Sensors & Transducers, Vol. 27, Special Issue, May 2014, pp. 258-263

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Development of Li^+ Selective Microelectrode Using PPy [3,3′-Co(1,2-$C_2B_9H_{11})_2$] as a Solid Contact

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Received: 31 December 2012 /Accepted: 10 August 2013 /Published: 26 May 2014

Abstract: Planar all solid-contact ion-selective microelectrodes (ASC-μISEs) with a conducting polymer (polypyrrole doped with cobaltabis(dicarbollide) anion [3,3′-Co(1,2-$C_2B_9H_{11})_2$]) as a solid contact layer between the polymeric membrane sensitive to lithium (Li) and the gold (Au) substrate were prepared and investigated. The N,N-dicyclohexyl-N′,N′-diisobutylyl-cis-cyclohexane-1,2-dicarboxamide (ETH 1810) was used as ionophore for Li recognition. The developed microelectrodes show a linear response for Li+ concentration between 6×10^{-5} M and 1×10^{-1} M with slope of 53±1 mV per decade and exhibits remarkably enhanced selectivity for Li over other cations. The calibration plots using artificial serum containing three different levels of sodium chloride (NaCl) (135, 145 and 155 mM) as a background electrolyte were shown a linear response with a slope of 50 mV per decade in the clinical range of interest (0.7-1.5×10^{-3} M Li^+). The developed microelectrodes will be used to determine Li^+ concentrations in serum samples of manic-depressive patients under Li treatment. *Copyright © 2014 IFSA Publishing, S. L.*

Keywords: Lithium-selective, All solid-contact ion-selective microelectrode, PPy [3,3′-Co(1,2-$C_2B_9H_{11})_2$], Potentiometry.

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1. Introduction

The development of miniaturized biosensors has increased over the last decades in clinical and biomedical analysis applications. Among these, all solid-contact ion-selective microelectrodes (ASC-μISEs) offer many advantages such as small size, robustness, fast response, and mass production. The ASC-μISEs display the inherent advantage, with respect to classical microelectrodes, of the removal of the inner filling solution. To produce such devices different layers of conducting polymers (CP), e.g., polyaniline (PANI) [1], poly(3-octylthiophene) (POT) and poly(3,4-ethylenedioxythiophene (PEDOT) [2], polypyrrole (PPy) [3], and carbon black [4] were placed as a solid internal contact between the metal and the ion-selective membrane to facilitate the charge transfer at the substrate-membrane interface. PPy was first used as a solid contact for sodium ISEs by Cadogan et al. [5]. The therapy of manic depressive psychosis with Lithium (Li) salts requires periodic measurements of the Li concentration in whole blood, plasma, urine or serum. The therapeutic concentration is in the range from 0.7 to 1.5 mM [6]. The analysis is difficult due to the low Li concentration when compared to the higher content of natural cations (especially sodium ions (Na^+)) [7]. However, as Li salts are prescribed for the treatment of manic-depressive patients [8], the borderline between the maximal therapeutic concentration and Li poisoning is relatively narrow and, therefore, an analytical method for its determination is necessary [9-10].

In this paper, we report on the potentiometric behavior of a Li ASC-μISEs based on silicon technology using a poly(vinyl chloride) (PVC) matrix membrane doped with N,N-dicyclohexyl-N′,N′-diisobutylyl – cis – cyclohexane – 1,2 -dicarboxamide (ETH 1810) as an ionophore. This sensitive membrane was deposited on the surface of a PPy film, doped previously with cobaltabis(dicarbollide) anions ($[3,3'\text{-Co}(1,2\text{-}C_2B_9H_{11})_2]$) [11-19] and electrodeposited onto gold microelectrodes. Finally, the prepared ASC-μISE was used for the determination of Li^+ in an artificial serum.

2. Experimentation

2.1. Reagents

Pyrrole (Aldrich Chemicals, France) was distilled under vacuum prior to its use. The cesium salt of cobaltabis(dicarbollide) Cs [3,3′-Co(1,2-C2B9H11)2] (KAT-CHEM, Hungary) was used as received without further purification. All the membrane components were of analytical reagent grade, namely: Lithium ionophore III (ETH 1810) (62558), Potassium tetrakis(4-chlorophenyl)borate (60591), 2-Nitrophenyl octyl ether (73732) and Poly(vinyl chloride) high molecular weight (81392) were purchased from Fluka, France. Standard solutions and buffers were prepared with deionized water.

