Review of progresses on clinical applications of ion selective electrodes for electrolytic ion tests: from conventional ISEs to graphene-based ISEs

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ABSTRACT

There exist several positively and negatively charged electrolytes or ions in human blood, urine, and other body fluids. Tests that measure the concentration of these ions in clinics are performed using a more affordable, portable, and disposable potentiometric sensing method with few sample volumes, which requires the use of ion-selective electrodes (ISEs) and reference electrodes. This review summarily descriptively presents progressive developments and applications of ion selective electrodes in medical laboratory electrolytic ion tests, from conventional ISEs, solid-contact ISEs, carbon nanotube based ISEs, to graphene-based ISEs.

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1. Introduction

As we know, there exist several positively and negatively charged electrolytic ions in human body environment, such as within cells, between cells, in the bloodstream, urine and other fluids throughout the body. Electrolytic ions with a positive charge include sodium (Na\textsuperscript{+}), potassium (K\textsuperscript{+}), calcium (Ca\textsuperscript{2+}), lithium (Li\textsuperscript{+}), magnesium (Mg\textsuperscript{2+}), and etc., while some examples of the ions with a negative charge include chloride (Cl\textsuperscript{-}), bicarbonate and phosphate, and etc. The concentrations of these ions in the human body remain fairly constant throughout the day in a healthy subject. Changes in the concentration of one or more of these ions can occur during various acute and chronic disease states and can lead to serious consequences.

Tests that measure the concentration of electrolytic ions are useful in the emergency room to obtain clues for the diagnosis of specific disease. Electrolyte tests are used for diagnosing dietary deficiencies, excess loss of nutrients due to urination, vomiting, and diarrhea, or abnormal shifts in the location of an electrolyte within the body. When an abnormal electrolyte value is detected, the physician may either act to immediately correct the imbalance directly (in the case of an emergency) or run further tests to determine the underlying cause of the abnormal electrolyte value. Electrolyte disturbances can occur with malfunctioning of the kidney (renal failure), infections that produce severe and continual diarrhea or vomiting, drugs that cause loss of electrolytes in the urine (diuretics), poisoning due to accidental consumption of electrolytes, or diseases involving hormones that regulate electrolyte concentrations.[1, 2]

Photoelectric flame photometry [3] is one of the oldest direct potentiometric methods commonly used to measure the concentrations of sodium (Na\textsuperscript{+}), potassium (K\textsuperscript{+}), lithium (Li\textsuperscript{+}), and etc., in serum and urine samples. It is a routinely used reference method, working on emission photometric principle. Nevertheless, this method has drawbacks such as low throughput, requiring manual operation, as well as being a time consuming procedure. No standardization methods are available to date for this technique.

The regular clinical need for the availability of these electrolytes with both patients presenting to emergency departments as well as with inpatients has paved way for the replacement of these techniques by newer ones. One such method is the electrolyte measurement by ion selective electrodes (ISEs).[4] ISEs are an important class of chemical sensors that have found wide spread uses today in a number of routine applications, including laboratory medical devices. A key driving force for their development is their implication in automated clinical analyzers for the high throughput determination of electrolytes in physiological samples.

The paper will descriptively present different methods based on ISEs, from conventional ISEs (C-ISEs), solid-contact ISEs (SC-ISEs), carbon nanotube based ISEs (CNT-ISEs), to recently developed graphene-based ISEs (G-ISEs).
2. Overview of ISEs

2.1. Potentiometry and ISEs

Electrochemical analysis based on potentiometry and C-ISEs is such a kind of electrochemical sensing and analytical technique with much higher performance characteristics that it is widely used in clinical blood gas analysis of hydrogen ion concentration (pH), partial pressure of oxygen (pO₂), partial pressure of carbon dioxide (pCO₂) and etc., as well as in tests of electrolytic ions (K⁺, Na⁺, Cl⁻, Li⁺ and etc.) due to its versatility, ease of use, and low cost.

In potentiometric analysis, the potential between the working electrode and the reference electrode is measured while the electric current (with high impedance) between them is maintained usually nearly at zero values. The signal is generated by the charge separation at the interface between the membrane and the solution, due to the selective partitioning of ionic species between these two phases. The potentiometric cell is composed of an ISE, whose potential is highly sensitive to a specific ion to be measured, less or no sensitive to other interferences, referring to the potential of the reference electrode, which is composed of Ag/AgCl typically, and whose potential is stable constant and known as the reference potential as Figure 1(a) shows.

