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Preparation and study of a naproxen ion-selective electrode

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ABSTRACT

Naproxen membrane electrodes based on different plasticizers and quaternary ammonium salt tetraoctylammonium (S)-6-methoxy-α-methyl-2-naphthaleneacetate (NAP–TOA) were prepared. The electrode response to naproxen has the sensitivity of −59.2 mV decade^{-1} over the linear range of 10^{-4}–10^{-1} mol L^{-1} and limit of detection 1.80×10^{-5} mol L^{-1}. This electrode has a response time 15–20 s and can be used in the pH range 5.5–9.5. The selective coefficients were determined in relation to some organic and inorganic anions and excipients of pharmaceuticals. The notable property and attractive quality of the naproxen electrode are low cost, comfortable application and very long lifetime—about 20 months. The electrode was successfully applied for determination of naproxen in urine samples and pharmaceuticals by the calibration curve method and standard addition method. The obtained results are comparable and sometimes better than those obtained by pharmacopoeial method.

1. Introduction

The quality of the medicinal product is a very significant and essential problem worldwide. In order to be safe and effective, the drug must be subjected to quality control. An important step of research in the process of evaluating the quality and usefulness of a medicinal substance is the determination of the content of active ingredient in the pharmaceutical preparation under investigation. This is a routine investigation in the process of drug production, and it may also be performed in the case when an appraisal is made to find out if the given drug has not been forged and if it contains the declared amount of the active ingredient. In most cases analytical techniques used in the pharmaceutical analysis (chromatographic methods, UV–VIS spectrophotometry, polarography) are sensitive, precise and selective, but quite expensive and complicated (for instance, the sample preparation is usually very time-consuming). That is why continuous investigations are being carried out in order to find cheaper, simpler and fast techniques that would also be precise and selective at the same time.

One of the solutions that permit effective cost reduction is the use of a well-known potentiometric technique. This technique, which makes use of ion-selective electrodes (ISE), has a competitive advantage over other expensive and complicated methods such as chromatography or spectrophotometry, because it is relatively simple to use, cheap, and at the same time it enables one to determine the examined compound in a selective, sensitive and precise way.

Non steroidal anti-inflammatory drugs (NSAIDs) are widely applied, thanks to their anti-inflammatory action, as analgesics and antipyretics. They also remain the main drugs used for treatment of patients with rheumatic disorders. The consumption of these compounds is very high in Poland and also in other countries. From the investigations, results show that during one day 30 million people worldwide take the NSAIDs, of whom 40% are over 65 years of age [1]. The popularity of these drugs results from the fact that the NSAIDs are available in most countries with no limitations as over-the-counter drugs. Because of wide applications of the NSAIDs the number of new preparations, based on these components, is constantly growing. As a result new analytical problems arise concerning the production and quality control of these drugs.

One of medicines belonging to NSAID-s group is naproxen, (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid (Fig. 1). Both the acid and its sodium salt are used in the treatment of rheumatoid arthritis and other rheumatic or musculoskeletal disorders, dysmenorrhea, and acute gout [2]. This drug is used more and more frequently. Therefore new, improved methods of determining its concentration in various matrixes need to be introduced. The applied methods to quantitatively determine of naproxen in the routine control have been described in Polish Pharmacopoeia [3], British Pharmacopoeia BP [4] and United States Pharmacopoeia USP [5].

Several methods available in the literature for the determination of naproxen in pharmaceuticals and biological fluids are reported. They include chromatographic method: HPLC [6], TLC with densitometry [7], gas chromatography–mass spectrometry [8], capillary electrophoresis [9], spectrophotometry [10], spectrofluorymetry [11], chemiluminescence [12], potentiometric titration [13] and other electrochemical methods [14]. These methods are characterized by long and complicated preparation of a sample for analysis as well as expensive instrumental apparatus.

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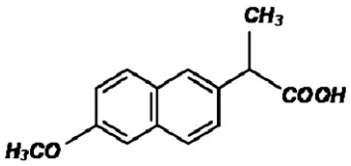

Fig. 1. Naproxen (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid.

On the basis of the literature, there are limited scientific works on the use of ion-selective electrodes for naproxen determination [15–18]. These electrodes have different constructions: the electrode [15] with liquid membrane type, based on the use of tetraheptylammonium naproxenate, the electrode with polymeric membrane type with methyltrioctylammonium naproxenate [16], the electrode with graphite membrane based on mercury(I) naproxenate [17], and electrodes based on other quaternary ammonium salt in chloride and bromide forms with inner solution of naproxenate in NaCl solution [18].

The purpose of this research was to sensor design as soon as possible better analytical parameters than the so far developed electrodes. In this work new naproxen ion-selective membrane electrode was prepared based on tetraoctylammonium 6-methoxy-α-methyl-2-naphthalenate (NAP–TOA) ion-pair complex in PVC membrane phase. In contrast to most of the previously described membrane sensors sensitive to naproxen, the presently proposed sensor is characterized by very long lifetime (over 20 months). This is due to the construction of naproxen electrode and kind and properties of used ion exchangers. The presently proposed naproxen sensor is characterized by a 20-month lifetime. After this time, the regeneration of the second membrane layer is simple. It consists in cutting of second membrane layer with sharp tool. Then the preparation of new membrane is analogous to phase of dissolution of membrane composition mixture in THF.

