Talanta 160 (2016) 56–65

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Solid contact potassium selective electrodes for biomedical applications – a review

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ARTICLE INFO

Article history:
Received 8 February 2016
Received in revised form
17 June 2016
Accepted 24 June 2016
Available online 25 June 2016

Keywords:
Potentiometry
ISE
Potassium
Solid-state
Conducting polymers
Conducting nanomaterials

ABSTRACT

Ion-selective electrodes (ISE) are used in several biomedical applications, including laboratory sensing of potassium concentration in blood and urine samples. For on-site determination of potassium concentration and usage in other applications such as determination of extracellular potassium concentration, miniaturization of the sensors is required. To that extent, solid contacts have proven to be an adequate substitute of liquid contacts as inner layer for ion-to-electron transduction, allowing industrial production of miniaturized ISEs. This review paper covers relevant developments of solid-state ISEs in the past decade, critically compares current potassium ISEs and discusses future prospects for biomedical applications. Performances of three main types of solid contact materials in potassium sensing are compared, namely polypyrrole, polythiophenes and conducting nanomaterials. With these new materials, numerous improvements in stability, selectivity and time response of solid-state ISEs have been made. Current developments are new operational methods of sensing, flexible miniaturized sensors and multi-electrode designs able to measure electrolyte concentrations in one-drop blood samples or transmembrane ionic flows.

Contents

1. Introduction

Determination of potassium concentration in human blood is of great importance in both chronic illness and acute menacing conditions [1]. Especially in critical care medicine, rapid on-site

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http://dx.doi.org/10.1016/j.talanta.2016.06.050
0039-9140/

measurement is beneficial for detecting acute changes in electrolyte levels and monitoring treatment [2]. Furthermore, localized fluctuations in extracellular potassium concentration of the human brain may be related to a number of important brain diseases. Intracranial electrodes with high potassium selectivity and a short response time may visualize these fluctuations, which is essential to increase understanding of the underlying pathophysiological processes [3]. For on-site measurement of potassium concentration in blood as well as localized measurement of extracellular potassium concentration in the brain, miniaturization of the sensor is needed [1,3].

Over the last two decades, many improvements have been made in miniaturization of ion-selective electrodes (ISE) [4]. This paper reviews literature from the past decade relevant for miniaturized potassium ISEs and discusses current developments in operational sensing methods and sensor design. Production processes are not covered. Previous reviews in the field have focused on ISE modeling and application [4], development of solid-state ISEs [5] and properties of conducting polymers [6]. This review combines these aspects to critically compare stability, selectivity and time response of solid contact potassium ISEs. To start with, this review covers essential theory of ISE sensing and a short history of ISE development. Subsequently, specifications of current biomedical potassium ISEs are compared and emerging developments are presented.

2. Theory of ion-selective electrodes

The goal of ion-selective electrodes (ISEs) is to convert activity of a specific ion into an electrical potential measured as output signal. An ISE is an electrochemical cell minimally consisting of a working electrode covered with an ion-selective membrane and a reference electrode. An intermediate or inner layer is commonly placed between the ion-selective membrane and the electrode to facilitate ion-to-electron transduction. Ideally, potential drops are only present at phase boundaries (a high impedance voltmeter provides near-zero current) and all interfaces except for the membrane|sample interface exhibit a constant potential difference. Changes in electrode potential are then only dependent on the membrane|sample interface. We will first present a brief overview of the exchange process at the membrane, which governs specificity of the electrode. Next, theoretical conditions for stable potentials of the remaining electrode interfaces along with the commonly applied method for testing potential stability are provided.

