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Recent advances of electrochemical and optical enzyme-free glucose sensors operating at physiological conditions

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ABSTRACT

Diabetes is a pathological condition that requires the continuous monitoring of glucose level in the blood. Its control has been tremendously improved by the application of point-of-care devices. Conventional enzyme-based sensors with electrochemical and optical transduction systems can successfully measure the glucose concentration in human blood, but they suffer from the low stability of the enzyme. Non-enzymatic wearable electrochemical and optical sensors, with low-cost, high stability, point-of-care testing and online monitoring of glucose levels in biological fluids, have recently been developed and can help to manage and control diabetes worldwide. Advances in nanoscience and nanotechnology have enabled the development of novel nanomaterials that can be implemented for the use in enzyme-free systems to detect glucose. This review summarizes recent developments of enzyme-free electrochemical and optical glucose sensors, as well as their respective wearable and commercially available devices, capable of detecting glucose at physiological pH conditions without the need to pretreat the biological fluids. Additionally, the evolution of electrochemical glucose sensor technology and a couple of widely used optical detection systems along with the glucose detection mechanism is also discussed. Finally, this review addresses limitations and challenges of current non-enzymatic electrochemical, optical, and wearable glucose sensor technologies and highlights opportunities for future research directions.

1. Introduction

According to the world health organization (WHO), diabetes is predicted to be the world's 7th leading cause of death by 2030. It is one of the most commonly diagnosed diseases with an elevated number of affected people every year, which is anticipated to reach 592 million by 2035. In 2016, about 1.6 millions of deaths were recorded directly because of diabetes, and in 2012, 2.2 millions of deaths were registered due to the high glucose level in the blood (Diabetes, 2018). Diabetes is caused by the deficiency of insulin production induced by the destruction of the β-cells of the pancreas (type I or juvenile-onset diabetes) or because target cells became resistance to insulin/insulin deficiency (type-2 or adult-onset diabetes) (Xiao et al., 2019). The causes of diabetes are multifactorial and include both genetic and environmental factors induced, for instance, by virus and life-style (Murea et al., 2012). Among the various types, about 5-10% and 90-95% of global diabetes are accounted for type-1 and type-2 diabetes, respectively (American Diabetes Association, 2012). To maintain the blood glucose level of diabetic patients within the normal range (<100 mg/dL, while fasting <140 mg/dL; 2 h after eating) with proper metabolic functions, sugar levels should be measured five times a day for type-1 and several times a week for type-2 diabetes (American Diabetes Association, 2012; Strakosas et al., 2019) The easiest and economical way for diagnosis and prognosis of diabetic patients is the precise detection of glucose levels using easy, portable, and exact quantifiable glucose sensor devices. To this purpose, various detection methods, based on techniques such as fluorescence, UV–vis spectroscopy, mass-spectrometry and electrochemical have been applied to glucose determination (Hwang et al.,

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2018; Tian et al., 2014). Among these techniques, electrochemical approaches have received increasing interests due to their advantages over other techniques, such as low-cost, fast response and user-friendly. In particular, in clinical analysis, enzymatic glucose sensors with electrochemical transduction are widely used and commercialized (Dincer et al., 2019; Monzó et al., 2015). Although accurate, they suffer from long term stability, due to loss of the enzyme biological activity (Monzó et al., 2015). In fact, the commonly used glucose oxidase (GO_x) enzyme has low-stability and require complex immobilization processes of GO_x onto the sensor surface (Du Toit and Di Lorenzo, 2014). In addition, GO_x is irreversibly damaged at a temperature >40 °C, loses its catalytic activity bellow pH 2.0 or higher than pH 8.0, and can be affected by surfactants at a certain pH (Mitsou et al., 2017; Wang et al., 2018).

