Sensors and Actuators B 145 (2010) 133–138

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

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

Novel flow-through bulk optode for spectrophotometric determination of lithium in pharmaceuticals and saliva

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ARTICLE INFO

Article history:
Received 28 July 2009
Received in revised form
12 November 2009
Accepted 20 November 2009
Available online 3 December 2009

Keywords:
Flow-through optode
Sensor
Lithium
Pharmaceuticals
Human saliva

ABSTRACT

A new flow-through spectrophotometric bulk optode for the determination of lithium is reported. The optode membrane incorporates a lipophilic pH indicator (chromoionophore XIV), a lipophilic neutral ionophore (lithium ionophore VIII) and potassium tetrakis[3,5-bis(trifluoromethyl) phenyl] borate (ionic additive) as active constituents in a plasticized poly(vinyl) chloride membrane, entrapped in a cellulosic support. The composition of the membrane was tested using two different plasticizers. The optode was incorporated in a flow-injection system optimized for the determination of lithium. The analytical performance of the optode was evaluated, obtaining a linear concentration range of two decades of concentration (1×10^{-4} to 1×10^{-2} M), a limit of detection of 1.4×10^{-4} M, a fast sample throughput (25–4 samples h^{-1}) and good reproducibility and selectivity. The sensor was seen to exhibit a fully reversible response. The proposed FI method is applied to the determination of lithium in pharmaceuticals and human saliva with satisfactory results.

1. Introduction

Lithium ion sensors are currently in demand for their potential biomedical applications. The therapeutic effects of lithium salts have proved useful in the treatment of manic depressive, hyperthyroidism and certain types of cancer, and have also been proposed for help in the prevention of Alzheimer's disease [1].

Lithium salts, normally administered as lithium carbonate, have widely been employed in the control of bipolar disorder symptoms [2] and have been seen to be efficient at plasmatic concentrations higher than 0.50 mmol l^{-1}. However, some cases of severe intoxication at lithium concentrations above 1.5 mmol l^{-1}, and even death at concentrations 2–2.5 mmol l^{-1}, are related in the literature [3,4], emphasising the narrow therapeutic window available. Therefore, the monitoring of lithium levels in drugs and biological fluids is important to ensure adequate and safe treatment.

A review of the literature revealed that several analytical methods have been described for lithium monitoring in different kinds of sample, including spectrophotometry [5,6], flame photometry [7], fluorimetry [8], chromatography [9,10], potentiometry [11,12] and atomic absorption and emission [13,14].

The use of optical sensors is considered a simple, quick and inexpensive method of analysis. The development of optical chemical sensors (optodes) as viable alternative to other types of sensor is of great interest [15] and several optodes have been applied in the trace analysis of heavy metals in control processes and environmental and medical analyses [16]. One type of optode makes use of a plasticized polymeric membrane and is based on the reversible mass transfer of analyte from the sample into the bulk of the sensing layer. This type of optical sensor was named "bulk optode membrane" by Seiler and Simon, who described the basic principles and techniques that can be used with it [17]. Several ionophores and appropriate lipophilic pH indicator dyes introduced into the membranes have been used to design optical cation-sensing systems [18]. Optical transduction is based on the protonation and deprotonation of the pH indicator dye related with the cation concentration present in the membrane.

The performance of reversible bulk optodes is probably best tested in flow-injection systems (FI), a configuration that provides greater flexibility and the possibility of automation, in addition to a wider applicability to real samples. Some optodes for lithium determination have been proposed in the literature [19–25].

The goal of this work was to develop and optimize a flow-through bulk optode for the FI-spectrophotometric determination of lithium in pharmaceuticals and human saliva. The originality of the present paper with respect to previous lithium optodes was to exploit the analytical possibilities in flow-injection systems and to cope with the analysis of saliva samples.

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doi:10.1016/j.snb.2009.11.053

2. Experimental

2.1. Reagents and materials

All chemicals were of analytical reagent grade and Milli-Q water was used throughout. Polyvinyl chloride (PVC) of high molecular weight, 2-nitrophenyl octyl ether (NPOE), bis(2-ethylhexyl) sebacate (DOS), 2-[2-9-acridinyil)vinyl]-5-(diethylamino)phenyl stearate (chromoionophore XIV), potassium tetrakis[3,5-bis (trifluromethyl)phenyl]borate, *N,N,N′,N′,N″,N″*-hexacyclohexyl-4,4′,4″-propylidynetris(3-oxabutyramide) (lithium ionophore VIII) and tetrahydrofuran (THF) were obtained from Fluka. Filter paper 235 from Albet. Lithium chloride solution (8 M solution) from Sigma.

A 0.02 M buffer solution of pH 4.5 was prepared by mixing appropriate amounts of $MgAc_2$ and HAc solutions.

Lithium working solutions within the concentration range 1.0×10^{-4} M to 1.0×10^{-2} M were prepared by serial dilutions of the 8 M lithium chloride solution with the Ac^-/HAc buffer of pH 4.5.

Pharmaceutical: Plenur tablets (FAES FARMA, Vizcaya, Spain) containing 400 mg of lithium carbonate and excipients.

