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Cyclodextrin based potentiometric sensor for determination of ibuprofen in pharmaceuticals and waters

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ABSTRACT

In this work, a potentiometric sensor for ibuprofen monitoring in pharmaceuticals and waters is described. The sensor development relied on comparative performance evaluation of membranes based on several commercial cyclodextrins. The optimum membrane comprised 1.2 wt.% α-cyclodextrin, 65.6 wt.% o-nitrophenyloctylether plasticizer, 42% mol (relative to the molar concentration of the ionophore) of tetradodecylammonium bromide and 32.8 wt.% PVC. A conductive polymeric resin coated with the membrane used as low impedance solid contact completed the sensor device. The sensor presented a constant sensitivity of $-59.0\,mV\,dec^{-1}$ in the concentration range of 3.87×10^{-6} to 10^{-2} M, for samples with pH adjusted to 9. The response time was fast <15 s and reproducible (±0.8 mV) with constant performance over more than 6 months. The practical limit of detection was of $(3.34 \pm 0.03) \times 10^{-6}$ M ibuprofen. Sample analysis enabling accurate and reproducible results as well as the ability to be coupled to samples front-end conditioning procedures used in environmental analysis is also evidenced.

1. Introduction

Ibuprofen, the 2-(4-isobutylphenyl) propanoic acid (Fig. 1), is a weak acid with cyclooxygenase inhibition activity, commonly used to relieve pain in arthritis or otherwise consumed in illness conditions associated to inflammation and fever.

It is one of the most prescribed generic drugs according the worldwide sales ranking [1] and due to high consumption and the several ways of discharge it may contaminate aquatic environment including drinking water [2–4]. Key aspects of ibuprofen as environmental pollutant are related with toxic effects observed on non-target organisms even at low concentrations [5] and absence of data on the chronic exposure by humans. Commonly, analytical determinations in waters are accomplished with the use of chromatographic methods such as GC–MS [6] or LC with tandem mass spectrometric detection [7]. The concentration levels determined by these techniques are quite low but performed by highly skilled technicians at expense of laborious front end sample treatments and thus hardly suitable for screening tasks purposes. For pharmaceutical formulations the British Pharmacopoeia [8] reports a visual titrimetric method for the determination of ibuprofen tablets. On the other hand, US Pharmacopoeia [9] reports a high-performance liquid chromatography (HPLC) method. The titrimetric method is fairly problematic since suffers interference from tablet matrix, whereas the HPLC method is sensitive despite requiring the use of organic solvents and an expensive equipment. The alternative resort to sensor technologies could be envisaged and the use of potentiometric sensors came recently into play in this context [10–12]. Potentiometric sensors offer the advantages of simple design, implementation and use additionally providing reversible and reproducible measurements at modest costs [13,14]. Several ion-selective electrodes for ibuprofen were described in literature either based on ion-exchangers [15–17] or hard Lewis base [18], metallic [19] and organometallic ionophores [20,21] to bring perm-selectivity into the electrode membrane. However, with the exception of the electrode based on a commercially inaccessible In(III) porphyrinate [21] the reported practical limits of detection are poor (generally above 10^{-5} M), the selectivity insufficient for analysis in complex matrices, or are implemented with use of high toxic compounds [19]. Generally, the adopted electrode configurations require an internal reference solution containing ibuprofen in high concentration which hampers an adequate performance due to transmembrane fluxes towards membrane/sample interface as well as it contributes to the continuous leakage of the ionophore [22]. Aiming molecular complexation, cyclodextrins are widely used in many industrial products, technologies, analytical methods and especially in the preparation of chemical sensors [23]. They possess a cage-like supramolecular structure similar to those formed by cryptands, calixarenes, cyclophanes, spherands and crown ethers, being likely involved in host-guest chemical reactions where covalent bonds are not formed with the interacting molecules, ions or radicals. These compounds are capable of

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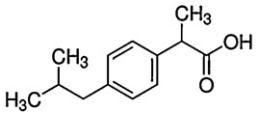

Fig. 1. Ibuprofen chemical structure.

forming inclusion complexes with drugs by taking up a whole drug molecule, or some part of it, into its hydrophobic cavity [24,25]. Its previous use as ionophore rendered potentiometric sensors with high durability and good performances concerning other drugs [26–28]. The implementation of an ibuprofen potentiometric sensor could be similarly envisaged with the use of cyclodextrins aiming a performance improvement that renders ability for monitoring tasks. In this work, different cyclodextrins available on the market are studied as ionophore materials after dispersion in a plasticized poly(vinyl chloride) matrix and applied directly in a contact solid based on a graphite conductive polymer. After performance evaluation, a procedure is developed and validated aiming the analysis of ibuprofen in water samples and in formulations available on the market.

2. Experimental

2.1. Reagents and solutions

Doubly deionised water (conductivity <0.1 $\mu S\,cm^{-1}$) and analytical grade chemicals were used throughout without further purification unless otherwise stated. Poly(vinyl chloride) (PVC), tetradodecylammonium bromide (TDDAB), tetrahexylammonium bromide (THAB), 2-nitrophenyloctyl ether (oNPOE), 2′-fluoro-2-nitrodiphenyl ether (FNDPE), α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), methyl-β-cyclodextrin (M-β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD), were from Fluka; tetrahydrofuran (THF) was from Riedel-de-Haën. The ibuprofen metabolic adducts carboxyibuprofen and 2-hydroxyibuprofen were purchased from Sigma–Aldrich.

