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Man-tailored biomimetic sensor of molecularly imprinted materials for the potentiometric measurement of oxytetracycline

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ABSTRACT

A novel biomimetic sensor for the potentiometric transduction of oxytetracycline is presented. The artificial host was imprinted in methacrylic acid and/or acrylamide based polymers. Different amounts of molecularly imprinted and non-imprinted polymers were dispersed in different plasticizing solvents and entrapped in a poly(vinyl chloride) matrix. Only molecularly imprinted based sensors allowed a potentiometric transduction, suggesting the existence of host–guest interactions. These sensors exhibited a near-Nernstian response in steady state evaluations; slopes and detection limits ranged 42–63 mV/decade and 2.5–31.3 μg/mL, respectively. Sensors were independent from the pH of test solutions within 2–5. Good selectivity was observed towards glycine, ciprofloxacin, creatinine, acid nalidixic, sulfadiazine, cysteine, hydroxylamine and lactose. In flowing media, the biomimetic sensors presented good reproducibility (RSD of ±0.7%), fast response, good sensitivity (65 mV/decade), wide linear range (5.0×10^{-5} to 1.0×10^{-2} mol/L), low detection limit (19.8 μg/mL), and a stable baseline for a 5×10^{-3} M citrate buffer (pH 2.5) carrier. The sensors were successfully applied to the analysis of drugs and urine. This work confirms the possibility of using molecularly imprinted polymers as ionophores for organic ion recognition in potentiometric transduction.

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1. Introduction

The response of ion-selective electrodes (ISEs) towards a single analyte ion occurs under the condition of thermodynamic equilibrium at the sample/membrane interface (Johnson and Bachas, 2003). Polymeric membranes are of hydrophobic nature and are doped with active sensing ingredients such as a lipophilic ion-exchanger and/or a highly selective ionophore (Bakker and Pretsch, 2005). The presence of the ionophore molecules is responsible for chemical sensing and signal generation in the electrochemical interface of a potentiometric sensor (Dybko and Wróblewski, 2002).

For ISEs to operate, ions in an aqueous phase must undergo a phase transfer into an organic medium and interact with the active ingredients in the membrane (Johnson and Bachas, 2003). If only an ion-exchanger is incorporated into the membrane, the driving force for ion extraction into the sensing layer is solely ion exchange, governed by the lipophilicity of the ions being exchanged (Bakker et al., 1997). The incorporation of a selectively binding ionophore into the ISE sensing layer lowers the overall free energy for ion transfer into the organic phase for those ions to which the ionophore binds (Bakker et al., 1997). For ions strongly complexed by the ionophore a great difference in the magnitude of observed selectivity coefficients *versus* the lipophilicity series is expected (Johnson and Bachas, 2003).

The use of an organic species as potentiometric ionophore is however limited. The complex formation constant between ion and ionophore cannot be so large so that ions bind tightly, and the complexation becomes kinetically irreversible. Furthermore, the complexation between ionophore and target ion must be kinetically fast. As a result, ionophores are required to have some degree of pre-organization and flexibility so that the overall free energy barrier for the free to complexed states is small enough for complexation to occur quickly (Johnson and Bachas, 2003).

For an improved selectivity, the ionophore should discriminate the target ion from other ions already present. This may be achieved by chemically imprinting the target molecule against a polymeric surface to produce molecularly imprinted polymers (MIPs). These materials can be easily tailored with selectivity for a guest molecule (Mayes and Whitcombe, 2005; Katz and Davis, 2000; Busi et al., 2004; Rimmer, 1998). The preparation of MIPs involves the polymerization of functional monomers in the presence of template molecules and initiators. After polymerization, the template molecules are removed, leaving sites with induced molecular memory that are capable of recognizing the previously imprinted molecules (Lad et al., 2008). They leave accessible bind-

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ing sites with specific shape and functional group complementarily to original print molecule in the polymeric network. These binding sites maintain the ordered arrangement of complimentary chemical functionalities of the template and the overall spatial configuration of the target molecule. MIPs hold many advantages over natural receptors, such as their stability at extremes of pH and temperature, biological stability, low cost, and reusability. These features have led to the development of various MIP applications, including chromatography (Hosoya et al., 1998; Sellergren, 1994; Peter et al., 2003), artificial antibodies (Lavignac et al., 2004; Nilsson et al., 1994; Ye and Mosbach, 2001; Manesiotis et al., 2005), solid phase extraction (Andersson, 2000; Lanza and Sellergren, 2000; Qiao et al., 2006; Ariffin et al., 2007) and chemical sensors (Marx et al., 2004; Hirayama et al., 2002; Kriz et al., 1997; Kamel et al., 2008).

The central part of a chemical or biosensor is the recognition element, which is in close contact with an interrogative transducer (Haupt and Mosbach, 2000). The recognition element is responsible for specifically recognizing and binding the target analyte in an often complex sample. In biosensors this recognition is made by a biomolecule. There have been numerous attempts to replace these natural receptors with more stable counterparts. One technique often used for this purpose is molecular imprinting. Typically, the MIP-based sensors are fabricated by assembling MIP materials onto the surface of the transducer, and thus the analyte binding is transformed into a measurable signal. In principle, many physical measurements such as electrochemical voltammetry, fluorescence, piezoelectricity and surface plasma resonance can be used for the signal detection in MIP-based sensors (Guan et al., 2008; Bossi et al., 2007).

