Construction of a Naproxen Ion-selective Electrode and its Application to Pharmaceutical Analysis

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A naproxenate-selective electrode with a liquid membrane consisting of a tetraheptylammonium - naproxenate ion pair dissolved in *p*-nitrocumene is described. The electrode exhibits a rapid and near-Nernstian response to naproxenate activity from 10^{-1} to 10^{-4} M at pH 9.0 (borate buffer). No serious interference from common ions and tablet excipients was found and the electrode was used for the direct assay of naproxen tablets by means of the calibration graph technique and of suppositories using the standard additions technique. A dissolution study of naproxen tablets was also carried out and the results compared favourably with those given by the USP XXI methods.

Keywords: *Naproxen; naproxenate-selective electrode; ion-selective electrode; pharmaceutical analysis; dissolution studies of naproxen formulations*

Naproxen [(+)-2-(6-methoxy-2-naphthyl)propionic acid] is a non-steroid drug with anti-inflammatory, analgesic and antipyretic properties. Formulated in tablets or suppositories it is used in the treatment of rheumatoid arthritis and other rheumatic or musculoskeletal disorders, dysmenorrhea and acute gout. The extensive use of naproxen formulations requires the development of a rapid, selective and accurate method that can be used in routine quality control.

Naproxen in commercial formulations has been determined by coulometry,[1,2] oscillometric titration,[3] first- and second-derivative UV spectrophotometry[4] and high-performance liquid chromatography (HPLC).[5] The United States Pharmacopeia XXI (1985)[6] describes a UV spectrophotometric method for the assay of naproxen tablets and for a dissolution study and an acid - base titrimetric method with sodium hydroxide for the determination of the pure substance. Biological fluids can be analysed for naproxen using HPLC,[7-9] GLC,[10] fluorimetry,[11] UV spectrophotometry[12] and mass fragmentography.[13]

Ion-selective electrodes (ISEs) have found many applications in pharmaceutical analysis.[14-17] The inherent advantages of ISEs, *i.e.*, simplicity, short measurement time, low cost, adequate precision and accuracy, adequate detection limits, wide analytical range and, particularly, the ability to measure the activity of various drugs directly and selectively and, in most instances without prior separation of the drug of interest from the formulation matrix in coloured or cloudy sample solutions, make the ISE potentiometric method very attractive for pharmaceutical analysis.[18-21]

In this paper, a naproxenate-selective electrode of the liquid membrane type, based on the use of a tetraheptylammonium - naproxenate ion pair as the ion exchanger, is described. The electrode was applied to the assay of commercial naproxen formulations and to a dissolution study of naproxen tablets.

Experimental

Reagents

All solutions were prepared in de-ionised water from analytical reagent-grade materials. Naproxen (pure) and its formulations were obtained from local manufacturers and their purity or content was determined using the official USP XXI procedures.[6] The various formulation additives, used in the interference experiments, were obtained from various commercial sources and were used as received.

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Borate buffer, 0.100 M, *pH* 9.0. Prepared by dissolving 6.18 g of boric acid in about 900 ml of water, adjusting the pH to 9.0, using saturated sodium hydroxide solution, and diluting to 1 l. A more dilute borate buffer solution (0.0100 M) was prepared by appropriate dilution.

Naproxenate standard stock solution, 0.100 M. Prepared by dissolving 5.76 g of naproxen in an equivalent amount of sodium hydroxide (*i.e.*, 25.0 ml of a 1.00 M NaOH solution) and diluting to 250 ml with the 0.100 M buffer. This solution was stable for long periods (at least 2 months) when stored in a refrigerator (8 °C). More dilute working standard solutions of naproxenate were prepared by appropriate dilution of the stock solution with 0.0100 M borate buffer.

Dissolution media. Phosphate (0.0100 M, pH 7.4) and acetate (0.0100 M, pH 4.0) buffers were prepared according to the usual laboratory procedures.

