



## Review

## Applications of nanomaterials in potentiometric sensors

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## ABSTRACT

Nanomaterials play an important role in the fabrication of chemosensors and biosensors, due to their unique physical and chemical properties, such as large surface area/volume ratio, good conductivity, excellent electrocatalytic activity and high mechanical strength. We review recent advances in the applications of these nanomaterials in potentiometric sensors. We highlight the development of stable solid-state polymeric membrane ion-selective electrodes (ISEs). We describe ISEs based on ionophore-modified nanomaterials. Also, we present highly-sensitive potentiometric biosensors based on nanomaterials.

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## 1. Introduction

Potentiometric sensors are an important class of electrochemical sensors, which detect the relationship between the activity of

analyte species and the observed potential response with the two-electrode system comprising an indicator electrode and a reference electrode. Ion-selective electrodes (ISEs) with polymeric membranes containing selective carriers (ionophores) are the most commonly-used potentiometric sensors. They have been widely used for directly determining various inorganic and organic ions in medical, environmental and industrial analyses [1,2]. Compared

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with other analytical techniques, ISEs have some unique characteristics, such as small size, ease of operation, portability and low cost. In the past few years, ISEs have made great progress in improving the lower limit of detection (LOD), exploiting new membrane materials, proposing new sensing concepts and developing deeper theoretical research about potentiometric responses [2].

Nanomaterials, including nanotubes, nanowires, nanofibers, nanorods, nanoparticles, nanocomposites and other nano-structured materials, have been widely applied to fabricate a variety of chemosensors and biosensors based on their unique physical and chemical properties, such as large surface area/volume ratio, good conductivity, excellent electrocatalytic activity and high mechanical strength [3]. In recent years, nanomaterials were gradually introduced into potentiometric sensors (Fig. 1). For example, the exceptional electrical properties and good hydrophobicities of nanomaterials make them suitable as solid contacts for solid-state ISEs. The immobilization of the ionophore on nanomaterials not only eliminates its leaching from the ion-selective membrane, but also develops an alternative sensing membrane. Also, potentiometric biosensors with new sensing concepts have been developed based on the functionalization of nanomaterials with receptors. The most important contributions of nanomaterials to the field of potentiometry are shown in Table 1.

Based on the significant development of advanced materials, this review summarizes the applications of nanomaterials in

potentiometric sensors, including the stable solid-state ISEs based on nanomaterials as solid contacts, ISEs based on ionophore-modified nanomaterials and nanomaterial-based potentiometric biosensors.

## 2. Nanomaterial-based solid-state ion-selective electrodes

### 2.1. Nanomaterials as solid contacts

Solid-contact ISEs are regarded as the most promising generation of potentiometric ion sensors, due to their durability, ease of miniaturization and low maintenance. A solid contact between an electronic conductor and an ion-selective membrane is the essential element for fabricating a stable solid-state polymeric membrane ISE, since its intrinsic property significantly influences the potential stability and reproducibility for long-term use [4]. In the past few decades, various electroactive materials with ionic and electronic conductivities have been extensively investigated as solid contacts in order to obtain stable analytical performance. Conducting polymers, such as polypyrrole (PPy), poly(3-octylthiophene) (POT) and poly(3,4-ethylenedioxythiophene) (PEDOT), are commonly used ion-to-electron transducer materials, as reviewed by Bobacka et al. [2,5]. However, these materials suffer from some limitations, such as light sensitivity [6], uptake of POT by the membrane [7], remnants of salt from the polymerization process that

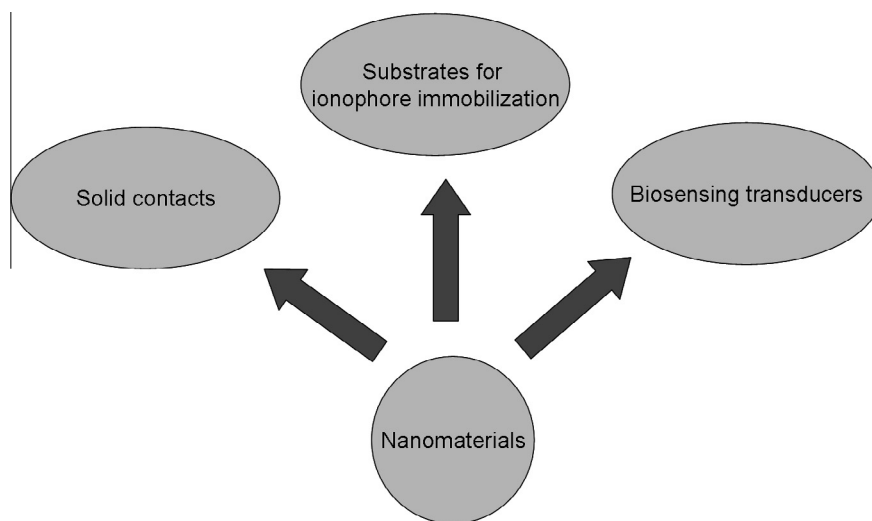


Fig. 1. The most important applications of nanomaterials in potentiometric sensors.

