



Amperometric sensing of sodium, calcium and potassium in biological fluids using a microhole supported liquid/gel interface



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ABSTRACT

In this paper, we successfully applied a cost-effective and simple amperometric sensing design featuring a single microhole-water/organic gel interface to determine native sodium, calcium and potassium ion concentrations in biological fluids. The detection was based on measuring current changes associated with the transfer of each cation type across a microhole supported water/polyvinylchloride-2-nitrophenyl octylether gel interface. Three different sensing platforms were applied to the same biological sample with each only differing in the selective ionophore incorporated into the organic phase: dibenzo-18-crown-6 for sodium, calcium ionophore II (ETH 129) for calcium and valinomycin for potassium ions. Assisted transfer reactions of each ion from the aqueous to the organic gel layer by the corresponding ionophores were first characterized using cyclic voltammetry and then further analyzed using differential pulse stripping voltammetry. A linear dynamic range from 5 μM to 100 μM was achieved for each ion target. This enabled quantitative measurements of native concentrations of Na^+ , Ca^{2+} and K^+ in biological fluid samples including serum and plasma. The amperometric measurements were also validated by comparing with inductively coupled plasma mass spectrometry.

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1. Introduction

Concentration levels of electrolytes in biological fluids have been used as clinical indicators [1]. For example, sodium imbalance in the body is associated with blood pressure, kidney damage, atherosclerosis and risks of gastric cancer and dementia [2], while calcium is involved in the regulation of endocrine functions, blood coagulation, neuromuscular activity, tooth and bone metabolism [1]. Potassium level is also important for a range of metabolic purposes including maintenance of heart rhythm, nerve impulse transmission, water balance and muscular constriction [2]. Conventional methods used for analyzing electrolyte levels in biological samples are ion chromatography [3], inductively coupled plasma mass spectrometry (ICP-MS) [4], capillary electrophoresis [5–7], and flame photometry [8].

In addition, there have been extensive efforts made on developing different types of ion sensing devices and extensive reviews can be found in the literature [9–11]. One of the most commonly developed platforms is the use of ion selective electrodes (ISEs) based on the measurement of a potential difference when the target ionic species in an aqueous phase complexes with target selective ionophores present in organic membranes [12–14]. Like ISEs, the current associated with ion transfer processes across a polarized aqueous/organic phase assisted

by a selective ligand present in the organic phase can be an excellent alternative for the measurement of ion concentrations. Significant developments have been made over the past two decades on designing different sensing platforms based on an interface between two immiscible electrolyte solutions (ITIES) including a microhole or microarray or micropipette supported interface with one of the phases gelified [15–17]. One of the great advantages of using ITIES as a sensing platform is that the current increases proportionally with respect to the target ion concentration transferring across the interface. Incorporation of specific ionophores in the organic gel layer often drastically improves the selectivity of the ITIES sensor via the selective formation of an ionophore–target ion complex [15,18]. For example, the facilitated transfer of sodium and potassium ions by dibenzo-18-crown-6 (DB18C6) and valinomycin through microhole array supported water/polyvinylchloride-2-nitrophenyl octylether (PVC-NPOE) gel interfaces were applied for lake water analysis [19]. The same ionophores have also been widely applied for the assisted transfer of Na^+ and K^+ across different types of ITIES [20–22]. Ca^{2+} ion transfer facilitated by ETH 129 has also been demonstrated utilizing micropipette supported ITIES [23] for the analysis of commercial ultrapure water [24]. However, only a few studies have been reported on cation transfer reactions across the ITIES applied to analyze biological fluids [25–28]. For instance, the concentrations of Na^+ and K^+ in blood serum were determined based on the assisted transfer of the ions by DB18C6 across a hydrophilic membrane stabilized ITIES in conjunction with a flow injection technique [28].

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In this paper, we successfully applied a cost-effective and simple amperometric sensing design featuring a single microhole-water/organic gel interface to determine native sodium, calcium and potassium ion concentrations in biological fluids. This work represents the first successful attempt to use a microhole-water/gel based platform design for ion sensing in serum and plasma solutions and also that multiple target cations can be detected and concentrations compared in small sample volumes. This was achieved by individually including DB18C6, calcium ionophore II (ETH 129) and valinomycin into the PVC-NPOE gel phase to improve the selectivity for sodium, calcium and potassium ions, respectively (see Scheme 1). Cyclic voltammetry (CV) and more sensitive differential pulse stripping voltammetry (DPSV) measurements were both used to characterize facilitated cation transfer across a single microhole-liquid/gel interface. The determination of native cation concentrations in serum and plasma samples was also independently validated using inductively coupled plasma mass spectrometry (ICP-MS).

