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Research paper

Graphene-Based Wearable Electrochemical Glucose Biosensor: A Review

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Abstract

An overview of recent advancement in wearable glucose biosensor has been reviewed. The large sensing area, superior conductivity and high tensile strength has become key factors of graphene as material for flexible and wearable electronic device. This review discusses development and challenges based on graphene and its related materials of recent electrochemical glucose biosensor towards fast response, good selectivity, superb reproducibility and outstanding flexibility. A details comparison in terms of sensitivities, low detection limits and long-term stabilities are included. This review will also provide new insight into invasive and non-invasive methods as future prospect of wearable glucose biosensor.

Keywords: *Electrochemical sensor; glucose biosensor; graphene; non-invasive biosensor.*

1. Introduction

Wearable glucose biosensors are electronic devices which can be worn or patch onto human skin to monitor glucose concentration. The increasing demand for on-site, continuous glucose monitoring have driven development for wearable sensor due to elimination of fixed, bulky measuring device and non-disruption to users' daily activities. A flexible, stretchable and mechanically strong and high sensitivity materials are necessary to build such wearable sensor. Recent trend shows soaring numbers of research based on graphene due to its superior performance; high Young's modulus strength, atomic thin size and high conductivity [1]. Therefore, ggraphene and graphene based materials; graphene oxide (GO) and reduced graphene oxide (rGO) have been widely adopted in many types of glucose biosensor [2].

The first commercialized glucose biosensor is electrochemical type by Yellow Spring Instrument (YSI) in 1975 [3]. Electrochemical biosensors have advantages such as wide linear response range, low detection limits, reproducibility and optimum stability, which lead to their greater usage as compared to thermal, piezoelectric or optical biosensor. The robustness, compatibility with new microfabrication technologies, disposability, low cost, ease-of-operation, independence from sample turbidity and minimal power requirements has led electrochemical as largest market value holder among biosensors [4].

The latest glucose biosensor in market has offered continuous glucose monitoring (CGM) system such as by [5]. However, sensor cycle is limited thus requires new sensor replacement and calibration resulting in higher maintenance cost and long start up hour. Plus, invasive method is adopted where sensor is inserted under the skin to measure glucose concentration in blood. Since diabetic is found in any ages, invasive method has always become a challenge for measuring sample in infants, kids and elders. Thus, many efforts have been poured to achieve minimal invasive or non-invasive measuring method using saliva, sweat or tears as samples.

This paper will review on recent electrochemical glucose biosensor using graphene in terms of basic principles, analytical performance (sensitivity, low detection limit, linear range) and the present status of wearable glucose biosensor. First section will focus on invasive method followed by non-invasive method in section

2. Invasive Electrochemical Glucose Biosensor

Electrochemical sensing requires three types of electrodes; working electrodes, reference electrode and counter electrode. Here, transparent conductive electrode (TCEs) are essential for flexible, stretchable electrochemical sensor compared to conventional indium tin oxide (ITO) [6]. Work in [7] reported highly sensitive, non-enzymatic and enzymatic device using platinum (Pt)-decorated graphite to detect glucose as shown in Fig. 1. The reported linear range is between 0 mM - 0.9 mM, sensitivity up to 105 μA cm^{-2} mM^{-1}, and low detection limit (LOD) of 10 μM. The device can be elongated to 75% of its initial length to show its maximum strain. Plus, correlated results between sample from sweat and blood offers alternative for non-invasive glucose sensor. However, superior performance is obtained from enzymatic device (using GOx) compared to non-enzymatic device thus putting strain to sensor cycle time.

Next, another flexible electrode is proposed in [8] based on graphene paper with 3D nanoporous gold scaffold plus a layer of Platinum/cobalt nanoparticles as in Fig. 2. The PtCo possess high electrocatalytic activity towards electro-oxidation of glucose. This nonenzymatic device shows wide linear range from 35 μM - 30 mM, a LOD of 5 μM and a high sensitivity of 7.84 μA cm^{-2} mM^{-1}. It offers good selectivity, long-term stability and reproducibility but consumes high production cost due to various material adopted. Another similar work that proposed nonenzymatic device based on graphene paper is reported in [9]. An ionic liquid with

