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A REVIEW OF GLUCOSE BIOSENSORS BASED ON GRAPHENE/METAL OXIDE NANOMATERIALS

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In recent years, considerable attention has been paid to developing economical yet rapid glucose sensors using graphene and its composites. Recently, the excellent properties of graphene and metal oxide nanoparticles have been combined to provide a new approach for highly sensitive glucose sensors. This review focuses on the development of graphene functionalized with different nanostructured metal oxides (such as copper oxide, zinc oxide, nickel oxide, titanium dioxide, iron oxide, cobalt oxide, and manganese dioxide) for use as glucose biosensors. Additionally, a brief introduction of the electrochemical principles of glucose biosensors (including amperometric, potentiometric, and conductometric) is presented. Finally, the current status and future prospects are outlined for graphenelmetal oxide nanomaterials in glucose sensing.

Keywords: Enzymatic sensor; Glucose biosensor; Graphene; Metal oxide; Nonenzymatic sensor

INTRODUCTION

Diabetes mellitus is a group of endocrine disorders marked by an elevated level of sugar in the blood. It is a leading cause of major health problems such as blindness and kidney failure (Bastaki 2005). The World Health Organization (WHO) estimated that 366 million people with diabetes in 2011 represented a 30% increase from the estimated 285 million in 2010 (Whiting et al. 2011), and this total will increase to 439 million by 2030. The worldwide increase in the number of diabetic patients has been troubling most developed societies and has encouraged the development of glucose biosensors.

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Historically, the idea of glucose enzyme electrode was proposed by Clark and Lyons in 1962 (Clark and Lyons 1962). During the 1980s, self-monitoring of blood glucose had been introduced to check the level of glucose in blood at a given point in time. The first electrochemical glucose meter was a pen-sized electrode strip and was launched in 1987s as ExacTech by Medisense Inc. It used an enzyme electrode strip contained glucose oxidase and ferrocene (an electron transfer mediator). The reduction process of the mediator produced a current which was then detected by an amperometric sensor (Matthews et al. 1987). More recently, there is increasing interest in nanostructured materials with grain sizes less than 100 nm because of the expectation of their unique properties, reflecting the growing emphasis on nanotechnology.

Graphene, a single atomic layer of graphite, is the building block of all sp^2 bonded carbon materials including graphite and carbon nanotubes. The explosion of recent interest in graphene is in large part due to its exceptional electronic properties and its potential applications, such as for nanoelectronic devices and chemical/bio-sensors (Schedin et al. 2007; Ohno et al. 2009). Unlike carbon nanotubes, with a two-dimensional structure, the monolayer graphene has its whole volume exposed to the environment, which can maximize the sensing effect. Graphene-based electrochemical sensors and biosensors have recently received increasing attention in the field of electroanalysis (D. Chen, Tang, and Li 2010; Pumera 2010; Pumera et al. 2010; Shao et al. 2010), such as direct electrochemistry of enzymes (Lu et al. 2007; Shan et al. 2009; K. Liu et al. 2010; G. H. Wu et al. 2013), and small biomolecule detection (Shang et al. 2008; M. Zhou, Zhai, and Dong 2009; Alwarappan et al. 2010).

Being an unrolled carbon nanotube, graphene has a high specific area ($2630\ m^2\ g^{-1}$) that can serve as a superior platform for building nanocomposites. Furthermore, its unique two-dimensional crystal structure makes it extremely attractive as a support material for metal oxide nanoparticles due to its photophysical and electrochemical properties. Deposition of nanoparticles, such as zinc oxide, titanium dioxide, copper oxide, and nickel oxide, on graphene sheets reveals special features in new hybrids that can be widely utilized in chemical/bio-sensors. These graphene-based hybrid materials have shown greater versatility as enhanced electrode materials for electrochemical sensors and biosensor applications. Graphene/metal oxide biosensors exhibit good direct electrochemistry without any electron mediator, as well as good sensitivity and fast response time towards molecule detection (S. Chen, Zhu, and Wang 2010).