**Table 1**  
Timeline of the most important contributions of nanomaterials to the field of potentiometry

Year	Nanomaterials	Applications
2003	Biotin-modified gold nanopores	Label-free potentiometric protein sensor
2007	3DOM carbon <sup>a</sup>	Solid contact
2008	Carbon nanotubes	Solid contact
2009	Polycarbonate nanopore membrane	Ion-channel mimetic sensor for protein detection
	Aptamer-modified carbon nanotubes	Potentiometric aptasensor
2010	Ionophore-modified gold nanoparticles	Ionophore immobilization
2011	Gold nanoparticles	Solid contact
	Graphene	Solid contact
	Ionophore-modified carbon nanotubes	Ionophore immobilization
	Ionophore-modified gold nanopores	Solid-state ion-channels
2012	Gold nanocluster	Solid contact
	Ionophore-modified gold nanoparticles	Potentiometric sensing membrane

<sup>a</sup> 3DOM carbon, Three-dimensionally ordered macroporous carbon.

may lead to water uptake [8] and undesired side reactions with redox interferences and sensitivity to dissolved oxygen and CO<sub>2</sub> during the ion-to-electron transduction processes [2]. It is therefore necessary to develop alternative solid-contact materials to obtain stable, reliable potential responses.

To develop new electroactive materials as solid contacts, the following prerequisites are required:

- (1) reversible transition from ionic to electronic conductivity and sufficiently high bulk (redox) capacitance in order to obtain the potential stability [4];
- (2) good hydrophobicity in order to eliminate the undesired water layer between the electronic conductor and the ion-selective membrane [9–11]; and,
- (3) excellent chemical stability and absence of any side reactions during the process of ion-to-electron transduction [12].

Over the past few years, various nanomaterials, such as carbon-based nanomaterials, Nanoparticles (NPs) and nanoclusters, have been used as solid contacts to develop solid-state ISEs for detection of K<sup>+</sup>, Ca<sup>2+</sup>, Ag<sup>+</sup>, ClO<sub>4</sub><sup>-</sup>, pH and choline (Table 2).

### 2.1.1. Carbon-based nanomaterials

Fullerenes are recognized as three-dimensional electron-acceptor materials [13]. They can reversibly accept several electrons and form stable intermediate multi-anions [14]. A self-assembled monolayer (SAM) of the lipophilic and redox-active fullerene derivative was proposed by Pretsch and co-workers [15] to act as a novel solid contact for K<sup>+</sup>-ISE. They demonstrated that the redox and lipophilic properties of SAM are essential for obtaining a stable potential response and eliminating the aqueous layer between the ion-selective membrane and the underlying contact. However, one limitation of SAM is its inherently low redox capacitance, which is unfavorable for solid-contact ISEs [4]. Solution-cast fullerene-C<sub>60</sub> films on carbon substrates have been reported to be efficient charge-transfer mediators [16]. Based on the specific characteris-

tics of fullerene-C<sub>60</sub>, Chaniotakis et al. [17] cast a C<sub>60</sub> film on the glassy-carbon (GC) electrode as an electrochemical mediator of the solid-state K<sup>+</sup>-ISE. Electrochemical studies based on electrochemical-impedance spectroscopy (EIS) showed that the electrochemically-active layer of the interfacial C<sub>60</sub> favors efficient ion-to-electron transduction between the polymeric ion-selective membrane and the underlying GC electrode, which is essential for obtaining a stable potential response of the solid-state ISE.

Three-dimensionally ordered macroporous (3DOM) carbon, which is fabricated with colloidal crystal templating, was introduced by Bühlmann and Stein et al. [18] to act as a solid contact for the solid-state K<sup>+</sup>-ISE. The 3DOM carbon-based K<sup>+</sup>-ISE exhibits an excellent long-term potential stability with a low potential drift of 11.7 μV h<sup>-1</sup>, due to the specific pore and wall structures of 3DOM carbon with a large interfacial area and the high capacitance [19]. Moreover, no significant potential drifts were observed in measuring the effects of O<sub>2</sub>, light and redox interferences on the potential stability. Also, there is no clear evidence for an aqueous layer forming between the polymeric sensing membrane and the underlying contact, due to the hydrophobic surface of 3DOM carbon. The applications of the 3DOM carbon-based solid-contact ISEs were further investigated [20] and the LODs of 1.6 × 10<sup>-7</sup> M and 4.0 × 10<sup>-11</sup> M were obtained for K<sup>+</sup> and Ag<sup>+</sup> ions, respectively.

