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Design and characterization of novel all-solid-state potentiometric sensor array dedicated to physiological measurements

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ABSTRACT

A novel construction of all-solid-state potentiometric sensor array designed for physiological measurements has been presented. The planar construction and elimination of liquid phase creates broad opportunities for the modifications in the sensing part of the sensor. The designed construction is based on all-solid-state ion-selective electrodes integrated with the ionic-liquid based reference electrode. Work parameters of the sensor arrays were characterized. It has been shown that presented sensor design indicates high sensitivity (55.2 ± 1 mV/dec, 56.3 ± 2 mV/dec, 58.4 ± 1 mV/dec and 53.5 ± 1 mV/pH for sodium-, potassium-, chloride- and pH-selective electrodes, respectively in 10^{-5}–$10^{-1.5}$ M range of primary ions), low response time (t_{95} did not exceed 10 s), high potential stability (potential drift in 28-h measurement was ca. ± 2 mV) and potential repeatability ca. ± 1 mV. The system was successfully applied to the simultaneous determination of K^+, Cl^-, Na^+ and pH in the model physiological solution and for the ion flux studies in human colon epithelium Caco-2 cell line as well.

1. Introduction

One of the fundamental issues in physiology is homeostasis and all aspects of this phenomenon, especially ion transport in human cells and tissues. Disturbed ion transport is the reason of many genetic and lethal diseases e.g. polycystic kidney disease [1], asthma [2], pulmonary edema [3], stroke [4], Alzheimer's disease [5], cystic fibrosis [6]. Moreover, there are many controversies around mechanism of ion transport in this diseases as proposed elucidations are often contradictory. Abundance of various ion channels (e.g. potassium-, sodium-, chloride- selective), ion transporters and ion pumps in human cells creates complex network of transporting proteins regulating and interacting mutually. Understanding physiological processes mechanisms in human is often experimental challenge that requires the use of various sophisticated techniques. The gold standard for investigation of particular ion channels in cells is patch-clamp technique [7]. The technique needs isolation of a single cell and is not appropriate when ion transport in cell layer is needed to be observed. Typically ion transport studies are carried out within the cell layer or tissue in the Ussing chamber [8]. However, this method is limited because of lack of selectivity toward a specific ion. The current signal obtained from Ussing chamber measurements results from the total ion fluxes in the cell layer or tissue (net flux) and it is not possible to distinguish particular ion contribution in the observed current change. The method has no chemical selectivity, thus obtained results give only outline information on the ion transport. More information about the particular ion (e.g. potassium, sodium, chloride) transport can be obtained with radioactive traces. Radiotracer flux method, though has many advantages, is limited by a low time resolution and is connected with the production of radioactive waste, their storage and utilization [9]. The safety and environmental hazards have led to abandoning the use of isotopic labeling and replacing them with other techniques.

The expectations of non-toxic, non-invasive, real-time monitoring of all ion fluxes in a cell layer or tissue have met potentiometric methods, especially ion selective electrodes (ISE). Besides the selectivity toward a specific ion, the simple construction and possibility of miniaturization were the main reasons for ISE to gain popularity in biological and medical applications. That is why ion-selective electrodes have gradually replaced spectroscopic methods in clinical analysis for continuous determination of ionic composition of human whole blood. In biology and medicine there have been numerous adaptations of ISEs in different configurations. Tahirbegi et al. described a method for fabrication of disposable all-solid-state ion-selective electrodes in an array of a

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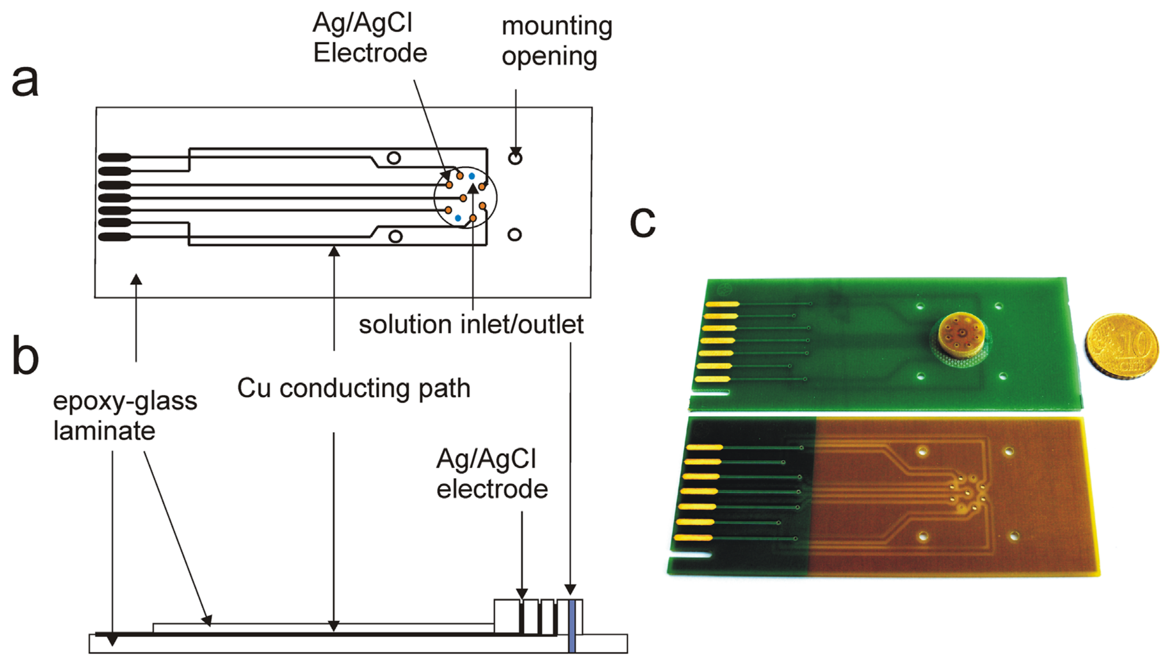