This review particularly focuses on the development of graphene functionalized with different nanostructured metal oxide [such as copper oxide, zinc oxide, nickel oxide, titanium dioxide, iron oxide, cobalt oxide, and manganese dioxide] based glucose biosensors. Additionally, a brief introduction of electrochemical principles of glucose biosensors (including amperometric, potentiometric, and conductometric) is presented. Finally, the current status and future prospects are outlined for graphene/metal oxide nanomaterials in glucose sensing.

GRAPHENE/METAL OXIDE NANOCOMPOSITES

Graphene offers a unique two-dimensional environment for fast electron transport and has potential applications in the field of electrochemical sensors and

biosensors (Rao et al. 2009; Choi et al. 2010; Kuila et al. 2011). It exhibits a theoretical surface area of $2630\,m^2\,g^{-1}$, which is approximately 260 times greater than graphite and twice that of carbon nanotubes. Thus, graphene enhances the electrochemical catalytic activity of materials by greatly increasing the surface area (X. M. Chen et al. 2011). Besides, the four edges of a graphene sheet offer significant number of centers for fast heterogeneous electrons (F. Chen and Tao 2009), as compared to single-walled carbon nanotubes for which heterogeneous electron transfer occurs only at the two ends of the nanotube (Pumera 2009). Therefore, graphene may have good potential in electrochemistry sensing (Shao et al. 2009; Brownson and Banks 2010).

With a large surface area and the unique properties, graphene is an attractive choice as the matrix material for metal oxide catalyst nanoparticles. Functionalization of graphene with various metal oxide nanoparticles can further enhance the properties of graphene for glucose detection as metal oxide nanoparticles make excellent catalysts, due to their high ratio of surface atoms with free valences to the cluster of total atoms and may even provide electrochemical reversibility for redox reactions (Hrapovic et al. 2006; Katz, Willner, and Wang 2004; Rahman et al. 2010). In other words, the combination of graphene with metal oxide nanoparticles provides a new solution for highly sensitive graphene-based glucose sensors for which metal oxide nanoparticles can act as the active site to enhance the specificity and sensitivity, whereas graphene offers fast electron transfer in the electrochemical reaction (Solanki et al. 2011; Z. Zhu et al. 2012).

There are various growth processes to produce metal oxide nanostructures on graphene sheets such as in situ chemical synthesis (S. Chen, Zhu, and Wang 2011; L. Zhu et al. 2013; Teymourin, Salimi, and Khezrian 2013), hydrothermal processes (Pan and Liu 2012; Qin, Luo, and Chang 2012; Golsheikh et al. 2013), microwave heating (S. Wang, Jiang, and Wang 2011), and electrodeposition (J. Luo et al. 2012; L. Luo, Zhu, and Wang 2012; Y. Zhu et al. 2010). The growth mechanism of metal oxide nanostructures on graphene is due to the attraction of positively-charged metal/metal-oxide ions by the polarized bonds of the functional groups on the graphene (such as –OH, C=O of carboxylic, O=C-O of carboxylate, C-O and O-C-O) (Y. Zhu et al. 2010; Sheshmani and Amini 2013). For example, tin oxide nanoparticle/graphene nanocomposites have been developed by a facile microwave method (Zhao et al. 2011). When graphene oxide was mixed with Sn^{2+} ions in the presence of sodium hydroxide, a platform was provided for electrostatic interaction between the negatively charged oxide functional group of graphene oxide and the positively charged Sn^{2+} ions. Nucleation process occurred at the sites, resulting in the growth of tin oxide nanoparticles on the graphene nanosheets during the microwave process. Graphene oxide was reduced to graphene due to the simultaneous presence of Sn^{2+}, sodium hydroxide, and microwave treatment (Lim et al. 2012).

GLUCOSE BIOSENSORS BASED ON GRAPHENE/METAL OXIDE NANOCOMPOSITES

Generally, there are two derivatives of graphene: graphene oxide and reduced graphene oxide. Graphene oxide is functionalized graphene with various oxygen-bearing groups (such as C=O, C−O, and −OH), while reduced graphene oxide is

Table 1. Graphene/metal oxide nanocomposites available for glucose biosensors and their functional properties