Carbon nanotubes (CNTs), including single-walled CNTs (SWCNTs) and multi-walled CNTs (MWCNTs), have unique characteristics, such as large surface area/volume ratio, high charge-transfer capacity, hydrophobicity and chemical stability. These properties are favorable for acting as solid contacts, as demonstrated by Rius and co-workers in developing a series of solid-state ISEs for ions – K<sup>+</sup> [21], choline [22], Ca<sup>2+</sup> [23], pH [24] and ClO<sub>4</sub><sup>-</sup> [25]. These ISEs not only are insensitive to light and species displaying redox behaviors, but also show the absence of the aqueous layer between the ion-selective membrane and the electronic conductor. Furthermore, Rius et al. [26] discussed in detail the transduction mechanism of the SWCNT film as a solid contact. They demonstrated that the SWCNT film with small resistance

**Table 2**  
Solid-state polymeric membrane ion-selective electrodes (ISEs) based on nanomaterials as solid contacts

Solid contact	ISM <sup>a</sup>	Primary ion	Potential drift (μV h <sup>-1</sup> )	Aqueous layer	Effects of interferences on potential stability				Ref.
					O <sub>2</sub>	CO <sub>2</sub>	Redox	Light	
Fullerene-C <sub>60</sub>	PVC/DOS <sup>b</sup>	K <sup>+</sup>	–	–	–	–	No	–	[17]
3DOM carbon	PVC/ <i>o</i> -NPOE <sup>c</sup>	K <sup>+</sup>	11.7	No	No	Yes	No	No	[18]
SWCNTs <sup>d</sup>	MMA/nBA <sup>e</sup>	K <sup>+</sup>	–	No	No	No	–	–	[21]
		Choline	224	No	–	–	–	–	[22]
		Ca <sup>2+</sup>	493	No	–	–	–	–	[23]
		pH	500	No	–	–	–	–	[24]
		ClO <sub>4</sub> <sup>-</sup>	220	No	–	–	–	–	[25]
MWCNT <sup>f</sup>	MMA/nBA	ClO <sub>4</sub> <sup>-</sup>	220	No	–	–	–	–	[25]
PEDOT(MWCNTs) <sup>g</sup>	PVC/DOS	K <sup>+</sup>	–	No	No	No	–	–	[27]
CRGO <sup>h</sup>	PVC/ <i>o</i> -NPOE	K <sup>+</sup>	12.6	No	No	No	No	No	[30]
Graphene sheets	PVC/DOS	K <sup>+</sup>	–	No	–	Yes	–	–	[31]
ERGO <sup>i</sup>	PVC/ <i>o</i> -NPOE	Ca <sup>2+</sup>	14.7	No	No	No	No	No	[32]
Carbon black	PVC/ <i>o</i> -NPOE	K <sup>+</sup>	15.1	No	No	No	No	No	[33]
PANI-NP <sup>j</sup> /K <sup>+</sup> -ISM	PVC/DOS	K <sup>+</sup>	–	–	–	–	–	–	[35]
PANI-NP	SR <sup>k</sup> /DOS	Ca <sup>2+</sup> /Ag <sup>+</sup>	–	No	No	–	–	No	[36]
Au@C4/C8 <sup>l</sup>	PVC/DOS	K <sup>+</sup>	380/660	No	–	–	–	–	[38]
MPCs <sup>m</sup>	PVC/DOS	K <sup>+</sup>	10.1	No	No	No	No	No	[41]

<sup>a</sup> ISM, Ion-selective membrane.

<sup>b</sup> DOS, bis(2-ethylhexyl) sebacate.

<sup>c</sup> *o*-NPOE, *o*-nitrophenyl octyl ether.

<sup>d</sup> SWCNTs, Single-walled carbon nanotubes.

<sup>e</sup> MMA/nBA, Methyl methacrylate/*n*-butylacrylate.

<sup>f</sup> MWCNTs, Multi-walled carbon nanotubes.

<sup>g</sup> PEDOT(MWCNTs), Poly(3,4-ethylenedioxythiophene) doped with multi-walled carbon nanotubes.

<sup>h</sup> CRGO, Chemically-reduced graphene oxide.

<sup>i</sup> ERGO, Electrochemically-reduced graphene oxide.

<sup>j</sup> PANI-NPs, Polyaniline nanoparticles.

<sup>k</sup> SR, Silicone rubber.

<sup>l</sup> Au@C4/C8, Gold nanoparticles modified with butylthiol/octanethiol.