The construction of the proposed electrode in this work is simple and cheap. The making of proposed electrode is very comfortable. Unlike other sensors with inner solution, it does not have to be stored in a vertical position and does not require an external solution for storing the electrodes between the measurements. The sensor may be kept in air, it is characterized by mechanical resistance and it is a self acting sensor.

The constructed electrode exhibits favourable analytical parameters like Nernstian slope of characteristic, a wide range of linearity, selectivity towards inorganic ions, organic ions, pharmaceutical excipients, and short response time. The naproxen determination in tablets and urine using new sensor was carried out to show the feasibility of the potentiometric sensor. The results obtained for naproxen determination are characterized by an accuracy and precision typical of potentiometric determination methods and are comparable and sometimes better than pharmacopoeial method.

The novelty of this work consists of obtaining sensor that may correctly work on a much longer time than other electrodes. Proposed method allows the selective, sensitive, the exact and above all cheap, comfortable determination of naproxen in pharmaceuticals and biological samples. In addition, there was no analytical literature describing so far sensor for naproxen of identical design and analytical parameters.

2. Experimental

2.1. Reagents

All chemicals were of analytical reagent grade. The components of the membrane: tributyl phosphate (TBP; Merck), dioctyl adipate (DOA; Prolabo, Rhône Poulenc), bis(2-ethylheksyl)sebacate (DOS; Merck Schuchard), dibutyl phthalate (DBP; Merck Schuchard), diisobutyl phthalate (DIBP; Fluka), 2-nitrophenyloctyl ether (NPOE; Fluka), emulsion PVC (Tarwinyl Tarnów, Poland), tetraoctylammonium chloride (TOA-Cl; Fluka). The sodium salts of interferent ions are obtained from Fluka. The other reagents are naproxen sodium salt (Sigma–Aldrich), naproxen tablets, 250 mg Hasco Lek SA (Poland), 500 mg Polfarmex, (Poland) tetrahydrofuran (THF; Merck) and the ionic strength stabilizing solution—sodium acetate of pH 8.0. and 6.5.

2.2. Potentiometric measurements

Before each measurement the electrodes were conditioned in 10^{-3} mol L^{-1} naproxen solution for 10 min. EMF potentiometric measurements of the cell – reference electrode (Orion 90–02) with salt bridge 1 mol L^{-1} CH_3COOLi solution–naproxen electrode – were made in the main ion and interfering ions solutions at the concentrations of 10^{-5}–10^{-1} mol L^{-1} of pH 8.0. During the measurements the solutions were stirred with a mechanical stirrer and the potential (±0.5 mV) was recorded after stabilization. The measurements of the electromotive force of the system naproxen electrode–reference electrode were carried out at 22±2 °C using a multifunctional computer device (CX–721 Elmetron (±0.1 mV); Poland) with APE1 attachment, which ensured efficient multiplexing of the electrodes.

2.3. Preparation of ion pair

The quaternary ammonium salt, tetraoctylammonium (S)-6-methoxy-α-methyl-2-naphthaleneacetate (TOA–NAP), was acquired through a process of periodic ion-exchange extraction of naproxen anion from aqueous phase to organic phase. In order to prepare this complex, 60% (v/v) solution of TOA-Cl in 1-decanol was extracted with 10^{-1} mol L^{-1} naproxen solution [19]. The organic phase volume was 2 mL, the aqueous phase volume was 2–3 mL. When the extraction was over, the organic phase was separated from the aqueous phase and deaerated until a clear solution was obtained. The complex was stored at +4 °C and was then used in membrane phase preparation.

2.4. Electrode construction

The description of the electrode construction and membrane phase preparation was presented in earlier papers [20–22]. The construction of the proposed electrode is very simple. The body of the electrode is made from insulating substance. The Teflon sensor is connected with the electrode body by the screw thread. In the body, the cable is placed in which the Ag/AgCl electrode is soldered.

The membrane phase of the electrode consists of two layers placed in a Teflon holder: the inner layer containing plasticized PVC in which the Ag/AgCl electrode is placed and the outer layer contacting with the tested solution and containing the potential-creating substance apart from the inner layer components. The internal layer is composed of the following: 30% wt. PVC, 70% wt. of mixed plasticizers—95% wt. DOA, or DBP or DIBP, or DOS, or o-NPOE and 5% wt. TBP. The outer layer consists of: 30% wt. PVC, 10% wt. ion pair (TOA–NAP) complex, 60% wt. mixed plasticizers (95% wt. DOA or DBP or DIBP or DOS or o-NPOE and 5% wt. TBP). In the author's earlier studies and unpublished data, the role and amount of the plasticizers and TBP were previously tested. Addition of TBP causes an increase in conductivity membranes.

The potential of the internal reference Ag/AgCl electrode is stable and determined by Cl^- ions originating from PVC degradation as well as from dissolution dissociation of AgCl in TBP [23]. The potential of these construction electrodes with solid contacts is reproducible and stable in time. The electrodes prepared were stored in air between the measurements.

2.5. Determination of naproxen in pharmaceuticals and urine samples

Samples to determine naproxen were prepared: 10 tablets of naproxen 250 mg, 500 mg were weighed and then ground in a mortar