Electrode matrix	Enzymatic/ nonenzymatic	Sensitivity/detection limit (μM)	Response time (s)/ applied potential (V)	Ref.
CuO/graphene	nonenzymatic	1065 μA $mmol^{-1}$ L cm^{-2}/1	−/+0.60	Hsu et al. 2012
Cu_2O/graphene nanosheet	nonenzymatic	−/1.2	<3/+0.45	Qian et al. 2012
CuO nanocubes/graphene	nonenzymatic	1360 μA mM^{-1} cm^{-2}/0.7	<5/+0.55	L. Luo, Zhu, and Wang 2012
CuO/graphene nanosheets	nonenzymatic	1480 μA mM^{-1} cm^{-2}/0.29	3/+0.40	Li et al. 2013
CuO/graphene	nonenzymatic	−/6.7 × 1	3/+0.55	Yu et al. 2013
CuO/rGO/CNF	nonenzymatic	912.7 μA/0.1	<2/+0.60	Ye et al. 2013
CuOG-SPCE	nonenzymatic	2367 μA mM^{-1}/34.3 × 10^{-3}	−/−	C. L. Sun et al. 2013
Cu_2O/GNS	nonenzymatic	−/3.3	<9/−0.4	M. Liu, Liu, and Chen 2013
Cu_2O/rGO	nonenzymatic	19.5 μA/mM^{-1}/−	−/−	F. Xu et al. 2013
RGOs-Cu_2O	nonenzymatic	185 μA mM^{-1}/0.05 μM	3 s/0.60	D. L. Zhou et al. 2014
ZnO/nanographene sheets	enzymatic	2.5 mL/min/0.02	−/−	Norouzi et al. 2011
rGO/ZnO	enzymatic	18.97 μAmM^{-1}/0.02 mM	−/0.40	Palanisamy, Vilian, and Chen 2012
Graphene-ZnO	nonenzymatic	−/−	−/−	Kavitha et al. 2012
Graphene-Ni/NiO	nonenzymatic	3410.3 μA/μM/0.28	/0.2 and 0.8	Kumary et al. 2013
NiO-graphene	nonenzymatic	−/5.0	<3/+0.35 V	L. Zhu et al. 2013
NiONPs/GO	nonenzymatic	1087 μA mM^{-1} cm^{-2}/1.00	−/+0.6	Yuan, Xu, Liu, et al. 2013
GNS/NiO hybrids	nonenzymatic	−/2.5	<8/+0.6	Lv et al. 2012
NiONFs/GO	nonenzymatic	1100 μA mM^{-1} cm^{-2}/0.77	<5/+0.6	Y. Zhang et al. 2012
RGO-TDN	nonenzymatic	35.8 μA mM^{-1} cm^{-2}/4.80	10/−0.7	Z. Luo et al. 2013
Ti_2O-graphene	nonenzymatic	6.2 μA/mM cm^2/	/−0.6	Jang et al. 2012
Fe_3O_4/GRO	nonenzymatic	−/3.2	<5/−	Kong et al. 2012
Nafion/EGO/Co_3O_4	nonenzymatic	560 μA $mmol^{-1}$ L cm^{-2}/0.30	−/+0.76	Ensafi, Asl, and Rezaei 2013
PtAu-MnO_2/graphene	nonenzymatic	58.54 μA cm^{-2} mM^{-1}/0.02 mM	−/−	Xiao et al. 2013
Cu_2O/NiO_x/GO	enzymatic	−/−	−/−	Yuan et al. 2013

CuO: copper oxide; Cu_2O: cuprous oxide; CuO/rGO/CNF: CuO nanoneedle/graphene/carbon nanofiber; CuOG-SPCE: CuO/graphene-modified screen-printed carbon electrode; Cu_2O/GNS: Cu_2O nanocubes graphene nanosheets; Cu_2O/rGO: cuprous oxide-reduced graphene oxide; ZnO: zinc oxide; rGO/ZnO: reduced graphene oxide/zinc oxide; Ni/NiO: nickel/nickel oxide; NiONPs/GO: nickel oxide nanoparticles/graphene oxide; GNS/NiO: graphene nanosheet/nickel oxide; NiONFs/GO: nickel oxide nanofibers/graphene oxide; RGO-TDN: reduced graphene oxide- highly dispersed titanium oxide nanoclusters; Ti_2O: titanium dioxide; Fe_3O_4/GRO: reduced graphene oxide/ferroferric oxide nanocomposites; Nafion/EGO/Co_3O_4: Nafion/exfoliated graphene oxide-cobalt oxide; PtAu-MnO_2: platinum-gold alloy and manganese dioxide.