<sup>m</sup> MPCs, Monolayer-protected Au clusters. No, Absence/ Insensitive; Yes, sensitive.

and large bulk capacitance is an asymmetric capacitor where one side is formed by electrons (holes) in the walls of the SWCNTs and the other side is formed by cations (anions) in the ion-selective membrane, when acting as an ion-to-electron transducer. Also, Ivaska et al. [27] electrochemically synthesized poly(3,4-ethylenedioxythiophene) (PEDOT) doped with carboxyl-functionalized MWCNTs [PEDOT(MWCNT)] as an ion-to-electron transducer of the solid-contact  $K^+$ -ISE. The experimental results from cyclic voltammetry (CV) and EIS show that the electroactive film, PEDOT(MWCNT), has the capability to act as a solid contact, due to its high redox capacitance. However, the incorporation of PEDOT may bring back the inherent problems of conducting polymer-based solid contact.

Interestingly, SWCNTs are also employed as an effective transducer layer for fabricating reliable, stable solid-state reference electrodes (SSREs), due to their hydrophobicity and UV/Vis light insensitivity [28,29]. For example, Riu et al. [28] fabricated a series of SSREs using SWCNTs as efficient ion-to-electron transducers and polyacrylic polymers as the reference membranes containing the  $Ag/AgCl/Cl^-$  ion system. They investigated photo-polymerized and thermo-polymerized polyacrylic polymers as the  $Ag/AgCl/Cl^-$  ion-system reservoirs for the SWCNT-based SSREs. The photo-polymerized poly(*n*-butylacrylate) membrane solid-state reference electrode showed better results, including satisfactory medium-term stability in 0.01 M KCl ( $-1.1 \pm 0.2$  mV/h) and insensitivity to pH, room light and various salts.

The same group [29] prepared octadecylamide-functionalized SWCNTs (SWCNTs-ODA) as the transducer layer to fabricate a disposable screen-printed solid-state reference electrode. The proposed reference electrode not only is insensitive to various ions, small charged molecules, proteins, pH, redox species and ambient light, but also shows a medium-term potentiometric stability ( $-0.9 \pm 0.2$  mV  $h^{-1}$ ) in  $10^{-3}$  M KCl and a long shelf life (8 months).

Graphene, as a two-dimensional carbon nanomaterial, has similar characteristics to CNTs, such as large specific surface area, fast electron-transfer capability, excellent conductivity and electrocatalytic activity. It has been used as a solid contact to develop solid-state ISEs. For example, the chemically-reduced graphene oxide (CRGO) was proposed by Wu et al. [30] as a solid-contact layer of the solid-state  $K^+$ -ISE. The CRGO-based electrodes show excellent potentiometric behaviors, such as potential stability, fast response time, and insensitivity to  $O_2$ ,  $CO_2$ , light and redox interferences. Similarly, graphene sheets were used by Zhang and Niu et al. [31] as a transducer layer to fabricate the solid-contact  $K^+$ -ISE. However, the CRGO film as solid contact is usually fabricated by the multi-step drop-casting method, which is time consuming and complicated. A simple, rapid, efficient one-step electrodeposited technique was subsequently proposed by Wu et al. [32] to prepare GO film as an ion-to-electron transducer for the screen-printed  $Ca^{2+}$ -ISE.

Carbon black (CB), as a form of amorphous carbon, shows advantages of low production cost, large surface area, high conductivity and hydrophobicity. These properties are favorable in acting as a solid contact for the solid-state  $K^+$ -ISE, as demonstrated by Paczosa-Bator [33].

### 2.1.1.2. Nanoparticles and nanoclusters

Polyaniline (PANI) has been extensively studied for numerous practical applications, due to its excellent electrical properties, good environmental stability and processability. PANI contains three kinds of oxidation state, which depend on the pH of sample solution [34]. Among them, the electrically-conducting emeraldine salt (ES) form is regarded as the most useful, stable form of PANI. The membrane with the pure PANI NPs, mainly in the ES form, was found to display an exceptionally good pH stability [35]. Lindfors et al. [35] prepared the homogenous mixture of PANI

NPs and plasticized PVC membrane as an internal ion-to-electron transducer of the solid-contact  $K^+$ -ISE. The geometrically well-defined internal solid contact with good mechanical strength is favorable for improving the reproducibility of the solid-contact ISEs. Additionally, Lindfors and Gyurcsányi et al. [36] used PANI NPs as a solid contact to develop silicone rubber (SR)-based  $Ca^{2+}$ -ISEs and  $Ag^+$ -ISEs. The impedance of the proposed solid-contact ISEs was found to be lowered, which is due to the presence of PANI NPs between the ion-selective membrane and the underlying electronic conductor.

Gold NPs (AuNPs) with excellent physical and chemical characteristic have been extensively used to fabricate various chemical and biological sensors [37]. Michalska et al. introduced AuNPs to act as a solid contact for the solid-state  $K^+$ -ISE [38]. To increase the lipophilicity, AuNPs were modified with aliphatic thiols using the Brust-Schiffrin method in a two-phase liquid-liquid system [39,40]. The proposed electrode shows a highly stable potential response, due to the high capacitance and lipophilicity of the aliphatic thiol-modified AuNPs.

