Novel naproxenate screen-printed potentiometric sensors

Elmorsy Khaled[a], Eman M. Shoukry[b], Mona F. Amin[b], Basmat A.M. Said[b], Mahmmoud S. Abd-Elmonem[c]

[a]Microanalysis Laboratory, Applied Organic Chemistry Department, Industries Research Division, National Research Centre, Giza, [b]Chemistry Department, Faculty of Science (Girls), Al Azhar University, Naser City, [c]National Organization of Drug Control and Research, Cairo, Egypt

Correspondence to Prof Elmorsy Khaled, Microanalysis Laboratory, Applied Organic Chemistry Department, Industries Research Division, National Research Centre, El Bohouth Street, Dokki, Giza 12622, Egypt.
Tel: +20 100 378 1777; fax: +20233370931;
e-mail: elmorsykhaled@yahoo.com

Received 23 May 2018
Accepted 26 June 2018

Egyptian Pharmaceutical Journal 2018, 17:201–211

Background and objectives
Naproxen (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid (or sodium salt) belongs to a group of pharmaceuticals known as NSAIDs. The aim of this study is to describe the construction and performance characteristics of naproxen (NAP) screen-printed sensors.
Materials and methods
Various sensor fabrication protocols have been applied including bulk modification with NAP-surfactants ion pairs (IPs), in-situ modification with ion pairing agents and soaking the plain electrode in IP suspension solutions. Qualitative and quantitative matrix composition optimization was done referring to the effect of modifier and plasticizer. Conductometric measurements were performed for the determination of the solubility products of NAP-surfactants ion associates.
Results and conclusion
The fabricated sensors showed Nernstian compliance in the concentration range from 10^{-7} to 10^{-2} mol/l (detection limit 8.0×10^{-8} mol/l) with fast response time (4 s) and long operational lifetime (3 months). The developed electrodes have been successfully applied for the potentiometric determination of NAP in pure and dosage forms under standard addition and potentiometric titration conditions with average recoveries agreeable with the reported official methods. The solubility products of various NAP-IPs were determined conductometrically.

Keywords:
modification, naproxen, pharmaceutical preparations, screen-printed potentiometric sensors

Egypt Pharmaceut J 17:201–211

1687-4315

Introduction

Naproxen (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid belongs to a group of pharmaceuticals known as NSAIDs. Naproxen (NAP) is used for the treatment of rheumatoid arthritis and other rheumatic or musculoskeletal disorders, dysmenorrhea, and acute gout [1]. This drug is used more and more frequently; therefore, new improved methods of determining its concentration in various matrixes need to be introduced.

Several analytical methods are available in the literature for the determination of NAP in pharmaceuticals and biological fluids. They include chromatographic method: high-performance liquid chromatography [2], thin layer chromatography with densitometry [3–5], gas chromatography–mass spectrometry [6], capillary electrophoresis [7], spectrophotometry [8,9], spectrofluorometry [10], and nonaqueous potentiometric titration [11]. Most of these methods require prior derivatization or the extraction step and involve the use of expensive apparatus.

On the contrary, the inherent advantages of electrochemical methods are simplicity, adequate precision, and accuracy with short measurement time [12–14]. To the best of our knowledge, few ion-selective electrodes for NAP determination can be found in the literature [15–19]. These electrodes differ in their construction and sensing element: for instance, there is the electrode [20] with liquid membrane type based on the use of tetraheptylammonium naproxenate ion associates, the electrode with polymeric membrane type without the inner solution using methyl trioctyl ammonium naproxenate [21] ion associate, or tetraoctylammonium naproxenate [22], the electrode with graphite membrane based on mercury (I) naproxenate [23], and the electrodes based on other quaternary ammonium salts in the chloride and bromide forms with the inner solution of naproxenate in the NaCl solution [24].

Poisoning of the traditional polyvinylchloride (PVC) electrode surface during biological sample measurements by proteins and other contaminants besides their bulk size limited their widespread applications for biomedical monitoring. Miniaturization of the sensing element is crucial for the development of the

analytical method. Several shapes and designs of disposable electrochemical sensors based on the screen printing technology have been produced for economic and practical feasibility [25,26].

The aim of the present work is to introduce disposable screen-printed electrodes constructed with different fabrication protocols as potentiometric sensors that can be used in drug quality control of NAP. The proposed electrodes are without the inner solution, so they are easy to use with inexpensive equipments.

Experimental

Reagents

All reagents were of analytical grade, and bidistilled water was used throughout the experiments. 2-fluorophenyl 2-nitrophenyl ether (*f*-PNPE) from Sigma was used as electrode plasticizer. Other types of plasticizers, namely, *o*-nitrophenyloctylether (*o*-NPOE), dioctylphthalate (DOP), dioctylsebacate (DOS), and tricresylphosphate (TCP) were purchased from Sigma, Avocado, and Fluka, respectively. PVC (relative high molecular weight) and graphite powder (synthetic 1–2 μm) were purchased from Aldrich.

Ion pairing agents such hyamine 1622 (Hy; Fluka), cetylpyridiniumchloride (CPCl; Fluka), tridodecyldimethylammonium chloride (Sigma), cetyltrimethylammonium bromide (CATB; Fluka), and Septonex [1-(ethoxycarbonyl) pentadecyltrimethylammonium bromide] was purchased from Slovakofarma (Hlohovec, CZ) (SEP; Hlohovec, Czech Republic) were used for preparation of different NAP ion associates.

Authentic samples

NAP authentic sample was kindly provided from National Organization of Drug Control and Research, Giza, Egypt. Stock solution (1×10^{-2} mol/l) was prepared by dissolving the appropriate amount of the active ingredient in 5×10^{-2} mol/l NaOH solution and kept at 4°C.

Pharmaceutical preparations

Naprosyn tablets (250 mg NPA/tablet; Misr Pharmaceutical Industries, Cairo, Egypt) were purchased from local drug stores. One tablet was dissolved in 5×10^{-2} mol/l NaOH, filtered and completed to 250 ml with the same solution.

Apparatus

All the potential measurements were carried out using a 692-pH meter (Metrohm, Switzerland) with Ag/AgCl double-junction reference electrode (Metrohm 6.0726.100) and a combined pH glass electrode (Metrohm 6.0202.100). 46-Range Digital Multimeter (Radioshack, Radiosack, China) with PC interface was used for response time measurements. Lyophilizer, Snijders Scientific b.v. (Tilbury, Holland), Stek-no: S1084 was applied for separation of different NAP ion associates. A conductivity meter model 4510 Jenway (England) was used for conductance measurements. The bridge is connected with a thermocouple for temperature measurements, and the cell constant, K_{cell}, is 1.0. Elemental analysis was performed at Elementar (Vario El, Germany).