It can be summarized as:

\[
\text{ISE} \leftarrow \begin{array}{c}
\text{Ag/AgCl} | 0.1 \text{ M KCl} | \text{Membrane} | \text{Sample} \parallel \text{Ref} \\
\end{array}
\]

Where, ISE is formed of internal reference and internal interface. The phase boundary potentials between internal interface and external interface are well defined, and assumed not to influence one another.

![Figure 1](image1.png)

Figure 1. The composition of a potentiometric cell including a reference electrode, a working ISE and a high impedance potentiometer.

Table 1. Representative example of ion selective electrodes for analytes.

| Analyte | Construct of electrode | Selectivity coefficients |
|---------|------------------------|-------------------------|
| Na⁺     | 11% Na₂O, 18% Al₂O₃, 71% SiO₂ | \(K_{Na⁺,Na⁺} = 1000\), \(K_{Na⁺,K⁺} = 0.001\), \(K_{Na⁺,Li⁺} = 0.001\) |
| Li⁺     | 15% Li₂O, 25% Al₂O₃, 60% SiO₂ | \(K_{Li⁺,Na⁺} = 0.3\), \(K_{Li⁺,K⁺} = 0.001\) |
| K⁺      | 27% Na₂O, 5% Al₂O₃, 68% SiO₂ | \(K_{K⁺,Na⁺} = 0.05\) |

Actually, being an electrochemical sensor, it has three main different parts: (1) the ion-selective membrane (ISM) with the selective ionophore entrapped in a polymeric matrix; (2) the transducer element to convert the ionic current into electronic current; and (3) the detector, in this case a potentiometer. The elements used to make the membranes for Na⁺, pH, K⁺, and Cl⁻ are glass with lead sodium silicate, valinomycin and polyvinyl chloride, metal chloride, respectively. Figure 1(b) shows the surface interface adopted between the ISE capillary tube (a kind of membrane) and the blood solution for Na⁺ and pH tests, while Figure 1(c) shows the point interface adopted between the ISE membrane and the blood solution for K⁺, Ca²⁺ and Cl⁻ tests.

Table 1 shows the membrane composition and representative measurable characteristics of glass membrane ion selective electrodes for analytes used in clinics.

2.2. Solid-contact ISEs

As we introduced above, the ISEs is a transducer that converts the activity of a specific ion dissolved in a solution into an electrical signal (potential). The voltage theoretically depends on the logarithm of ionic activity, according to the Nernst equation. The sensing part of the electrode is usually an ion-specific membrane, along with a reference electrode. In order to eliminate drawbacks of the C-ISEs, such as the drying out the inner filling solution, electrode orientation, temperature variations and the pressure range, SC-ISEs or ion-sensitive sensors is invented by researchers, which are more durable and easier to miniaturize than their conventional counterparts.[5]

A SC-ISEs is an asymmetrical sensor, where the membrane on one side is in contact with a solid-contact
instead of an inner solution, and on the another side it is in contact with the aqueous solution, as Figure 2 shows. Table 2 shows some representative testing characteristics of analytes based on SC-ISEs.

### 2.3. Carbon nanotube based ISEs

Carbon materials, such as graphite pellet substrates coated with an ion-exchanger or ionophore-doped hydrophobic liquid [6, 7] have been explored as popular electrode components in ISE. Graphite with a surface-confined redox buffer system has also been used in SC-ISE. [8] Recently, carbon materials with a much higher surface area, e.g. carbon nanotubes (CNTs) [9, 10] three dimensionally ordered macroporous carbon (3DOM carbon) [11, 12] and fullerenes [13] have been used as solid contacts.

The single-walled carbon nanotubes based electrode material is sprayed onto a non-conducting poly (vinyl chloride) rod as mechanical support; this electrode also has a Nernstian slope, selectivities, and limits of detection that are comparable to other solid-contact electrodes. [14] Hamid Reza Rajabi et al. [15] has reported a voltammetric sensor for selective recognition and sensitive determination of mercury ions using glassy carbon (GC) electrode modified with an ion imprinted polymeric nanobeads and multi-wall carbon nanotubes. And, the designed modified electrode showed a linear response in the range of 1.0 × 10⁻⁸ to 7.0 × 10⁻⁴ mol/L of Hg²⁺ ion with a detection limit of 5.0 × 10⁻⁹ mol/L.