Preparation of the Liquid Ion Exchanger

A 0.10 M solution of tetraheptylammonium bromide (Aldrich) in *p*-nitrocumene (4-isopropylnitrobenzene) (Fluka) was shaken three times with an equal volume of the 0.100 M naproxenate standard stock solution to exchange bromide with naproxenate. The aqueous phase was decanted each time and, finally, the organic phase was dried thoroughly with anhydrous sodium sulphate and used for preparation of the electrode. The liquid ion exchanger thus obtained consists of the tetraheptylammonium - naproxenate ion pair dissolved in the initial organic solvent (*p*-nitrocumene).

Assembly of the Electrode

An Orion liquid-membrane electrode body (Series 92) was used with Orion polycellulose acetate membranes (*e.g.*, 92-07-04 nitrate membranes) and the above naproxenate ion exchanger. The internal reference solution was a 0.1 M naproxenate solution containing 0.1 M NaCl and saturated with AgCl. The external reference electrode was an Orion 90-01 Ag - AgCl single-junction electrode filled with 4 M KCl as the electrolyte solution.

The measuring cell can be represented as

Ag-AgCl	Internal reference solution 0.1 M naproxenate 0.1 M NaCl	Membrane saturated with naproxenate ion exchanger	Test solution	KCl salt bridge	AgCl-Ag

The electrode was conditioned in a stirred 0.01 M naproxenate solution for 12 h before use and stored in this solution when not in use.

Apparatus

E.m.f. values were measured with an Orion Model 801 digital pH - millivoltmeter; the values could be read to within ±0.1 mV. All measurements were carried out in a 50-ml double-walled glass cell, thermostated at 25.0 °C, with constant magnetic stirring of the test solutions. For pH measurements, a Metrohm Model E-350 B pH meter with a combination glass electrode was used.

For the dissolution studies of the tablets, the USP XXI rotating basket apparatus (apparatus 1)[22] was used, with a rotation speed of 60 rev min^{-1}.

Procedures

Direct potentiometric assay of pharmaceutical preparations

Tablets. The official procedure of the USP XXI[6] was followed for sampling and homogenisation. An appropriate, accurately weighed amount of the homogenised powder, equivalent to about 180–230 mg (0.8–1.0 mmol) of the drug, was transferred into a 100-ml calibrated flask. An equimolar amount of NaOH was added (using a 1.00 M solution) to dissolve and ionise the naproxen and the solution was made up to the mark with 0.010 M borate buffer. Dissolution of the sample was assisted by means of a mechanical shaker or ultrasonic bath and the undissolved excipients were removed by filtration or centrifugation (3.0×10^3 rev min^{-1}). The e.m.f. values (E) of the resulting sample solutions were measured and the naproxenate concentration (c) was determined using a calibration graph of E *versus* log c, prepared from working standard solutions in the same buffer with concentrations of 1–100 $\times 10^{-4}$ M. No difference in the results was found between the two methods used for removing the undissolved excipients (filtration or centrifugation).

Suppositories. An accurately weighed amount of the sample, equivalent to about 230 mg (1.0 mmol) of the drug, was transferred into a beaker and 100 ml of a 0.010 M NaOH solution were added. By gentle heating and simultaneous swirling, the sample was melted and a homogeneous solution was obtained. The solution was transferred quantitatively into a 250-ml calibrated flask, 25 ml of the 0.10 M borate buffer were added and, after cooling, the solution was made up to the mark with water. The undissolved excipient was removed by filtration or centrifugation and the naproxenate concentration in the resulting solution was determined using the standard additions method. To a 25.00-ml volume of the sample solution, for which the e.m.f. value, E_1, had been measured, were added 5.00 ml of a 5.00×10^{-2} M working standard naproxenate solution and the e.m.f. value, E_2, was then measured. The slope, S, of the naproxenate electrode was determined using standard solutions containing the same amount of the melted excipient as that used in the suppository formulation. The naproxenate concentration in the sample solution, c_u, was calculated using the following equation:

$$c_u = \frac{5\,(\text{ml}) \cdot 5 \times 10^{-2}\,(\text{mmol ml}^{-1})}{(25\,\text{ml} + 5\,\text{ml}) \cdot 10^{E_2 - E_1/S} - 25\,(\text{ml})} \quad \ldots \quad (1)$$

