

Recent trends in the development of electrochemical glucose biosensors

Abstract

Glucose sensing is of great significance as diabetes is becoming one of the biggest health care challenges of the near future. Substantial effort has been made to design and develop novel glucose monitoring devices. The aim of this review is to provide a brief overview of the recent trends in the development of glucose biosensors based on electrochemical detection procedure. A brief introduction to glucose biosensor is presented, with attention given to the challenges in non-enzymatic and enzymatic electrochemical glucose biosensors. Special emphasis is given to discussion on biocompatible conducting polymer and its derivatives used in the fabrication of electrochemical glucose biosensors.

Keywords: glucose, biosensor, electrochemical, enzymatic, non-enzymatic

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Abbreviations: PANI, polyaniline; GOx, glucose oxidase; SWCNH, single-walled carbon nanohorns

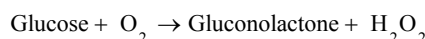
Introduction

The research interest behind the development of glucose monitoring systems is in fact firmly related to diabetes mellitus, a group of endocrine disorders marked by abnormal levels of glucose in the blood.^{1,2} World Health Organization (WHO) has recently reported about 422 million people around the globe suffered from this disease.³ Diabetes is categorized mainly into two types. In type 1, the immune system wrongly identifies and attacks pancreatic beta cells that are responsible for insulin production. As a result, not enough insulin is produced by the pancreas. In case of type 2, human body become insensitive to insulin due to persistent overexposure to glucose.⁴ Regardless of the cause of diseases, both types are equally contributing to the complications such as kidney failure, blindness, cardiovascular disease, non healing of wounds, and neurological disorders.^{4,5} Therefore, maintaining the level of glucose in human blood is of great clinical importance, and accordingly the glucose biosensors industry is growing rapidly. In the last 30 years, a lot of struggles have been made to develop sensitive and selective glucose biosensors.⁶ For the detection of glucose, two methods namely optical and electrochemical have been used. In optical methods, photons are measured which do not require wire connection, thereby making them very useful for bioimaging and *in vivo* biosensing. These methods include absorptiometry, reflectometry, surface plasmon resonance and fluorescence.^{7,8} Electrochemical methods, especially amperometric methods, have been extensively employed in glucose sensing because of its promising characteristics such as rapid response, high sensitivity, and convenient operation.⁹

Discussion

There are two categories of glucose sensors i.e., enzymatic and nonenzymatic. The conventional enzymatic glucose sensors involve the use of glucose oxidase (GOx), where GOx catalyzes the oxidation of glucose in the presence of O₂ to produce hydrogen peroxide. During this reaction, two electrons and protons are exchanged. The reaction with glucose oxidase enzyme is shown in the following equation:

GOx



Glucose concentration is determined by monitoring either the consumption of O₂ or the generation of H₂O₂ during this process. Oxygen measurement is usually limited by the error associated to dissolved oxygen. When there is oxygen deficiency in the body fluid, this method cannot be used. On the other hand, the amount of H₂O₂ produced is usually determined by amperometric method by oxidation at the working electrode. This method however utilizes high anodic potential which results in electroactive interference, thus affecting the response signals. Non-enzymatic glucose sensing is a direct approach of monitoring glucose level based on the oxidation or reduction of glucose without using enzymes. This method is rapid and cost-effective. Usually noble metals such as Pt and Au and their composites have been utilized to fabricate non-enzymatic biosensors.^{10,11} However, direct electrooxidation of glucose on noble metals leads to a number of issues such as sluggish glucose oxidation kinetics, poisoning of the electrodes due to adsorbed intermediate species and poor selectivity.¹² Apart from Pt and Au, other materials such as graphene and carbon nanotubes have also been tested as electrode material for the development of non-enzymatic glucose biosensors^{13,14} (Table 1).