conductive ink formulated by 3D porous graphene-carbon nanotubes (CNT) is printed on the graphene paper. The platinum/gold alloy nanoparticles is then deposited on the paper for glucose sensing. The linear range is from 0.1 mM - 11.6 mM, with a sensitivity of 0.19 mA cm^{-2} $mM^{-1}$and a detection limit of 8.0 µM. The sensitivity is lower but compensated with easier preparation method.
Other than conductive metals, few research suggest smart fabrics for biocompatible sensor as reported in [10]. It used silk fibroin as substrate and platform for GOx immobilization and encapsulated with graphene field effect transistor (FET) as referred to Fig. 3. This CVD grown graphene FET biosensor detected glucose range in 3-10 mM the biocompatibility of silk is reported to improve stability of enzyme for long time measurement
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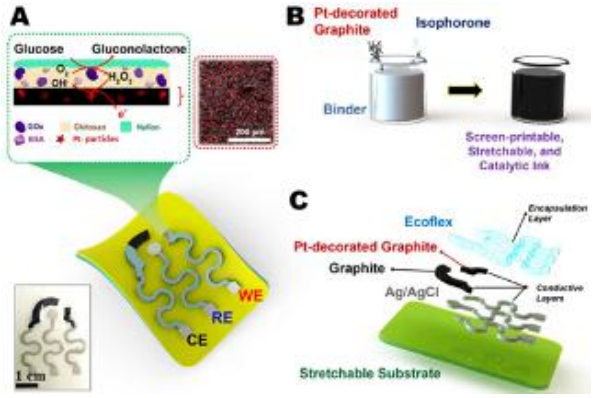

Fig. 1: Design of stretchable screen printed biosensor using Pt-Graphite ink onto flexible PU as in [7]. Preparation method is simple and low cost.

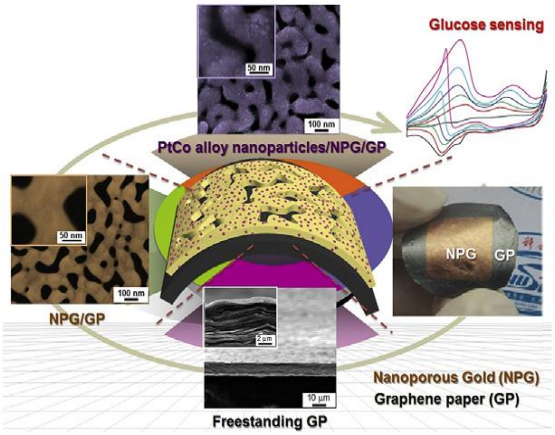

Fig. 2: Free standing, flexible GP and NPG electrodeposited with PtCo for nonenzymatic biosensor in [8].

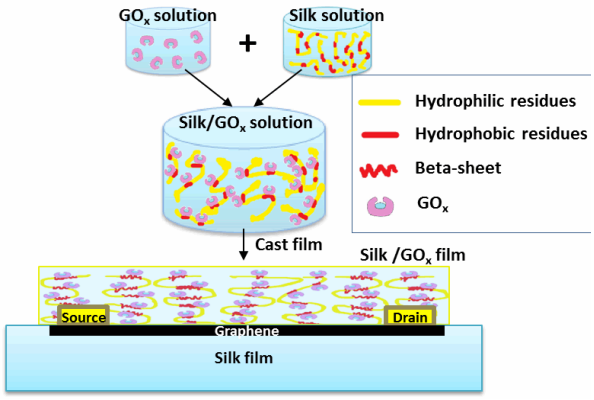

Fig. 3: Stabilized graphene/FET on biocompatible silk film in free standing, flexible GP and NPG electrodeposited with PtCo for nonenzymatic biosensor in [10].

Table 1 summarize analytical performance and sensing method for the discussed works.