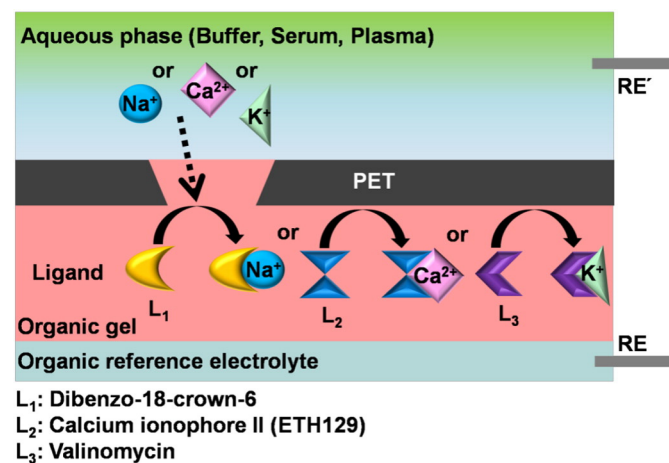
2. Experimental section

2.1. Reagents

Calcium (II) chloride (CaCl_2 , Duksan Pure Chemical Company Ltd.), calcium ionophore II (ETH 129, Fluka), dibenzo-18-crown-6 (DB18C6, 98%, Sigma-Aldrich), lithium chloride (LiCl, Fluka), lithium tetrakis(pentafluorophenyl)-borate etherate (LiTB, Boulder Scientific Co.), 2-nitrophenyloctylether (NPOE, Fluka), polyvinylchloride (PVC, high molecular weight, Sigma-Aldrich), potassium chloride (KCl, Merck), sodium chloride (NaCl, Merck), tetraoctylammonium bromide (TOABr, Fluka), tetraoctylammonium chloride (TOACl, Sigma-Aldrich), tris(hydroxymethyl)-aminomethane ($\geq 99.9\%$, Sigma-Aldrich), valinomycin ($\geq 98\%$, Sigma-Aldrich), normal human serum (Millipore), plasma from human (Sigma-Aldrich) were all used as received. Tetraoctylammonium tetrakis(pentafluorophenyl)borate (TOATB) used as an organic supporting electrolyte was prepared using the previously reported method [29]. Millipore-filtered water was used to prepare all aqueous solutions. All biological fluids were diluted in 20 mM Tris buffer (pH 9) at a desired level.

2.2. Fabrication of a microhole-ITIES

A single elliptical microhole on a thin polyethylene terephthalate (PET) film (thickness = 12 μm) was fabricated using a sharp needle [30]. Major and minor axis lengths of the elliptical hole were ranged from 44 to 108 (± 2) μm and 25 to 69 (± 2) μm , respectively. The



Scheme 1. Schematic presentation of the assisted transfer of Na^+ , Ca^{2+} and K^+ ions by DB18C6, ETH 129 and valinomycin, respectively across a microhole interface between a water phase and 3% PVC-NPOE gel.

variation in the hole size is due to the mechanical force applied when punching a hole on a thin film with a needle. The organic gel phase consisted of PVC (3.0% wt/wt), 10 mM TOATB and 10 mM of chosen ionophores dissolved in NPOE. Three different ionophores, DB18C6, ETH 129 and valinomycin were individually dissolved in the organic gel phase for the selective detection of Na^+ , Ca^{2+} and K^+ ions, respectively. Eight microliters of the PVC-NPOE mixture at 70 °C were casted on the exit side of a microhole and the gel was formed by keeping it for at least 6 h at room temperature.

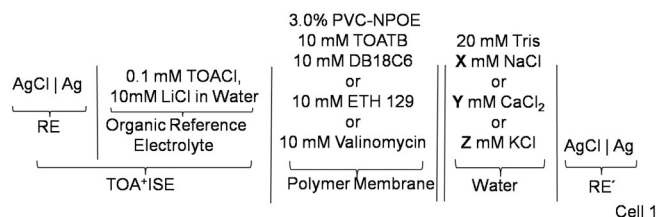
2.3. Electrochemical measurements

All electrochemical experiments were performed at room temperature unless otherwise stated using a potentiostat (Autolab PGSTAT30, Ecochemie) in a two electrode mode without IR any drop compensation. CV and DPSV were used throughout the experiments with the parameters were as follows: a scan rate of 10 mV/s for CV. For DPSV, preconcentration time for 30 s at 0.7, 0.3 and 0.4 V (vs. Ag/AgCl) for Na^+ , Ca^{2+} and K^+ ions, respectively with a constant step potential of 10 mV/s, a pulse amplitude of 50 mV and pulse duration of 50 ms.

3. Results and discussion

3.1. Detection methodology for Na^+ , Ca^{2+} and K^+ ions

Prior to characterizing the assisted transfer of Na^+ , Ca^{2+} and K^+ ions by selective ionophores across a microhole interface between the water and PVC-NPOE gel phases (see Scheme 1), the direct transfer of Na^+ , Ca^{2+} and K^+ ions in the absence of any ionophores in the gel was first characterized. The electrochemical cell set-ups for Na^+ , Ca^{2+} and K^+ ion transfer studies are shown in Cell 1.



Since they are the potential limiting species, the increases in current at the positive potential limit with respect each Na^+ , Ca^{2+} and K^+ ion concentrations are indicative of direct Na^+ , Ca^{2+} and K^+ transfer processes (Fig. S1) along with negatively charged organic supporting electrolyte such as TB^- ions and positively charged aqueous electrolyte such as H^+ ions. Also, high negative currents at the positive potential limit for the differential pulse stripping voltammetry (DPSV) data were observed (see Fig. S1) mostly associated with the transfer process of TB^- and H^+ ions in addition to the direct transfer of target metal ionic species. The variation in current values at the positive or negative potential limits are likely due to size variation of the mechanically drilled microhole supported the water/organic gel interface. Thus, current densities were utilized for further quantitative analysis.

For the assisted transfer of Na^+ , Ca^{2+} and K^+ ions, DB18C6, ETH 129 and valinomycin were chosen respectively with these selective ionophore complexations established previously [19–24]. The addition of an ionophore to the organic phase assists the ion transfer process across the polarized interface by selective metal ion-ligand complexation. This improves selectivity and also helps lowering the standard Gibbs energy of cation transfer and enables full voltammetric responses for the ion transfer reaction to be obtained [22,31]. In the absence of the target metal cations, the potential window was set by the transfer reaction of H^+ or TB^- ions and TOA^+ or OH^- ions across the interface at the positive and negative ends of the applied potential, respectively. The addition of Ca^{2+} and K^+ at low concentrations resulted in the occurrence

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