2.2. Apparatus

Cyclic voltammetry (CV) measurements were performed with a multichannel electrochemical analyzer, VMP3 (Bio-logic-Science Instrumentation, France). The electrochemical cell contains three electrodes: a platinum (Pt) counter electrode, a saturated calomel reference electrode (SCE), and the integrated microelectrodes with an area of 9×10^{-4} cm^2 based on gold (Au) were used as the working microelectrode. The electrochemical measurements were performed in phosphate buffered saline (PBS) (10 mM) at pH 7.4 with $Fe(CN)_6^{3/4-}$ (5 mM) at room temperature (25 ± 0.5 °C). A potential range of - 0.4 V to 0.6 V was applied with a scan rate of 100 mV/s.

The potentiometric measurements were carried out at room temperature, using a homemade data acquisition system set-up with four multi-channel microelectrodes connected and controlled by a personal computer. LabVIEW software was used for data manipulation. Measurements were made relative to a silver/ silver chloride (Ag/AgCl) double junction reference electrode (Thermo Orion) under magnetic stirring. Calibration curves were obtained by adding successive aliquots of lithium chloride (LiCl) solutions (prepared within a concentration range of 10^{-1} to 10^{-5} M by serial dilution) to 25 mL of Tris-HCl (0.05 M at pH=7.2) to increase the Li^+ concentration from 10^{-8} to 10^{-1} M.

The variations in the potential were recorded after stabilization and the value was plotted as a function of the logarithm of the Li activity. The activities of the metal ions in the aqueous solutions were calculated according to Debye-Huckel equation [20]. The behavior of the microelectrodes was also tested in the presence of other cations (Mg^{2+}, K^+, NH_4^+, Ca^{2+}, and Na^+). The fixed interference method (FIM) was used to obtain the selectivity coefficients [20].

2.3. Microelectrodes Fabrication

The microelectronic fabrication process for the microelectrodes was performed at the “Centro Nacional de Microelectronica” (CNM, Spain). The process has only two photolithographic steps. The starting material is p-type <100> silicon 100 mm diameter wafers with a nominal thickness of 525 μm. The process starts with a thermal oxidation process to grow a thick oxide layer (8000 Å). A first photoresist layer was then applied and patterned on the wafer surface. For improving the adhesion of Au microelectrodes, first, a titanium (Ti) layer (10 nm) was introduced and then the 250 nm layer of Au was sputtered onto the surface. After that, a photoresist layer was spin-coated and then exposed to UV light with a patterned mask. Etching away the exposed photoresist was then performed, and this left the photoresist of the required microelectrodes pattern. The next step consisted in the deposition of two PECVD (Plasma-Enhanced Chemical Vapor Deposition) layers of SiO_2 (4000 Å) and Si_3N_4 (4000 Å), acting as a passivation layer. The second photolithographic process was performed to open the passivation on the active Au microelectrodes (300 μm × 300 μm) and on the soldering pads. Finally, the wafer was diced and the devices were glued to a printed circuit board (PCB) and the connections were wire-bonded in the usual manner. The bonding area of the devices, the bonding of the wires, and the copper tracks of the PCB were then encapsulated using an epoxy resin (Epo-Tek H77, from Epoxy Technology) to protect them from the liquid environment.

2.4. Fabrication of the Ion Selective Microelectrodes

2.4.1. Electropolymerization of PPy [3,3′-Co(1,2-$C_2B_9H_{11})_2$]

It is well-know that, upon exposure to a non-clean room laboratory environment the Au surface is subject to numerous ambient contaminations, thus, the electrochemical characteristics of the developed devices can be affected [21]. It is for this reason that Au microelectrodes, especially evaporated Au, must be cleaned before the electropolymerization of the conductive polymer. Therefore, the microelectrode samples were cleaned for 20 min using UV/Ozone (BioForce UV/Ozone ProCleaner). The microelectrodes were then characterized before and after UV/Ozone cleaning.

The microelectrodes were then characterized by CV with the measurements performed in 5 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ in PBS at pH 7.4. The microelectrodes were scanned between -0.4 and 0.6 V, with a scan rate of 100 mV/s. Fig. 1 shows both oxidation and reduction peaks at ~ 0.263 V and 0.177 V respectively. Such values indicate a cleaner and more electrochemically active microelectrodes surface [22].

