Opportunities and Challenges of using Ion-Selective Electrodes in Environmental Monitoring and Wearable Sensors

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Abstract

Great opportunities exist for Ion-Selective Electrodes (ISEs) in the fields of environmental monitoring and of wearable applications for example as the sensing part in wireless networks. In this review special attention is given to the recent results obtained with Solid Contact Ion-Selective Electrodes and Solid Contact Reference Electrodes. Their combination as disposable sensing platform may offer the best solution to eliminate issues commonly experienced with ISEs and lead in a short term to their commercialization. Future research will likely focus on the miniaturization of the current devices and on the further development of non conventional potentiometric methods, *e.g.*, controlled potential thin-layer coulometry.

Contents.

1. Introduction

Sensors integration within wireless networks [1] would represent a pivotal step for remote analytical monitoring, not limited to pollutants in the environment or engineered units and facilities [2-4] but also for the diagnostics and personal health monitoring [1, 5, 6]. The major advantages of this strategic vision are the cutting of the costs linked to conventional techniques avoiding also artefacts introduced during sampling [2, 3, 7-9], the increase of spatial and temporal resolution in the analyte/s monitoring, allowing the creation of early warning systems [2, 3, 7-9]. For instance, it has been shown that most toxic forms of metals in environmental waters may vary in concentration on a time scale less than one hour [3]. Higher spatial and temporal resolutions are fundamental not only for a better modelling of the complex interactions between pollutants and environment but also for the current epidemiology studies as they would allow more definitive association between exposures to specific chemicals and health of individuals and communities [10].

Despite great progresses in the biosensing field, we are still far from a practical realization of the above vision [1, 3, 5]. The revolutionary step from handheld battery operated instruments to deployed sensing platform and wearable sensors requires a more holistic approach to solve the multi-disciplinary challenges involved [1, 5]. From a chemistry perspective, insufficient long term stability of the sensing interface, active interferences in the sample, drift over time, difficult and/or repetitive calibration, biofouling due to the environmental conditions in joint with the typical need of low detection limits are major issues which have not entirely solved [2, 3, 11]. Thus, high level of maintenance, *e.g.*, need of recalibrate and rejuvenate the sensors, precludes their use in long term applications [12, 13]. The final hurdle to be overcome is validation, which is a very important issue for their realistic integration within monitoring controlled programs [6, 9].

Within the above current scenario Ion-Selective Electrodes (ISEs) compete against other electrochemical and optical sensors. Among the electrochemical sensors, ISEs offer an easy-to-use and cheap tool for analysis of several ions found in natural waters [12] and body fluids although in the latter case they have been mainly limited to determination in blood [14]. The list of detectable analytes with ISEs today approaches 100 species and ISEs offer also an extended dynamic range (in some case more than eight order of magnitude) which is a not so common feature of analytical methods [15]. Although more than ten analytes were reported to be detectable at nano- and, in some favourable cases, at pico-molar ranges [15] often this is not done in real samples [16]. Indeed, for trace element in environmental monitoring ISEs have to catch up with voltammetric probes (based on stripping analysis) whose sensing platform are already at commercial level although at very prohibitive cost [16]. In this regard, it is worthwhile to note that European directives play an important role in matter of environmental legislation and development of new devices using priority hazardous substances, *e.g.*, mercury, as reported in the Water Framework Directive (WFD), leads to a commercial dead-end and a waste of resources [3]. Considering that the majority of sensors for heavy-metals rely on anodic stripping voltammetry based on mercury films, the WFD legislation dictates a shift from mercury to other type of films or to new analytical techniques [3]. Finally, the detection of other harmful ions in the environment, *e.g.*, thiocyanate, azide, not at trace level remains important and ISEs can also aim at this market [17-19].

