Different Techniques and Ionophores Used For Sensing Sodium Ion

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ABSTRACT

Sodium ion is one of the essential elements of human body; mostly exist in blood and extracellular fluid. Sodium ions along with potassium ions maintain the osmotic pressure of the cell and participate in the normal functioning of nerves, heart and muscles. The optimum concentration range sodium ion required for normal physiological functioning of human body is 134-145 mM/L, above which it causes hypernatremia and sodium level below 135 mM/L causes hyponatremia. Present day, with the point-of-care in health sector, monitoring sodium ion concentration in real time with high selectivity is of great interest. Analytical techniques led to the developments of portable devices in the form of optical sensors/optodes, ion-selective electrodes (ISEs), electrochemical sensors, ion selective field effect transistors (ISFETs) and surface plasmon resonance (SPR) based sensors. A variety of crown ethers, cryptands and calixarenes based sodium ion specific ionophores have been employed in construction of sodium sensors. Evolution of sodium ion sensors employing different techniques and variety of ionophores has been summarized in present review article.

Keyword: Sodium; Ion-Selective Electrodes; sensors; crown ethers; cryptands; ionophores

INTRODUCTION

Alkali metal cations are of great significance in clinical chemistry, biochemistry and environmental studies. Monitoring blood electrolytes especially sodium, potassium and lithium has been quite challenging due to their quite similar chemical properties. Sodium and potassium are required for the proper functioning of our nerves and the contraction of our muscles. Sodium ions predominate in the extracellular fluid of body whereas potassium is found mainly in the inside of the cells, the intracellular fluid. These two electrolytes need to be in constant dynamic balance for movement of nutrient and waste across the cell membranes. Sodium is necessary to maintain fluid balance, electrolyte balance and pH (acid/alkaline) balance in the body [1-5].

In fact, sodium ions are so important, that humans have a specific sensor on the tongue that can detect the sodium salt. Thousands of years ago, when the diet of humans was potassium-rich and sodium-poor, this sensor for salt was a crucial survival tool. Nature, in her infinite wisdom, devised a way to help humans and animals to seek out salty foods so they could be assured of receiving adequate sodium from their diets. However, our body requires a fixed concentration of sodium ion (135 to 145 mM/L), the increase in Na+ concentration above 145 mM/L causes hypernatremia and concentration below 135mM/L causes hyponatremia. The
danger is not excess, rather a lack of sodium. Excess sodium will raise blood pressure but will be excreted in the urine. A person suffering from a lack of sodium or hyponatremia can die quickly from the brain swelling or the heart stopping [6-9]. Therefore, Na\(^+\) ions need to be in constant dynamic balance, for which it is important to monitor the concentration of sodium ions accurately. Na\(^+\) needs to be in constant dynamic balance, for which it is important to monitor its concentration accurately.

Number of analytical methods for sodium ion detection and quantitation have been developed and evaluated for their practical applicability [10-13], including flame photometry, enzymatic assay, electrophoresis, potentiometry, optical techniques, amperometry, surface plasmon resonance spectroscopy etc. Analytical techniques led to the developments of portable devices in the form of optical sensors/optodes, ion-selective electrodes (ISEs), electrochemical sensors, ion selective field effect transistors (ISFETs) and surface plasmon resonance (SPR) based sensors. A variety of crown ethers, cryptands and calixarenes based ionophores listed in table 1 have been employed in construction of sodium ion sensors. Present review paper gives an updated account of various ionophores used in the fabrication of sodium ion selective electrodes and sensors of different categories.