Dissolution study. In this instance, 900-ml volumes of 0.010 M phosphate (pH 7.4) and 0.010 M acetate (pH 4.0) buffers, thermostated at 37 °C, were used as dissolution media. Aliquots (ten for each study) of 10.0 ml were withdrawn every 10 min using glass syringes with an accuracy of ±0.05 ml. The sample solutions were filtered through filter-paper contained in in-line plastic holders (Millipore, USA) fitted on the syringe tips. The volume of solution withdrawn was substituted immediately with fresh dissolution medium kept at the same temperature. To each sample filtrate, 5.00 ml of 0.100 M borate buffer were added to adjust the pH to 9.0 and the e.m.f. was measured. The naproxenate concentrations were calculated using a calibration graph (E *versus* log c) constructed from working standards prepared in the corresponding dissolution medium, the pH of which was adjusted to 9.0 as described above for the sample solutions. The concentration of the dissolved naproxen at the various time intervals was corrected for the volume of solution substituted using the equation[23]

$$c_{r,n} = \frac{c_{m,n} V_m + V_s \sum_{i=1}^{n-1} c_{m,i}}{V_m} \quad \ldots \quad (2)$$

where $c_{r,n}$ is the corrected drug concentration in the nth sample, $c_{m,i}$ the drug concentration in the ith sample determined from the calibration graph, V_m the volume of the dissolution medium (900 ml) and V_s the sample volume (10 ml). From the corrected drug concentration at each time interval the percentage dissolved drug was calculated.

Results and Discussion

Choice of Optimum Liquid Ion Exchanger

Various bulky quaternary ammonium cations (octadecyltrimethylammonium, hexadecyltriethylammonium, hyamine, tetraheptylammonium and 1-hexadecylpyridinium) were tested as ion-pairing cations with naproxenate for use as possible liquid ion exchangers in the construction of the electrode. *p*-Nitrocumene was used as the organic solvent because of its excellent characteristics,[24] *viz.*, insolubility in water, low vapour pressure (b.p. 122 °C), relatively high viscosity, high extractability of the ion pair (ensuring an adequate association constant of the ion pair), low dielectric constant, high relative molecular mass, sufficient purity and stability to light.

The tetraheptylammonium - naproxenate ion pair was found to have the optimum characteristics (with regard to slope, detection limit and freedom from interferences).

Effect of pH

In order to study the pH-dependence of the electrode potential, graphs of E/mV *versus* pH were constructed at various naproxenate concentrations. The pH of the initial solution (containing also 0.100 M Na_2SO_4 to adjust the ionic strength) was varied by the addition of very small volumes of appropriate NaOH or H_2SO_4 solutions. A typical plot for a 1.0×10^{-3} M naproxenate concentration (Fig. 1) shows that

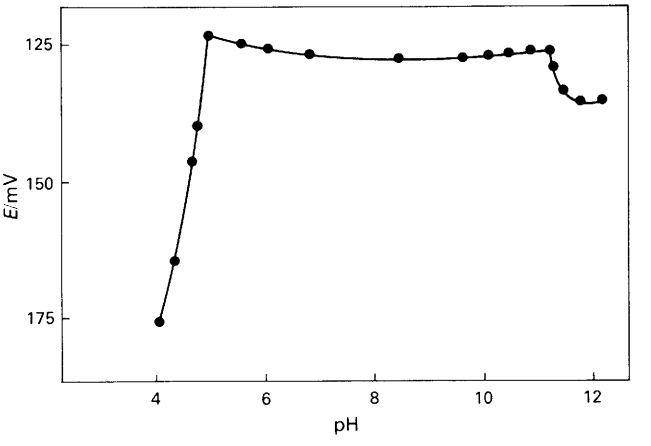

Fig. 1. Effect of pH on the potential of the naproxenate electrode. Naproxenate concentration, 1.0×10^{-3} M in the presence of Na_2SO_4 (0.100 M); T = 25 °C