On the wearable side, for example, levels of sodium, potassium and chloride in sweat have been used as early diagnostic tool of cystic fibrosis (CF) [20-24]. However, it is worth to note that, to date, the US Cystic Fibrosis Foundation has not approved the use of ISEs for in sweat diagnosis of cystic fibrosis [24]. Significantly, ISEs are commonly employed in the analysis of electrolytes in real blood samples [14]. The latter fact would support their potential use in wearable applications in the monitoring of clinical important analytes in sweat, saliva and interstitial fluids when good correlation between blood plasma with these body fluids exists. The current focus on point-of-care and self diagnostics encourages the use of ISEs for these applications [9, 20, 24]. There are many analytes in sweat and saliva whose monitoring would be extremely important [24-34] and hereafter few examples are reported. pH could provide a method to relate acid build-up in muscle cells during exercise [23] and, although Hanna (www.hannainst.co.uk) supplies on-skin pH meters, they are not appropriately wearable. Lithium in saliva correlates to lithium carbonate intake which is used for treatment of maniac depressive and hyperthyroidism disorders [15]. Li-ISEs are generally sensitive to high sodium concentration [14, 15] but in saliva the sodium levels are three order of magnitude lower [35]. However, to date, examples of convincing wearable ISE-sensors are few and limited to sodium and chloride [20, 24]. Significantly, the results in the two latter references correlated with the ones from Atomic Absorption Spectroscopy (AAS) which is surely an encouragement to push forward into this direction.

At the light of the above scenario, exciting opportunities exist for ISEs to have a leading role in the sensors arena as low cost and easy-to-operate devices which will offer simplification in the software/hardware [11, 36, 37] interface and small power consumptions. In the last decade sensors design has shifted from conventional electrodes to screen printed disposable ones [38, 39] to cut costs and boost their commercialization. This trend has also interested ISEs both for wearable and environmental applications and in the next section more details will be given.

The opportunities which lie in front of ISEs are somehow hampered by challenges which are not completely solved yet. The fact that ISE measures activity is an advantage because the latter is a more useful parameter in health disorders [15] and bioavailability [16] although reporting values in terms of concentration is preferred for historical reasons [14]. Factors like ionic strength, temperature, liquid-junction potentials [14] may be compensated or taken in account [16]. Leaching of membrane components, *i.e.*, biocompability/toxicity, can be limited by use of membranes based on polyacrylate [15] or perfluorocarbons. Because of the properties of the latter, *e.g.*, chemical stability, decreased affinity to proteins and lipids, perfluorocarbons may offer significant benefits in terms of development of biocompatible and more rugged membranes [15]. Perhaps, matrix effect in real samples of body fluids and/or environmental waters, *e.g.*, speciation of ions, lipophilic elements affecting the membrane properties, *etc*., is the main hurdle. The use of standard addition to overcome the matrix effect is hardly compatible with the wearable concept and surely affects the cost of the sensing platform for environmental analysis [16]. For wearable applications, difficulties in the sampling, *e.g.*, sweat evaporation [24], concur also in a delay in the introduction of ISEs as commercial devices. Finally, the practical realization of wearable chemical sensors and deployed autonomous systems for environmental trace analysis require significant efforts from mechanical and electronic engineers to solve other problems, *e.g.*, passive pumping, sensor integration in fabric, microfluidic design, wireless transmission of the data [1, 5].

Excellent reviews on Ion-Selective Electrodes can be found in the literature. Privett *et al.* [40] describe the use of ISEs in relation to the more general topic of electrochemical sensors. Diamond *et al.* [16] analyse the ISEs in the context of environmental monitoring within autonomous sensing platform. Bakker *et al.* [41, 42] discuss recent trends in potentiometry in relation to new technique approaches beyond classical potentiometry, miniaturization and novel applications. Bobacka *et al.* [43-47] discuss the uses of conducting polymers in solid-state ion selective electrodes. Lindner *et al.* [48] review the topic of solid-contact polymeric membrane ion-selective electrodes with focus on criteria for their quality control. Guth *et al.* [49] review designs of solid-state reference electrodes for potentiometric sensors. Makarychev-Mikahailov *et al.* [15] review some of the recent trends in the ISEs field. Lewenstam [14] describes the use of ISEs for clinical monitoring of electrolytes in blood samples.

2. Recent Advances in Solid-Contact Ion-Selective Electrodes (SC-ISEs)

The principles of operation and good theoretical background for potentiometric ion selective electrodes can be found elsewhere [47, 50-53]. Potentiometric sensors employ ionophore agents like crown compounds and calixarenes and they are usually applied to ion monitoring. Molecular imprinting techniques [54] has enabled a larger range of molecules to be screened, *e.g.*, pesticides, drugs, antibiotics, *etc.* [40, 54, 55] although much work is still needed [15, 16] to implement ISEs into general practise for the analysis of the latter. The field of potentiometric sensors has gone through a revolution in the last ten years with a major effort focused in the theoretical developments [56-60] which has led not only to a deeper understanding of these devices, but significantly in dramatic improvements in the detection limits, which has opened up new opportunities in environmental monitoring [12, 61-64]. For instance, reference [47] highlights the importance of the diffusion potential and its variation from sample-to-sample and over time. Theoretical models offer tools to tackle and predict the latter aspect [47] which would be extremely beneficial for engineering more robust ISEs.