### Table 1: List of Ionophores used for development of sodium ion sensors

<table>
<thead>
<tr>
<th>Ionophores</th>
<th>Detection Range, M</th>
<th>LOD, M</th>
<th>POTENTIOMETRY &amp; FET Techniques</th>
<th>Selectivity</th>
<th>Li(^+)</th>
<th>K(^+)</th>
<th>Cs(^+)</th>
<th>Rb (^+)</th>
<th>NH(^+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di(o-methoxy)stil benzo-24-crown-8 [38]</td>
<td>9×10(^{-6}) 1×10(^{-2})</td>
<td>-</td>
<td>-</td>
<td>-3.69</td>
<td>-0.74</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-1.60</td>
</tr>
<tr>
<td>Methyl p-t-butyl calix[4]arylacetic [40]</td>
<td>10(^{-4}) - 10(^{-1}) 10(^{-4})</td>
<td>10(^{-4})</td>
<td>59.4</td>
<td>-3.24</td>
<td>-3.66</td>
<td>-4.84</td>
<td>-3.45</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>bis[(12-crown-4)-2-2-2-dodecyl-2-methyl malonate [41]</td>
<td>-</td>
<td>&gt;10(^{-5})</td>
<td>-</td>
<td>-2.94</td>
<td>-2.59</td>
<td>-1.57</td>
<td>-</td>
<td>-3.1</td>
<td>5</td>
</tr>
<tr>
<td>Cryptand derivative [42]</td>
<td>10(^{-4}) - 10(^{-3}) 5.5×10(^{-6})</td>
<td>59.4</td>
<td>6×0.5×10(^{-6})</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Molybdenum oxide bronze [44]</td>
<td>10(^{-4}) - 10(^{-1}) 1×10(^{-5})</td>
<td>-</td>
<td>52</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>16-Crown-5 derivative [45]</td>
<td>-</td>
<td>&gt;10(^{-4})</td>
<td>-</td>
<td>-2.5</td>
<td>-2.0</td>
<td>-3.5</td>
<td>-3.5</td>
<td>-2.8</td>
<td></td>
</tr>
<tr>
<td>4-tert-butylcalix[4]arene-tetraacetic acid tetraethyl ester [46]</td>
<td>1.3×10(^{-5}) 2.3×10(^{-3})</td>
<td>1.3×10(^{-5})</td>
<td>59.4</td>
<td>-3.1</td>
<td>-2.5</td>
<td>-4.5</td>
<td>-4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-tert-butylcalix[4]areneethyl ester [47]</td>
<td>3.0×10(^{-6}) 1.0×10(^{-1}) 1.45×10(^{-6})</td>
<td>58.65</td>
<td>3.0×10(^{-6}) 1.3×10(^{-6}) 30.9±0.1</td>
<td>-2.97</td>
<td>-2.20</td>
<td>-3.04</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenhytine sodium with tungstosilicic acid [48]</td>
<td>5×10(^{-6}) 5×10(^{-3})</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>B12C4 with anodised Indium Tin Oxide [50]</td>
<td>10(^{-4}) - 10(^{-1})</td>
<td>29.96</td>
<td>-</td>
<td>-3.11</td>
<td>-</td>
<td>-</td>
<td>-4.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B12(12-crown-4) [51]</td>
<td>-</td>
<td>1.3×10(^{-6})</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ionophore</th>
<th>Detection range/LOD (M)</th>
<th>Wavelength (nm)</th>
<th>Interfering Ions</th>
</tr>
</thead>
<tbody>
<tr>
<td>N,N,N'-triheptyl-N,N',N'-trimethyl-4,4',4''-propyldiyne-tris(3-oxabutylamine) [15]</td>
<td>20 – 200 x 10^-3</td>
<td>460</td>
<td>K⁺, Ca²⁺, Mg²⁺</td>
</tr>
<tr>
<td>N,N'-dibenzyl-N,N'-diphenyl,1,2-phenylene-dioxy-diacetamide [16]</td>
<td>1 - 100 x 10^-3</td>
<td>540</td>
<td>K⁺, Ca²⁺</td>
</tr>
<tr>
<td>Calix[4]arene sodium binding benzofuran isophthalate acetoxy - methylester [18]</td>
<td>10^{-4} - 10^{-7}</td>
<td>480</td>
<td>Li⁺, K⁺</td>
</tr>
<tr>
<td>Ru(bpy)₃(15-C-5-bpy)²⁺ [19]</td>
<td>&lt; 1 x 10^{-3}</td>
<td>450</td>
<td>-</td>
</tr>
<tr>
<td>Calix[4]arene derivative [20]</td>
<td>0.01 - 2.0</td>
<td>583</td>
<td>K⁺</td>
</tr>
<tr>
<td>Benzo-15-crown-5 ether [21]</td>
<td>&lt; 0.4 x 10^{-3}</td>
<td>480</td>
<td>Na⁺, Ca²⁺</td>
</tr>
<tr>
<td>1-aza-15-crown-5 [22]</td>
<td>&lt; 5 x 10^{-3}</td>
<td>550</td>
<td>-</td>
</tr>
<tr>
<td>(bis[(12-crown-4)methyl] dodecylmethylmalonate [24]</td>
<td>10^{-4} - 10^{-1}</td>
<td>-</td>
<td>Li⁺, K⁺, Ca²⁺, Mg²⁺</td>
</tr>
<tr>
<td>C14-DD16-Crown-5 [26]</td>
<td>10^{-5} - 10^{-1}</td>
<td>510</td>
<td>K⁺</td>
</tr>
</tbody>
</table>