Table 1. Effect of pH on the response characteristics of the naproxenate-selective electrode at 25 °C

Buffer*	Slope/mV decade^{-1}	Lower linear limit/M
Phosphate (pH 7.4)	101.7	3.9×10^{-4}
Phosphate (pH 8.0)	80.6	3.3×10^{-4}
Phosphate (pH 8.5)	66.4	1.8×10^{-4}
Borate (pH 9.0)	61.0	1.4×10^{-4}

* Buffer concentration, 0.010 M.

the potential is almost independent of pH in the pH range 5–11. As naproxen is a weak acid, with a pK_a of 4.15, a marked increase in potential (decrease in naproxenate concentration) is observed below pH 5.0.

The pH was also found to affect the detection limit and the slope of the electrode. From calibration graphs, constructed in various buffered solutions, it was concluded (Table 1) that pH 9.0 (0.010 M borate buffer) was the optimum, giving a near-Nernstian slope and a lower linear limit of about 1×10^{-4} M.

Operative Life and Characteristics of the Electrode

The electrode was found to have an operative life of about 2 months, with a slope ranging from 58 to 61 mV decade^{-1} and a linear concentration range from 1×10^{-4} to 1×10^{-1} M naproxen. The response time was fairly short (about 2.5 s for a ten-fold increase in the concentration); also, when the potentials were measured over the range 1×10^{-4}–1×10^{-1} M naproxen (from low to high concentrations and *vice versa*), no significant hysteresis phenomena were observed.

Interferences

The interference of various common anions was studied by the mixed solution method. The potentiometric selectivity coefficients for acetate, sulphate, hydrogen phosphate and chloride were found to be 0.0048, 0.0045, 0.0059 and 0.029, respectively (naproxenate concentration, 5×10^{-4}–1×10^{-3} M; interferent concentration, 1×10^{-3}–5×10^{-3} M in pH 9.0 borate buffer). The slightly increased interference from chloride is probably caused by the formation of a tetraheptylammonium chloride ion pair in the membrane.

In order to examine the effect of common excipients used in tablet formulations, synthetic mixed solutions containing 1.00×10^{-3} M naproxenate and 0.50 mg ml^{-1} of the various additives were analysed following the measurement procedure used for tablets. The recovery results, shown in Table 2, reveal that there is no interference from the excipients studied, with the exception of sodium chloride, with an average recovery of 99.8%. However, large amounts of sodium chloride (as an excipient) are not commonly found in tablets. Hence the proposed method is suitable for the assay and dissolution study of naproxen tablets using the calibration graph technique without any error from excipients.

As suppositories are formulated using oleaginous, water soluble or hydrophilic bases, the effect of some of these types of excipient on the electrode slope was studied. A calibration graph was constructed for the electrode using solutions obtained by melting or dispersing 500 mg of each additive in 250 ml of 0.010 M borate buffer (pH 9.0) as described under Suppositories. As can be seen from Table 3 the slope of the electrode decreases in these media (by about 16–19% compared with the slope obtained in the pure buffer). Therefore, the standard additions technique and calculation of the electrode slope [equation (1)] in the presence of the suppository excipients were used to develop a successful direct assay of naproxen in suppositories. The developed procedure was then evaluated by performing recovery experiments on 230 mg of naproxen dispersed in 1000 mg of various suppository excipients. As shown in Table 4 a mean recovery of 101.8% (range 97.8–103.9%) was obtained, demonstrating the ability of the procedure to eliminate the effect of the excipients. The precision of these determinations, expressed as the relative standard deviation (RSD), ranged from 1.3 to 3.3%.