normally obtained through chemical reduction of graphene oxide (Y. Sun, Wu, and Shi 2011; Singh et al. 2011). Recently, nanocomposites of graphene and metal oxides have been successfully prepared on the basis of either graphene oxide or reduced graphene oxide. An electrochemical technique has attracted tremendous attention for producing glucose biosensors due to their sensitivity and selectivity, lower detection limits, faster response times, better long term stability, and low cost (Jetkins, Heinemen, and Halsall 1988; Kvist et al. 2006; Park, Boo, and Chung 2006; Heller and Feldman 2008; Toghill and Compton 2010). Sensing materials without damaging the system (Arora et al. 2011) and the possibility to use samples with small volumes (Ronkainen-Matsuno et al. 2002) are some other advantages of electrochemical biosensors. In this section, the application of graphene/metal oxide nanocomposites for electrochemical glucose sensor is reviewed. Table 1 shows graphene/metal oxide nanocomposites applicable to glucose biosensors reported thus far and give brief descriptions in terms of the availability of enzymatic or nonenzymatic operations, sensitivity, detection limit, response time, and applied potential.

COPPER OXIDE GRAPHENE BASED GLUCOSE SENSORS

Recent advances in nanotechnology have revealed the potential of copper oxide nanoparticles with application to glucose oxidation and hydrogen peroxide detection with good stability (McAuley et al. 2008; X. Wang et al. 2010). As a *p*-type semiconductor with a narrow band gap of 1.2 eV, copper oxide nanomaterials are promising in the development of glucose sensors because of highly specific surface area, good electrochemical activity, and the possibility of promoting electron transfer reactions at a lower overpotential (Reitz et al. 2008; Zhuang et al. 2008). The incorporation of graphene with copper oxide nanoparticles produces synergistic effects leading to improved glucose detection. For example, a graphene/copper oxide glucose sensor has been developed by electrodepositing copper oxide nanocubes on graphene sheets (L. Luo, Zhu, and Wang 2012). The effects of copper electrodeposition time, pH, and applied potential have been studied for optimization of the sensing conditions. An optimized copper electrodeposition time (120 s), 0.1 M of sodium hydroxide solution, and +0.55 V of applied potentials were selected for further investigation. Under the physiological condition, a linear range up to 4 mM with a sensitivity of 1360 μA $mM^{-1} cm^{-2}$ at a positive potential (i.e., +0.55 V) was obtained.

The particle sizes of copper oxide nanoparticles can affect the sensitivity of glucose detection. In a related study by Hsu et al. (2012), graphene/copper oxide nanocomposites were prepared via electrodeposition on a glassy carbon electrode for electrochemical detection of glucose. A larger capacitance of cyclic voltammogram was shown by the graphene/copper oxide electrode compared to the graphene and copper oxide nanoparticle modified electrodes, respectively. A linear range up to 8 mmol L^{-1} glucose was achieved by this sensor, with a detection limit of 1 μmol L^{-1} (signal/noise = 3) at a detection potential of +0.60 V. The authors proposed that the particle sizes of copper oxide nanoparticles were influenced by pH values in the solution. However, it might have been helpful to provide more details on the size-dependent sensitivity of graphene/copper oxide nanocomposites towards glucose in real samples. In addition, the growth processes of copper oxides on graphene, the probability of toxicity, the reproducibility, and stability still requires attention.

In recent years, various approaches have been performed to reduce graphene/metal oxide nanocomposites via a green chemical route which does not involve any hazardous chemicals. Qian et al. (2012) have decorated copper oxide on the surface of graphene nanosheets at a low temperature using sodium citrate as the reductant and stabilizer in alkaline medium. Higher sensitivity and selectivity towards glucose was shown by graphene/copper oxide nanosheets with a good linear dependence on glucose concentration and a detection limit of 1.2 μM (at signal/noise = 3). High catalytic active sites for the glucose oxidation were provided by the decoration of copper oxide nanoparticles on the surface of graphene nanosheets, which may be attributed to the involvement of Cu(II) and Cu(III) surface species in the oxidation of glucose in alkaline medium (Wei et al. 2009; H. X. Wu et al. 2010).

