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Characteristic of a new sensor for indomethacin determination

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Abstract

Indomethacin membrane sensors based on different plasticizers and quaternary ammonium salt tetraoctylammonium 1-(p-chlorobenzoyl)5-methoxy-2-methyl-3-indolylacetate (INDO–TOA) were prepared. The electrode (with PVC membrane plasticized with dibutylphthalate) response to indomethacin has the sensitivity near Nernstian (-59.8±1.5 mV decade^{-1}) over the linear range of 1x10^{-5} ÷ 1x10^{-2} mol L^{-1} and limit of detection 3.16x10^{-6} mol L^{-1}. The present electrodes show clear discrimination of indomethacin ions from several inorganic, organic and some common drug excipients. This electrode has a response time 12 s and can be used in the pH range 6.0÷10.0. The notably property and attractive quality of the indomethacin sensor is low cost, comfortable application.

Keywords: ion-selective electrode; indomethacin; tetraoctylammonium cation; polymer membrane

1. Introduction

The quality of the medicinal product is a very significant and essential problem in 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. Apart from routine pharmacopoeial methods used in the process of production control and quality control of pharmaceutical drugs (UV-VIS spectrophotometry, chromatographic methods, polarography and volumetric methods of analysis, such as potentiometric, conductometric and amperometric titration), new and more precise conditions of analyses of medicinal substances are being worked out. One of these techniques is

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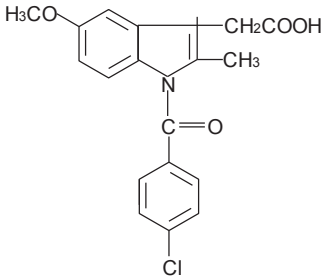
potentiometry which makes use of ion-selective electrodes (ISE), which are used in pharmaceutical analysis [1].
The group of drugs widely applied thanks to their anti-inflammatory, analgesics and antipyretics action, are the non steroidal anti-inflammatory drugs (NSAIDs). Because of wide applications of the NSAIDs the number of new preparations, based on these components is constantly growing.
One of medicines belonging to NSAID-s group is indomethacin (1-(p-chlorobenzoyl)-5-methoxy -2-methyl-3-indolylacetic acid) (Fig 1). It is commonly used to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins. Indomethacin is a potent drug with many serious side effects and should not be considered an analgesic for minor aches and pains or fever. The drug is best used as an anti-inflammatory, rather than an analgesic.



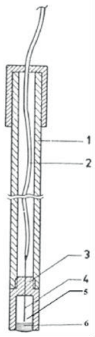


Fig. 1. Structure of (1-(p-chlorobenzoyl)-5-methoxy -2-methyl-3-indolylacetic acid) INDO

Fig. 2. The construction of the indomethacin electrode. 1-body, 2-cable, 3-Teflon container, 4-Ag/AgCl electrode, 5- membrane phase, the inner layer, 6- membrane phase, the outer layer

On the basis of the literature, there are a lot of other technics for indomethacin determination but only two scientific works on the use of ion-selective electrodes for indomethacin determination [2,3].

2. Preparation of ion-pair and construction of the electrode

The ion - pair: tetraoctylammonium 1-(p-chlorobenzoyl) 5-methoxy -2-methyl -3-indolylacetate (INDO-TOA) was used as the active substance. It was obtained by the process of periodic ion-exchange extraction of INDO anion from aqueous phase to organic phase (tetraoctyl ammonium chloride dissolved in 1-dodecanol). The indomethacin concentration in the aqueous phase was $1x10^{-2}$ mol L^{-1}. The construction of the research electrode was presented in the Fig. 2, and was described in the earlier paper [4]. The electrode membrane phase 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 active substance apart from the inner layer components. In order to prepare the inner layer , 0.3 g PVC, 0.665 g plasticizer (DOS, DBP, TEHP or NPOE), 0.035 g TBP were weighed respectively. The components were mixed and the mixture was de-aerated. 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 minutes. In order to prepare the outer layer, 0.05g INDO - TOA complex was dissolved in a mixed plasticizer (0.015g TBP+0.285g other plasticizer), with 0.15 g emulsion PVC added. The mixture was dissolved in THF and placed in drops on the inner layer, leaving THF to evaporate at room temperature. This was repeated for several times.