Table 1: Graphene based invasive glucose biosensor

Sensing Material	Sensor Preparation	Sensitivity	Linear Range	LOD (µM)	Ref.
*Pt-NPs-graphite/PU	Screen printed	105 µA $cm^{-2}mM^{-1}$	0-0.9 mM	10	[7]
**GP/Au-NPs/PtCo	Ultrasonic electrodeposition	7.84 µA $cm^{-2}mM^{-1}$	35µ-30mM	5	[8]
***GP/rGO-CNT-IL/PtAu	Screen printed	0.19 mA cm^{-2} mM^{-1}	0.1-11.6 mM	8	[9]
Silk/FET	graphene: CVD Silk: aqueous	-	3-10 mM	-	[10]

*Pt: Platinum, NP: Nanoparticle, PU: polyurethane
**GP: Graphene paper, Au: Gold, PtCo: Platinum-Cobalt
***rGO: Reduce graphene oxide, CNT: Carbon nanotube, IL: ionic liquid

3. Non-Invasive Electrochemical Glucose Biosensor

A non-invasive method is very useful for continuous monitoring due to elimination of conventional finger pricking. This method not only lessen users' pain, but very convenience for infants and kids. Sweat glucose has been found in the concentration range of 0.28–1.11 mM and possibly correlated with blood glucose (4–8 mM) relevantly [11]. Consequently, the accurate measurements of its values can be used to estimate the level of glucose in the blood of the especially type 1 and type 2 diabetic patients. This shows progress of a non-invasive glucose biosensor by measuring glucose in sweat/saliva or tears; other than blood. One of early work using sweat control is reported in [12]. This works used sweat-uptake layer (Nafion) to gather sweat sample and graphene doped with gold and combined with a gold mesh to form wearable patch not only for monitoring, but for including thermo-responsive needle for drug delivery. The glucose concentration tested is between 10µM to 0.7mM. The sensitivity is stable despite patch deformity and it is not affected by other presence of lactate, ascorbic acid and uric acid.

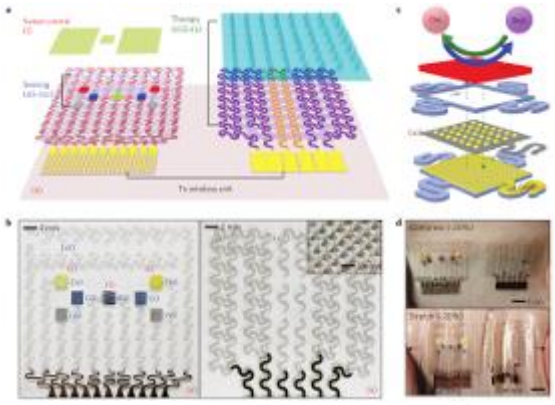

Fig. 4: Schematic drawings and corresponding images of the graphene-hybrid electrochemical devices and thermoresponsive drug delivery microneedles in [12]. Graphene doped with gold and gold mesh is adopted in sensing area to improve sensitivity.

An electrochemical transistor using polypyrrole (PPy) nanowires and reduced graphene oxide (rGO) [13] shows novel design of fibre transistor for glucose detection. It shows fast a response time 0.5 s, a linear range of 0.1 µM - 5 µM and low detection concentration of 0.1 µM with good stability after long cycle. This is due to that reduced graphene oxide, which help induce the growth and increase the amounts of polypyrrole nanowires that further enhance the fiber's conductivity. This fibre transistor can be integrated with textiles for a wearable sensor. Electro position of gold participles onto graphene layers for working electrodes in [14-15] has improved sensitivity of sensors. The electrodes are fabricated on polyimide substrate using flexible printed circuit board for integration within microfluidic chip. It measures glucose concen-

tration in interstitial fluid (ISF) rather than blood for minimal invasive method. The achieved linear range is 0 mM - 2.22mM and LOD of 16.6 µM. However, the accuracy of glucose reading using ISF is still in debate due to concentration of glucose in ISF is much lower than in blood sample. Work in [16] offer novel design of electrochemical sensor which employed graphene paper with Molybdenum disulphide (MoS_2) nanocrystals monolayer grown on top of it. The use of copper submicron buds for glucose detection results in llinear ranges between 1.775 mM - 5µM and LOD of 0.500 µM respectively. The obtained value enables glucose monitoring in human perspiration.

A simpler and low cost fabrication of micropatterned reduced graphene oxide onto a flexible polyimide substrate is reported in [17] which uses electron-beam evaporation system. The electrodes are patterned using photolithography technique. The working electrode consist of rGO deposited with gold and platinum alloy before integrated with chitosan-glucose-oxidase. The reports results are detection range of 0.1–2.3mM, sensitivity of 82 µA/mMcm^2, a short response time (12 s) and high linearity (0.99). The low detection limit is 5 µM. The biosensor also tested with human sweat and shows remarkable different of glucose reading between before eating and after eating conditions.