In addition to the graphene/copper oxide glucose sensor, recently Li et al. (2013) synthesized a nonenzymatic glucose sensor by immobilizing nanocomposites on glassy carbon electrode with Nafion. A remarkable electrocatalytic activity towards the oxidation of glucose has been shown by the graphene/copper oxide nanocomposites glassy carbon electrode and led to an enzymeless glucose sensor with a wide linear range between 2.0 μM to 0.06 mM, and a lower detection limit of 0.29 μM (signal/noise = 3). A much larger peak current was displayed by the graphene/copper oxide/Nafion/glassy carbon electrode compared to bare glassy carbon electrode and copper oxide/Nafion/glassy carbon electrode. This demonstrated that graphene/copper oxide nanocomposites have a larger electroactive surface than the copper oxide nanoparticles and can thus act as a promoter to enhance the electrochemical reaction for glucose detection. The findings are clearly presented as they also examined the poisoning possibility of chloride to the activity of graphene/copper oxide nanocomposites and also anti-interference property toward dopamine, uric acid, and ascorbic acid.

ZINC OXIDE GRAPHENE GLUCOSE SENSOR

Zinc oxide nanomaterial is a wide band gap (3.37 eV) semiconductor having a large excitation binding energy of 60 meV at room temperature, high specific surface area, nontoxicity, chemical stability, and high electrical conductivity (Nakahara et al. 2001; Lu, Ng, and Yang 2008). A high isoelectric point (IEP) of about 9.5 and the positively charged of zinc oxide are helpful to immobilize the negatively charged glucose oxidase (IEP = 4.2) at the reduced graphene oxide/zinc oxide composite in the physiological pH (7 to 7.4) (F. F. Zhang et al. 2004; Zang et al. 2007).

Several investigations have been performed to produce graphene/zinc oxide nanocomposites for glucose detection. In the work by Norouzi et al. (2011), an enzymatic glucose biosensor was synthesized based on zinc oxide nanoparticles doped in nanographene sheets. Nafion was used in the construction of the biosensor to prevent loss of the enzyme molecules. The authors claimed that the large quantity of well-dispersed zinc oxide nanoparticles on the graphene sheet were suitable for the immobilization of the glucose oxidase enzyme and thus led to a sensitive glucose sensor with a linear response range between 0.1 to 20 μM and lower detection limit of 0.02 μM at a signal-to-noise ratio of 3. However, the authors offered no information on the size distribution of the zinc oxide nanoparticles.

A similar approach has been reported by Palanisamy, Villian, and Chen (2012). An enzymatic glucose sensor was prepared using reduced graphene oxide/zinc oxide

nanocomposites on a glassy carbon electrode by electrochemical approach at room temperature. Good electrocatalysis toward the reduction of oxygen and oxidation of glucose was exhibited by the as-fabricated reduced graphene oxide/zinc oxide/glucose oxidase composite with a linear range from 0.02 to 6.24 mM and a detection limit of 0.02 mM. The authors found that the reduction current decreased linearly with the addition of glucose indicating excellent catalytic activity for glucose. However, this study offered no explanation on the effect of different concentration of glucose toward the sensitivity of glucose detection using graphene/zinc oxide/glucose oxidase composite film modified glassy carbon electrode.

In other work, Kavitha et al. (2012) introduced a glucose oxidase biosensor using graphene nanosheets decorated with zinc oxide nanoparticles through the in situ thermal decomposition at a moderate temperature. The sensitivity toward glucose was improved using graphene/zinc oxide nanocomposites compared to bare graphene. The enhanced performance of the graphene/zinc oxide biosensor was attributed to the synergistic influence of graphene (large surface area-to-volume ration and the high conductivity) and zinc oxide nanoparticles (good biocompatibility), thus provided good enzyme activity, which eventually resulted in direct electron transfer between the redox sites of the enzyme and electrode's surface (Kavitha et al. 2012). Nevertheless, the evidence cited in this article does not support the overall conclusion as this research did not take into account the toxicity test, anti-interference test, and stability test of the graphene-nickel/nickel oxide composite towards glucose. It has to be admitted that the current study is still far from being conclusive and further studies must be undertaken.