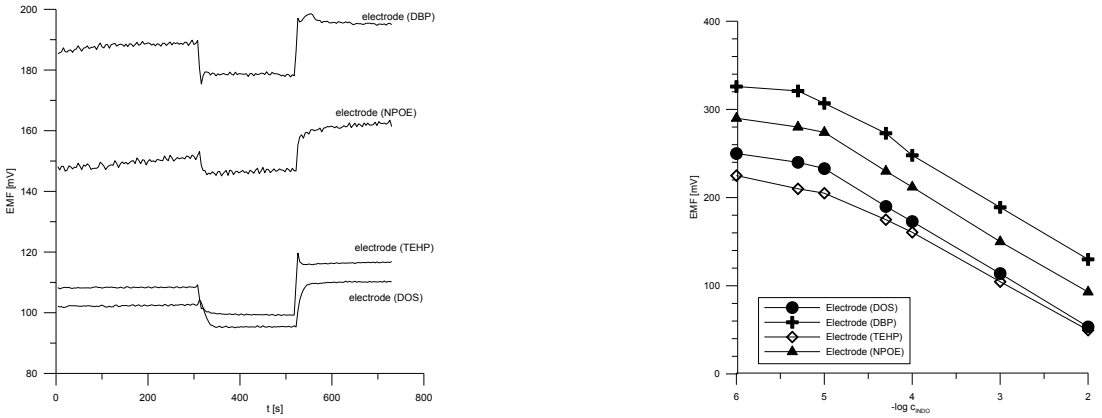
The outer layer of the electrode was acquired in this way. The sensors were conditioned for 1 hour before the measurements in the $5x10^{-4}$ mol L^{-1} indomethacin solution.

The construction of electrode is simple and cheap. The making uses of proposed electrode is very comfortable. The sensor may be kept in air, do not need to be stored in a vertical position. It is characterized by mechanical resistance and it is a self acting sensor.

3. Determination of analytical parameters

The electrode's basic parameters, such as the slope of characteristics, selectivity (Table 2), response time (Figure 1a), lifetime, the influence of pH on the electrode's potential, were established. (Table 1)
The calibration curves were determined in the main ion and interfering ions solution at pH 8.8 in the range of concentration 10^{-2} – 10^{-6} mol L^{-1}. (Figure 3b).

The best values of selectivity coefficient in respect of inorganic ions NO_3^- > Br^- >Cl^- > $H_2PO_4^{--}$, organic ions: acetate > propionate > formate > citrate > tartrate > oxalate and amino acids: glutamic acid > glicine > aspartic acid were obtained for the DBP electrode.



(a) (b)

Fig. 3. (a) Response time of indomethacin electrodes; (b) Potentiometric response of indomethacin sensors

4. Application of indomethacin electrode

The analytical usefulness of indomethacin electrode was examined by determining indomethacin inpharmaceutical preparations containing (1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid in "Metindol Retard" – ICN Polfa Rzeszów SA, Poland. The determination was performed by the calibration curve method and the method of standard addition. Statistical parameters prove to be typical of analytical methods using ion-selective electrodes: the accuracy (0.8 -2.5 % and the precision (RSD 0.8 - 5.5 %).

Table 1. Analytical parameters of indomethacin sensor .

Parameter	Electrode (DPB)
Characteristic slope S [mV decade-1]	-59.8 ± 1.5
Linearity range, [mol L^{-1}]	$10^{-5} \div 10^{-2}$
Correlation coefficient (r)	0.9980
Intercept E^0 [mV]	10.4
Potential drift mV/day	7
pH range	6.0 ÷ 10.0
Response time [s]	12
Life time, months	2

Table 2. Selectivity coefficients of indomethacin electrode

Selectivity coefficients	Column A (*t*)
Cl-	$1{,}17 \times 10^{-3}$
Br-	$8{,}88 \times 10^{-3}$
NO^{3-}	$5{,}13 \times 10^{-2}$
SO_4^{2-}	$6{,}64 \times 10^{-5}$
H_2PO^{4-}	$1{,}14 \times 10^{-4}$
propionate	$1{,}87 \times 10^{-3}$
citrate	$1{,}78 \times 10^{-4}$
formate	$1{,}21 \times 10^{-3}$
acetate	$2{,}08 \times 10^{-3}$
oxalate	$9{,}38 \times 10^{-5}$
tartrate	$1{,}15 \times 10^{-4}$
glutamic acid	$6{,}33 \times 10^{-4}$
aspartic acid	$5{,}6 \times 10^{-4}$
glycine	$5{,}19 \times 10^{-4}$
malonate	3.47×10^{-3}
D-mannitol	9.12×10^{-4}
glucose	$6{,}16 \times 10^{-4}$
lactose	$6{,}20 \times 10^{-4}$

5. Conclusion

In contrast to most of the previously described membrane sensors sensitive to indomethacin the presently proposed sensor is characterized by wider linear range ($1 \times 10^{-5} \div 1 \times 10^{-2}$ mol L^{-1}), lower limit of detection (3.16×10^{-6} mol L^{-1}), (Fig. 3a., Table 1) better selectivity towards Cl^-, SO_4^{2-}, NO^{3-}, tartrate ions. This is due to the construction of naproxen electrode and kind and properties of used ion exchangers. The electrode was successfully applied for determination of indomethacin in pharmaceuticals by the calibration curve method and standard addition method.

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