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Direct-printed, solid-contact pH sensor for clinical applications: Challenges of non-specific adsorption

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Summary: We present a solid-contact pH sensor based on an hydrogen ion-selective membrane (ISM). The sensor substrate was fabricated using direct printing technology. A conducting polymer, polyazulene (pAz), was applied as an ion-to-electron transducer layer. Metrological characterization demonstrated that the sensor operates over a wide range of hydrogen ion concentrations, exhibiting a fast Nernstian response. Additionally, surface plasmon resonance (SPR) was employed to study the non-specific adsorption of organic molecules on the ISM-coated gold chip. Studies have shown that for proteins, the non-specific adsorption to ISM is dependent on the isoelectric point. In the case of drugs, it was shown that the non-specific adsorption of ibuprofen is much higher than that of acetaminophen.

Keywords: pH sensor, Direct printing, Potentiometry, Non-specific adsorption

Introduction

pH sensors based on ion-selective membranes are leading analytical tools for determining hydrogen ion concentration in clinical applications. Their ability to provide reliable and rapid measurements makes them indispensable in pH monitoring in body fluids. However, one of the major challenges in the practical application of these potentiometric sensors is the non-specific adsorption of various organic compounds on the sensor surface, which can lead to signal drift and reduced performance over time. Therefore, research focused on enhancing sensor sensitivity and improving resistance to non-specific adsorption is essential. Advances in these areas are critical for the further development of potentiometric sensor technology, enabling their broader applications in continuous monitoring and clinical diagnostics.

Methods

Electrodes were manufactured using direct printing technology. The direct printing was processed using a programmable microdispensing robot. The basic structures of the electrode were fabricated on a nonconductive polyester foil, with consecutively deposited silver paste, carbon paste, and insulating layers [1]. Electroconducting polymer (ECP), polyazulene (pAz), was deposited onto the graphite direct-printed electrode by cyclic voltammetry technique [2]. Modified electrodes were covered with an hydrogen ion-selective membrane (ISM) cocktail. The cocktail was composed of 0.5 wt.% potassium tetrakis(*p*-chlorophenyl)borate, 1 wt.% tridodecylamine, 65.5 wt.% bis-(2-ethylhexyl)-sebacate, and 33 wt.% polyvinyl chloride. Surface plasmon resonance (SPR) was used as a technique for monitoring the non-specific adsorption of various organic compounds to ISM. The ISM was deposited onto the surface of a gold SPR chip using the spin-coating technique. The non-specific adsorption was studied for selected organic molecules, including proteins: lactoferrin (Lf), fibrinogen (Fib), bovine serum albumin (BSA); amino acids: phenylalanine (Phe), methionine (Met), alanine (Ala), lysine (Lys), nucleic acids (calf thymus DNA); small biomolecules: glucose (Glu); and commonly used drugs: ibuprofen (Ibu), acetaminophen (Acph). The applied concentrations reflect typical clinical and physiological ranges.

Results

The pH sensors featuring a pAz transducer layer were characterized in terms of metrological parameter and response (Table 1 and Fig. 1).

Table 1 Metrological parameters of pH sensor based on pAz.

S \ mV/dec	pH range	$T_{95\%}$ \ s
55.4±0.1	2-10	7

The selectivity coefficients determined for the pH sensors (Table 2) confirmed their suitability for pH measurements in complex matrices, including human plasma.

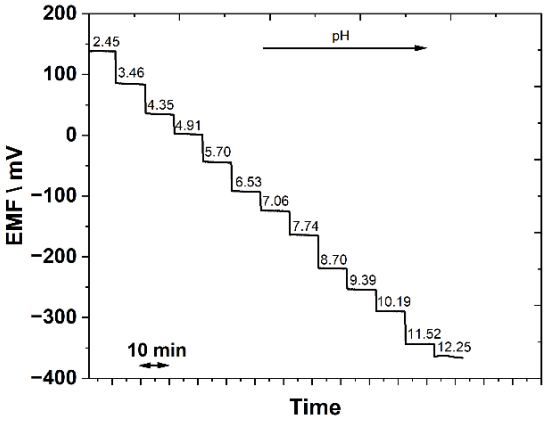

Fig. 1. Response of a direct-printed pH sensor to changes H^+ concentration.