Following this principle, the sensing element in the membrane of the ISE could be a MIP. MIPs may provide a means for selectivity enhancement and it is likely that electrodes made using imprinted polymers may more closely approach the exclusivity desire in such device (Yanming et al., 1999). The creation of a membrane potential does not require the template to be extracted from the membrane, and ionic species do not have to diffuse through the membrane, providing no size restrictions on the template compound (Lopez et al., 2004). The potentiometric response may also be governed by stereo-chemical interactions if the changes in membrane potential are induced by host–guest complexation, which implied the molecular recognition effects at the interface of the modified electrode and the aqueous solution. Therefore, this behavior should not be observed on PVC membrane ISEs when non-imprinted polymers (NIPs) are used as sensing materials, but no work in the literature has reported this. This concept and possibility are here applied using oxytetracycline (OXY) as target molecule of MIP sensing elements and comparing their behavior with that of NIP.

OXY belongs to the group of the tetracycline antibiotics. This drug is used in various human and veterinarian applications, being the preferred tetracycline drug in aquaculture. In particular, the wide use of tetracyclines in meat and fish food production species led to environmental and food spread of antimicrobials, and may result in the emergence of antibiotic-resistant bacteria (Cabello, 2006; Maki et al., 2008; Samulesen, 1989). Therefore, reliable analytical methods are required for monitoring OXY in aquatic environments as well as in biological samples and in the commercial drugs.

Analytical procedures suggested in the literature for OXY detection and quantification regard microbiological methods (Jevinova et al., 2003; Gesche et al., 2001; Piriz et al., 2001; Myllyniemi et al., 2000; Okerman et al., 2001; Tantillo et al., 1997; Markakis, 1996; Wanner et al., 1994; Hasselberger, 1993; Jinbo et al., 1992; Roudaut et al., 1987; Muellerbrennecke et al., 1980) or liquid-chromatographic techniques (Khosrokhavar et al., 2008; Fletouris and Papapanagiotou, 2008; Maia et al., 2008; Kowalski and Pomorska, 2007; Biswas et al., 2007; Fritz and Zuo, 2007; Miller et al., 2007; Kowalski et al., 2006; Hosseini et al., 2006; Poapolathep et al., 2008; Yegorova et al., 2006; Pena et al., 2005; Rupp and Anderson, 2005; Lu et al., 2004; Schneider et al., 2007; Kim et al., 2006). The former is unsuitable for routine control procedures considering that each trial may take several days, and analytical laboratories also require proper facilities to handle biological compounds safely. On the other hand, chromatographic techniques are accurate, precise and robust, but they are not as expeditious as required for routine control purposes. They may also contribute to the emission of effluents of high toxicity. The same comments may apply to the electrophoretic-based procedures reported in the literature (Wu et al., 2005; Nozal et al., 2004; Hernandez et al., 2003; Tjornelund and Hansen, 1997). Other methods reported in the literature are based on immunoassays (Kim et al., 2006; Himmelsbach and Buchberger, 2005; Mascher et al., 1996); although they provide specific responses, the overall procedure is time-consuming and too expensive for routine analytical measurements.

Alternative and advantageous methods should rely on expeditious and efficient procedures providing highly specific and sensitive measurements. Ion-selective sensor's utility and simplicity have replaced for long other wet analytical methods, because they offer high precision and rapidity, low cost of analysis, enhanced selectivity and sensitivity over a wide range of concentrations (Cosofret and Buck, 1993; Bakker et al., 1994). Improved selectivity may also be achieved by means of using MIP sensing elements.

Therefore, the present work describes the development of OXY MIP-based ISEs. The sensor is synthesized with methacrylic acid (MAA) and acrylamide (AA) functional monomers cross-linked by ethylene glycol dimethacrylic acid (EGDMA) and using OXY as template. The sensing materials are dispersed in PVC matrix plasticized with *o*-nitrophenyl octyl ether (*o*NPOE). The sensors are evaluated in steady state and flowing media, and applied to the analysis of complex samples.

2. Experimental

2.1. Apparatus

All potential measurements were made by a Crison μpH 2002 decimilivoltammeter (±0.1 mV sensitivity), at room temperature, and under constant stirring in a Crison, micro-ST 2038. The output signal in steady state evaluations was transferred to a commutation unit and reconnected to one of the six ways out, enabling the simultaneous reading of six ISEs.

The assembly of the potentiometric cell was as follows: conductive graphite | OXY-selective membrane | buffered sample solution (citrate, 5×10^{-3} M, pH 2.5) || electrolyte solution, KCl | AgCl(s) | Ag. The reference electrode was an Orion Ag/AgCl double-junction (Orion 90-02-00). The selective electrode was prepared in conventional or tubular configurations (Kamel et al., 2009) for batch and flow mode evaluations. These devices had no internal reference solution and epoxy–graphite as solid contact. The electrode body consisted of a Perspex® cylinder (7 mm i.d. and variable length) with a shielded electrical cable inside having a copper plate in one end to establish the electrical contact to a graphite-based conductive support. This plate was mounted at about 1 cm of the edge of the cylinder, keeping a small cavity (about 1 cm deep and 7 mm ∅) for application of the conductive graphite/epoxy (2:1) paste. After drying, a small cavity was drilled (about 1.0 mm depth) on the graphite surface; the selective membrane was applied over it, filling this cavity. The tubular-shape electrodes were constructed similarly, but the Perspex® tubes were only 1 cm long and their inner cavity was filled with a graphite–epoxy conductive

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