Procedures

Ion pair preparation

Different NAP ion pairs (IPs) were precipitated by drop-wise addition of different cationic surfactants solutions to 50 ml of 1×10^{-2} mol/l NAP solution with continuous stirring for 10 min. The aqueous IP solution was kept at −18°C for 24 h, lyophilized for removing of water and kept dry in dissector. The chemical compositions of the resultant IPs were confirmed by elemental analysis.

Sensor construction

The potentiometric bielectrode strips were printed on a ceramic support (dimensions 5×35 mm) using silver-based and graphite-based pastes for reference and working electrodes, respectively [27]. A pseudosilver/silver chloride reference electrode was firstly printed using homemade PVC ink [prepared by mixing 0.9 g silver/silver chloride mixture (65 : 35%) with 0.8 g 8% PVC solution in acetone/cyclohexanone mixture 1 : 1] and curing at 50°C for 30 min. The conducting carbon track was printed using homemade carbon ink prepared by mixing 5-g PVC solution and 3-g carbon powder.

The unmodified sensing cocktail, containing 360-mg *f*-PNPE and 240-mg PVC dissolved in 6-ml tetrahydrofuran, was printed on the surface of the graphite/PVC conducting track and left to dry at 50°C for 24 h. A layer of an insulator was then placed onto the printed electrodes, leaving a defined rectangular shaped (5×5 mm) working area and a similar area on the other side for the electrical contact. The fabricated sensors were soaked in different freshly prepared NAP IP suspensions for 24 h. On the contrary, the modified electrodes were fabricated in the same manner via incorporation of either 10.0 mg of NAP-Hy or 10.0 mg of Hy as sensing materials and used directly in the potentiometric measurements after 60 min preconditioning in 1×10^{-3} mol/l NAP solution.

Calibration of sensors

The developed sensors were calibrated by immersing the bielectrode strip in different NAP solutions covering the concentration range from 10^{-7} to 10^{-2} mol/l at 25°C. The potential readings were recorded and plotted against drug concentration in logarithmic scale [28].

Potentiometric determination of naproxen in pharmaceutical preparations

The content of NAP in pharmaceutical preparation was potentiometrically determined using the developed sensors by standard addition and potentiometric titration technique. For standard addition method, known increments of 10^{-2} mol/l NPA standard solution were added to the sample solution, and the electrode potentials for each increment were used to calculate BP concentration in the sample solution [29]. Under potentiometric titration, aliquots of the sample solutions containing 2.3–16.1 mg of NPA were titrated against standardized Hy solution [15] using the fabricated NPA bielectrode strip as indicator electrode. The potential readings were plotted against volume added, and the equivalence points were estimated from the first derivative of the sigmoid-shape titration curves. The obtained recoveries were compared with the official pharmacopoeial method including classical titration of (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid in alcohol medium [16].

Conductometric measurements

Aliquots of working solutions containing 2.3–23.03 mg of NAP were transferred to 25-ml volumetric flask and made up to the mark with bidistilled water. The contents of the volumetric flask were transferred to the measuring cell and titrated against 1.0×10^{-2} mol/l of the tested cationic surfactants solutions. The conductance was measured after 1–2 min after each addition of reagent through stirring.

The conductance reading was corrected for dilution assuming that conductivity is a linear function of dilution [17,18]:

$$\Omega_{corr} = \Omega_{obs}[(\upsilon_1+\upsilon_2)/\upsilon_1]$$

where Ω_{corr} and Ω_{obs} are the corrected and the observed electrolytic conductivities, respectively; υ_1 is the initial volume; and υ_2 is the volume of the added reagent (corr., corrected; obs., observed).

A graph of corrected conductivity values versus the volume of the added titrant was constructed and the end point was determined. The drug-titrant ratio is then determined from the intercept of the two linear segments of the graph.

Conductometric determination of the solubility product of the ion associates

A series of solutions of different concentrations (c) was prepared for NAP, Hy, SEP, CTAB, or CPCl. The conductivities of these solutions were measured at 25°C and the specific conductivities (λ_0), corrected for the effect of solvent, were calculated and used to obtain the equivalent conductivities (λ) of the solutions. Straight-line plots of λ versus $\sqrt{c}$ were constructed, and $\lambda_{0\ (NAP)}$; $\lambda_{0\ (Hy)}$, $\lambda_{0\ (CTAB)}$, $\lambda_{0\ (CPCl)}$ or $\lambda_{0\ (SEP)}$ were determined from the intercept of the respective line with the λ axis. The activity coefficients of the ions employed were taken as unity because all the solutions were sufficiently diluted (5×10^{-5}–2×10^{-3} mol/l). The values of $\lambda_{0\ (NAP)}$; $\lambda_{0\ (Hy)}$, $\lambda_{0\ (CTAB)}$, $\lambda_{0\ (CPCl)}$, and $\lambda_{0\ (SEP)}$ were calculated using Kohlrausch's law of independent migration of ions [19].

The solubility (s) and solubility product (K_{sp}) of a particular ion associate were calculated using the following equations:

$$S = K_s \times 10000/\lambda_{0(\text{ion associate})},$$

$$K_{sp} = S^2 \text{for } 1:1 \text{ ion associates,}$$

where K_s is the specific conductivity of a saturated solution of the ion associate, determined at 25°C and corrected for the effect of solvent. The saturated solution was made by stirring a suspension of the solid precipitate in distilled water for 15 min at 25°C.

Results and discussion

Conductometric determination of the ion-associates solubility products

Conductance measurements are used successfully in quantitative titration of systems in which the conductance of the solution varies before and after the equivalence point. One of the valuable features of the conductometric method of titration is that it permits the analysis of the components of a precipitation reaction. In this case, the formation of a precipitate alters the number of ions present in the solution and consequently the conductance varies. After the equivalent point, the addition of excess titrant increases the number of ions and so the conductance increases.