Table 2: Selectivity coefficients $K_{H,j}$, required (req.) and experimentally estimated (exp.) values for constructed pH sensor determined using fix interference method (FIM) recommended by IUPAC.

interfering ions (j)	C_{phys} \ mM	$\log(K_{H,j})_{req.}$	$\log(K_{H,j})_{exp.}$
Na^+	150	-7.8	-9.7
K^+	5	-6.4	-8.3
NH_4^+	0.05	-4.4	-7.2
Ca^{2+}	2	-6.7	-8.8
Mg^{2+}	2	-8.2	-8.8

To investigate the non-specific adsorption, the ISM used in the sensor was deposited onto a gold SPR chip using the spin-coating technique. A series of organic compounds (Lf, Fib, BSA, DNA, Phe, Met, Ala, Lis, Glu, Ibu, Acph) were dissolved in a phosphate buffered saline solution (PBS, pH = 7.4), and their non-specific interactions with the ISM were monitored using SPR apparatus (Fig. 2. A). The surface loading density of these molecules on the membrane was quantified (Fig. 2. B). The results indicate that the level of membrane loading under constant environmental conditions varied depending on the type of organic compound. In the case of proteins, adsorption was strongly influenced by their isoelectric point (pI), with Lf (pI = 8.7, MW = 80 kDa) adsorbing at levels exceeding 3 ng/mm², Fib (pI = 7.4, MW = 340 kDa) reaching approximately 1.5 ng/mm², and BSA (pI = 4.5, MW = 66 kDa) showing minimal adsorption below 0.5 ng/mm². In contrast, small amino acids did not display a clear dependence on pI, suggesting that alternative mechanisms, such as hydrophobic interactions, may govern their adsorption behaviour. Furthermore, Ibu, one of the tested drugs, demonstrated non-specific binding to the ISM, in contrast to Acph, which exhibited negligible adsorption. Notably, the hydrophobic character of the ISM and near neutral pH of the PBS solution likely played a significant role in mediating these non-specific interactions. Collectively, these findings highlight that membrane hydrophobicity, the pH of the surrounding environment, and the isoelectric point of the organic molecules are key factors influencing non-specific adsorption onto ISM.

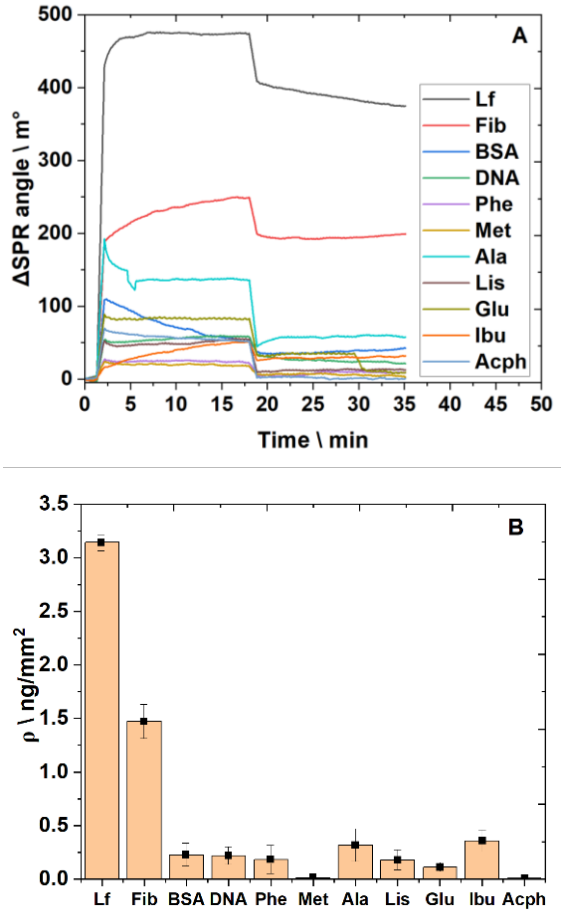

Fig. 2. A. Sensorgrams of non-specific adsorption of organic compounds onto the ISM; B. The loading density of the ISM with the applied organic molecules.

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