NICKEL OXIDE GRAPHENE GLUCOSE SENSOR

Various metal/metal oxide nanoparticles and graphene have been prepared so far due to the special properties of these materials. In practice, the high cost of the electrode using metal materials may limit their commercial application (Cao et al. 2011; Mu et al. 2011). Thus, some researchers have concentrated on the use of low-cost metal oxide materials such as nickel oxide nanomaterials. Nickel oxide based graphene nanocomposites have received considerable attention in electrochemical sensors, especially in glucose sensor due to its excellent electrocatalytic, inexpensive properties, and absence of interferences by other elecroactive species, such as ascorbic acid, dopamine and uric acid (Lv et al. 2012; Y. Zhang et al. 2012; Kumary et al. 2013; Zhu et al. 2013; Yuan et al. 2013).

Zhu et al. (2013) developed a nonenzymatic glucose sensor by directly electrodepositing nickel on a glassy carbon electrode with a graphene modifier. Then, the nickel was oxidized to nickel(II) oxides by potential cycling (Zhu et al. 2013). A high electrocatalytic activity for the oxidation of glucose was shown by the graphene/nickel oxide/glassy carbon electrode as there was a great enhancement of the anodic peak current while the cathodic peak current obviously decreased. A linear range up to 4.5 mm glucose level was achieved by this electrode sensor with a detection limit of 5 μM (at a signal/noise = 3) and the response time was very short (<3 s). These results are consistent with the goal of this research to prepare nickel (II) oxides and graphene nanocomposites modified glassy carbon electrode for the amperometric determination of the glucose concentration with high sensitivity and stability.

Recently, solving the problem of irreversible agglomeration of graphene sheets using solution based techniques has received considerable attention to synthesize graphene/metal oxide nanocomposites. Kumary et al. (2013) prepared a graphene-nickel/nickel oxide composite via solar exfoliation of graphite oxide/nickel acetate precursor for glucose sensor application. An alkaline medium (0.1 M of sodium hydroxide solution) was chosen as the supporting electrolyte because it provided the best peak current response to glucose (Qiao and Zheng 2012). A linear range up to 5 μM with a sensitivity of 3.410.3 μA/μM and a detection limit of 0.28 μM was obtained at a substantially positive potential (0.2 and 0.8 V). The discussion consistently relates the key findings in this research.

In other work, the graphene/metal oxide hybrids showed a poor water-dispersing ability which caused obstacles for the fabrication of the sensing electrodes and thus, appropriate dispersants (such as DNA, alcohol, sulfonated poly(ether-ether-ketone) were required (Lv et al. 2010). Lv et al. (2012) introduced a nonenzymatic glucose sensor through a self-assembly process of powdered graphene nanosheets/nickel oxide. Then, *ss*-DNA (single-strand DNA) was employed to disperse the powdered graphene nanosheets/nickel oxide hybrid in aqueous solution. Electrocatalytic activity toward the oxidation of glucose with a linear range between 1 μM to 200 μM and a detection limit of 2.5 μM at a detection potential of 0.6 V has been reported when using the obtained graphene nanosheets/nickel oxide/DNA hybrids for glucose sensing. The findings are clearly presented using schematic diagrams and a graph of electrochemical performance of the graphene nanosheets/nickel oxide glassy carbon electrode toward glucose.

OTHER METAL OXIDE-GRAPHENE GLUCOSE SENSORS

Other graphene/metal oxide nanomaterials such as graphene/titanium dioxide, graphene/iron oxide, graphene/cobalt oxide, and graphene/manganese dioxide have been reported for glucose sensing application (Z. Luo et al. 2013; Jang et al. 2012; Kong et al. 2012; Ensafi, Asl, and Rezaei 2013; Teymourin, Salimi, and Khezrian 2013; Xiao et al. 2013). Titanium dioxide nanomaterials are biocompatible, environmentally-friendly, and have been shown to have promising applications [130]. Z. Luo et al. (2013) developed a highly dispersed titanium dioxide nanocluster on reduced graphene oxide under microwave irradiation. The reduced graphene oxide/titanium dioxide nanocluster is responsible for the high loading of glucose oxidase and a short response time (10 s) with sensitivity 35.8 $\mu A\,mM^{-1}\,cm^{-2}$. In addition, a detection limit of 4.8 μM has also been reported.