Monolayer-protected Au clusters (MPCs) doped with tetrakis (4-chlorophenyl) borate were prepared by Niu et al. [41]. They demonstrated that the new material has the unique properties to act as an effective solid contact of the solid-state  $K^+$ -ISE, such as high redox capacitance, sufficient ion-exchange property, good long-term chemical stability, low electrical resistance, excellent hydrophobicity and insensitivity to  $O_2$ ,  $CO_2$ , light and redox interferences.

### 2.2. Nanomaterials directly dispersed in ion-selective membranes

Nanomaterials can be directly dispersed in the ion-selective membrane to fabricate all-solid-state ISEs. However, the dispersion of nanomaterials in the ion-selective membrane is critical for forming the homogeneous sensing membrane. For example, Abbaspour et al. [42] dispersed MWCNTs in PVC-based ion-selective membrane with the ultrasonic technique to develop a  $Cr^{3+}$ -ISE. Bobacka et al. [43] mixed MWCNTs or poly(3-octylthiophene) (POT) with the  $K^+$ -ion-selective membrane components to develop all-solid-state  $K^+$ -ISEs. By comparison, they demonstrated that MWCNTs are more suitable to act as an ion-to-electron transducer than POT, due to their high electronic conductivity and large redox capacitance [43]. Moreover, the selectivities of the proposed electrodes were found to be insignificantly influenced by the amount of MWCNTs or POT in the ion-selective membrane. Qin et al. [44] found that MWCNTs can be well dispersed in ion-selective membranes with poly(ethylene oxide) (PEO)-poly(propylene oxide) (PPO)-poly(ethylene oxide) block copolymers (PEO-PPO-PEO, Pluronic F127) as dispersant. They used the MWCNTs/F127-based ion-selective membranes with different ionophores to develop all-solid-state  $K^+$ ,  $Na^+$ ,  $Ca^{2+}$ -ISEs and  $Cu^{2+}$ -ISEs [44,45]. The proposed electrodes display similar selectivities to those of the corresponding liquid-contact PVC-based ISEs.

The plasticizer-free polyacrylate-based polymer membranes with low diffusion coefficients are regarded as an alternative membrane material for fabricating ISEs [46]. However, the high electrical resistance of polyacrylate membranes significantly limits their applications. Platinum NPs (PtNPs) were incorporated by Michalska et al. [47] into the photopolymerized poly(*n*-butyl acrylate)-based ion-selective membrane for lowering the electrical resistance. Interestingly, the potential stability of the proposed polyacrylate-based electrode was found to be improved, because PtNPs facilitate ion-to-electron transduction between the solid contact (POT) and the ion-selective membrane. However, the presence of PtNPs in the ion-selective membrane may lead to serious oxygen interference.

### 2.3. Ionophore-modified nanomaterials dispersed in ion-selective membranes

The immobilization of the ionophore in the polymeric membrane matrix offers a robust approach to eliminate leaching of the ionophore from the ion-selective membrane to the sample solution, which is requisite to fabricate the ISE with a long operating lifetime. For example, Gyurcsányi et al. [48] fabricated ionophore-AuNP conjugates based on the self-assembly of the Ag<sup>+</sup>-selective ligand onto the surface of AuNPs. The conjugates were incorporated into the ion-selective membrane to develop the Ag<sup>+</sup>-ISEs with nanomolar LODs. The methodology with ionophore immobilized on AuNPs can effectively lower the mobility of ionophore in the membrane phase and eliminate the light sensitivity of the sensing membrane.

Blondeau et al. [49] synthesized a hybrid material with benzo-18-crown-6 (lead ionophore) covalently immobilized onto MWCNTs to develop potentiometric Pb<sup>2+</sup> sensors. The hybrid material acts as not only a recognition receptor, but also an ion-to-electron transducer of the solid-state Pb<sup>2+</sup>-ISE. The proposed sensors show excellent intermediate-term potential stability without leaching out of the ionophore from the ion-selective membrane. Also, the selectivity of the electrodes was dramatically improved, because the specific structure of the hybrid material favors the formation of sandwich complexes between the Pb<sup>2+</sup> ion and the two ionophore molecules.

### 2.4. Nanomaterial-based potentiometric sensing membranes

Conventional polymeric membrane ISEs suffer from some limitations, such as leaching of the membrane components into the sample solution and extraction of lipophilic molecules into the polymeric membrane. Moreover, they cannot be applied in non-aqueous solutions. Consequently, some nanomaterial-based potentiometric ion sensors have been developed without polymeric membranes matrix. For example, gold nanopores, which are fabricated by electroless deposition of gold onto the surface of track-etched polycarbonate nanopore membranes, are used to immobilize Ag<sup>+</sup>-selective ionophore to develop solid-state ion channels for potentiometric sensing [50]. The nanopore-based Ag<sup>+</sup>-ISE shows fast Nernstian potential responses with the LOD in the sub-nM range. Moreover, the proposed electrode displays extraordinary ion-recognition selectivities.