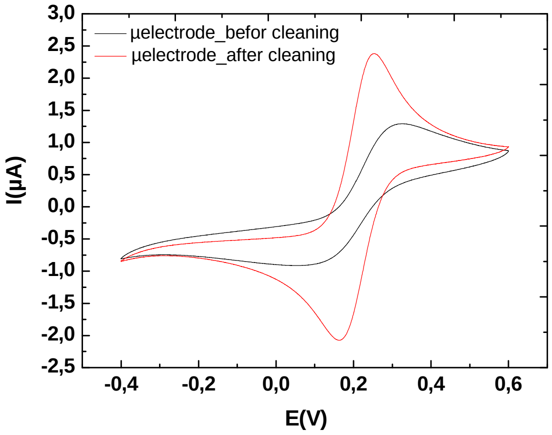

Fig. 1. CV response of the characterization of Au microelectrode before (black) and after (red) treatment with UV/Ozone in 5 mM K3[Fe(CN)6]/K4[Fe(CN)6] in PBS at pH 7.4 with a scan rate of 100 mV/s.

After this step, the electropolymerization of PPy doped with cobaltabis(dicarbollide) anion [3,3′-Co(1,2-$C_2B_9H_{11})_2$] (PPy [3,3′-Co(1,2-$C_2B_9H_{11})_2$]) on the cleaned gold microelectrode was made by galvanostatic method using a potentiostat galvanostat (Voltalab PGZ401), in a single compartment cell with a standard three-electrode system using a constant current of 100 μA for 20 s. The solution for the electropolymerisation was Pyrrole (0.1 M) and Cs[3,3′-Co(1,2-$C_2B_9H_{11})_2$] (0.035 M) in acetonitrile (MeCN) (1 wt. % in water) [11]. Fig. 2 shows the images of the microelectrodes before and after growing the PPy[3,3′-Co(1,2-$C_2B_9H_{11})_2$] layer.

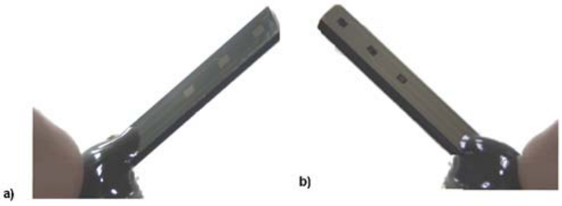

Fig. 2. Images of the gold planar microelectrodes with (a) before and (b) after growing PPy [3,3′-Co(1,2-$C_2B_9H_{11})_2$].

2.4.2. Preparation of Lithium Membrane

The composition of the ion-selective membrane sensitive to Li was the same as those normally used for the same ion in PVC-based ion–selective electrodes (ISEs) with internal filling solution [23]. The composition of the electroactive membrane was 1.2 wt. % of Li ionophore III (ETH 1810), 32.8 wt. % of PVC, 65.6 wt. % of plasticizer, and 0.4 wt. % of Potassium tetrakis(4-chlorophenyl)borate in 3 mL of tetrahydrofuran (THF). The membrane cocktail (~ 2μL) was deposited onto the surface of the microelectrodes doped PPy [3,3′-Co(1,2-$C_2B_9H_{11})_2$] using a pipette. The solvent was then allowed to evaporate overnight. Finally, before each use for measurements, the Li-selective microelectrodes were conditioned in 1×10^{-3} M LiCl solution for 30 minutes.

3. Results and discussion

3.1. Sensor Sensitivity

The performance of all the ASC-μISEs was characterized by the slope of the calibration graph, the response time, the detection limit, and the selectivity coefficients. The Li^+-selective microelectrodes exhibited linear responses to the activity of Li^+ over the range of $6x10^{-5}$ to $1x10^{-1}$M with a slope of 53 ± 1 mV/decade and a correlation coefficient of 0.9993 (n = 25) (See Fig.3). The developed microelectrodes showed a very stable response over time. Even after repeated calibrations (9 weeks) the microelectrodes still showed the linear response in the same range of the Li activity. The electrochemical characteristics of the developed microelectrodes exhibited a better performance compared with those measured for a polymeric membrane PVC [10, 24-28] and NASICON membrane [29] with respect to sensitivity and selectivity.

The detection limit was evaluated as the abscissa of the crossing point of extrapolation of the two linear parts of the calibration graph with a value of 3×10^{-5} M. In order to confirm this sensitivity, microelectrodes with a membrane without the ionophore were tested. They have shown a very low slope and detection limit when compared to those obtained with membranes containing the ionophore ETH 1810 (Fig. 3).