With the above sensors, the measurements are typically made using a small drop of blood (ca. 1 μL), obtained from the fingertip or forearm using a lancet. The blood droplet is spread onto the sensor surface and an electrochemical reaction occurs that allows the quantification of glucose under physiological conditions (Meyerhoff et al., 2014). However, these disposable and self-monitoring electrochemical glucose sensors are invasive and painful to diabetic patients, especially in those cases where it is necessary to carry out the measurements five times a day (Bruen et al., 2017). Considering the discomfort and the will to reduce the pain of diabetic patients, scientists and companies have directed their efforts towards the development of noninvasive or minimally invasive continuous glucose monitoring devices (implantable and wearable type) for blood and other biological fluids (e.g., sweat, tears, urine, etc.), using combination of transduction systems, including both electrochemical and optical approaches (Gonzales et al., 2019). The optical transduction systems are highly competitive since they allow the continuous tracking of glucose level in every 1-5 min with high accuracy. Yet they are expensive with a short lifetime (maximum one week) and require frequent calibrations (i.e., usually 5–8 times a day) (Gonzales et al., 2019). As a matter of fact, because of the above issues, there are still a large number of reports dealing with the electrochemical and optical, implantable and wearable systems for continuously tracing of glucose in body fluids, which can work in an invasive, non-invasive, or minimally invasive manner (Gonzales et al., 2019).

For the fabrication of efficient, sensitive, selective, low-cost, and highly stable enzyme-free glucose sensors, it is crucial to develop either suitable effective electrocatalysts, for electrochemical sensing, or molecular recognition compounds, for optical sensing. In addition, they should be able to detect the glucose concentration in biological samples under their physiological conditions, without any pre-/post-treatment (Niu et al., 2016b; Zhang et al., 2015). Contrary to enzyme-based sensors, non-biological nano-catalysts or molecular recognition elements have the advantage of being highly stable and cheap (Jiang et al., 2018; Toi et al., 2019). In this regard, nanotechnology plays an important role (Tian et al., 2014). To date, various nanomaterials have been developed for the direct electrochemical oxidation of glucose and include metals (Au, Ag, Ni, Cu, Co, etc.) (Ansari et al., 2019; Niu et al., 2016a,b), metal-oxides (NiO, CuO, Co_2O_3, etc.) (Rahman et al., 2010; Zhu et al., 2016) metal sulfides (Kim et al., 2017; Niu et al., 2016a; Rahman et al., 2010) metal-organic framework (MOF) (Li et al., 2019b; Lopa et al., 2018), and metal azolate frame work (MAF) (Lopa et al., 2019). Even though these nanomaterials can successfully oxidize the glucose without the necessity of GO_x, most of them do not work at physiological pH, rather they are electroactive at a much higher pH (Cash and Clark, 2010; Rauf et al., 2016; Si et al., 2013). Pt- and Au-based nanomaterials behave differently and are actually able to catalyze electrochemical oxidation of glucose at physiological pH conditions. They include Au/Pt-black/Nafion composites (Lee et al., 2016), carbon-supported PtxFe alloy nanoparticles (Mei et al., 2015a), Pt_3Pd nanoparticles and reduced graphene oxide composite (Zhao et al., 2015), titanium dioxide nanowire–poly(3-aminophenyl boronic acid)–Au nanoparticle ternary nanocomposite (Muthuchamy et al., 2018), and Au nanoparticles deposited carbon nanotubes (Branagan and Breslin, 2019). The non-enzymatic glucose sensor technology based on the latter compounds is promising to move from bench to commercial applications, and the development of noninvasive or minimally invasive wearable type devices (Bruen et al., 2017; Si et al., 2013). In contrast, a few molecular recognition compounds have been reported for the development of noninvasive, enzyme-free optical glucose sensors. They include phenylboronic acid-functionalized hydrogels, boronic acid-containing fluorophores, and boronic acid derivatives. These devices have been employed successfully for the detection of glucose directly in body sweat, tears, and saliva (Zhang et al., 2014a,b; Yuan et al., 2018; Shen and Xia, 2014).

This review article summarizes the state-of-the-art research activities and the recent progress for the development of non-enzymatic electrochemical, optical, and their related wearable sensors to detect glucose in biological fluids based on nanomaterials and molecular recognition elements. The fundamental aspects of electrochemistry and optical technologies related to the detection mechanism of glucose are highlighted. Additionally, the challenges of current non-enzymatic electrochemical, optical, and wearable glucose sensor technologies are discussed by emphasizing the opportunities for future research directions.