Optical spectroscopy, which includes pump-probe spectroscopy, Raman spectroscopy and photoemission spectroscopy. Other examples of optical techniques are interferometry, ellipsometry, optical tweezers, imaging and sensing [14]. Zhujun et al. [15] developed an optical spectroscopy, which includes pump-probe spectroscopy, Raman spectroscopy and photoemission spectroscopy. Other examples of optical techniques are interferometry, ellipsometry, optical tweezers, imaging and sensing [14]. Zhujun et al. [15] developed an optical spectroscopy, which includes pump-probe spectroscopy, Raman spectroscopy and photoemission spectroscopy. Other examples of optical techniques are interferometry, ellipsometry, optical tweezers, imaging and sensing [14]. Zhujun et al. [15] developed an optical spectroscopy, which includes pump-probe spectroscopy, Raman spectroscopy and photoemission spectroscopy. 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optical sensor for sodium ion based on ion-pair extraction and fluorescence, where-in a sodium-selective ionophore \([N,N',N''-\text{triethyl-N},N',N''-\text{trimethyl-4,4',4''-propyldyne-2-(5-oxabutylamide)}\) was immobilized on silica. The selectivity of sodium ion is in the range of 20 to 200 X 10^{-3}. Schaffar et al. [16] have developed an ion selective optrode for selective determination of sodium ion based on a potential-sensitive dye Rhodamine BC-18 ester together with sodium selective ionophore ETH 157. The detection limit of sensor was 1 to 100 × 10^{-3}. Jin et al. [17] have used calix[4]arene for Na⁺ sensor based on change in fluorescent characteristics specifically when complex is formed with Na⁺, the selectivity range was found to be 10-4 to 10-7M. Buchholz et al. have developed a new fibre-optical sodium sensor based on an immobilized fluorescent sodium ion carrier. The sodium selectivity was in the range from 2 × 10^{-5} to 1 × 10^{-1}M. Lai et al. [19] employed electrogenerated chemiluminescence method for the detection of sodium ion using 15-crown-5 ether derivative as a sodium ion selective ionophore. The detection limit of this sensor was found to be < 1× 10^{-3}M. Benco et al.[20] have used calix[4]arene for the development of sodium ion sensor. This sensor works in the concentration range of 0.01 to 2.0 M. Ramachandran et al. [21] have used benzo-15-crown-5 ether as ionophore for sodium ion to construct a fluorescence based Na⁺ sensor, with detection limit as < 0.4 × 10^{-3}M. Poronik et al. [22] have developed a probe which exhibits high sensitivity and good selectivity for Na⁺, based on the complexation of the Na⁺ by ionophore 1-aza-15- crown-5, which induces a prominent fluorescence enhancement via quenching of electron-transfer. The detection limit of sensor was < 5 × 10^{-3}M. Leray et al. [23] have used calix[4]arene derivative as a ionophore because of its selective complexing property towards sodium ion. Wang et al. [24] described an ionophore-based ion-selective optode platform on paper for the first time with a sodium optode by Cellulose paper is shown to be an excellent substrate for adsorption of the required chemoionophore, ionophore, and ion-exchanger species. These adsorbed components form a hydrophobic phase that enables heterogeneous optical ion sensing in the absence of any plasticizer or organic polymer phase. They used sodium ionophore VI for this purpose. Shortreed et al. [25] described a micrometer-size, fluorescent fiber-optic sodium sensor, based on a highly sodium-selective, calix[4]arene as ionophore. The optode have excellent sodium selectivity, with other physiologically relevant cations (e.g., potassium, calcium, and magnesium). Hisamoto et al. [26] have developed a rapid flow-through analysis system for sodium ion which was based on ionophore C14-DD16C5. The ionophore exhibits high selectivity for sodium ion over potassium ion. The selectivity range was from 10⁻⁵ to 10⁻¹ M. Zha et al. [27], developed a novel sodium ion sensor.