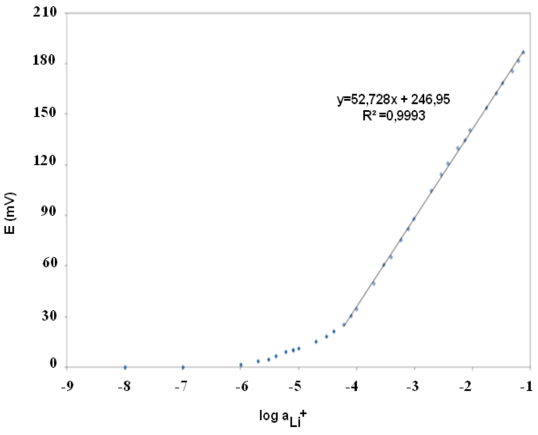

Fig. 3. Potentiometric response of the Li+ ASC-µISE.

3.2. Response Time

The response time of an ISE is an important factor. In this study, the practical response time was recorded after step changes in the concentration of Li in solution, and it was determined by measuring the time required to achieve a 95 % steady potential when the Li concentration is increased. The corresponding potential versus time for the microelectrode is shown in Fig. 4. As observed, the microelectrode reached the equilibrium response in a very short time of ~ 4.4 s.

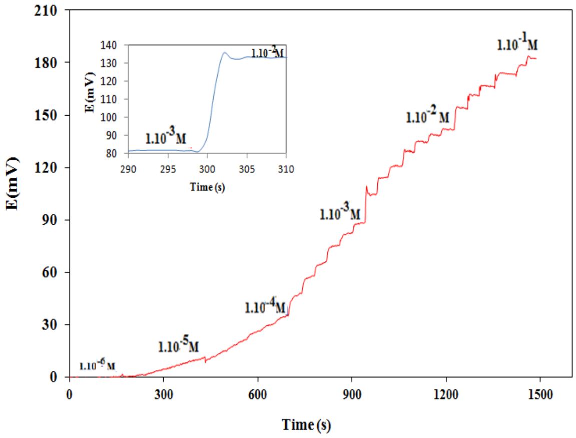

Fig. 4. Dynamic response of Li+ microelectrodes for step changes in the concentration of Li+ from 10^{-6} to 10^{-1} M and response time at $t_{95\%}$ was ~4.4 s.

3.3. Effect of pH

The influence of pH on the potentiometric response of the microelectrode was examined by following the potential variation over a pH between 1.5 and 11 at a fixed concentration of Li$^+$ (1.10^{-3} M). The pH of the solution was adjusted by the addition of small volumes of chloridric acid (1 M and 0.1 M) to decrease the pH. Fig. 5 shows that the potential remained constant between pH 7 and 10, particularly in the field of physiological pH (pH 7.31 to 7.45). This scale will be taken as the working range.

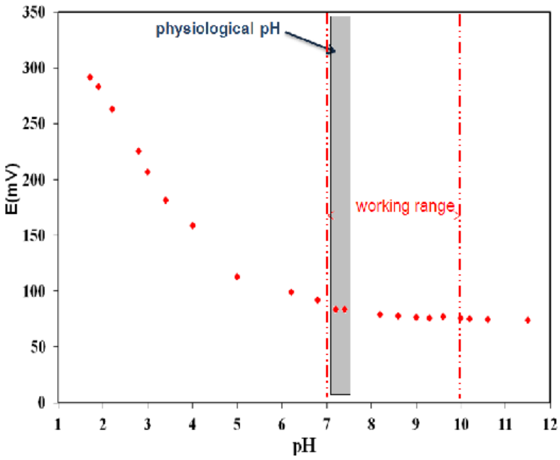

Fig. 5. Effect of pH on the Li ASC-µISE response at 1×10^{-3}M Li$^+$ concentration.

3.4. Selectivity of Membrane

The ASC-µISE response was examined in the presence of various foreign ions. The selectivity coefficients were evaluated from potential measurements on solutions containing a fixed concentration of interfering ion (1.0 × 10^{-2} M) with a varying amount of the primary ion. Therefore, the selectivity coefficient is calculated for these electrodes from the following equation and listed in Fig. 6:

$$K_{Li,M}^{pot} = \frac{a_{Li^+}}{(a_j)^{\frac{Z_{Li^+}}{Z_j}}}, \tag{1}$$

where a_{Li^+} is the activity of the primary ion (Li$^+$) at the lower detection limit in the presence of interfering ion j with activity of a_j and charges Z_{Li^+} and Z_j. Common cations, such as K$^+$, NH_4^+ and Mg^{2+} do not disturb the good Li$^+$- response of the sensor, while only Na$^+$ and Ca^{2+} are the interfering ions. As observed, the obtained $K_{Li,M}^{pot}$ values for the proposed microelectrode are superior in most cases to those previously reported for the ISE selective to Li [10, 24-29].