The titration curve, representing the relation between the conductance and the volume of the titrant added, can be constructed as two lines intersecting at the end point. Naproxenate anion forms ion associates with different cationic surfactants which can be applied for conductometric titration of NAP. Parameters affecting the end point, such as temperature, and concentration of both titrant and drug, were studied. The reagent concentration in each titration must not be less than 10 times that of the drug solution to minimize the dilution effect on the conductivity throughout the titration. The optimum concentration of the reagents is 10^{-2} mol/l to achieve a constant and highly stable reading within 1–2 min of mixing. Lower concentrations led to unstable readings and longer time to achieve constant conductance values. Temperatures up to 50°C show no effect on the end point. The systems under investigation showed a regular rise in conductance up to the equivalence point where a sudden change in the slope occurs.

Representative conductometric titration curves are shown in Fig. 1. The system showed a regular rise in conductance up to the equivalence point where a sudden change in the conductance was observed as obviously shown from the first derivative plots sustaining the elemental analysis data with the formation of (1 : 1) (drug:reagent) ion associates.

Conductance of the investigated solutions has been employed to find out the solubility product of the formed precipitates. The solubility products together with the parameters related to ion pairing of NAP are listed in Table 1 and illustrated in Fig. 2.

The calculated equilibrium constant values (*K*) are high enough to show the high degree of completeness of the ion pairing reactions. At equilibrium, the solubility of the undissociated ion-associates in water (the intrinsic solubility) was omitted as it has an insignificant contribution to the total solubility because the ion-associates are sparingly soluble in water and their saturated solutions are consequently very dilute.

Naproxen potentiometric sensors

Limited scientific reports on the use of ion-selective electrodes for NAP determination have been found in literature [20–24]. These are based on the ion associates between naproxenate ions and different cationic surfactants as well as mercury (I) nitrate. Usually, the ion-associates preparation protocol involves preparation of main ion solution, preparation of ion exchanger solution, several repetitions of extraction of the ion associated into the organic phase, washing of the organic phase from interfering ions, and finally possible centrifugation or drying of the complex until a clear solution is obtained. Owing to the toxic effect of organic solvent and tedious extraction conditions, the present work describes a simple and reliable green protocol for preparation of NAP ion associates with different cationic surfactants applying lyophilization as an efficient tool for separation of formed IPs from their aqueous solutions.

Moreover, incorporation of a suitable ion pairing agent in the membrane matrix followed by soaking the electrode in the target analyte solution will lead to formation of analyte–IP complexes at the electrode surface, which are subsequently extracted into the electrode bulk by the plasticizer [30,31]. Both ion pairing agent and IP have been incorporated as ion exchangers during the fabrication of ISEs, where modification with ion pairing agent is called in-situ mode.

In addition to the aforementioned methods for electrode fabrication, a simple and reliable suggested procedure could be applied by soaking the plain electrodes in the aqueous suspension of the lipophilic IP, where the electrode mediator (plasticizer) extracts IP and becomes gradually saturated with this IP. In such a case, there is no need to incorporate either IP or the ion pairing agent into the electrode matrix during its fabrication [32,33].

Optimization of the electrode performance under batch condition

The investigation of the experimental variables that contribute to the electrode response led to the development of a simple, selective, and reliable method for NAP determination.

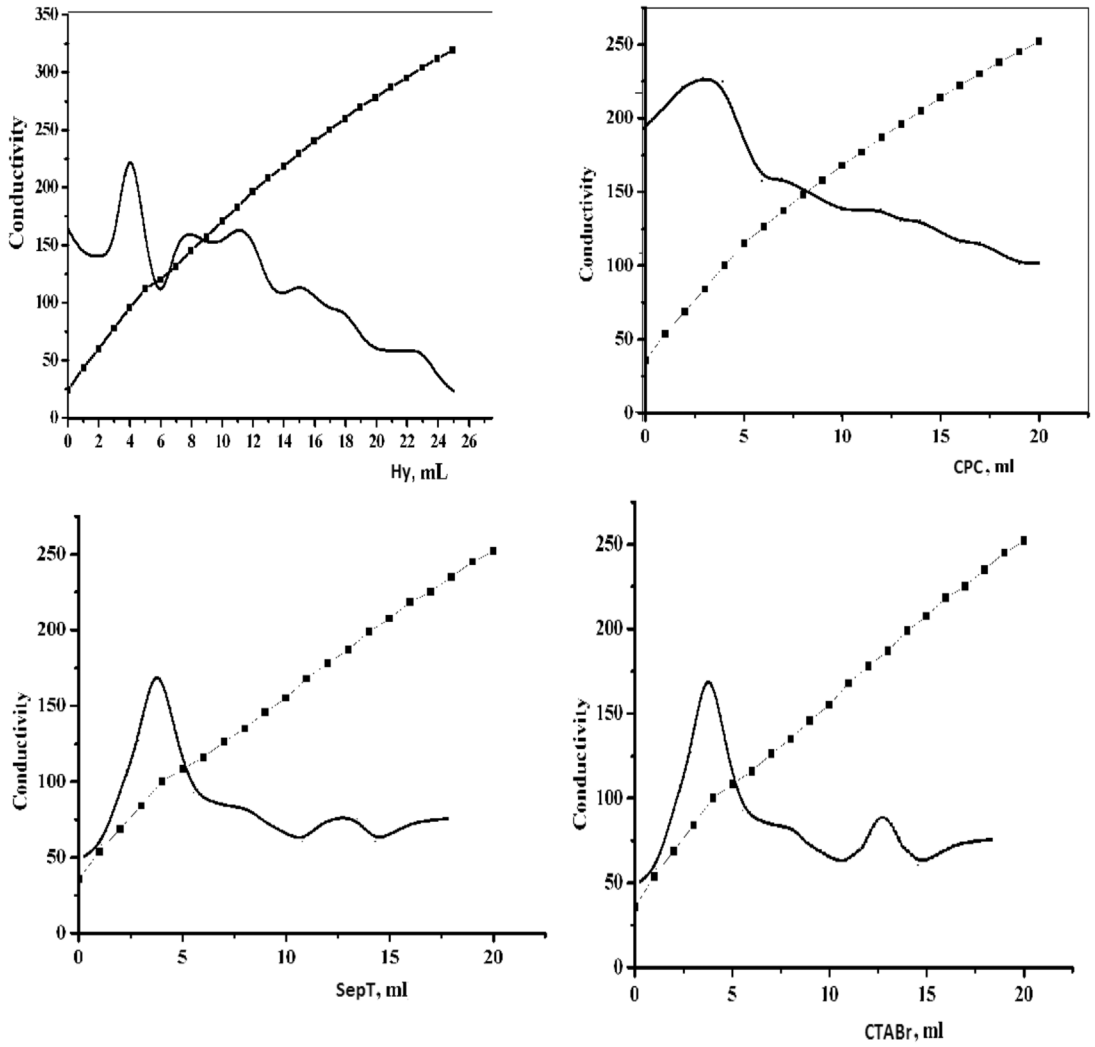
Both unmodified (plain) and modified electrodes (either with NAP-surfactant IPs or surfactants) were prepared and tested for nature and content of modifier, plasticizer, pH effect, response time, selectivity, and applications.