2.2. Apparatus

All spectroscopic measurements were made using a Metrohm LTD CH-9100 (Herisau, Switzerland) photometer equipped with light-guide cell for direct measurements, available wavelength range 400–700 nm and with an analogue-to-digital converter. The FI system (Fig. 1(a)) consisted of a carrier solution (2.0×10^{-2} M Ac^-/HAc buffer of pH 4.5) propelled by a peristaltic pump through polytetrafluoroethylene (PTFE) tubing (0.5 mm i.d.) at a flow rate of 0.8 ml min^{-1}. The sample injections (230 μl) were made by an Omnifit injection valve fitted with a sample loop. A home-made flow-through cell (Fig. 1(b)) designed by the authors and described previously [26] was used in the FI system. The body consists of two separate Perspex blocks (length 5.5 cm, width 1.7 cm and height 1.5 cm) tightly pressed together by screws. The upper block was drilled (1.3 cm) to fit the optical fiber, and a glass window was sealed in the lower part of this hole with epoxide cement. The upper block was also drilled to accommodate the inlet and outlet PTFE tubes. A mirror was placed on to the lower block to avoid any loss of light. A gasket of parafilm paper was placed on the mirror and the membrane optode was then pressed firmly on to the gasket. Finally, a thick gasket made of parafilm paper folded to obtain twelve layers, through which a hole was made, was placed between the two blocks. The solution cavity was defined by the front window of the cell, the thick gasket and the optode membrane.

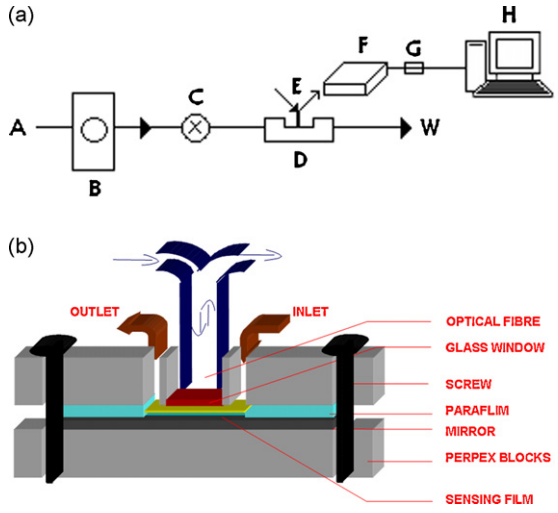

Fig. 1. (a) Flow-injection system. A, carrier Ac^-/HAc buffer solution pH 4.5; B, peristaltic pump (0.8 ml min^{-1}); C, sample injection valve (230 μl); D, flow-through cell; E, optical fiber; F, spectrophotometric detector; G, analogue-to-digital converter; H, personal computer; W, waste. (b) Schematic representation of the flow-through cell.

2.3. Optode membrane preparation

The optode membrane was prepared by dissolving 50 mg of PVC, 100 mg of DOS, 1.6 mg of chromoionophore XIV, 2.8 mg of lithium ionophore VIII and 2.2 mg of ionic additive in 3.0 ml of THF. Then, 50 μl of this mixture was deposited on a cellulose filter paper. After a few minutes, the THF had evaporated giving rise to a plasticized PVC membrane, containing the dissolved reagents, entrapped into the cellulose paper. A piece (2.0 cm × 3.0 cm) was cut out and incorporated into the flow-through cell, which was then incorporated into the FI system selected.

2.4. Procedures

2.4.1. Calibration of the sensor

Spectroscopic measurements were carried out in the flow-injection mode. Aliquots (230 μl) of lithium working solutions (1.0×10^{-4} to 1.0×10^{-2} M) were injected in the FI system to obtain a calibration graph by monitoring the peaks of the different working solutions. The corresponding peaks height values obtained were plotted against the corresponding concentrations and were fitting to a linear regression.

2.4.2. Determination of lithium in pharmaceutical

The lithium content in tablets was determined by analysing three tablets separately, each one powdered and dissolved with 10 ml of water. The mixture was then introduced into an ultrasonic bath for 30 min, filtered through a filter paper and the filtrate was diluted with Ac^-/HAc buffer of pH 4.5 in a 200-ml calibrated flask. Adequate aliquots of this solution were diluted with Ac^-/HAc buffer of pH 4.5. The lithium concentration was obtained following the recommended procedure described above, making the measurements in triplicate and obtaining the corresponding concentration from the calibration graph.

2.4.3. Determination of lithium in saliva

In the absence of saliva samples containing lithium, known amounts of lithium were added to different saliva samples obtained from untreated volunteers. About 5 ml of saliva sample was centrifuged at 3000 rpm for 15 min and aliquots of 1.0 ml of the supernatant were diluted with 1.0 ml of Ac^-/HAc buffer of pH 4.5. The lithium concentration was determined following the recommended procedure described above. A saliva blank (saliva without any lithium added) was also run to correct the values.

3. Results and discussion

3.1. Principle of operation

The proposed flow-through optode membrane was prepared by incorporation of an ionophore (L) which selectively forms complex with Li^+ acting such as neutral ligand, and a chromoionophore (Ind) that interacts with the reference ion (H^+) and changes optical properties upon protonation (the indicator is green in its acidic form and yellow in its basic form). The third component involved in the mechanism response is a lipophilic cation-exchanger (R). Because the concentration of cation-exchanger in the matrix is limited, the competition between the two ions for the cation-exchanger sites affects the fraction of protonated chromoionophore ($IndH^+$) and