**Ion-Selective Electrodes**

Development of ion selective electrodes (ISE) was a breakthrough discovery specially for alkali metal monitoring. ISEs are based on potentiometric methods have advantages such as good selectivity and give results in short time. Electrodes can simply be produced with a very low cost and above all they allow to analyze the solution without pre-treatments. Some of them are in solid state such as selenite, sulfate and hydroxide electrodes [28-30], some of them are prepared using PVC membrane such as iodide and glucose electrodes [31,32]. An ion-selective electrode (ISE), also known as a specific ion electrode (SIE), is a transducer (or sensor) that converts the activity of a specific ion dissolved in a solution into an electrical potential. The voltage is theoretically dependent on the logarithm of the ionic activity, according to the Nernst equation. Ion-selective electrodes are used in analytical chemistry and biochemical/biophysical research, where measurements of ionic concentration in an aqueous solution are required [33,34]. Direct and indirect are two methods commonly used in biochemistry laboratories in order to measure the electrolytes employing ion selective electrodes [35]. In direct method samples are not diluted while in indirect method samples are diluted. In the clinical practice, it’s the sodium concentration in plasma water -measured by direct ISE- which is important to consider as it is responsible of water movements between the liquid compartments. Knowing the difference between direct and indirect ISE, especially with sodium and inappropriate therapeutic decisions could be taken if the clinician is not aware of
this difference. The increase and the decrease in plasma water volume are the situations that distort the results of the indirect ISE because this method, after a dilution step, does not take into account the real percentage of plasma water of the patient in the determination of the concentrations leading to pseudohyponatremia, pseudonormonatremia or pseudohypernatremia. In the direct ISE, the sample is not diluted and the results are correct even if the volume of plasma water is modified.

Moore et al. [36] determined sodium in body fluids by using sodium aluminium silicate glass electrode. The reported electrode produces highly accurate and reproducible results. The sample need not require further dilutions. The LOD was 0.01M. Levy [37], worked on determination of sodium ion in serum with ion-selective electrode, the selectivity of this electrode was found to be 145 X 10⁻³ M. Zhou et al. [38] prepared Sodium ion-selective electrode which was based on ionophore di(o-methoxy)stilbenzo-24-crown-8 ether. The lower detection limit of this sensor is 9×10⁻⁶ – 1×10⁻² M. Ladenson [39] proposed a direct potentiometric method for determination of sodium and potassium in whole blood. Diamond et al. [40] have developed sodium ion-selective electrode based on methyl p-t-butyl calix[4]arene acetate as the ionophore. The electrode works in the range 10⁻⁴–10⁻¹ M. Moody et al. [41] developed an potentiometric sensor employing bis[(12- crown-4)-2-ylmethyl]-2-dodecyl-2-methyl malonate. Electrode slopes were near-Nernstian, with detection limits of less than 10⁻⁵ M.