Michalska et al. [51] synthesized dithizone-decorated AuNPs to act as an alternative potentiometric sensing membrane for the Cu<sup>2+</sup> ion. The membrane shows Nernstian potentiometric responses in the absence of a polymeric membrane matrix, due to the interaction between Cu<sup>2+</sup> ions and the ligand immobilized on the AuNP layer. Moreover, the proposed membrane shows selectivity superior to the PVC-based Cu<sup>2+</sup> polymeric membrane, due to not only the intrinsic properties of the applied ligand, but also the stable conformation of the complex on the surface of AuNPs.

## 3. Nanomaterial-based potentiometric biosensors

### 3.1. Solid-state potentiometric aptasensors based on carbon nanotubes

Based on  $\pi$ - $\pi$  stacking interactions between the nucleic-acid bases and the CNT walls [52], CNTs are used as transduction elements to develop solid-state potentiometric aptasensors. These aptasensors represent a promising research area, in which the polymeric membranes are replaced by nanomaterials. The sensing mechanism is quite different from the well-established phase-

boundary potential model for the traditional polymeric membrane ISEs.

Rius et al. [53] covalently immobilized the 5'-NH<sub>2</sub>-functionalized 15-mer thrombin-binding aptamer (TBA) on the carboxylated SWCNTs using the carbodiimide-mediated wet-chemistry method [54] to develop a solid-state potentiometric aptasensor for detecting thrombin. The aptasensor displays a direct potentiometric response to thrombin in concentration range 10<sup>-7</sup>-10<sup>-6</sup> M with the sensitivity of 8.0 mV/log a<sub>thrombin</sub> and the LOD of 80 nM. The biosensing mechanism is based on competitive binding between thrombin and SWCNTs for TBA. That is, in the absence of thrombin, TBA is self-assembled on CNTs by  $\pi$ - $\pi$  stacking interactions between the aptamer bases and SWCNT walls; however, in the presence of thrombin, the affinity interaction between TBA and thrombin induces a conformational change in the aptamer, which separates the phosphate negative charges of TBA from the SWCNT sidewalls and subsequently leads to a potential change.

Similarly, pathogens, such as *Salmonella typhi* (*S. typhi*) [55], *Escherichia coli* (*E. coli*) [56] and *Staphylococcus aureus* (*S. aureus*) [57], have been detected based on potentiometric aptasensors using CNTs as transducers and proper aptamers as recognition elements. These sensors offer a simple, selective method for detecting and identifying pathogens. However, the low sensitivities (<2 mV/decade), the narrow response ranges and the rigorous experiment conditions, such as the constant ionic strength of the sample solution and the elimination of the other charged species that would interfere with the potential change, would limit their real-world applications.

### 3.2. Nanoparticle-based potentiometric biosensors

Based on their unique optical and electrochemical properties, NPs, such as metal NPs (gold, silver) or semiconductor dots, have been extensively applied in biosensing [58]. The applications of NPs as labels in biosensors represent an interesting field of research and applications. The pioneering work was done by Mirkin and Letsinger et al. [59], who developed a scanometric DNA-array-detection system based on oligonucleotide targets labeled with AuNPs. Afterwards, Wang et al. [60–62] used AuNPs or silver-enhanced colloidal gold as labels for electrochemical detection of DNA hybridization. These NP-based electrochemical biosensors typically employ the stripping voltammetric technique as the read-out principle due to the “built-in” preconcentration step that obtains ultratrace-level LODs.

Potentiometric ISEs are recognized as an attractive tool for determining trace metals in confined samples, because the potential signal or LOD is independent of the sample volume and electrode surface. Miniaturized ISEs have been reported to detect femtomole amounts of ions in microvolume samples [63,64], so ISEs/ion-selective microelectrodes (ISEs/IS $\mu$ Es) based on NPs have been employed for highly-sensitive bioassays (Table 3).