SC-ISEs are more convenient for remote monitoring than liquid filled ISEs as they are compatible with microfabrication technologies and they are easier to miniaturize [43, 47, 48, 51, 65]. In a SC-ISE, the internal reference electrode and the inner filling solution are replaced by a solid material which should be nonpolarizable upon the input current of the measuring amplifier and have suitable redox and ion-exchange properties [43, 46-48, 66].

Despite these advantages, it should be noted that the control of the ion fluxes across the SC-ISEs membrane cannot be established in the same way as in inner liquid filling ISE. For instance, incorporation of a complexing agent into the SC layer, conditioning steps, increasing polymer content or using different polymeric membranes may help in achieving this control [15, 48]. CPs have received particular attention as solid contact despite unresolved issues around the effects of the polymer chemical/redox layer properties on the sensor's analytical performance [44, 46, 48, 51, 61, 67-76]. Conducting polymer based SC-ISEs have produced significant results for the detection of lead at concentrations comparable with the current legislation requirements [46, 61, 67, 77].

For example, significant results in the detection of lead have been achieved in Diamond's group [78, 79]. Employing screen printed electrodes as substrates for poly(3,4-ethylenedioxythiophene) SC-ISEs, and coupling the latter electrodes to solid state reference electrodes (SC-REs) lead concentrations down to ppb levels in real samples were detected when standard addition methodology was employed [79]. These results are significant because obtained with real samples and because the good correlation shown with the ICP-MS method [3]. Researchers from the same group showed that the calibration trends of these sensors are significantly distorted upon exposure with environmental samples [80]. This finding may indicate that sensors can be used only in combination with the standard addition method to compensate for the matrix effect although the latter may give rise to anomalous super Nearstian responses [12]. It was also shown that Electrochemical Impedance Spectroscopy (EIS) may represent a powerful self-diagnostics for remotely deployed chemical sensors in order to decide when sensor calibration is needed [80].

Poly(3-octylthiophene) (POT) has been used as solid contact because of its hydrophobicity to improve membrane adhesion and limit water uptake [48, 81] particularly in combination with polyacrylate membranes which improved the limit of detection (LOD) in several cases by reducing ion diffusivities [67, 82]. Formation of a water layer at the POT/electrode interface does not occurs while the incorporation of water (in form of nanodroplets) occurs within the membrane but at a slower rate than ISEs based on PVC membranes requiring ~ 450 hours to reach equilibration [67]. Therefore, it has been suggested that silicone membranes may represent a significant option to polyacrylate ones [69] although poor solubility of ionophores and high bulk impedance are the main drawbacks [70].

While effects of layer deposition, *e.g.*, dropcast *vs.* electrodeposition, oxidation state of CP, ion content, have been analyzed at some extent [75, 83, 84] nanostructured conducting polymers in the solid contact has not been extensively investigated and it may represent an interesting research line [85]. For instance, Lindfors *et al.* [70] used polyaniline (PANI) nanoparticles as solid contact in combination with a silicone membrane for the detection of silver showing enhanced selectivity than ones reported for PVC and polyacrylate membranes. Kisiel *et al.* [85] used polypyrrole microcapsules as solid contact of Ca-ISEs showing that the control of the electrolyte composition of the microcapsules can tune the LOD. It should be also noted that the type of CP used as solid contact may be important in relation to the ion analyte. For instance, a comparison of PANI and PEDOT commercial dispersions in SC-ISEs highlights the importance of the CP redox state during the analysis for silver but not for lead [75].