Schindler et al. [42] developed a High-ion selective sensor by incorporating cryptand derivative into the PVC membrane. The selectivity of sodium ion was found to be greater than 5.5×10⁻⁶ M. Lukyanenko et al. [43] developed a sodium-selective electrodes based on PVC membranes containing bis(10-crown-3)-hexamethylenebis(3,6,10-trioxacycloundecane).The selectivity of this sensor is 1×10⁻⁵–1 M. Shuk et al. [44] prepared a sodium ion sensitive electrode based on a molybdenum oxide bronze. This sensor responded to Na⁺ concentration in the range of 1–10⁻⁴ M. Suzuki et al. [45] designed and synthesized a Sodium Ion-Selective Ionophores which was based on 16-Crown-5 derivative with two decalino subunits (DD16C5) for an Ion-Selective Electrode. This electrode exhibited a Na⁺ selectivity > 10⁻⁴ M. Wygl et al. [46] designed a miniaturized backside contact sensors with polymeric Na⁺ selective membranes based on ionophore 4-tert-butylcalix[4]arene-tetraacetic acid tetraethyl ester. The LOD was found to be 1.3×10⁻⁵–2.3×10⁻¹ M. Marques et al. [47] prepared sodium-selective potentiometric microelectrodes with a conducting polymer (polypyrrole doped with cobaltabis(dicarboxilide) ions ([3,3′-Co(1,2-C2B9H11)L]₂) as solid contact layer between the polymeric sensitive membrane and the platinum substrate. The p-tert-butylcalix[4]arene ethyl ester was used as ionophore for sodium recognition. The lower detection limit of Na⁺ was 1.45 × 10⁻⁶ M. Tohamy et al. [48] constructed sodium ion selective electrodes by incorporation tungstosilicic acid in PVC membrane. The LOD was observed to be 1.3×10⁻⁶ M. Ioannidis et al. [49] reported an aza-15-crown-5 derivative as a selective ionophore for sodium ion, this ionophore is suitable for detection of Na⁺ ion. Lin et al. [50] worked on anodized indiumtin oxide electrode for detection of sodium ion. This electrode shows good sensitivity in the range of 10⁻⁴ - 1 M.