2. Principles, historical and perspective of the electrochemical glucose sensors

The electrochemical glucose sensor is a device that converts the amount of glucose into a quantifiable electrical signal, typically a current or voltage (Grieshaber et al., 2008; Pohanka and Skládal, 2008). An electrochemical glucose sensor include the biological recognition element, the electrochemical transducer, and the signal processing and display system (Fig. 1a). Among them, the main component is the molecular recognition element, which catalyzes the electro-oxidation of glucose with high selectivity and sensitivity (Cash and Clark, 2010). Leland C. Clark introduced the first glucose sensor in 1962, at the New York Academy of sciences symposium, and was based on GO_x -modified Pt electrode (Heller and Feldman, 2008; Pohanka and Skládal, 2008). Another commonly used enzyme that catalyzes the oxidation of glucose is the glucose-1-dehydrogenase (GDH) along with the oxidized form of pyrroquinolinequinone (PPQ) (i.e., the PQQ-GDH system). These two families of enzymes are different from each other due to their different bond strength and redox potentials. GOx is more specific for glucose oxidation (about 5×10^3 per second in half of the electrochemical relevant reaction) (Heller and Feldman, 2008), while PQQ-GDH can catalyze the oxidation not only of glucose but also of other sugars (Heller and Feldman, 2008; Sato et al., 2001).

The basic principle of operation of the Clark's developed GO_x modified Pt glucose sensor is schematized in Fig. 1b **(first generation)**, and relies on the following reaction process:

$$\text{Glucose} + O_2 \xrightarrow{GO_x} \text{Gluconic acid} + H_2O_2$$

$$H_2O_2 \xrightarrow{Pt} 2H^+ + O_2 + 2e^-$$

It involves the GO_x catalyzed oxidation of glucose by molecular O_2 with the production of gluconic acid and H_2O_2. The generated H_2O_2 is oxidized at the Pt electrode, and the electron flow induced by this oxidation reaction is proportional to the amount of glucose present in the sample. This is considered as 1st generation glucose sensor and has been widely used for the self-monitoring of blood glucose level at physiological pH.

Even though Clark's glucose sensor is highly selective towards glucose oxidation, the detection mechanism of this sensor is greatly dependent on the concentration of O_2 in biological fluids. Therefore, the variation of humidity and the restricted solubility of O_2 in biological fluids (known as the "oxygen deficit") can significantly influence the responses of the 1st generation glucose sensor performance (Yoo and Lee, 2010). To overcome this limitation, the 2nd generation glucose

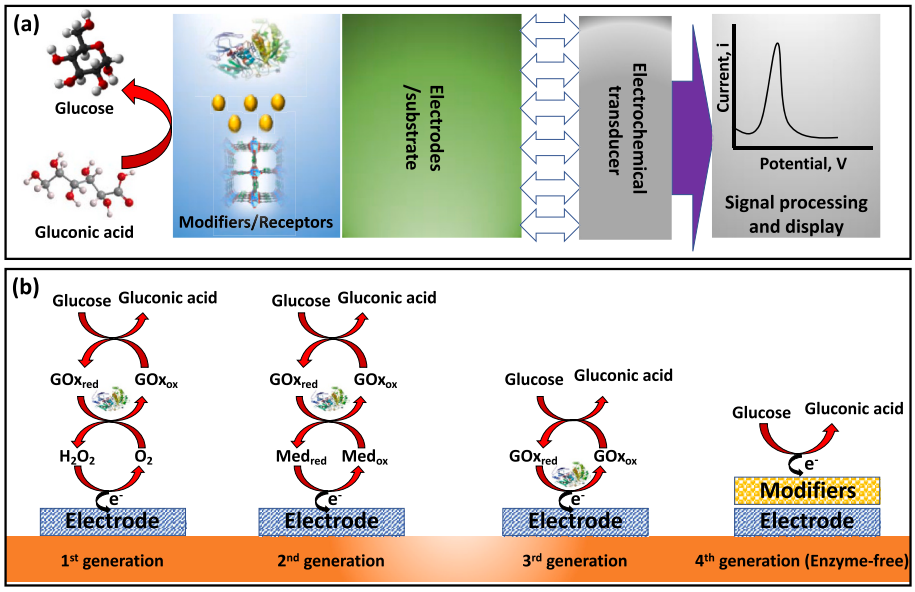

Fig. 1. (a) General scheme and (b) working principle of different generations of an electrochemical glucose sensor.