Table 2. Recovery of naproxen from various tablet additives

Additive*	Recovery, %
Galactose	95.8
Lactose	100.1
Saccharose	101.9
Mannitol	99.7
Sorbitol	101.0
Carbowax 4000†	99.2
Pharmacoat‡	103.3
Talc	101.0
Magnesium stearate	96.2
Sodium chloride	124.5

Mean (except sodium chloride): 99.8

* Naproxen, 1.00×10^{-3} M; additive, 0.50 mg ml^{-1}.
† Polyethylene glycol 4000.
‡ Hydroxypropylmethylcellulose.

Table 3. Effect of suppository excipients on the slope of the naproxenate electrode

	Equation of electrode response†	
Additive*	Intercept (±SD)/ mV decade^{-1}	Slope (±SD)/ mV decade^{-1}
None (pure borate buffer, 0.010 M, pH 9.0)	−56.3 ± 1.1	58.6 ± 0.4
Glycerin	−27.4 ± 1.2	48.9 ± 0.4
Gelatin	−27.7 ± 1.7	49.3 ± 0.6
Massa esterinum‡	−26.3 ± 1.5	47.6 ± 0.5
Witepsol-W-35‡	−28.1 ± 1.1	47.5 ± 0.4
Witepsol-H-15‡	−28.1 ± 1.4	47.5 ± 0.5

* A 500-mg amount of each additive was melted or dispersed in 250 ml of borate buffer as described under Procedure.
† Naproxenate concentration range, 1×10^{-4}–1×10^{-2} M ($n = 5$).
‡ Hard-fat alternatives to *theobroma* oil with various contents of triglycerides.

Table 4. Recovery of naproxen from various suppository additives. A 230-mg amount of naproxen was dispersed in 1000 mg of each additive and determined according to the proposed procedure

Additive	Naproxen found ± SD/mg*	Recovery, %
Glycerin	225 ± 3	97.8
Gelatin	239 ± 6	103.9
Massa esterinum	239 ± 8	103.9
Witepsol-W-35	234 ± 5	101.7
Witepsol-H-15	234 ± 3	101.7
		Mean: 101.8

* Average of three measurements.

Applications

The proposed potentiometric method for the determination of naproxen was evaluated further by analysing commercial formulations and comparing the results obtained with those given by the official USP XXI procedures.[6] As can be seen from Table 5 the results show good agreement, and demonstrate the applicability of the naproxen electrode to routine analysis. The precision (RSD) of the potentiometric method was 0.8 and 2.9% ($n = 3$) for tablet and suppository assays, respectively.

The simplicity, rapidity and reliability of the proposed potentiometric method were evaluated by means of dissolution studies of commercial naproxen tablets. As shown in

Table 5. Comparison of results obtained by the proposed potentiometric and the official USP XXI methods for the determination of naproxen in commercial formulations

Formulation	Nominal content/mg	Amount found ± SD/mg: Proposed method	Amount found ± SD/mg: Official method*[6]	Difference, %	*t*-test†
Naprosyn tablets . .	250	253 ± 2	254 ± 3	−0.4	0.482
Naprosyn suppositories . .	250	238 ± 7	240 ± 8	−0.8	0.326

* UV spectrophotometric method for tablets, extraction with sodium hydroxide and UV spectrophotometry for suppositories.
† *t*-theoretical = 2.776 (95%), based on three determinations.