Takami et al. [51] used sub-micropeptide probe by incorporating ionophore bis(14-crown-4) into a PVC matrix. The LOD of this electrode was found to be 1.3×10⁻⁶ M for Na⁺. Hübl et al. [52] have evaluated the effect of hemolysis, icteric discoloration, lipemia, paraproteinemia, and uremia on enzymatic methods for determining sodium, potassium, and chloride, according to the National Committee for Clinical Laboratory Standards EP7-P proposals for testing interference from endogenous substances. The sodium determination was done employing beta-galactosidase. The detection range was 2.9-1.2mM/L. Cadogan et al. [53] prepared a sodium-selective electrodes with polymeric membranes containing ester and ketone derivatives of p-tet-butyl calix[4]arene. The electrodes were prepared with 2-nitrophenyl octyl ether as the solvent mediator and potassium tetrakis(p-chlorophenyl)borate as the ion-exchanger in a poly(vinyl chloride) matrix. Several of the ligands examined produced electrodes with near-Nernstian slopes, detection limits was 10⁻⁶ M for sodium. Diaz et al. [54] prepared an ion-selective electrode based on methyl p-t-butylcalix[4]arene acetate have been prepared that are responsive to sodium ions using a PVC membrane. Examination of the general
performance of the electrodes revealed excellent characteristics in terms of Nernstian response, selectivity, stability, reproducibility and response time. Chandra et al. [55] used ionophore 1-methyl-1-vinyl-14-crown-5 with potassium tetrakis(p-chlorophenyl)borate to prepare Na⁺-selective electrode. The response of the electrode was linear with a Nernstian slope of 55.0 mV/decade. The selectivity range was 3.16 × 10⁻⁴ to 1.0 × 10⁻¹ M and LOD was 2.81 × 10⁻⁶ M. Machini et al. [56] developed a new voltammetric sensor which was based on nanostructured ausmannite-type manganese oxide for the detection of sodium ions. Lee et al. [57] prepared a self-plasticised acrylic membrane recipe for Na⁺ and K⁺ ion selective electrodes. Ammann et al. [58] prepared a new, synthetic, and electrically neutral ligand in a membrane solvent incorporated in a PVC-matrix. In this sensor system, two different membrane solvents are compared in respect to selectivity, pH-dependence, lifetime, working range and dynamic response. Both electrodes show a linear response to sodium ion activities in the range of 10⁻¹ M to about 10⁻⁵M in unbuffered systems, with a selectivity over potassium, calcium and magnesium which permits measurements in blood serum. Analytical characteristics and sensing mechanism of sodium ion-selective electrodes based on NaCl-Ga₃S₅-GeS₂ glasses have been investigated by Vlasov et al. [59]. Chalcogenide glass electrodes containing 10% NaCl in the membrane showed near-Nernstian response in the concentration range from 10⁻⁵ to 1M. These sensors were superior to the conventional pNa oxide glass electrodes in selectivity in the presence of hydrogen ions and in Na⁺ ion sensitivity in fluoride media. A new sodium ion image sensor containing a CCD-type semiconductor and a plasticized PVC sodium ion selective membrane was developed by Hattori et al. [60]. The output potential slope was linear for sodium ion concentrations from 10⁻⁵ to 1⁻¹ M. The optimum membrane possessed a near Nernstian response and high selectivity to sodium ions. Sauvage et al. [61] developed a potentiometric ion sensor employing Na₂MnO₄ powder. Nernstian response (55 mV/dec) was obtained for concentrations ranging from 1 to 2 × 10⁻⁴ M. The sodium ion sensor developed by Liu et al. [62] has an outer electrolyte which is insensitive to water and has a high transport activity for sodium ions and an inner electrolyte bound by a thin membrane having very high sodium ion selectivity. The sodium ion sensor having such an electrolyte is sensitive only to the transport of sodium ions and may be operated in aqueous solutions without buffering and in the presence of other alkali ions and alkaline earth metal ions. Tavakkoli [63] prepared a sodium ion- selective electrode based on ionophore dibenzopyridino-18-crown-6. The electrode exhibits a Nernstian response for Na⁺ ions within the concentration range of 10⁻⁴ to 10⁻¹M with a slope of 58.5 mV/decade and the LOD was 9.0 × 10⁻⁷M.