Modification with ion pair

NAP can form insoluble IP complexes with oppositely charged cationic surfactants such as Hy, CPCl, CATB, and SEP, which can be used as ion exchangers for NAP sensors construction. The stoichiometric ratios were estimated from elemental analysis and conductometric titration data. NAP forms 1 : 1 IPs with both the tested ion pairing agents.

Preliminary experiment declared that the blank electrodes fabricated without incorporation of the

Figure 1



Conductometric titration of 5.0 ml of 10^{-2} mol/l NAP with 10^{-2} mol/l surfactant solutions. CPCl, cetylpyridiniumchloride; CTAB, cetyltrimethylammonium bromide; Hy, hyamine; SEP, Septonex; NAP, naproxen.

Table 1 Conductometrically measured solubility (s), solubility products (K_{sp}), and formation constants (*k*) of various drug-ion associates

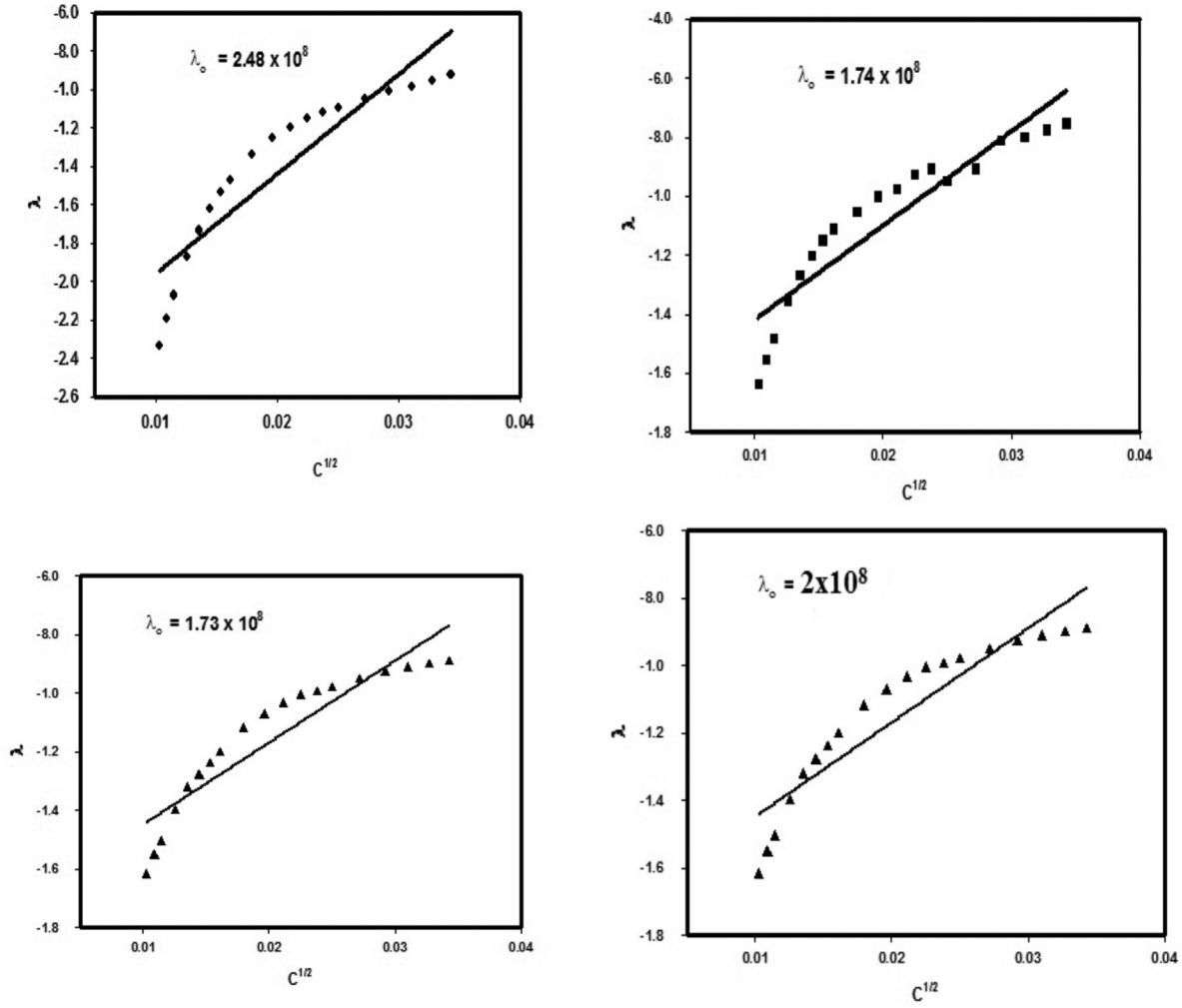
Ion pairing agent	K_s	λ_o	$\lambda_{ion\ asso}$	$s=K_s\times_{1000/\lambda}$	K_{sp}	K
CPCl	1516	2.09	9.26	163.7×10^3	2.68×10^{10}	3.7×10^{-11}
SEP	1780	1.74	8.91	199.7×10^3	3.99×10^{10}	2.5×10^{-11}
Hy	2140	1.73	8.90	240.5×10^3	5.78×10^{10}	1.7×10^{-11}
CTAB	1950	1.98	9.05	215.5×10^3	4.64×10^{10}	2.16×10^{-11}

CPCl, cetylpyridiniumchloride; CTAB, cetyltrimethylammonium bromide; Hy, hyamine; SEP, Septonex.

sensing materials showed poor Nernstian response toward NAP (slope value was −24.0±0.8 mV/decade), whereas those modified with different IPs gave performances depending on the IP used (Fig. 3a). Sensors incorporated with NAP-Hy IP showed the highest performance indicated (Nernstian slope was 59.0±0.6 mV/decade in the concentration range from 10^{-7} to 10^{-2} mol/l). Sensors containing other NAP-IPs showed either lower Nernstian slope values or narrow working concentration ranges.