#### 3.2.1. Release of metal ions by nanoparticle dissolution

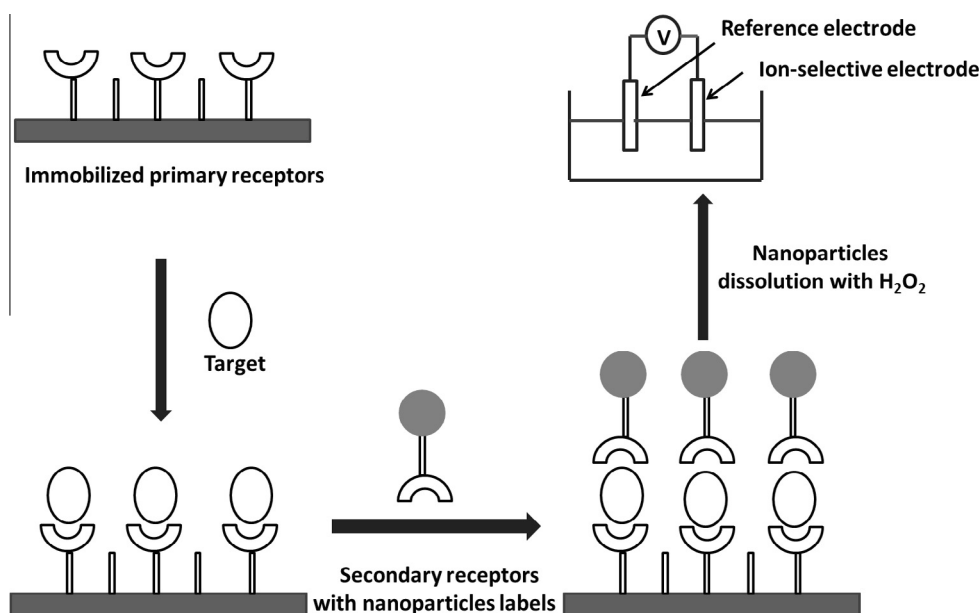
Fig. 2 shows potentiometric biosensors using NPs as labels. The sensing mechanism is based on a sandwich assay, where the target is first captured by the immobilized primary receptor and then attached to the NP-labeled secondary receptor. Potentiometry is finally used to detect the dissolution products of NPs after a release step with H<sub>2</sub>O<sub>2</sub>.

In the past few years, several kinds of NPs have been used as labels to develop highly-sensitive potentiometric biosensors using ISEs/IS $\mu$ Es for signal transduction. For example, Bakker and co-workers [65] developed a potentiometric IgG immunosensor based on silver-enlarged AuNP labels. A silver IS $\mu$ E (Ag<sup>+</sup>-IS $\mu$ E) was used to detect the released silver ion with H<sub>2</sub>O<sub>2</sub>. The proposed immunosensor offers a promising method for highly-sensitive bioaffinity



**Table 3**  
Nanoparticle-based potentiometric biosensors using ion-selective electrodes/microelectrodes (ISEs/ISμEs) for signal transduction

Nanoparticles (NPs)	Target	Signal transduction	Linear range	LOD	Ref.
Silver-enhanced AuNPs	IgG	Ag <sup>+</sup> -ISμE	0.5–7.5 μg mL <sup>-1</sup>	12.5 pmol/50 μL	[65]
CdS quantum dots	DNA	Cd <sup>2+</sup> -ISμE	0.01–300 nM	2 fmol/200 μL	[66]
CdS quantum dots	Thrombin	Cd <sup>2+</sup> -ISμE	10–250 μg mL <sup>-1</sup>	28 fmol/200 μL	[67]
CdSe quantum dots	IgG	Cd <sup>2+</sup> -ISμE	0.15–4.0 pmol/150 μL	<10 fmol/150 μL	[68]
AgNPs	Glucose	Ag <sup>+</sup> -ISE	0.1–3 mM	1.0 × 10 <sup>-5</sup> M	[69]
AuNPs	NADH	Cu <sup>2+</sup> -ISE	1 × 10 <sup>-5</sup> –1 × 10 <sup>-2</sup> M	–	[71]
AuNPs	DNA	Ag <sup>+</sup> -ISμE	100 fM–10 nM	0.2 amol/4 μL	[72]



**Fig. 2.** Potentiometric biosensors using nanoparticles as labels.

assay, with an LOD of around 12.5 pmol of IgG in the 50-μL sample solution. The same group [66] developed a potentiometric microsensor for detection of DNA hybridization based on CdS quantum dots (QDs) labeled on a secondary oligonucleotide. After the sandwich DNA hybridization, the captured CdS QDs were dissolved in H<sub>2</sub>O<sub>2</sub> and the released Cd<sup>2+</sup> ions were measured by a Cd<sup>2+</sup>-ISμE. The potentiometric immunosensor exhibited a wide linear response range of 0.01–300 nM of the target DNA, with a low LOD of 2 fmol in 200-μL sample solution. CdS QDs were also used as labels to develop an aptamer-based potentiometric biosensor [67]. Also, a potentiometric immunoassay based on CdSe QDs as labels was developed by Pretsch and co-workers [68] and the LOD of <10 fmol IgG in 150-μL sample solution was obtained.