To improve the performance of glucose biosensors, efforts have been made to search out new materials with enhanced electrical and surface properties. Conducting polymers present unique class of materials with intriguing properties such as high electrical conductivity, low energy optical transitions, high electron affinity, and low ionization potential. Because of these properties, they are considered as promising materials for the development of glucose biosensors.^{27,28} Various conducting polymers have been studied, including polypyrrole, polythiophene, polyacetylene, and PANI.²⁹ In glucose biosensor, the function of these polymers is to provide a matrix for enzyme immobilization and facilitate the electron transfer in enzymatic or redox reaction. Among the conducting polymers, PANI has got recent attention due to its interesting characteristics such as high conductivity, good opto-electronic properties, environmental and electrochemical stability, biocompatibility, low cost, and easy doping de-doping chemistry.³⁰

Table 1 PANI and its composites for electrochemical glucose sensing

Electrode	Enzyme immobilization	Selectivity	Detection range	Detection	Reference
GOx/PANI	Entrapment of GOx in PANI matrix	Permeable to oxygen	0-5 mM	Oxygen	15
GOx/poly(p-phenylenediamine)	Entrapment	Interfering species such as Lactose, sucrose, urea	1-6 mM	Hydrogen peroxide	16
GOx/Poly-2-aminoaniline	Covalent	Interference from ascorbic acid	0.2-20 mM	Amperometry	17
GOx/PANI/polyisoprene	Entrapment	Limit ascorbic acid	0.01-12 mM	Hydrogen peroxide	18
Nafion/GOx/AuNPs/PANI	Cross-linking	Negligible interference from ascorbic acid	0.001-0.8 Mm/L	Hydrogen peroxide	19
GOx-PANI nanofibers	Covalent	No effect on the response with addition of ascorbic acid, uric acid and 4-acetamidophenol	0.01-1 mM	Direct electrochemistry	20
GOx-PANI nanotubes	Entrapment	No effect on the response with addition of ascorbic acid, uric acid and 4-acetamidophenol	0.01-5mM	Direct electrochemistry	21
GOx/dendrimer-encapsulated Pt nanoparticles/PANI/CNT	Cross-linking	Effective screening of uric acid, acetaminophen, ascorbic acid	0.001-12 mM	Hydrogen peroxide	22
GOx/PtNPs/MWCNT-PANI	Covalent and adsorption	Any interferences	0.003-8.2 mM	Amperometry	23
GOx/AuNPs/PANI nanowires	Covalent	Any interferences	0.001-20 mM	Amperometry	24
GOx/TiO ₂ /PANI/GC	Cross-linking	Negligible effect with addition of uric acid, ascorbic acid, and L-cysteine	0.02-6 mM	Direct electrocatalysis	25
GOx/PANI-TiO ₂ nanotubes	Immobilization via Nafion	Efficient elimination of interferences of uric acid, ascorbic acid, and acetaminophen	0.01-2.5 mM	Direct electrochemistry	26

Shinohara et al. reported for the first time the use of PANI as a matrix for the immobilization of GOx in the fabrication of electrochemical biosensor.¹⁵ The quantity of glucose was determined by measuring the decrease in oxygen concentration due to the enzymatic reaction. Two approaches have been adapted for the GOx attachment to polyaniline. One, GOx is introduced during the synthesis of PANI which resulted the entrapping of GOx in the matrix of polymer. This method is simple and cost effective however leads to the inactivation of enzyme. Second approach accounts for the synthesis of PANI, followed by enzyme immobilization. With this, the reactivity of enzyme could be retained but the stability is affected, particularly when the size of the polymer particle is less than the enzyme molecule and enzyme just adsorb on the polymer surface. To increase the stability, Pan et al. introduced the template assisted immobilization of GOx on PANI. Their results showed good stability and improved glucose sensing performance of the designed sensor.³¹ In addition, PANI derivatives such as poly(p-phenylenediamine) and poly(o-amino benzoic acid) have been used for the construction of glucose biosensors.^{32,33} However, low stability and interference from cooxidizable substances such as ascorbic acid, uric acid etc., were the main bottlenecks in these systems.