Chemical and photochemical sensitivity of CPs has motivated investigations of other materials as solid contact. Single-walled carbon nanotubes (SWCNT) thanks to their hydrophobicity and lack of redox capacity appear promising [86]. However, Pb-ISEs based on SWCNT dispersed in poly(ethylene-*co*-acrylic acid) showed only slightly submicromolar LOD and no report on real water sample was presented [63]. Single-piece solid contact ISEs with polymer-Multi-Walled Carbon Nanotubes (MWCNTs) applied for the detection of sodium, copper, potassium and calcium did not show submicromolar detection limits [87]. Ordered macroporous carbon solid contact on the other hand allowed the preparation of ISEs for the monitoring of potassium and silver with LOD of 1.6×10^{-7} M and 4.0×10^{-11} M respectively [88]. Considering that potassium is an important electrolyte in sweat and that silver concentration above 0.17 μg L^{-1} are considered toxic to fish these results could be significant for wearable and environmental applications, respectively [88]. Finally, very recently potentiometric strip cells were produced on screen printed substrates and applied to test potassium in saliva samples [89] although diluted with buffer (to equalize ionic strength and pH). These strips contained SWCNT-based SC-ISEs and SC-REs, employed polyacrylate membranes and they were plugged into a 2-way edge connector [89]. The values of potassium were determined using a calibration plot generated with the measurement of 5 standard solutions and validated with AAS showing no statistical difference [89].

Ionic liquids (IL) were also applied to ISEs replacing ionic additives, ionophores, plasticizers in the membrane phase [90] and, perhaps more significantly, they were used as solid contact (after gellation in PVC membrane) providing double layer capacitance to stabilize sensor response [91]. The latter sensors could detect 40 ppm of lead in spiked tap, river and waste water using standard addition method in good correlation with the data obtained from anodic stripping voltammetry [91]. Graphite modified with hydroquinone was used as solid contact in ISEs and the ratio of the surface confined redox species (= a_{ox}/a_{red}) was tuned to 1 to improve the stability of the potential of the solid contact [92].

Among the limits fixed by the Water Framework Directive [3] for four heavy metals, *i.e.*, lead, cadmium, mercury and nickel, it appears that research on ISEs has been largely focused on lead at the required nano-molar level [77, 81], and potentiometric detection at these levels for other important toxic ions, *e.g.*, manganese and arsenate, has so far not been reported [93] or it is below the environmental policy requirements, *e.g.*, Cr(VI) [94]. In this regard it is worthwhile to note that the measurement of cadmium at 1 ppb levels, *i.e.*, compatible with some water regulation policies, in concentrated NaCl samples (simulating sea water) with ISE was reported [95]. A pre-concentration step at a bismuth-coated electrode and subsequent release in a different media allowed this measurement, however, these sensors were not tested in real sea water samples [95].

In spite of extensive research in the area, it seems that obtaining SC-ISEs with reproducible standard potentials is still a great challenge [47] and it should be noted that most of the ISEs designs described above rely yet on the use of standard macroelectrodes. In this regard, encouraging results employing screen printed electrodes have been recently obtained. For instance, Saltisza *et al.* [79] prepared Pb-ISEs which show superimposing calibration curves down to 10 nM ranges. In addition, Musa *et al.* [96] prepared a solid state ISE for pH using screen printing technology and a photo-polymerizable ion selective membrane deposited directly on the carbon surface but their performances upon exposition to real samples was not investigated.

3. The Miniaturization of ISEs

Ultra-Microelectrodes (UMEs) have received enormous interest thanks to several favourable characteristics, *e.g.*, compatibility with small sample, reduced amount of material used per device, and the great demand for miniaturized sensors [15, 47, 97, 98], and their use was also applied to potentiometry measurements [99]. For example, potentiometric ion selective microelectrodes for pH and silver have been reported [81, 100] but are based on glass pipette microelectrodes which limits their applicability as environmental and wearable sensors due to the cost and fragility. It should be also noted that the miniaturization of the ISEs may cause lower potential stability because of the smaller redox or double-layer capacitances, the leakage of membrane components, the adherence and the exfoliation of membranes [15, 47, 48] and overall, a trade-off in decreasing the size of the electrode may exist.

Despite the benefits of microelectrodes and microelectrodes arrays, their manufacture is still complex and the long term-stability sometimes problematic [48, 101-107]. To date, convincing designs of low-cost ion-selective microelectrodes which can be easily mass-produced and are applicable to environmental monitoring and wearable applications seem to be missing. Finally, multi-calibration in an array becomes complicated and time consuming as the array response pattern becomes important and, as each electrode drifts, the pattern is unstable in use [15, 108]. In conclusion there is still much work to do in order to develop low cost and reliable potentiometric micro- and microarray sensors for untreated samples [15, 109].