For biomedical potassium sensing, relevant contributors to the potential at the membrane|sample interface are potassium itself and interfering ions. For most applications a solvent polymeric membrane is used. Permselectivity, the membrane's ability to discriminate between cations and anions, is a necessary condition for cation selectivity and is achieved by incorporating anionic sites in the membrane [7]. Cation selectivity, i.e. the membrane's ability to discriminate between ions of positive charge, is attained by addition of an ion complexing agent or ionophore to the membrane. Many ionophores have been tested, but valinomycin, a naturally occurring antibiotic discovered over 50 years ago, is used in most potassium ISEs [8]. The working or linear range of an ISE describes the concentration range of the target ion in which the ISE exhibits a Nernstian response. The upper limit of detection is explained by a loss of permselectivity (Donnan exclusion failure) at high ionic concentrations [9]. The activity of interfering ions usually determines the lower limit of detection in biological samples [10]. To quantify an ISE's selectivity for the target ion relative to interfering ions, the selectivity coefficient $K_{A,B}$ in the semiempirical Nikolsky-Eisenman is recommended by the International Union of Pure and Applied Chemistry [11].

$$E_{meas} = E_0 + \frac{RT}{z_A F}\ln\left(a_{A,s} + K_{A,B}^{pot}(a_{B,s})^{z_A/z_B}\right) \quad (1)$$

with $a_{A,s}$ the activity of the target ion in the sample, $a_{B,s}$ the activity of an interfering ion in the sample and z the ion valency. R is the universal gasconstant, T is temperature, F is Faradays constant and E_0 is the potential (presumed constant) over all interfaces except the membrane|sample interface. In order to determine the selectivity coefficient, different methods can be used, such as the Fixed Interference Method or the Separate Solution Method. In both methods, described and recommended by the IUPAC [11], the potential of several solutions with known concentrations of ions A and B is measured, after which the coefficient can be calculated.

For stability of the electrode potential, Nikolskii and Materova [13] formulated the necessary conditions of a sufficiently fast and reversible ion-to-electron transduction without contribution of parallel side reactions. For conventional ISEs with liquid inner contact, a reversible redox reaction of the inner solution containing a salt of the target ion fulfills these conditions. For the solid contact ISEs considered in this review, two ion-to-electron transduction mechanisms are important. A schematic representation of both mechanisms is given in Fig. 1. The reader is referred to Lewenstam et al. [14] and Hu et al. [12] for detailed descriptions of these transduction mechanisms. The first concerns redox-reaction based transducers, which provide reversible ion-to-electron transduction through redox reactions of the solid contact that involve the target ion and/or its hydrophobic counterion in the membrane. These redox reactions involve oxidation/reduction of e.g. a conducting polymer doped with small anions or larger electroanalytes (p-doping). The doping substance and level of doping during production allows control over redox capacitance [12] and electronic conductivity of the polymer [15]. The second mechanism is described by formation of an electrical double layer at the solid contact|membrane interface. In analogy to a capacitor, this interface is referred to as a double-layer capacitance formed by ions at the membrane site and electrons or holes in the solid contact site. Interfacial potential is dependent on the quantity of charge in the double layer.

Stability of the potential at the interfaces of the solid contact depends on redox capacitance and susceptibility to interferences of e.g. light, O2 and CO2 and may be improved by implementing a

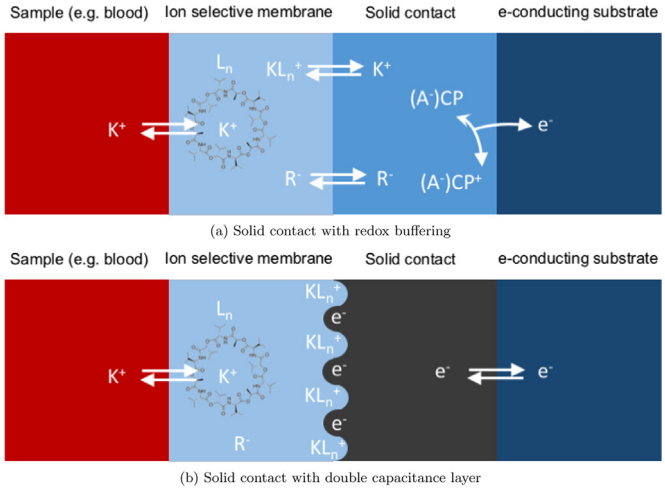

Fig. 1. Schematic representation of ion-to-electron transduction mechanisms in a solid contact potassium ISE. L_n=neutral carrier (valinomycin is depicted as example), R^-=hydrophobic counterion, CP=conducting polymer possibly doped with a small anion (e.g. R^-) or a larger electrolyte (A^-) (Adapted from Hu et al. [12]).