In addition, PANI composites have been widely investigated for the design and development of glucose sensing devices. Polyaniline-benzoquinone and GOx-poly(o-aminobenzoic acid) mediated with

tetrathiafulvalene and ferrocene carboxylic acid were employed for glucose sensing.^{33,34} The resultant structures showed better charge transport properties and overall enhanced glucose sensing performance. Hybrid structures of PANI and other materials such as carbon nanotubes (MWCNTs-PANI), Au nanoparticles (AuNPs/PANI), and Pt nanoparticles (PtNPs-PANI) have shown excellent performance with high stability, rapid response, and high selectivity.³⁵⁻³⁷ Besides, nanostructured PANI such as nanofibers, nanotubes, nanojunctions, and nanofibers have been tested for improving the performance of PANI-based glucose biosensors.^{20,21,28} They can be used as suitable matrix for enzyme immobilization and overall the development of stable and reliable glucose biosensors.

Moreover, carbon based-conducting materials such as graphene and carbon nanotubes have been largely exploited for glucose detection owing to their intriguing electrochemical and electrical properties. For instance, Hossain et al.³⁸ combined glucose-treated graphene oxide-activated carbon (GRGO/AC) with Pt nanoparticle (PtNP)-glucose oxidase chitosan (Chit-GOx) and utilized it for glucose detection. The electrode exhibited a broad linear range from 0.002–10 mmol/L in urine sample. Other systems such as graphene/copper oxide nanocomposite,³⁹ direct laser engraved graphene (DLEG) with pulse deposited copper nanotubes (CuNCs),⁴⁰ zinc oxide (ZnO) nanorods on chemically reduced graphene (CRG),⁴¹ nickel oxide decorated

graphene nanosheets (NiO/GNS),⁴² and copper nanowire decorated reduced graphene oxide (CuNWs/rGO)⁴³ have been reported for electrochemical glucose sensing. Similarly, Single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) in its composite form have shown promising results in the detection

of glucose as summarized in Table 2. Particularly, the sensor prepared by decorating silver nanoparticles on organic functionalized MWCNT glucose detection limit of as low as 0.03 μ M and a linear dynamic range of 1.3 to 1000 μ M.⁴⁷

Table 2 Graphene and carbon nanotubes based materials for glucose biosensors

Electrode composition	Sensitivity/ μ A mM ⁻¹ cm ⁻²	Linear range/mM	Limit of detection/ μ M	Reference
PtNP/GRGO-Chit-GOx	61.06	0.002-10	2	38
CuO/graphene	1065	0.001-8	1	39
CuNCs/DLEG	4532.2	0.025-4	0.25	40
ZnO/CRG	17.64	0.2-1.6	NA	41
NiO/GNS	NA	0.005-4.2	5	42
CuNWs/rGO	1625	Up to 11mM	0.2	43
Polyelectrolyte-SWCNTs	157	0.5-5	5	44
Nafion-SWCNH	15	0-6	6	45
MWCNTs-Chit nanowires	5.03 μ A mM ⁻¹	10-Jan	NA	46
AgNPs/F-MWCNTs	1057.3 μ A mM ⁻¹	0.0013-1.0	0.03	47

Conclusion

In summary, this review article highlights the recent research trend in the development of electrochemical glucose biosensors. Conducting polymer PANI, which is benefitted with many attractive properties such as high electrical conductivity, favorable storage ability, and biocompatibility, plays significant role in glucose sensing systems. It provides a favorable matrix for the immobilization of glucose oxidase enzymes thus reducing the loss of enzymes loss during reaction. In addition, it can act as electron mediator and therefore facilitates the charge transfer in enzymatic or redox reaction. Derivatives of PANI have shown promising results in glucose sensing devices. A lot of literature is dedicated to the use of PANI composites for electrochemical glucose sensing. Recently, the research focus is shifted to carbon-based conducting materials such as graphene and carbon nanotubes. Significant improvement in the sensitivity and performance has been achieved for electrochemical glucose sensing using graphene and CNT based nanostructured materials. These materials are expected to be ideal models for the fabrication of stable, sensitive, reliable glucose biosensors.

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Conflict of interest

The author declares no conflict of interest.

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