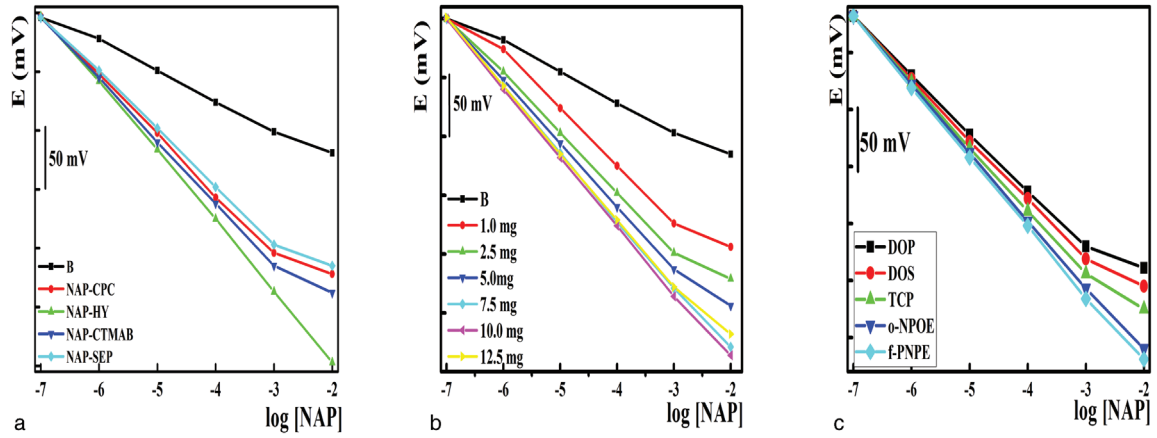
On constructing an ion selective electrode (ISE), the amount of the sensing material in the electrode matrix should be sufficient to obtain reasonable complexation at the electrode surface that is responsible for the electrode potential. If the sensing material presents in excess, over-saturation occurs in the network hindering the equilibrium process at the electrode surface leading to unsatisfactory measurements. Thus, the influence of the NAP-Hy IP content within the electrode matrix was varied from 0 to 12.5 mg (Fig. 3b). The sensor performance was improved via incorporation of the sensing material, and the Nernstian slope value increased from −49.3±0.2 to −58.6±0.7 mV/decade by rising the ionophore content from 1 to 10%, then decreased with higher IP concentration.

Figure 2



Equivalent conductance (λ_{eq}) versus the square root of concentration $C^{1/2}$ for Hy, SEP, CPCl and CTAB, respectively. CPCl, cetylpyridinium-chloride; CTAB, cetyltrimethylammonium bromide; Hy, hyamine; SEP, Septonex.

Figure 3



Effect of (a) nature of the ion associate, (b) NAP-Hy ion associate concentration, and (c) nature of plasticizer on the performance of naproxen screen-printed sensor. Hy, hyamine; NAP, naproxen.

Plasticizers play an important role on the ion-selective electrode behavior as they improve the solubility of the sensing material and lower the overall bulk resistance of the electrode owing to their dielectrical constant (ε) [34]. Different membrane plasticizers with different dielectric constants were employed, namely, DOP,

DOS, TCP, *o*-NPOE, and *f*-PNPE (ε=3.8, 5.2, 17.6, 24, and 50, respectively). Improved performances were recorded for electrodes containing high polar plasticizers (*o*-NPOE and *f*-PNPE), whereas other tested plasticizers showed lower Nernstian slopes in a narrow working concentration range (Fig. 3c). The recorded slope values were −50.6±0.5, −53.1±0.6, −56.5 ±0.5, −58.8±0.59, and −60.6±0.7 mV/decade for DOP, DOS, TCP, *o*-NPOE, and *f*-PNPE, respectively.

Modification *in situ*

Incorporation of a suitable ion pairing agent in the electrode matrix followed by soaking the electrode in the drug solution will lead to the formation of an ion exchanger at the electrode surface, which will be subsequently extracted by the plasticizer into the electrode bulk. Such technique will reduce the time required for the electrode fabrication, as there is no need for IP precipitation, and it offers simpler approaches for oily nature IPs and tinny precipitate that cannot be separated by traditional methods.

The effect of the ion pairing agent type was tested via incorporation of different cationic surfactants within the electrode matrix, including Hy, CPCl, tridodecyldimethylammonium chloride, CATB, or SEP (Fig. 4a). The obtained results revealed the superiority of Hy indicated by the highest slope (59.2 ±0.2 mV/decade in the concentration range from 10^{-7} to 10^{-2} mol/l), which may be attributed to the high polarity of Hy compared with other tested surfactants. Moreover, the Hy content was varied from 0 to 15 mg, and incorporation of 10 mg was the most proper.

Similar to those modified with NAP-IPs, the influence of the membrane plasticizer on the electrode performance was tested. Sensors fabricated using *f*-PNPE showed the highest slope value (−58.7±0.3 mV/decade) compared with other tested plasticizer (Fig. 4c).

Modification by soaking

In such type of sensors, membranes fabricated without incorporation of the sensing material were soaked in the aqueous suspension of the lipophilic IPs where the membrane plasticizer extract such IPs and hence, there is no need to add either IP or the ion pairing agent into the electrode matrix during its fabrication. The IP concentration in the electrode phase increases with increasing both the extractability and the solubility product of the IP formed [35].