Silver NPs (AgNPs) were also used as a potentiometric redox marker to develop a potentiometric glucose biosensor [69]. The product, H<sub>2</sub>O<sub>2</sub>, generated by the enzyme-substrate reaction between glucose and glucose oxidase, is used to oxidize AgNPs to free Ag<sup>+</sup> ions, which are related to the concentration of glucose and can be detected by an Ag<sup>+</sup>-ISE. The proposed sensor shows good repeatability and high reproducibility for detection of glucose with an LOD of 1.0 × 10<sup>-5</sup> M.

### 3.2.2. Reduction of metal ions by nanoparticle-induced biometallization

Due to their intrinsic properties, metal NPs can also be applied to catalyze the reduction of metal ion by an enzymatically-generated reducing agent [70]. Such biometallization processes can be monitored by ISEs in real time. For example, a potentiometric NADH biosensor was successfully proposed by Wang et al. [71]

based on monitoring the NADH-stimulated catalytic reduction of Cu<sup>2+</sup> in the presence of AuNPs with a Cu<sup>2+</sup>-ISE. The presence of the AuNPs in the enzyme-mediated reduction of metal ions was found to be crucial in improving the sensitivity.

Wang et al. [72] reported a highly-sensitive potentiometric biosensor for detecting DNA hybridization based on monitoring the depletion of Ag<sup>+</sup> ions in the presence of AuNPs induced by the biocatalytic reaction of alkaline phosphatase (ALP)-enzyme labels with a solid-contact Ag<sup>+</sup>-ISμE. The proposed method does not need to dissolve the nanocrystal tracer with H<sub>2</sub>O<sub>2</sub> or to have a preconcentration step. The sensor has been used to detect DNA and 16S rRNA of *E. coli* pathogenic bacteria with LODs of 50 fM and 10 CFU in 4-μL sample solution, respectively.

### 3.3. Nanopore-based potentiometric biosensors

Gold nanopores were employed by Gyurcsányi and Pretsch et al. [73] for potentiometric protein detection. They modified the inner walls of gold nanopores with biotin and monitored the change of the zero-current flux of Ca<sup>2+</sup> ion through the modified nanopores with a Ca<sup>2+</sup>-ISE, which depends on the affinity biorecognition between biotin and avidin. The proposed method offers a novel label-free biosensing strategy for selective recognition of proteins.

Bakker et al. [74] detected surface-confined protein using an ion-channel mimetic chronopotentiometric polymeric membrane ion sensor. They covalently attached biotin to the backbone of the polymeric Na<sup>+</sup>-selective membrane so that avidin can be accumulated on the membrane surface through bioaffinity interaction, which may lead to partial blocking of the current-induced Na<sup>+</sup>-ion

transfer across the interface between the membrane and the sample solution and subsequently a large potential drop in the so-called super-Nernstian step. Furthermore, a poly(vinyl pyrrolidone)-wetted hydrophilic track-etched polycarbonate nanopore membrane, which can reduce the effective membrane surface area, was used to place at the surface of the biotinylated ion-selective membrane to improve the detection sensitivity.

#### 4. Nanomaterial-based potentiometric sensors for neutral species

SWCNTs are regarded as an excellent charge-transducing material, due to their special structure with  $\pi$  electrons on the side walls and the large surface area/volume ratio. The change in electrical characteristics of SWCNTs makes them suitable for potentiometric detection. For example, Rius et al. [75] used SWCNTs as a receptor layer to develop a potentiometric sensor for detecting neutral aromatic hydrocarbon in aqueous solutions with low ionic strength. The sensing mechanism is that the adsorption of aromatic hydrocarbons onto the side walls of the CNTs through hydrophobic and  $\pi$ - $\pi$  stacking interactions could lead to the change of the interfacial double-layer capacitance between the CNTs and the sample solution and subsequently influence the potential response.

#### 5. Conclusions and outlook

This review summarizes recent advances in applications of nanomaterials in potentiometric sensors. The unique, attractive properties of nanomaterials, such as excellent electrical properties and good hydrophobicities, make them ideal solid contacts in developing stable, reliable polymeric membrane solid-state ISEs.

The functionalization of nanomaterials (i.e. ionophore-modified AuNPs and CNTs) is favorable for developing stable ISEs with long operating lifetimes, due to the effective elimination of ionophore leaching from the ion-selective membrane to the sample solution.

Gold nanopores and AuNPs can be applied as alternative receptor layers to eliminate the limitations of the traditional polymeric membrane ISEs, such as the leaching of the membrane components into the sample solution and the extraction of lipophilic molecules into polymeric membrane.

Also, the incorporation of CNTs with aptamers opens up a new type of potentiometric aptasensor. Metal NPs and QDs can be used for signal transduction and amplification to develop highly sensitive potentiometric biosensors.

In conclusion, the applications of nanomaterials in potentiometric sensors are a promising research area and we expect further innovative work, such as developing other new nano-structured materials as solid contacts and applying more functionalized nanomaterials for reliable, stable, sensitive potentiometric sensors.

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