4. Recent Advances in the Reference Electrode

Potentiometric methods require the use of a reference electrode, whose stability over time is particularly important, *i.e.*, a ± 1 mV change would result in a ± 4 % change in the estimated activity for a monovalent ion and ± 8 % for a divalent one [52]. Several solutions have been proposed [110] but only few are technically compatible with mass production, *e.g.*, planar-type designs, screen printing technologies, solid state functional components [49]. The employment of an ISE for a background ion, whose concentration is relatively stable, as reference electrode [41] is applicable only in few cases, *e.g.*, when the ion can be added to the sample as a reagent held within the instrument. Preparations employing hydrogels with KCl can dry up if not stored under appropriate conditions while more conventional designs based on junction diffusion can result in short effective lifetime due to electrolyte leakage [40, 49, 111, 112]. Good results have been obtained with hydrophobic ionic liquid gels saturated with AgCl although the electrodes still suffer from component leaching and instabilities due to chloride interference [49, 113]. Metal oxide based reference electrodes have been prepared but they suffer of pH and redox species interferences [49, 114]. The coating of the metal oxide and of the ionogel reference films with ISEs membranes reduced interferences in the latter two designs. Perhaps, solid contact reference electrode prepared by coating an Ag/AgCl or a conducting polymer-electrode interface with membranes containing lipophilic salts [78, 115] appears to be an interesting alternative although the response time is slow (few minutes) and the batch reproducibility needs to be optimised.

5. Conclusions

In future research special attention will probably be given to establish more standard procedures for the preparation of SC-ISEs and SC-REs which would help their evaluation among different laboratories and trigger their commercialization as disposable sensors. For instance, guidelines for standardizing a conditioning protocol or for defining storage conditions are not widely agreed [48] although these steps appear to be essential in order to achieve low detection limits. Some efforts have been done in this direction [56, 62, 116, 117]. For instance, Michalska *et al.* [118] compared two different CPs as solid contact for Pb-ISEs in terms of their potential stability over time showing that they depend on the storage conditions. Future research would possibly focus on the integration of ISEs within a microfluidic device capable of switching between sample, conditioning and washing solutions, and able to add an appropriate solution for the measurement. This path seems a feasible way to develop sensors with extended lifetime and avoid the reconditioning [48, 53] of the sensors after long time exposition to the sample although it may be more hardly applicable to wearable sensors due to the demanding miniaturization of such devices.

It should be noted that other techniques have been proposed for remote chemical sensing in order to overcome some restrictions of the classical zero-current potentiometry [41, 42, 119]. Among these, pulsed chrono-potentiometrically controlled ISEs [120], is particularly interesting as it eliminates the *i*R drop effects, lowers the limit of detection, decreases analysis time [40] and has been employed with SC-ISEs for the sensing of potassium, sodium and calcium [121, 122]. However, some limitations related to this approach should also be considered. A post-measurement conditioning step was found to be necessary in order to stabilize the potentiometric plots, because of the redox effects at the solid contact and because of the ionic fluxes at the two interfaces which causes concentration polarization of the ionophore [122, 123]. In addition, it was pointed out that the polarization at the CP/membrane under applied current can lead to the disruption of the sensor response function at relatively small current densities, which may impose a serious limitation on the development of CP-based solid-contact ion-selective pulsed galvanostatic sensors [121].

Controlled potential thin-layer coulometry using ISEs seems a very intriguing and powerful approach to achieve calibration free analysis and independence from the reference electrode potential, temperature changes and other processes which may alter the diffusion kinetics [42, 124-126]. Recent work give guidance on the sensor design highlighting that the level of interferences is more severe than in direct potentiometry, and that sample volumes need to be precisely reduced but also suggesting solutions for the limitation due to non-Faradaic processes [124, 125, 127]. With this approach silver and calcium could be detected in water solution at μM levels. These results may be significant for wearable sensors in case of analytes present at these concentrations but the achievement of trace analysis seems still far. Coulometric detection has been also used for determination of drugs [128] but calibration using known concentrations was employed which seems to reduce the significance of the results.

Future research will most probably explore the use of new materials in order to improve ISEs performance. For instance, conducting polymers that contain ion-recognition sites represent an interesting approach for the preparation of sensing membranes although selectivity is generally lower than with traditional membranes [47]. At the present state, the preparation of disposable ion-selective electrodes seems the simplest solution in order to deliver low cost sensors applied to environmental and wearable applications but new approaches are mostly needed yet to increase ruggedness, shelf- and operational life-time of these devices. This conclusion brings back to the fundamental research in nanotechnology as the key strategy to design, engineer and control the sensing layer at the electrode interface thus addressing these needs.

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7. References

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