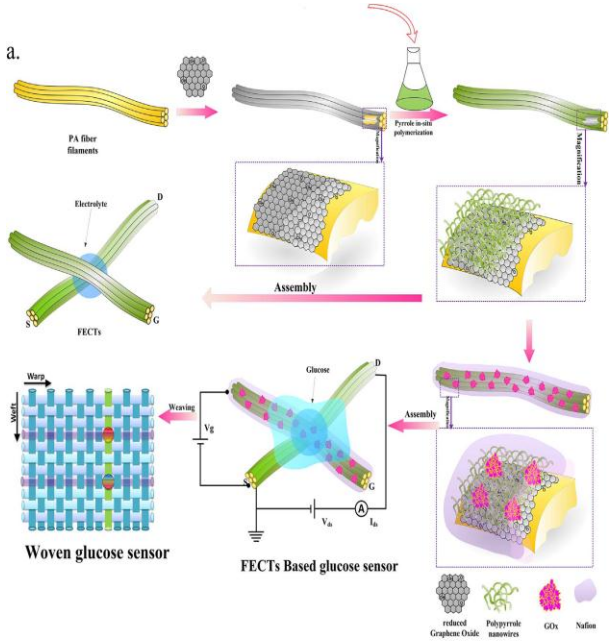

Fig. 5: Preparation of woven fiber organic electrochemical FET using PA fiber in [13].

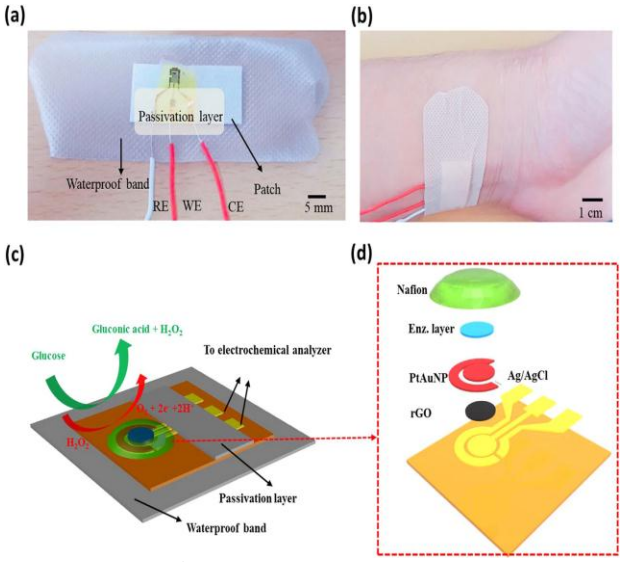

Fig. 6: Image of patchable sweat based glucose biosensor in [17].

Table 2: Graphene based non-invasive glucose biosensor

Sensing Material	Sensor preparation	Sensitivity	Linear Range	LOD (µM)	Ref.
*Graphene/Au/Au mesh/PB	Graphene: CVD		10µ-0.7mM	-	[12]
**PPy/rGO/PA6 FET	Dipping	-	0.1µ-5 µM	0.1	[13]
***Graphene/Au-NPs/PI	PCB inkjet printing	-	0 m-2.2mM	16.6	[14]
****GP/MoS_2/Cu buds	Electrodeposition	-	1.78 m - 5µM	0.5	[16]
rGO-Au-Pt/PI	Photolithography	82 µA/mMcm2	0.1–2.3mM	5	[17]

*PB: Prussian Blue
**Ppy: polypyrrole
***PI: polyimide
**** MoS_2: Molybdenum disulphide, Cu: Copper

4. Conclusion

This review presents recent works on flexible, wearable graphene based electrochemical glucose biosensor focusing on invasive method and non-invasive method which is using humans' sweat primarily as sample. Graphene and its related material such as rGO have certainly improved performance of the sensors. There are also various methods adopted to design each sensor. This shows adaptability of graphene with different of materials as the substrates. A bright future of graphene-based biosensor advances can be expected to assist in designing comfortable, long lasting, low maintenance cost of continuous glucose monitoring system.

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