A stock solution of ibuprofen sodium salt (Fluka) was daily prepared by weighing about 0.2283 g of reagent into a 100 mL volumetric flask and subsequent dilution to the mark with ammonium buffer (I = 0.01 M, adjusted to pH 9.0). The working calibrating solutions were prepared from it by rigorous dilution with the same buffer solution.

A solution acetonitrile/chloroacetic acid-ammonium sulphate (pH 3.0), in the volumetric proportion 60:40 (v/v) was prepared to be used as mobile phase in chromatographic determinations.

2.2. Apparatus

All potential measurements were performed by means of a Crison micropH digital potentiometer (sensitivity ±0.1 mV) coupled with an Orion 605 switcher. An Orion 90-02-00, silver chloride/silver double junction electrode was used as reference electrode with a 10% of KNO_3 solution (Thermo Orion 900003) filling the external compartment.

The pH measurements were carried out with a Phillips GAH 110 combined glass electrode.

A chromatographic system Jasco, model LC-NetII/ADC equipped with a PU-2080 Plus Intelligent HPLC pump, a MD-2015Plus multiwavelengh detector, a 20 μL loop and a C18 column (Waters Spherisorb, ODS2, 5 μm; 250 mm × 4.6 mm) was used to enable the analysis according the reference procedure [9].

2.2.1. Potentiometric sensors

The selective membranes for potentiometric sensors were prepared by appropriate mixture of PVC, plasticizer and sensing material as listed in Table 1. The additives THAB or TDDAB were alternatively incorporated in the membrane formulations to provide the cationic sites indispensable either to neutralize the anionic sites from PVC impurities, for extraction of ibuprofen into the membrane and to ensure membrane electroneutrality. The PVC was previously dispersed in THF (6 mL) and later mixed with the plasticizer solution of additive and ionophore. For electrode construction, the resulting mixture was stirred and about 1 mL dropped directly on the conductive surface of the electrode, made up with a mixture of epoxy resin (Araldite) with graphite powder following the procedure previously described [28]. A membrane including only the additive was also prepared to ascertain about the mechanism of sensor response. Membranes were dried at room temperature for one day. To promote membrane hydration before use the sensors were soaked in deionized water for 30 min. Between usages the electrodes were kept dried.

2.3. Procedures

All potentiometric measurements were carried out at room temperature. The potential of the electrochemical cell was measured after stabilization to ±0.2 mV, in ibuprofen standard solutions with concentrations ranging from 1×10^{-7} up to 1×10^{-2} M, in fixed ionic strength (I = 0.01 M) conditions and with pH adjusted to 9.0 by means of the ammonium sulphate buffer solution. The effect of proton ion was assessed by imputing pH variations on 200 mL of a 1×10^{-4} M ibuprofen solution through small volume additions of either concentrated sulphuric acid or saturated sodium hydroxide solution, freshly prepared. The potentiometric selectivity coefficients against some common inorganic ions presented in waters, chemical species presented in formulations, and also both ibuprofen metabolites were assessed by means of the fixed interference method [29] using 1×10^{-3} M solutions of each interfering ion. The reproducibility was estimated by means of calibrations in the linear range of sensor response performed during a day and between days. The response time to achieve a steady potential response (±1 mV) using the proposed sensors was registered through addition of adequate volumes of more concentrated ibuprofen solutions to a 1×10^{-7} M ibuprofen basal solution.

2.3.1. Samples preparation

Pharmaceutical formulations (labelled amounts of 200, 400, 600 mg per tablet) were obtained from local drug stores. Twenty tablets from the same lot were weighed and finely crushed in an agate mortar. Afterwards, a portion of powder equivalent to the weight of about 30–120 mg was accurately weighed and dissolved in 50.00 mL of buffer solution (pH 9.0; I = 0.01 M), being the mixture sonicated during 3 min. Suitable aliquots were analyzed and the results extracted from the corresponding calibration plots.

All water samples were filtered under vacuum through 1.2 μm glass microfiber filters (GF/C, Whatman, UK), followed by 0.20 μm nylon membrane filters (Supelco, Bellefonte, PA, USA) and stored at −20 °C, until extraction. Prior analysis, the pH of samples was adjusted with hydrochloric acid (2 M) in order to pre-concentrate ibuprofen in water samples by means of a SPE procedure adapted from [30]. Samples were extracted under vacuum in LiChrolut RP-18 cartridges (Merck) previously conditioned with 5 mL of acetone followed by 5 mL of methanol, and 5 mL of water (pH 2.2 in order to prevent the analytes from taking their ionic form) at a flow rate of 3 mL min^{-1}. After the conditioning step, sample was loaded at 8 mL min^{-1}. Afterwards, the cartridges were washed with 5 mL of water at 5 mL min^{-1} and dried with vacuum during 1 h. Elution of ibuprofen was performed ten times with 1 mL of methanol. The extract was evaporated to dryness under a gentle stream of nitrogen