Fig. 1. a: Schematic presentation of the transducer array design on the example of configuration A; b: schematic cross-section of the transducer A design; c: photo of transducers used for the sensor array: configuration A (upper) and configuration B (lower).

needle shape dedicated to physiological applications [10]. According to this method all-solid-state potentiometric sensor array was constructed and used in gastroendoscope measuring pH in vivo [11]. The device was designed for measuring ischemia inside stomach. The electrodes used in the device were made by casting polymeric, ion-selective membrane solution directly on the gold electrode surface. As a reference electrode pseudo-reference Ag/AgCl was used. Electrodes indicated near-Nernstian responses, but their potential stability and repeatability were not investigated. An array of potentiometric sensors was also used for the simultaneous determination of potassium and urea. The electrodes were coated-wire type, obtained by casting PVC-based membrane on a conducting epoxy. However, low potential stability of the sensors' response and cross-talk between biosensors have been observed [12]. Dam et al. presented a flexible chloride sensor designed for chloride ions analysis [13]. Chloride-selective electrodes were made by screen-printing AgCl conducting paste on flexible polyethylene terephthalate sheet. The reference electrode was integrated on the same patch. It was made by adding a polyhydroxyethylmethacrylate hydrogel layer on the AgCl electrode. For the investigation of bacteria metabolism novel pH electrodes were designed. pH sensors were produced on silicon chips where thin layers of metal oxides were deposited. As a reference pseudo-reference Ag/AgCl was used [14]. However, there were no experimental data on the pH electrode potential repeatability, and short-/long-term potential stability. Walsh et al. described application of the silicon-based, potassium-selective ion-selective field-effect transistors (ISFET) for potassium efflux from mammalian cells and screening ion channels [15]. However, there has also been applied quasi-reference Ag/AgCl electrode which limits application of such array for other ions. In another group Ag/AgCl electrode was used as a chloride-selective electrode mounted in Ussing chamber [16]. It allowed for obtaining information about changes of chloride flux in the human epithelium. However, it needed using a macroscopic reference electrode. Recently, the construction of multielectrode bi-sensor system for ion flux measurements in human epithelia was described [17]. The construction was based on the ion-selective electrodes with liquid electrolyte solution and was applied to measurement of sodium and chloride ions fluxes across human bronchial epithelium.

In this work a novel design of all-solid-state array of potentiometric sensors enabling simultaneous determination of K^+, Cl^-, Na^+ ions and pH in cell monolayer and tissue has been presented. The measuring system is composed of two sensor arrays based on planar, all-solid-state ion-selective electrodes integrated with the reference electrode. According to our knowledge this is the first approach to all-solid-state miniaturized potentiometric system allowing for simultaneous determination of four physiologically important ions in cells and tissues. The paper shows introductory results of sensor system design and characteristics of its work parameters.

2. Experimental

2.1. Chemicals

All inorganic salts used were of analytical grade and were obtained from Fluka. The standard stock solutions (0.1 M) were prepared in redistilled water; working solutions were made by dilution of the stock solutions. The potassium-sensitive ionophore - valinomycin, hydrogen ionophore III, sodium ionophore X, tridodecylmethylammonium chloride, potassium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (KTFPB), potassium tetrakis[3,5-bis(trichloromethyl)phenyl] borate (KTClPB), sodium tetraphenylborate (NaTFPB), polyurethane Tecoflex (PU), plasticizer bis(2-ethylhexyl) sebacate (DOS) were purchased from Sigma-Aldrich. 1-dodecyl-3-methylimidazolium chloride was purchased from Iolitec (Germany). Freshly distilled tetrahydrofuran (THF) from Fluka was used as a solvent for the membrane components. Ringer solution was purchased from Baxter (Poland). All salts used for the measurements were purchased from Sigma-Aldrich.

2.2. Sensor array construction

The main part of the measuring system are two sensor arrays. The construction of arrays is based on epoxy-glass laminate (Fig. 1). The transducer part of the sensor array was produced