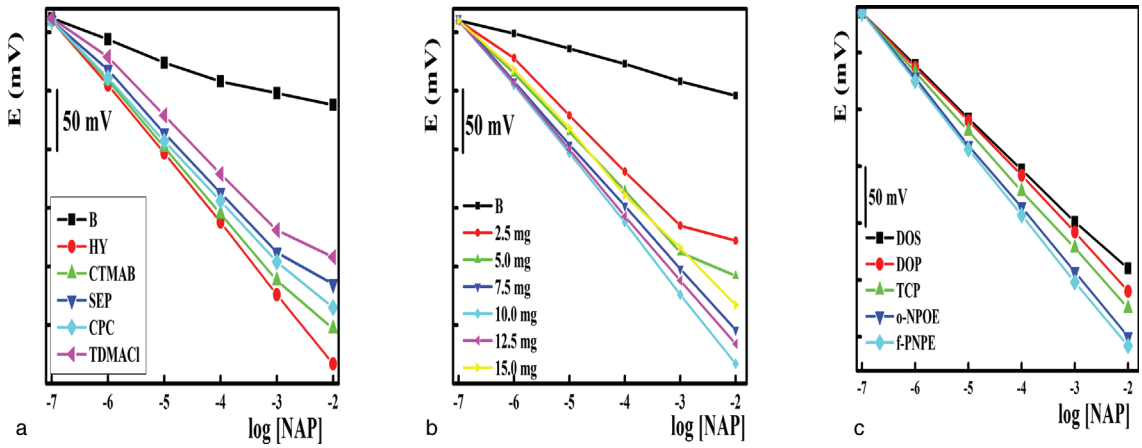
Results indicated that the electrodes soaked in the NAP-Hy ion part suspension possessed the best sensitivity (Fig. 5a) indicated by the highest slopes when compared with other IPs (−59.2±0.2, −55.8±0.7, −50.9±0.9, −47.8 ±1.4, and 51.0±1.3 mV/decade for sensors soaked in NAP-Hy, NAP-CTAB, NAP-CPCl, NAP-TDDMAC, and NAP-SEP, respectively) which is directly related to the solubility products of such IPs.

In addition to the nature of the IP, the membrane plasticizer affects the sensors performance through its ability to extract the formed IP from their aqueous solutions. From five different plasticizers, *o*-NPOE and *f*-PNPE were selected (Fig. 5b) with highest sensitivities (slope values were −59.5±0.3 and 58.4 ±0.2 mV/decade, respectively).

Sensors performance

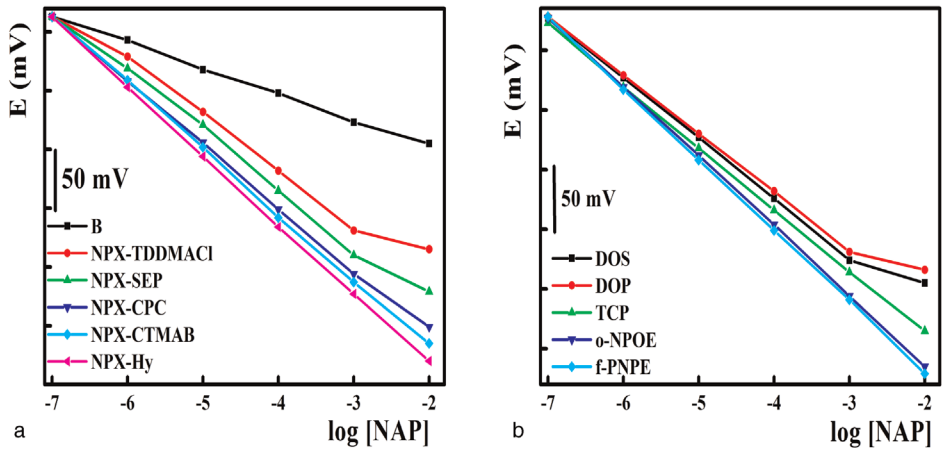
The potentiometric response characteristics of NAP disposable sensor fabricated with various modes were evaluated according to IUPAC recommendations [28].

Figure 4



Effect of (a) nature of the ion pairing agent, (b) Hy concentration, and (c) nature of plasticizer on the performance of naproxen (NAP) screen-printed sensor.

Figure 5



Effect of (a) nature of ion associate suspension and (b) nature of plasticizer on the performance of naproxen (NAP) screen-printed sensor.

Table 2 Analytical performances* of different naproxen screen-printed sensors

	Modified with NAP-Hy	Modified with Hy	Soaked
Concentration range (mol/l)	10^{-7}–10^{-2}	10^{-7}–10^{-2}	10^{-7}–10^{-2}
Slope (mV/decade)	−57.4±0.2	−56.8±0.7	−56.2±0.6
R	0.9997	0.9996	0.9999
LOD (mol/l)	1.0×10^{-7}	8.0×10^{-8}	1.0×10^{-7}
Response time (s)	4	6	6
Life time (months)	3	3	2
Titration potential jump for 2.3 mg NAP (mV)	115	122	145
Working pH range		8–12	

Hy, hyamine; LOD, lower detection limit; NAP, naproxen. *Average of five calibration graphs.

The developed sensors can be successfully applied for the potentiometric determination of NAP in concentration range 10^{-7}–10^{-2} mol/l with Nernstian anionic slopes depending on the type of the electrode and the method of modification. The lower limit of detection was 8.0×10^{-8} mol/l (Table 2).

As the fabricated sensors have the solid state nature, owing to the absence of internal reference solution, they showed a 12-week shelf lifetime, during which the Nernstian slopes did not change significantly (±1 mV/decade). Relatively shorter lifetime was found with soaked electrode as it needs dipping of the electrode in IP suspension to compensate for the sensing materials leached from the membrane during measurements. Meanwhile, the fabricated sensors are disposable; the same electrode can continuously operate up to more than 4 weeks without losses of performance. Screen printing technology offers the advantages of high fabrication reproducibility. The average Nernstian slope values for ten modified printed electrodes within the same batch were −56.2±0.7 mV/decade with standard potential of (E_o) −378.8±3.5 mV.

During the sensor fabrication protocol, both the sensing membrane and the conducting track contained PVC polymer matrix; therefore, copolymerization of both PVC matrices during printing takes place that prevents the formation of undefined layer between sensing membrane and conductor and improves the potential stability [36]. Thus, the fabricated electrodes showed stable potential reading after preconditioning in 10^{-3} mol/l NAP solutions for 60 min.

Table 3 Selectivity coefficient for naproxen sensors

Interferent	−log $K_{A,B}$	Interferent	−log $K_{A,B}$
Na^+	2.40	Starch	3.40
K^+	2.95	Maltose	3.20
Li^+	2.70	Glucose	3.15
NH_4^+	3.10	Sucrose	3.30
Ca^{2+}	3.31	Citrate	3.65
Mg^{2+}	3.05	Caffeine	3.80
Phosphate	3.30	Glycine	3.80
Citrate	2.60	Cysteine	3.80

For analytical applications, the response time of a new fabricated sensor is of critical importance. The dynamic response time of different NAP sensors was tested by measuring the time required to achieve a steady-state potential (within ±1 mV) after sudden increase in the NPA concentration from 1×10^{-7} to 1×10^{-3} mol/l. The

fabricated sensors showed fast response time ranging between 4 and 6 s.