sensor (Fig. 1b) was introduced by replacing O_2 with a non-physiological redox mediator that can transport electrons from the GO_x to the surface of the sensing electrode (Bollella et al., 2017). Afterward, a 3rd generation glucose sensor (Fig. 1b) was developed based on the direct electron transfer between the GO_x and the sensing surface, thus overcoming the necessity of both mediator and O_2. Even though these 2nd and 3rd generations GO_x based glucose sensors can successfully overcome the O_2 problem, the aforementioned stability issues of GO_x are still valid (Chen et al., 2013). Moreover, other drawbacks arise due to complex immobilization processes of GO_x, chemical deformation during its manufacturing process, storage, and use (Ren et al., 2019).

Recently, the introduction of non-biological catalysts has attracted significant attention for the detection of glucose, as, in principle, they can successfully solve all the limitations of 1st to 3rd-generation glucose sensors. The novel technologies led to a new class of glucose sensors, designated as enzyme-free or 4th generation glucose sensors.

In sections 4 and 6, recent developments of enzyme-free electrochemical and wearable glucose sensors, respectively, which can operate under physiological conditions, are reviewed.

3. Principles of the optical glucose sensor

Optical glucose sensors offer direct, label-free, and real-time detection of glucose (Damborský et al., 2016). Moreover, optical methods are free from reagents and can measure the glucose concentration in a short time (i.e., within 1-5 min). A variety of optical techniques, as transduction systems, have been reported and include Raman, fluorescence, near-infrared (NIR), surface plasmons resonance (SPR), Fourier transforms near-infrared (FT-NIRS), surface-enhanced Raman scattering (SERS) spectroscopy and optical coherence tomography (OCT) (Jernelv et al., 2019). Here, we deal mainly with fluorescence- and SPR-based non-enzymatic glucose sensors. Most of the spectroscopic methods utilize the change of intensity of the light, due to the nanomaterials or molecular recognition compounds, upon they bind the glucose molecules (Fig. 2a). For example, a fluorescence spectroscopy-based glucose detection system does not measure the glucose concentration directly, rather, it measures the readout signal from the molecular recognition compounds or fluorophores where glucose can bind reversibly (Klonoff, 2012; Moschou et al., 2004). The variation of fluorescence intensity of these fluorophores is directly proportional to the concentration of glucose (Fig. 2b). In an SPR based detection system, a glucose molecule binds on the surface of plasmonic nanoparticles functionalized molecular recognition compounds, which induces the variation of the angle of light reflectance (Nguyen et al., 2015). The change of the angle of light reflectance is proportional to the concentration of glucose (Fig. 2c).

4. Enzyme-free electrochemical glucose sensors

To date, a large number of reports are available on the non-enzymatic detection of glucose based on nanostructured metals, alloys, metal-oxides, metal-sulfides, MOFs, and MAFs modified electrodes (Ansari et al., 2019; Lopa et al., 2019; Niu et al., 2016a; Kim et al., 2017; Rahman et al., 2010). However, most of these nanostructured-based sensors are not able to catalyze the oxidation of glucose under physiological pH conditions, rather they work efficiently in alkaline medium (George et al., 2018; Li et al., 2019a). Nanostructures based on Pt, Au and their alloys/composites showed high catalytic activity for oxidation of glucose at neutral pH. For example, Shim et al. synthesized Au-incorporated Au@Pt core-shell nanoparticles (NPs), which were used to decorate the surface of a carbon electrode. The latter was then employed for the non-enzymatic detection of glucose at physiological pH (7.4) conditions (Fig. 3a) (Shim et al., 2019).

