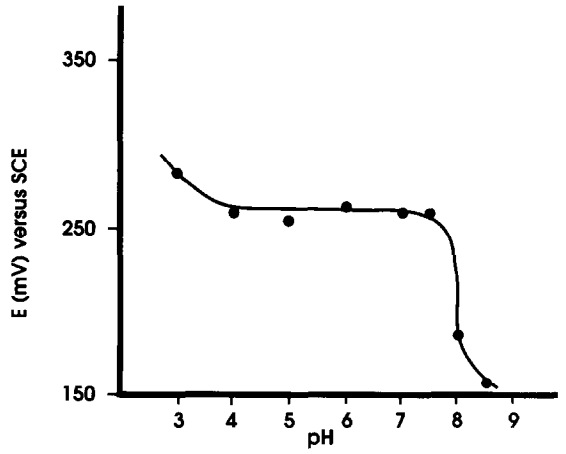

Fig. 2. Influence of pH on the response of the flurbiprofen sensor in 10^{-3} mol solution.

of small volumes of nitric acid and/or ammonium solution (1.0 M of each). The graph presented in Fig. 2 shows the linearity in the range 4.0–7.5 of the potential E (mV) versus pH function. At pH values higher than 8.0–8.5 the potential decreased slowly because of interference of the hydroxide anion.

3.3. Selectivity of the electrode

Potentiometric selectivity coefficients were evaluated by the mixed solution method.

The data presented in Table 2 show a good selectivity of the flurbiprofen membrane sensor over a number of potentially interfering ionic species where only the chloride and hydroxide ions interfere. The excipients usually used in the manufacture of the pharmaceutical preparations, such as corn starch, gelatine, lactose and sugar do not interfere.

Table 2
Selectivity coefficients for various anions with flurbiprofen sensor

Interfering species	$K^{pot}_{A,B}$
Acetate	$<10^{-4}$
Citrate	$<10^{-4}$
Chloride	1.12
Bromide	3.5×10^{-3}
Iodide	$<10^{-4}$
Hydroxide	2.3×10^{-2}
Nitrate	$<10^{-4}$

Table 3
The results of quantitative determination of flurbiprofen tablets using the standard addition method [a]

Pharmaceutical preparation	Sample	Found [b] (% of nominal)	R.S.D. (%)
FROBEN 50	1	99.7	1.4
sugar-coated	2	100.7	1.9
tablets	3	102.5	1.5
FROBEN 100	1	98.5	1.5
sugar-coated	2	102.1	1.7
tablets	3	99.3	0.9

[a] $V_s = 25.0$ ml, $V_a = 2.0$ ml, $C_s = 10^{-3}$ M flurbiprofen.
[b] All values are the average of four determination.

3.4. Analytical applications

The electrode proved useful for the assay of the flurbiprofen content in pharmaceuticals by using the standard addition method (sample addition to a standard). The results are given in Table 3. As can be seen, a high precision (R.S.D. < 2.0%) was obtained. Usually, the potentiometric assay could be accomplished within 15–20 min in contrast to the 1 h required for the assay by the chromatographic method.

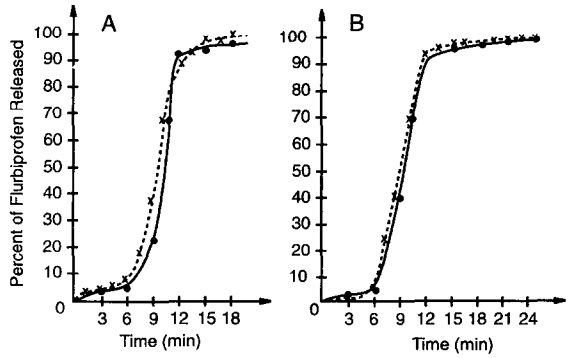

Fig. 3. Dissolution profile of the FROBEN® tablet. (A) FROBEN 50 mg sugar-coated, (a) potentiometric method (×), (b) spectrophotometric method (●). (B) FROBEN 100 mg sugar-coated, (a) potentiometric method (×), (b) spectrophotometric method (●).

The desirability of an in vitro test that adequately reflects the physiological availability of solid dosage form of drugs is now recognized. The advantage of the electrode technique for carrying out such test is that the electrode can monitor continuously and selectively the concentration of the active ingredient in the standardized dissolution cell.

Fig. 3 shows the dissolution profiles of sugar-coated flurbiprofen tablets (FROBEN 50 and FROBEN 100, respectively). For FROBEN tablets both methods (potentiometric and spectrophotometric, respectively) show similarity of the dissolution profiles procedure [17]. Taking into account the S-shape of the curves there are some possibilities for simulating all the physical processes. The simulation of the experimental data proved that the active component release follows the Hixson-Crowell [18] model; i.e., the dissolution involves two main steps: a first one (about 4 min) when the coating of the tablet is removed and a second step when a rapid dissolution take place

$$\sqrt[3]{W_0} - \sqrt[3]{W_t} = A \cdot (t - t_D) + B$$

where W_0 is the labeled amount of the active component, W_t is the unreleased amount at time t, t_D is the disintegration time period of the sugar-coated tablet, while A and B are the coefficients of the linearization of the experimental data using the least-squares method. All the other possibilities were found to be inadequate for these tablets.

4. Conclusions

The new flurbiprofen drug membrane sensor can be applied successfully for the potentiometric determination of FROBEN sugar-coated tablets without prior treatment if the standard addition method is used. Also, it is useful for the dissolution studies.

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