The influence of pH on the electrode response was checked by recording the electrode potential readings for NAP solutions containing 10^{-4} to 10^{-2} mol/l at different pH values (pH 6–12). The electrode responses were pH independent in the range from 8 to 12.

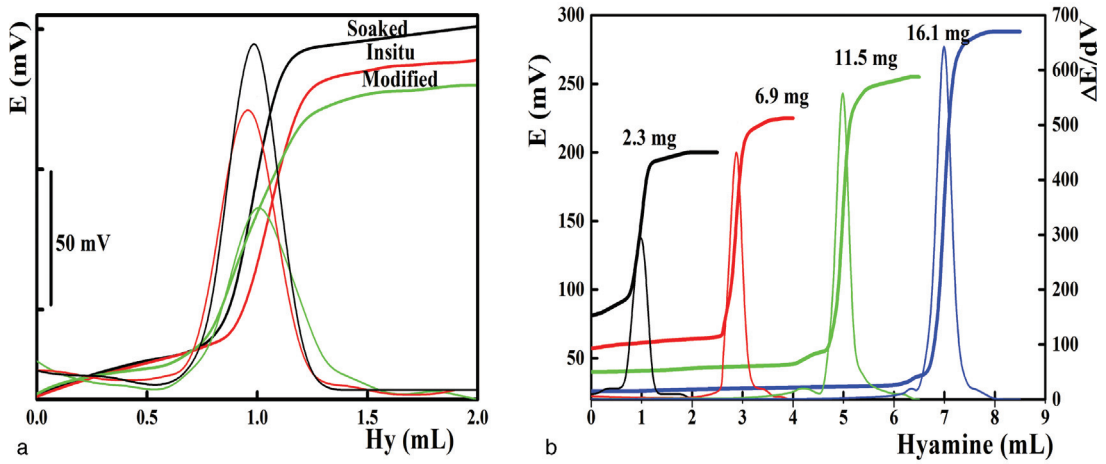
Selectivity is one of the most important characteristics of an ISE, as it measures the sensitivity to the target ion over interferents and hence determines the electrode reliability, and applicability to sample measurement is possible or not. Selectivity coefficient describes the ion discrimination ability and depends upon the nature and content of each electrode component including the recognition element, solvent, and the plasticizer [37,38]. In pharmaceutical analysis, it is important to test the selectivity of the method toward the excipients which are usually added to the pharmaceutical preparations, such as glucose, starch, talc, lactose, and sucrose. Selectivity of the prepared potentiometric sensors toward different species was tested applying matched potential method [38]. Results revealed a high selectivity toward NAP in presence of other interferents, additives, and fillers commonly introduced in pharmaceutical formulations (such as glycine, caffeine, citrate, maltose, sucrose, and starch); moreover, inorganic cations, such as Na^+, K^+, Li^+, Ca^{2+}, Mg^{2+}, and NH_4^+, did not affect the electrode potential (Table 3).

Potentiometric titration

In contrast to the direct potentiometric measurements requiring careful calibrations of measuring cells, the potentiometric titration techniques offer the advantage of high accuracy and precision, though the cost of increased time and consumption of reagents used as titrants [39]. The effect of the electrode fabrication techniques on the titration process was investigated and the plain electrodes showed the best titration curve compared with those modified with either the IP or with ion pairing agent (Fig. 6a).

Under the optimum conditions, the titration curves were symmetrical with a well-defined potential jump indicating the high sensitivity of the electrode. Concerning the titration process, the total potential changes were large (ΔE ranges between 120 and

Figure 6



Potentiometric titration of (a) 1.0 ml of 1.0×10^{-2} mol/l NAP with 1×10^{-2} mol/l hyamine (Hy) solution using different naproxen sensors and (b) different concentration of naproxen with 1×10^{-2} mol/l Hy using naproxen-soaked sensor. NAP, naproxen.

Table 4 Determination of naproxen in pure form and in pharmaceutical preparations

Sample	Taken (mg)	Found					
		Official method		Developed sensors			
				Standard addition		Titration	
		Recovery %*	RSD*	Recovery %*	RSD*	Recovery %*	RSD*
Authentic sample	2.30	95.22	3.1	96.18	2.7	97.30	2.1
	6.90	97.26	2.7	99.00	2.0	100.09	1.9
	8.14	98.40	2.0	101.16	2.2	102.10	1.1
Naprosyn tablets	6.90	96.60	3.2	95.10	3.0	99.27	1.9

RSD, relative standard deviation.*Mean recovery and SDs for five determinations.

260 mV) allowing the application of the electrode to determine NAP reaching down to 2.3 mg (Fig. 6b), with mean recovery of 101.3±0.8%.

Analytical applications

The obtained satisfactory sensitivity and selectivity of the fabricated disposable sensors toward NAP suggested their application as a suitable tool for assaying of NAP in pharmaceutical dosage samples with average recoveries in agreement with the official methods (Table 4).

Conclusion

The present work describes the fabrication of a novel NAP screen-printed sensors based on NAP ion associates with different cationic surfactants. Different fabrication techniques were employed involving modification with NAP-Hy ion associates, incorporation of cationic surfactant in the electrode matrix or soaking the blank electrode in the aqueous IP suspension. The fabricated electrodes showed anionic Nernstian compliance in the concentration range 10^{-7}–10^{-2} mol/l with fast response time (4 s) and long operational lifetime.

Studies on the determination of NAP in pharmaceutical formulations were carried out to illustrate the feasibility of the proposed method. Furthermore, as both the electrode and the standard potentiometric equipment are low cost, the developed procedure also allows small laboratories with limited resources to run NAP analyses for the aforementioned samples.

The developed disposable strips have several advantages including miniaturization, simplicity, versatility, and reproducibility of the preparation with low cost mass production. The proposed methods of electrode modification (*in situ* and soaked) allow the potentiometric determination of more anionic whose IPs cannot be isolated by traditional methods and avoid using of toxic organic solvent for extraction.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Index of Drugs, Practical Medicine, Naproxen: Cracow, 2009

2 Monser L, Darghouth F, Simultaneous LC. Determination of paracetamol and related compounds in pharmaceutical formulations using a carbon-based column. J Pharm Biomed Anal 2003; 32:1087–1092.

3 Ashutosh KS, Manidipa D, Seshagiri R, Gowri SD. A new bioanalytical method development & validation for simultaneous estimation of esomeprazole and naproxen in human plasma by using RP-HPLC. Br J Pharm Res 2014; 4:2312–2327.