**Electrochemical Sensors**

Electrochemistry is a branch of chemistry concerned with the effect of electrical potential on chemical reaction. It is named electrochemistry because it’s originated from the study of the movement of electrons in an oxidation-reduction reaction. Electrochemical methods are analytical techniques that use a measurement of potential, charge, or current to determine an analytes concentration or to characterize an analytes chemical reactivity. It is a qualitative and quantitative methods of analysis based on electrochemical phenomena occurring within a medium or at the phase boundary and related to changes in the structure, chemical composition, or concentration of the compound being analyzed. By the definition ISEs are also a type of electrochemical sensors based on potentiometry whereas so called electrochemical sensors are based on voltammetry or amperometry. Flink et al. [64] have reported an electrochemical sensor which was based on self-assembled monolayer (SAM) of 2-[6-mercaptohexyl]oxy)methyl-12-crown-4 onto the gold surface for selective sensing of sodium ion. The detection limit of this method is 1 × 10⁻³ M. Wujcik et al. [65] developed an electrochemical sodium ion sensor, composed of a multiwall carbon nanotube (MWNT) functionalized with ionophore cyclo-oligomeric calixarene on nylon-6 matrix. Range of detection is 5 to 60 × 10⁻³ M. Moore et al. [66] developed an electrochemical sensor based on cation-sensitive redox-active molecules (TTF-crown derivatives with R = C(O)(O)(CH₂)₅SH or CH₂SH) immobilized on a metal surface. Diba et al. [67] have successfully developed
amperometric sensor for sodium, calcium and potassium ion concentrations in biological fluids. The detection was based on measuring current changes associated with the transfer of each cation across a microhole supported water/polyvinylchloride-2-nitrophenyl octylether gel interface. Dibenzo-18-crown-6 was used as an ionophore for sodium ion detection in biological sample. 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 × 10-6 to 100 × 10-6M was observed. Schazmann et al. [68] developed a new method for the real-time quantitative analysis of sodium in human sweat. This temporal data opens up new possibilities in the study of human physiology, broadly applicable from assessing high performance athletes to monitoring Cystic Fibrosis (CF) sufferers. This compact Sodium Sensor Belt (SSB) consists of a sodium selective Ion Selective Electrode (ISE) integrated into a platform that can be interfaced with the human body during exercise. This method has confirmed the accuracy of the new continuous monitoring approach. Zhang et al. [69], developed sodium ion sensing voltammetric technique using sensing electrode containing sodium ionophore Bis[(12-crown-4)methyl]dodecyl methylmalonate, and 4-tert-Butyl[4]arene-teraaecetic acid tetraethylester.

A novel electrochemical approach using simple ionophores for the detection of alkali metal ion using redox probe as mediator ion has been reported by Kumbhat and Singh [70,71]. For sodium ion sensing 4-aminobenzo-15-crown-5 covalently bonded to thioic acid selfassembled monolayer functionalized gold electrode has been used. The sensor is highly selective for sodium ion over potassium, lithium and ammonium ions and is suitable for clinical application.

Ion Selective Field Effect Transistor (ISFET)

The concept of the ion-sensitive field-effect transistor (ISFET) was proposed by Bergveld in 1970s [72], wherein an ionophore is introduced in construction of field-effect transistor. Field-effect transistor (FET) is basically a type of transistor commonly used for weak-signal amplification for example, wireless signals. The device can amplify analog or digital signals. It can also switch DC or function as an oscillator. In the FET, current flows along a semiconductor path called the channel. At one end of the channel, there is an electrode called the source. At the other end of the channel, there is an electrode called the drain. The physical diameter of the channel is fixed, but its effective electrical diameter can be varied by the application of a voltage to a control electrode called the gate. The conductivity of the FET depends, at any given instant in time, on the electrical diameter of the channel [73]. A small change in gate voltage can cause a large variation in the current from the source to the drain.

A variety FETs with possible sensor applications such as pH, chemical and alkali metal ion sensing [74-78] and label-free biosensing [79-82] have been demonstrated using silicon nanowire FETs (Si NWFETs). Further kinetic studies on receptor binding and even intracellular recordings of action potentials could be realized by downsizing of the devices. The sensing principle is based on adsorption of charged species on the sensor surface, leading to a change in surface potential and hence a change in current in the FET channel. Thereby, the high-impedance input signal is transformed into a low-impedance output signal, which is an advantage against classic ion selective electrodes. The possibility of downsizing and integration [83] for the simultaneous detection of multiple parameters make Si NWFETs a promising platform to meet the demand for cheap, multifunctional, and scalable sensors. Wipf et al. [78] a developed a FET based sodium ion (Na+) sensor by applying a self-assembled monolayer (SAM) of dithiol onto the gold surface through which 4-aminobenzo-15-crown-5 was attached with a covalent bond, the detection range of this sensor was 10-3 to 1 M.