Au@Pt core-shell NPs were synthesized by the sonochemical method, then Au was electrochemically incorporated in the nano-gap of Pt shells to form Au@Pt core-shell structures. The Au@Pt/AuNPs-decorated carbon electrode exhibited current responses covering two wide dynamic ranges of glucose concentration, specifically, 0.5–10.0 μM and 0.01–10.0 mM in phosphate buffer saline (PBS) solution (pH 7.4), and a limit of detection (LOD) of 445.7 ± 10.3 nM. The excellent electrochemical performance of this Au@Pt/Au NPs was attributed to the enhanced electroactive surface area of Pt (6.19 m^2/g) and Au (0.8 m^2/g) in the Au@Pt/Au NPs. In another report, Abunahla et al. prepared novel Pt/CuO/Pt metal-oxide-metal and (metal oxide metal sensor) MOMSense devices on a glass wafer substrate by photolithography. Their application for non-enzymatic detection of glucose provided current against glucose concentration with a linear range from 2.2 mM to 10 mM at pH 7.0 (Fig. 3b and c) (Abunahla et al., 2019). The MOMSense device was incorporated in microfluidic channels, fed by human sample solutions (i.e., fluids simulating body fluids) containing glucose, extracted using a suitable separation technique. It must be considered that the MOM-Sense device was not tested for the detection of glucose in real biological fluids.

