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Preparation and characterization of a sulindac sensor based on PVC/TOA–SUL membrane

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ABSTRACT

A potentiometric sulindac sensitive sensor based on tetraoctylammonium (Z)-5-fluoro-2-methyl-1-[[p-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetate (TOA–SUL) was described. The electrode responded with sensitivity of 57.5 ± 1.6 mV decade^{-1} over the linear range 5×10^{-5}–1×10^{-2} mol L^{-1} at pH 6.0–9.0. It had the limit of detection 1.4×10^{-5} mol L^{-1}, a fast response time of 13 s and showed clear discrimination of sulindac ions from several inorganic and organic compounds and also amino acids. This electrode did not contain any inner solutions, so it was easy and comfortable to use. The proposed sensor was used to determine sulindac in clear solution and in urine sample solution.

1. Introduction

Pharmaceutical substances are determined in drug preparations and biological fluids. The quality of medicinal products is a very important problem worldwide. However, in recent years both in Poland and other countries, there are an increasing number of new drugs that are cheaper but forged, sold primarily via the Internet or at the market. Such drugs may fulfill the requirements concerning the content of the active ingredient, but in many cases they are characterized by considerable deviations from the requirements. The quality of guaranteed drugs is also deteriorating. The majority of medicinal raw materials that are not easy to produce for environmental reasons (for instance, utilization of wastes is very expensive) are imported from the East. Unfortunately, the quality of these products is not always guaranteed and thus the raw materials supplied to the pharmaceutical company may be of inadequate quality and may contain a varying number of impurities. As it is shown by the investigations, the pharmaceutical firms which base their production on state norms and European standards, have problems with quality control of the drugs.

Routine pharmacopeial methods have been used in the process of production control and quality control of pharmaceutical substances (UV–VIS spectrophotometry, chromatographic methods, polarography and volumetric methods of analysis, such as potentiometric, conductometric and amperometric titration), as a result of which new and more precise conditions of analyses of medicinal substances are being worked out. One of those techniques is potentiometry which makes use of ion-selective electrodes (ISE) that have been frequently used in pharmaceutical and biological fluid analysis in recent years [1–8].

The use of ion-selective membrane electrodes has several advantages in applications such as the determination of ionic drugs in vitro and in vivo in pharmaceutical and clinical analyses. Ion-selective electrodes constitute a simple, fast and inexpensive means of measuring the activity of an ionic analyte over a wide concentration range, typically 3–6 orders of magnitude without extensive sample preparation.

The aim of the composition was to create an electrode with a polymeric membrane phase with sulindac function on the basis of PVC as well as to establish its analytical parameters. Sulindac (Z)-5-fluoro-2-methyl-1-[[p-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetic acid (Fig. 1) is a nonsteroidal antiinflammatory drug. It belongs to a group of heterocyclic and arylic derivatives of acetic acid similarly as indomethacin and tolmethin. Sulindac, a yellow crystalline compound, is a weak organic acid practically insoluble in water below pH 4.5, sparingly soluble in ethanol and slightly soluble in ethyl acetate. It is very soluble as the sodium salt or in buffers of pH 6 or higher [9]. Sulindac is an indomethacin analog but it is less toxic. Sulindac is generally used to treat pain, fever and inflammation. It is also used to relieve pain and fever as well as to reduce swelling and tenderness of joints caused by the inflammation of rheumatoid arthritis, ankylosing spondylitis, gouty arthritis, osteoarthritis, and acute painful shoulder. Moreover, it is used to treat inflammation of soft tissues such as tendinitis and bursitis [10]. Recent studies have shown that sulindac may find application in the adjuvant treatment of a standard chemotherapy of ovarian cancer [11] and is of considerable importance in cardiovascular diseases as it gives high level ischemic protection to the heart [12].

Common analytical determinations of sulindac in plasma and serum are accomplished with the use of chromatographic methods such as LC

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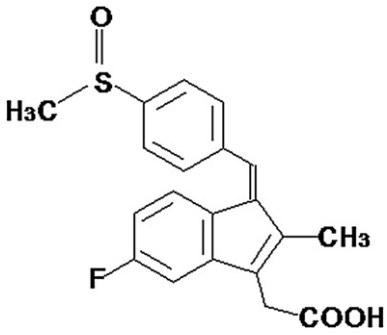

Fig. 1. Sulindac (Z)-5-fluoro2-methyl-1-[[p-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetatic acid.

[13], HPLC [14,15]. For pharmaceutical formulations, the US Pharmacopoeia [16] reports LC–UV of sulindac in tablets, while British Pharmacopoeia [17] reports potentiometric titration of sulindac with sodium hydroxide in methanol. The European Pharmacopoeia [18] recommends the LC method. In the literature there are also chromatographic determinations [19,20].

Sulindac reacts with quaternary ammonium salt tetraoctylammonium chloride to form an association complex that is only slightly soluble in water, which may therefore be used as a liquid exchanger in the membrane phase for the sulindac-sensitive electrode.

Previous studies from this laboratory dealt with the development of solid contact electrodes for other nonsteroidal antiinflammatory drugs such as ibuprofen, ketoprofen, or naproxen, and their applications in pharmaceutical research [21–26]. The investigations were performed on non-crystal electrodes with a microporous matrix (e.g. vinyl polychloride dissolved in an appropriate modifier) containing the ionophore as the main component which affects the electrode characteristics. The analytical parameters of such electrodes have considerably improved (e.g. the stability of electrode potential, or the lifetime) as compared with other electrodes selective to nonsteroidal antiinflammatory drugs [27–29].