Calix[4]arene derivatives are highly selective for sodium ion, these neutral carriers have been designed especially for sodium ion-sensitive field-effect transistors (Na+ ISFETs) [84-85]. Kimura et al. have used Calix[4]arene neutral carriers incorporating unsymmetrical structures and/or oligosiloxane moieties, in silicone rubber
and have realized high performance of silicone rubber-based sodium-ion sensors, with high sensitivity, selectivity, and durability [86]. The Na\(^+\) ISFETs based on silicone rubber membranes of the modified calixarene neutral carriers have proved to be reliable for sodium assay in human body fluids. Brunink et al. [87] developed an ion-sensitive field-effect transistor for sodium ions using Calix[4]arene derivatives incorporated in a poly(vinyl chloride)-based membrane provide the selectivity. A poly(2-hydroxyethyl methacrylate) interlayer between the silicon dioxide gate and the sensing membrane was necessary to obtain a Na\(^+\) sensitive ISFET with Nernstian behaviour. Chou et al. [88] have employed the extended gate field effect transistor (EGFET) to fabricate the sodium ion sensor and have studied the effect of interference ions on sodium ion. For this they used entrapment method to prepare the sodium ion membrane, and that the polyurethane incorporates the sodium ion ionophores (B12C4) to form on the window of EGFET. The present results indicate that the good sensitivity, linear regression, rapid response time, the temperature effect, low hysteresis voltage, long working lifetime, interference selectivity coefficients and working range as 1 M to 10\(^{-5}\) M of the sodium ion. Hsu et al. [89] have reported sodium and potassium ion sensors based on separated extended gate field effect transistors. Kimura et al. [90] have reported a high-performance sodium ion-sensitive field-effect transistors based on an unsymmetrical calix[4]arene ionophore/silicone rubber composite membrane. Caneiro et al. [91], used sodium super ionic conductor for detection of sodium ion by sol-gel route method. Parker et al. [92] proposed a highly selectivity and sensitivity sensor employing calix(4)crown based ionophore which acts as a receptor and offers a great affinity towards sodium over the simple crown ether receptor. On combining it with a switchable dye, the chromoionophore will selectively amplify the refractive index change upon binding sodium over other cations. Ho et al. [93] developed an ISFET based sensor by treating HfO\(_2\) sensing films with carbon tetrafluoride. The detection range of Na\(^+\) was 1 to 100 x10\(^{−3}\) M.

**Surface plasmon resonance based sensors**

Surface Plasmon resonance (SPR) is a surface-sensitive analytical method for chemical and biochemical sensing that is based on measuring changes in the refractive index (RI) on the noble metal surface. It is a powerful tool for the in situ real-time characterization of a solid/liquid interface and to study interactions between larger molecules [94-99]. Kurihara et al. [100] have reported a SPR based sensor for sodium ion using an ion selective optode membrane film incorporating sodium ionophore (DD16C5). This method was able to detect sodium ion in the range of 10\(^{-6}\) to 10\(^{-1}\) M. They proposed a new concept which was based on absorption that basically detects changes in the refractive index of complex due to the optical absorption. Benounis et al. [101] have used self-assembled monolayer of calix[4]arene-derivative immobilized on cysteamine modified gold disc of SPR. The LOD of proposed sensor 10\(^{-10}\) M and the range detection was 10\(^{-6}\) to 10\(^{-4}\)M.

**CONCLUSION**

Alkali metal ions are plays quite significant role in proper functioning of nerves and the contraction of muscles. Sodium ions predominate in the extracellular fluid of body whereas potassium is found mainly in the inside of the cells, the intracellular fluid. Selective detection of these ions has been quite challenging due to similar chemical properties. Need to monitor sodium ion concentration in clinical samples have led to development of various categories of sensors. Present review summarizes different categories of sensors and variety of ionophores used for the development of sodium ion sensor.

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**CONFLICTS OF INTEREST**

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