A large number of reports deal with nanostructured Pt or Pt-

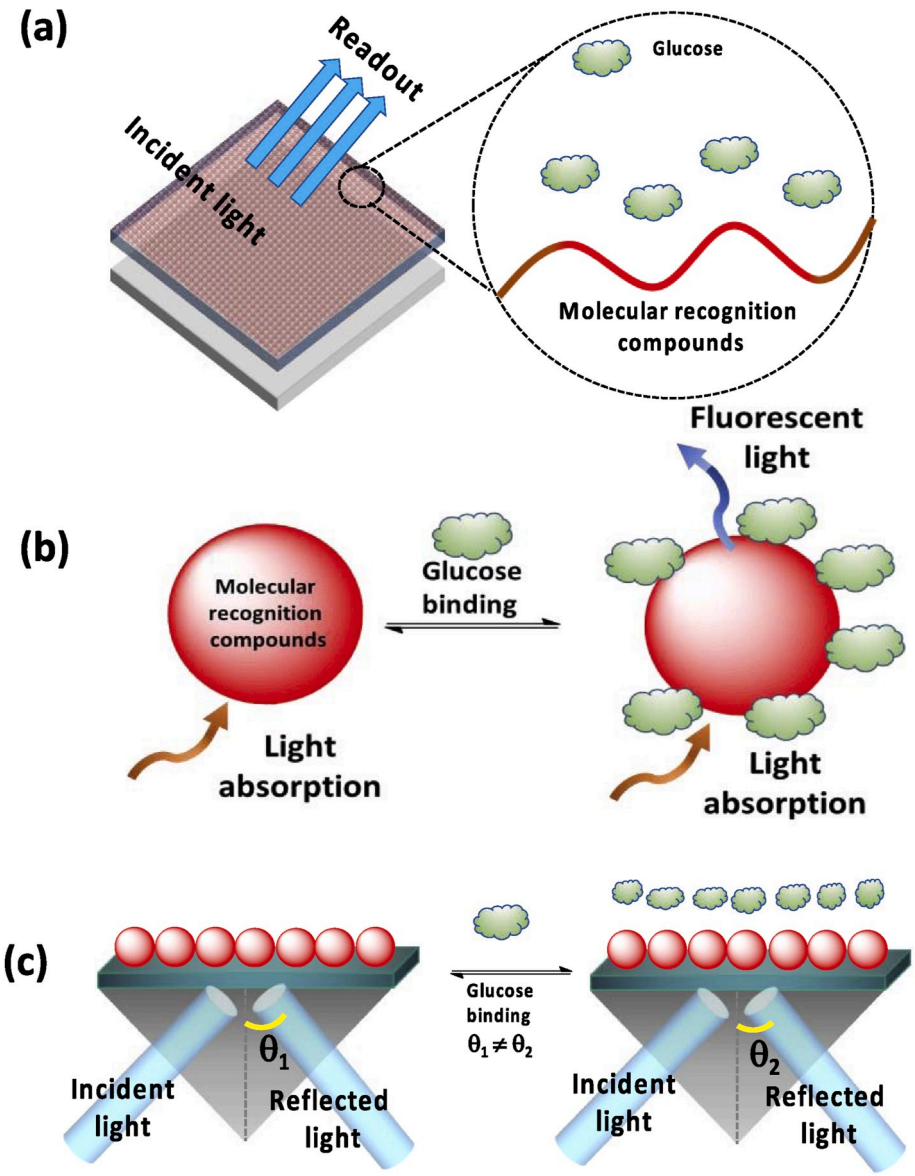

Fig. 2. (a) A general scheme of an optical (spectroscopic) (b) fluorescence and (c) surface plasmon resonance-based glucose sensor.

composites for the electrochemical detection of glucose at physiological pH. Table 1 summarizes articles published in the last ten years. Most of the reported sensors were successfully employed to detect glucose over the concentration range typically found in biological fluids and were suggested as promising systems or future commercialization. However, at physiological pH, they suffer from poisoning effect due to adsorbed intermediates of the oxidation process. Furthermore, Pt-based electrodes display strong capability of protein adsorption, and low selectivity to glucose oxidation due to their oxidizing ability of other organic molecules. Generally, these phenomena produce unstable current responses, which are difficult to correlate with accuracy to glucose concentration in real samples (Bruen et al., 2017; Cash and Clark, 2010). Therefore, as an alternative to Pt-based materials, researchers developed various nanostructures of Au and its composites for non-enzymatic electrochemical detection of glucose at physiological pH (Fu et al., 2015). This is because Au nanostructures make the surface-bound bio-receptors more accessible by increasing the surface area, which is also advantageous to obtain high sensitivity for glucose oxidation (Wang et al., 2013). Hsu et al. developed a non-enzymatic electrochemical glucose sensor that can operate at pH 7.0 based on the AuNPs thin film-modified hemisphere array of photoresist AZ-1518 onto a reclaimed silicon wafer (Fig. 3d and e). The as-prepared sensor showed a wider linear range (55.6 μM – 13.89 mM) with LOD and sensitivity of 9 μM and 749.2 μA/mM/cm^2, respectively (Hsu et al., 2016). To improve the performance of Au based glucose sensors, Fischer et al. prepared an AuNP-decorated diatom biosilica composite (Fig. 3f) for the catalytic oxidation of glucose. Biosilica, obtained from three different species (*Stephanopyxis turris*, *Eucampia zodiacus*, and *Thalassiosira pseudonana*) was used as a support material for the deposition of AuNPs using a covalent coupling method. Diatom biosilica was used as a support material for the deposition of AuNPs since it provides high catalytically active sites (up to 3.28×10^{-4} $mmol_{Glc}/s/mg_{Au}$ for *Thalassiosira pseudonana*) and homogeneous distribution of AuNPs with a loading of ca. 45 wt% (Fischer et al., 2016). A variety of other nanostructures of Au and its composites were prepared for non-enzymatic electrochemical detection of glucose at physiological pH, and Table 1 includes works published in the last ten years. It must be considered that also Au based sensors, in spite of their good performance in terms of sensitivity and LOD, at physiological pH, they also suffer from poisoning effect due to intermediates, while it is more expensive than Pt (Gnana Kumar et al., 2017). Thus, there is still a quest for the development of new nanomaterials that can catalyze the oxidation of glucose non-enzymatically, at low-cost, and free-from poisoning effects.