Functionalization of iron oxide nanomaterials on graphene has been explored for glucose sensing as the magnetic properties of these nanocomposites promise a greatly improved delivery and recovery of biomolecules (Rossi, Quach, and Rosenzweig 2004; Ma et al. 2012). However, there are only a few biosensor applications. Kong et al. (2012) introduced the application of graphene/iron oxide nanocomposites as an electrode material for glucose sensing. The nanocomposites were synthesized by a coprecipitation method. A low response time of less than 5 seconds with a detection limit of 3.2 μM ($S/N = 3$) was shown using the graphene/iron oxide electrode for glucose detection.

Ensafi et al. (2013) reported an amperometric glucose sensor based on a Nafion/exfoliated graphene oxide/cobalt oxide nanocomposite coated glassy carbon

electrode. A remarkable electrocatalytic activity towards the oxidation of glucose was shown by the Nafion/exfoliated graphene oxide/cobalt oxide coated glassy carbon electrode with a detection limit of $0.3\,\mu mol\,L^{-1}$ at a detection potential of 0.76 V. Experimental data for the glucose detection was in good agreement with results from the method performed in milk.

The growing attention for compact point-of-care medical devices and portable instruments for glucose sensing application has encouraged Xiao et al. (2013) to produce electrochemical biosensors based on free-standing graphene paper carrying binary nanocomposites of platinum-gold alloy and manganese. The coral-like platinum-gold/manganese dioxide nanocomposites were grown on the substrate through one-step template-free electrodeposition, leading to intimate contact between the platinum-gold alloy and manganese dioxide matrix. A greatly enhanced sensing performance such as wide linear range (0.1 mM to 30.0 mM), high sensitivity ($58.54\,\mu A\,cm^{-2}\,mM^{-1}$), and a low detection limit (0.02 mM, $\underline{S}/N = 3$) were reported using the platinum-gold/manganese dioxide manganese dioxide binary nanostructure-decorated graphene paper for glucose.

CONCLUSIONS: FUTURE PROSPECTS AND CHALLENGES

With the advent of nanotechnology, various materials have been investigated as biosensors for monitoring glucose without interference from other electroactive species. Metal oxide nanoparticles have large surface-to-volume ratios and can act as the active site to immobilize glucose oxidase and high isoelectric point (IEP). This review briefly summarized the most frequently-used electrochemical methods and metal oxides to functionalize graphene including copper oxide (IEP = 6.5), zinc oxide (IEP = 9.5), nickel oxide (IEP = 9.9–11), titanium dioxides (IEP = 3.9–8.2), iron oxide (IEP = 6.5–6.6), and manganese dioxide (IEP = 4–5) in glucose biosensors. Zinc oxide and nickel oxide which have high IEPs might be the most suitable graphene electrode materials for glucose biosensors. Additionally, the high IEP of zinc oxide and nickel oxide provide a better surface for glucose oxidase immobilization which further improves the sensitivity and selectivity during glucose monitoring.

Despite the impressive advances in glucose biosensor technology, there are still several challenges related to the achievement of stable and reliable glucose sensing based on graphene/metal oxide nanocomposites. The challenges include determining the toxicity and biocompatibility of graphene/metal oxide nanocomposites. The increases use of graphene/metal oxide nanocomposites in a variety of biomedical applications will require stringent toxicological assessment in vitro and in vivo. It is a challenge as there are a limited number of studies that have looked into the toxicity profile of graphene/metal oxide nanocomposites. Meanwhile, under biocompatibility, it is important to consider the effect of sensor upon the in vivo environment for a prolonged operation in the blood. It is a major challenge and significant progress must be made towards the continuous monitoring of glucose using graphene/metal oxide sensors.

Amperometric electrochemical biosensors for glucose play a leading role in this sensing area. Besides, the development of a cheap, sensitive and interference free sensor for nonenzymatic glucose detection is still greatly in demand. Indeed, research interest in glucose sensors will grow with increasing numbers of diabetic patients.

Taking into account the excellent individual properties of graphene and metal oxide nanomaterials, the combination of graphene with metal oxide nanomaterials provides a new solution for highly sensitive graphene-based glucose sensors.

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