Table 6. Comparison study for the dissolution of a naproxen tablet for the potentiometric and the USP XXI spectrophotometric methods (Naprosyn tablet containing 250 mg of naproxen. Dissolution medium, pH 7.4 phosphate buffer, 0.010 M; T = 37 °C)

Sampling No.	Time/min	Dissolved drug: mean ± SD, % (n = 3): Potentiometric method	Dissolved drug: mean ± SD, % (n = 3): Official USP method[6]	Relative difference, %	*t*-test*
1	10	11.6 ± 2.2	10.9 ± 1.0	+6.4	0.502
2	20	17.1 ± 2.5	19.1 ± 1.7	−10.5	1.146
3	30	26.7 ± 3.1	29.4 ± 0.6	−9.2	1.481
4	40	38.5 ± 3.0	42.2 ± 0.5	−8.8	2.107
5	50	52.5 ± 5.1	54.4 ± 1.0	−3.5	0.633
6	60	69.5 ± 6.8	73.3 ± 2.2	−5.2	0.921
7	70	80.7 ± 5.9	82.2 ± 1.2	−1.8	0.432
8	80	84.4 ± 3.4	85.0 ± 2.2	−0.7	0.257
9	90	85.6 ± 4.0	86.2 ± 3.2	−0.7	0.203
10	100	84.1 ± 3.3	86.9 ± 2.0	−3.2	1.257
				Mean: 5.0%	

* *t*-theoretical = 2.776 (95%).

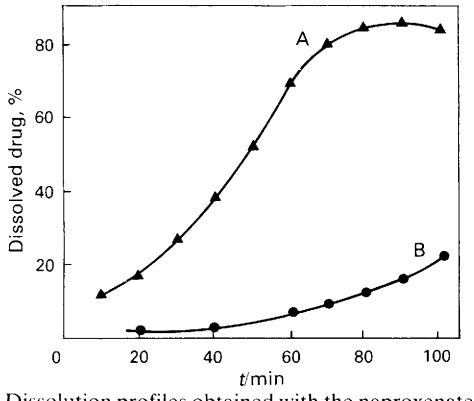

Fig. 2. Dissolution profiles obtained with the naproxenate electrode of a naproxen tablet (Naprosyn, 250 mg) in (A) phosphate (pH 7.4) and (B) acetate (pH 4.0) buffer

Table 6 the results obtained with the proposed potentiometric method for three dissolution experiments on tablets from the same batch compare favourably with those given by the spectrophotometric USP XXI method[6] (mean relative difference 5.0%, range 0.7–10.5%). The standard deviation (SD) of the measurements for the three tablets for all data points ranged from 2.2 to 6.8% dissolved drug (mean 3.9%), which was slightly higher than the SD of the spectrophotometric method (0.5–3.2% dissolved drug, mean 1.6%). The tablet to tablet variability is included in these precision data. From the results obtained the dissolution rate constant, K_d, can be calculated using the equation

$$c_t = c_\infty (1 - e^{-K_d t}) \quad . . \quad . . \quad . . \quad (3)$$

where c_t is the corrected drug concentration at time t [$c_{r,n}$, equation (2)] and c_∞ is the final theoretical concentration expected. Analysis of the data presented in Table 6, after logarithmic transformation and linearisation of equation (3), gave values for K_d of 0.0261 ± 0.0021 min^{-1} (r = 0.98) for the potentiometric method and 0.0267 ± 0.0021 min^{-1} (r = 0.98) for the spectrophotometric method.

The effect of pH on the rate of dissolution of naproxen tablets was also investigated with the potentiometric method by carrying out dissolution experiments in phosphate (pH 7.4) and acetate (pH 4.0) buffers. The dissolution profiles shown in Fig. 2 gave values for K_d of 0.0261 ± 0.0021 min^{-1} (r = 0.98) at pH 7.4 and 0.00332 ± 0.00017 min^{-1} (r = 0.996) at pH 4.0. Hence there is a decrease in the dissolution rate constant (87%) of the acidic drug naproxen at low pH, which was expected.

Conclusions

The proposed potentiometric method for the determination of naproxen using a naproxenate electrode has the advantages of simplicity and rapidity and it can be used for the direct assay of formulations without any interference from excipients. The recent increase in the use of dissolution tests, where a heavy analytical workload is involved, provides a potential area of application for a drug ion-selective electrode.

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