To search for an improved Li ASC-µISE for the determination of Li in serum, we have used a model acting as an artificial serum solution [8 mM NaH_2PO_4; 1.5 mM Na_2HPO_4; 2.0 mM $CaCl_2$; 0.8 mM $MgCl_2$; 4.5 mM KCl; 0.05 mM NH_4Cl; 4.7 mM glucose and 2.5 mM urea] in three different concentrations of NaCl (135, 145 and 155 mM). Fig. 7 shows the results for the calibration of Li in the artificial serum model. The response of the ASC-µISEs for the three carrier solutions was linear and a sensitivity of ~50 mV/decade in the clinical range of interest (0.7 – 1.5 mM Li^+) was observed. For instance, TRIS-HCl ($y = 52.73x + 246.95$ and $R^2 = 0.9993$); artificial serum + NaCl 135 mM ($y = 50.87x + 247.24$ and $R^2 = 0.9991$); artificial serum + NaCl 145 mM ($y = 50.48x + 143.29$ and $R^2 = 0.9903$); and artificial serum + NaCl 155 mM ($y = 47.31x + 128.50$ and $R^2 = 0.9926$); In addition, the presence of proteins in the artificial serum model did not interfere with the response of the ASC-µISEs.

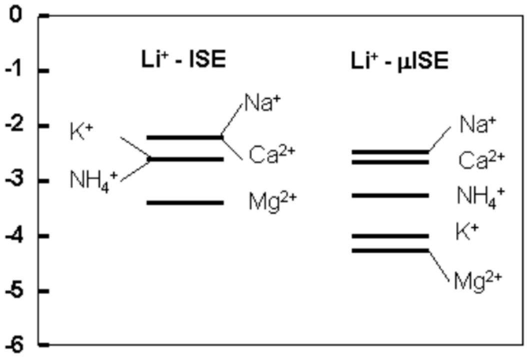

Fig. 6. Potentiometric selectivity coefficients $K_{Li,M}^{pot}$.

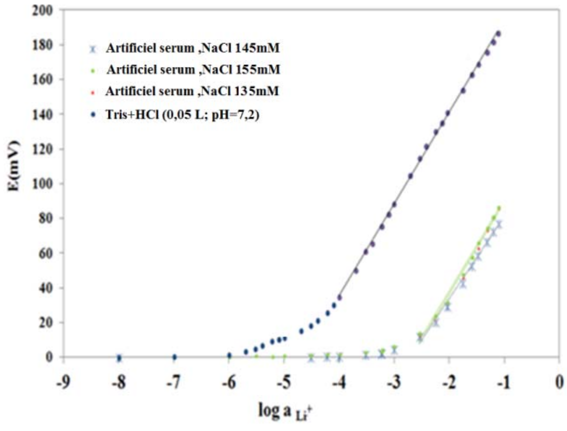

Fig. 7. Potentiometric Li response of the ASC-µISE based on Li Ionophore III in artificial serum containing various levels of NaCl. The sensitivity was ~50 mV/decade and a correlation coefficient of $R^2 = 0.99$ that was within the clinical range of interest (0.7 – 1.5 mM Li^+).

4. Conclusions

Planar ASC-ISEs of a Li sensitive microelectrode based on silicon technology with PPy doped with cobaltabis(dicarbollide) anion as the solid internal contact between the polymeric sensitive membrane and the Au substrate have been fabricated. The good potentiometric performance of the ASC-ISEs studied in this work indicates that PPy doped with cobaltabis(dicarbollide) anion is useful as a solid contact material. The tested ASC-µISE sensors showed a higher reliability in Li measurements in artificial serum that were within the significant range. Along with rapid measurements, economical use of reagents, use of small sample volumes, and a low cost for their production, these sensors are promising for the direct monitoring of Li^+ activities in blood serum during therapy of manic-depressive psychosis.

Acknowledgements

This work was funded by the European Communities Seventh Framework Programme (FP7/2007-2013) under the grant agreement No. 248763 (SensorART) and FP7-PEOPLE-2012-IRSES under the grant agreement No. 318053 (SMARTCANCERSENS) and SPS (NUKP. SFPP984173) NATO project.

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