The aim of the present work was to develop a sensitive, accurate and selective electrode for sulindac determination. To this purpose, the modifications of the membrane composition were studied and their potential responses towards the derivative of acetic acid — sulindac were tested. Then the basic analytical parameters (selectivity, response time, pH dependence of potential, lifetime) of the constructed ion-selective electrodes were determined.

A great advantage of the proposed sensor is its simple and cheap construction. In addition, this kind of electrode is very comfortable to use. The proposed electrode was satisfactorily applied to the determination of sulindac in urine samples. According to the literature data, the ion-selective electrode for sulindac has not yet been elaborated.

2. Experimental

2.1. Reagents

All chemicals were of analytical–reagent grade. The components of the membrane consisted of tributyl phosphate (TBP) (Merck, Germany), 2-nitrophenyloctyl ether (o-NPOE), bis(2-ethylhexyl) sebacate (DOS), bis(1-butylpentyl)adipate (BBPA), dioctyl adipate (DA), diisobutyl phthalate (DIBP), diisodecyl phthalate (DIDP), dibutyl phthalate (DBP) (Merck Schuchard), (Fluka), emulsion PVC (Tarwinyl Tarnów, Poland), suspension poly(vinyl)chloride (PVC) (Aldrich), and tetraoctylammonium chloride (TOA–Cl) (Fluka). The substances of the pharmaceutical excipients: lactose, glucose, D-mannit were obtained from POCh (Poland). The sodium salts of interferent ions were obtained from Fluka, Sigma. The other reagents were: Sulindac (SUL) (Sigma-Aldrich), tetrahydrofuran (THF) (Sigma), NAOH, HCl (POCh Standard, Poland). All aqueous solutions were prepared with deionized water (Mili-Q plus Milipore, Austria).

2.2. Apparatus

The measurements of the electromotive force of the system sulindac electrode–reference electrode (Orion 90-02) were carried out at 22 ± 1 °C using Electrochemistry EMF Interface system (Lawson Labs. Inc., USA) and an IBM PC computer. To automatically obtain appropriate concentrations of the working solutions during potentiometric measurements a Metrohm Dosino Liquino pump system was used. A Thermo Orion 81-72 glass electrode C using a Multifunctional Computer device CX-721 Elmetron (±0.1 mV) (Poland) was used for pH measurements.

2.3. Preparation of ion-pair

The quaternary ammonium salts: tetraoctylammonium (Z)-5-fluoro-2-methyl-1-[[p-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetate (TOA–SUL) was acquired in the process of sulindac anion's periodic ion-exchange extraction from an aqueous phase to an organic phase. In order to prepare the TOA–SUL complex, a 60% (v/v) solution of TOA–Cl in 1-decanol was extracted with 10^{-2} mol L^{-1} sulindac sodium salt solution. The organic phase volume was 1 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 complexes were stored at +4 °C and were then used in membrane phase preparation.

2.4. Construction of the electrode

An Ag/AgCl electrode was prepared by electrolytic covering of clean silver wire with silver chloride in the process of electrolysis for 5 min in 4 mol L^{-1} HCl with constant current 5 V voltage. Then the electrode was rinsed with water, dried using tissue-paper and covered by the inner membrane phase. The potential of the internal reference Ag/AgCl electrode was stable and determined by Cl^- ions originating from PVC degradation as well as from dissolution dissociation of AgCl in TBP [30].

The electrode membrane phase consisted of two layers placed in a Teflon holder: the inner layer containing plasticized PVC in which the Ag/AgCl electrode was placed and the outer layer, contacting with the tested solution and containing the active substance in addition to the inner layer components. In order to prepare the inner layer, 30% w/w of PVC, 70 wt.% of plasticizers (95 wt.% NPOE, DOS, BBPA, DA, DIBP, DIDP, DBP) and 5 wt.% of TBP were weighed, respectively. The components were mixed and the mixture was deaerated. The Teflon holder was filled with the mixture so that the silver–silver chloride electrode was immersed in it. Then the mixture was gelated at about 100 °C for 30 min. In order to prepare the outer layer, 10% w/w of the TOA–SUL complex was dissolved in a mixed plasticizer 60 wt.% (5 wt.% of TBP + 95 wt.% of another plasticizer), with 30 wt.% of emulsion PVC. The composition of the outer layer membrane phase is presented in Table 1. Because of the complex decomposition at the temperature higher than 60 °C, the method of gelating by THF evaporation was

Table 1
The composition of the polymer membrane (outer layer) of sulindac electrodes.

No. of El.	Composition of the membrane [mg]										
	PVC	TBP	NPOE	DOS	BBPA	DA	DIBP	DIDP	DBP	TOA–SUL	PVC
1	150	75	225	–	–	–	–	–	–	50	150
2	150	75	–	225	–	–	–	–	–	50	150
3	150	75	–	–	225	–	–	–	–	50	150
4	150	75	–	–	–	225	–	–	–	50	150
5	150	75	–	–	–	–	225	–	–	50	150
6	150	75	–	–	–	–	–	225	–	50	150
7	150	75	–	–	–	–	–		225	50	150