4 Abhilash PR, Rao JV. Development and validation of new RP-UPLC method for the quantitative estimation of naproxen in tablet dosage. Pharmacia Lett 2014; 6:325–329.

5 Bilal Y, Ali A, Fuat EA. HPLC method for naproxen determination in human plasma and its application to a pharmacokinetic study in Turkey. J Chrom Sci 2014; 52:584–589.

6 Bilal Y, Huseyin S, Fuat EA. Determination of naproxen in human plasma by GC-MS. J Sep Sci 2014; 37:997–1003.

7 Preinerstorfer B, Lmmerhofer M, Lindner W. Advances in enantioselective separations using electromigration capillary techniques. Electrophoresis 2009; 30:100–132.

8 El-Kommos ME, Mohamed NA, Abdel Hakiem AF. Extractive spectrophotometric determination of some nonsteroidal anti-inflammatory drugs using methylene blue. J AOAC Int 2013; 96:737–744.

9 Keyhanian F, Alizadeh N, Shojaie A. Spectrophotometric determination of Naproxen as ion-pair with bromophenol blue in bulk, pharmaceutical preparation and human serum samples. Curr Chem Lett 2014; 3:15–223.

10 Damiani P, Bearzotti M, Cabezón MA. Spectrofluorometric determination of naproxen in tablets. J Pharm Biomed Anal 2002; 29:229–238.

11 Aktas AH, Ertokus GP. Potentiometric determination of ibuprofen, indomethacin and naproxen using an artificial neural network calibration. J Serb Chem Soc 2008; 73:87–95.

12 Gupta V, Nayak A, Agarwal S, Singhal B. Recent advances on potentiometric membrane sensors for pharmaceutical analysis. Comb Chem High Throughput Screen 2011; 14:284–302.

13 Angnes D. Pharmaceutical and personal care products. In: Moretto L, Kalcher K, editors. Environmental analysis by electrochemical sensors and biosensors. Vol. 2. Springer; 2014.

14 Ozkan SA, Kauffmann J, Zuman P. Electroanalysis in biomedical and pharmaceutical sciences. xx: Springer; 2016.

15 Khaled E, Mohamed GG, T. Awad T. Disposable screen printed carbon paste electrode for the potentiometric titration of surfactant. Sensor Actuat B 2008; 135:74–80.

16 British pharmacopoeia. Vol. 1. London: The Stationary Office; 1999.

17 Lingane JJ. Electroanalytical chemistry. 2nd ed. New York: Interscience 1958.

18 Issa YM, Shoukry AF, El-Nashar RM. Conductimetric determination of reproterol HCl and pipazethate HCl and salbutamol sulphate in their pharmaceutical formulations. J Pharm Biomed Anal 2001; 26:379–386.

19 Antropov LL. Theoretical electrochemistry. Moscow: Mir 1977.

20 Valsami GN, Macheras PE. Construction of a naproxen ion-selective electrode and its application to pharmaceutical analysis. Analyst 1989; 114:387–391.

21 Lenik J, Dumkiewicz R, Wardak C, Marczewska B. Naproxen ion-selective electrode and its application to pharmaceutical analysis, Acta Pol Pharm 2002; 59:171–176.

22 Lenik J. Preparation and study of a naproxen ion-selective electrode. Mater Sci Technol C 2013; 33:311–316.

23 Santini AO, Oliveira JE, Pezza HR, Pezza L. A novel potentiometric naproxenate ion sensor immobilized in a graphite matrix for determination of naproxen in pharmaceuticals. J Braz Chem Soc 2006; 17:785–791.

24 Lenik J, Wardak C, Marczewska B. Properties of naproxen ion-selective electrodes. Cent Eur J Chem 2008; 6:513–519.

25 Mohamed HM. Screen printed disposable electrode pharmaceutical application and recent development. Trends Anal Chem 2016; 82: 1–11.

26 Couto RAS, Lima JLFC, Quinaz MB. Development of Nafion/MWCNT-SPCE based portable sensor for the voltammetric analysis of the anti tuberculosis drug Ethambutol. Talanta 2016; 146:801–814.

27 Khaled E, Kamel MS, Hassan HNA, Abdel-Gawad H, Aboul-Enein HY. Performance of the portable biosensor for the analysis of ethion residues. Talanta 2013; 119:467–472.

28 Buck RP, Lindner E. Recommendation for nomenclature of ion selective electrodes. Pure Appl Chem 1994; 66:2527–2536.

29 Baumann EW. Trace fluoride determination with specific ion electrode. Anal Chim Acta 1968; 42:127–132.

30 Katsu T, Furuno K, Yamashita S, Gomita Y. Ion selective electrode for procainamide determination in blood serum. Anal Chim Acta 1995; 312:35–38.

31 Zareh M, El-Sheikh R, Issa YM, Shoukry AF. Potentiometric determination of ephedrine hydrochloride using plastic membrane ion-selective electrode. Anal Lett 1992; 25:663–668.

32 Vytras K, Kalous J, Jezkova J. Automated potentiometry as an ecologic alterative to two-phase titration of surfactants. Egypt J Anal Chem 1997; 6:107–114.

33 Vytras K, Kaderabkova M, Socha J. Testing of some nitro compounds as new plasticizers of polymeric membrane-based electrodes. Sci Pap Univ Pardubice Ser A 1997; 3:323–337.

34 Morf WE. The principles of ion-selective electrodes and membrane transport. New York: Elsevier 1981.

35 Vytras K, Capoun T, Halamek E, Soucek J, Stajerova B. Potentiometric ion-pair formation titrations of N-alkyl-N-ethylpyrrolidinium cations using plastic membrane electrodes. Collect Czech Chem Commun 1990; 55:941–950.

36 Bobacka J, Lindfords T, McCarrick M, Ivaska A, Lewenstam A. Single piece all solid state ion selective electrodes. Anal Chem 1995; 67:3819–3823.

37 Umezawa Y Ed. Handbook of ion selective electrodes: selectivity coefficients. Boca Raton, FL: CRC Press 1990.

38 Umezawa Y, Buhlmann P, Umezawa K, Tohda K, Amemiya S. Potentiometric selectivity coefficients of ion-selective electrodes, part I. inorganic cations. Pure Appl Chem 2000; 72:1851–2082.

39 Vytras K. Determination of inorganic cations ionselective electrodes Ion-Sel Electrode Rev 1985; 7:77–144.

(DUPHAT 2019: www.duphat.ae)