### 2.4. Graphene-based ion selective electrodes

The success of CNTs, on the other hand, in advancing sensors is part of the reason for the incredible interest in graphene as a material that could potentially push the boundaries of this field even further, considering its unique structural, electronic, mechanical, optical, thermal, and chemical properties. In addition, due to their low cost, wide potential window, and electrocatalytic activity, graphene sheets have been extensively used in electrochemistry fields.
Table 3. The physicochemical properties of graphene.

| Items                  | Descriptions | Evaluation | Reference |
|------------------------|--------------|------------|-----------|
| Mechanical strength    | 1000 GPa     | Strong     | [24]      |
| Electrical conductivity| 1738 siemens/m| Excellent  | [25]      |
| Thermal conductivity   | 4.84 x 10^10 to −5.30 x 10^4 W/mK | Unparalleled | [26]      |
| Specific surface area  | 2000 m^2/g   | High       | [27]      |
| Functionalization      | /            | Easy       | [28, 29]  |

Table 4. Analytes tested based on G-ISEs.

| Analyte   | Construct or electrode | Linear range (mol/L) | Detection limit (mol/L) | Reference |
|-----------|------------------------|----------------------|-------------------------|-----------|
| Pb        | Graphene/Nafion        | 5.0 x 10^-11 to 5.0 x 10^-8 | 2.0 x 10^-4 | [30]      |
| Pb        | Carbonyl graphene      | 4.2 x 10^-1 to 4.2 x 10^1 | 2.0 x 10^-14 | [31]      |
| Cd        | Graphene/Nafion        | 1.5 x 10^-3 to 30 x 10^-3 | 2.0 x 10^-4 | [32]      |
| Cd        | Graphene/nano gold     | 2.5 x 10^-3 to 2.5 x 10^-2 | 1.8 x 10^-4 | [33]      |
| Cd        | Carbonyl graphene      | 2.9 x 10^-3 to 2.9 x 10^-1 | 2.0 x 10^-14 | [34]      |
| Hg        | Graphene               | 2.0 x 10^-2 to 8.0 x 10^-2 | 8.0 x 10^-4 | [35]      |
| Cu        | Graphene oxide/2-amino-5-mercaptop-1,3,4-thiodiazole | 1.0 x 10^-2 to 1.0 x 10^-1 | 4.0 x 10^-4 | [36, 37] |
| La        | Magnetic graphene hybrids/2,2-dithiodipyridine | 1.0 x 10^-9 to 1.0 x 10^-3 | 2.75 x 10^-10 | [36, 37] |
| Ag        | Carbon nanomaterials/Au nanoparticles/dithiocarbamate | 5.3 x 10^-7 to 1.0 x 10^-1 | 4.5 x 10^-7 | [36, 37] |

Figure 4 shows some representative testing characteristics of analytes based on G-ISEs.

3. Conclusions and outlook

Electrolytes are positively (sodium, potassium, calcium, and magnesium, and etc.) and negatively (chloride, bicarbonate and phosphate, and etc.) charged ions, which also exist in human blood, urine, and other body fluids. Tests that measure the concentration of electrolytes in clinics are usually performed to help investigate conditions that cause electrolyte imbalances such as dehydration, kidney disease, lung diseases, or heart conditions using a potentiometric sensing method with few sample volumes, which requires the use of ISEs and reference electrodes. Nowadays, ISEs are present not only in clinical laboratory instrumentation but also in blood gas analyzers and other point-of-care measuring devices, allowing real-time monitoring of electrolyte concentrations at the bedside. This review summarily describes progressive developments and applications of ion selective electrodes in medical laboratory electrolytic ion tests, from C-ISEs, SC-ISEs, CNT-ISEs, to G-ISEs.

By comparison between Tables 2 and 4, it can be inferred that G-ISEs can give more accurate results than
other methods used with wider linear range, and lower limit of detection. Additionally, it can be inferred that with the development of ISEs, more low cost, portable, disposable, accurate with low detection limit modern clinical laboratory electrolyte devices, including conventional devices for K⁺, Na⁺, Li⁺, Cl⁻, as well as new devices for Mg²⁺, Ca²⁺, Zn²⁺, Pb²⁺, and etc., base on ISEs will enter into clinical trials, and benefit patients suffered from electrolyte imbalances.

Disclosure statement

No potential conflict of interest was reported by the authors.

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