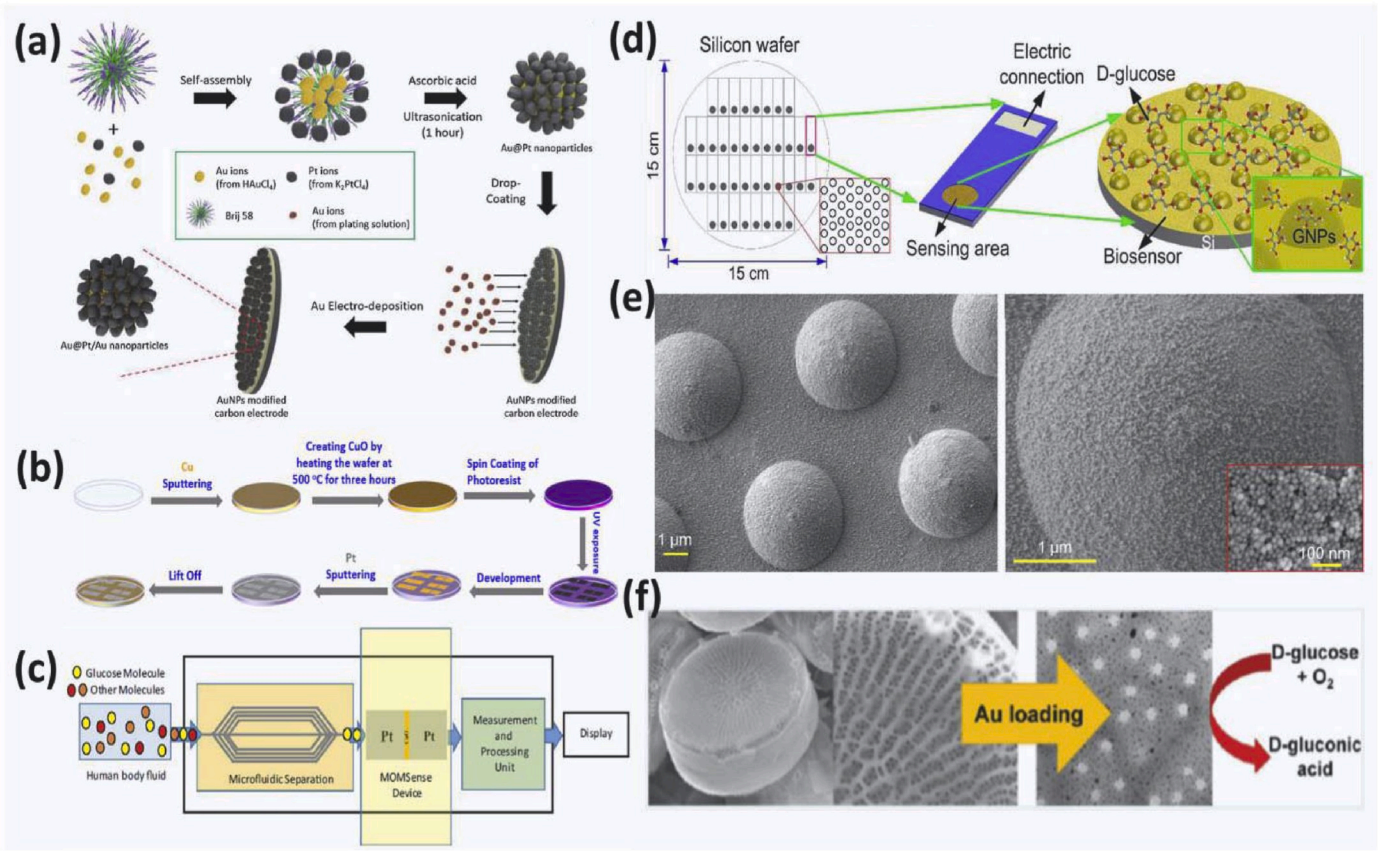

Fig. 3. *(a) Schematic illustration of the preparation of Au@Pt/Au NPs modified electrode (Reproduced with permission from Ref.* (Shim et al., 2019)*). (b) and (c) are the schematic illustration of the preparation of the MOMSense device and the block diagram of the lab-on-chip MOMSense device, respectively (Reproduced with permission from Ref.* (Abunahla et al., 2019)*). (d) and (e) schematic diagrams of the fabrication of AuNPs decorated hemisphere array of AZ-1518 and its corresponding SEM images, respectively (Reproduced with permission from Ref.* (Hsu et al., 2016)*). (f) SEM micrograph of AuNPs decorated diatom biosilica for glucose oxidation (Reproduced with permission from Ref.* (Fischer et al., 2016)*).*

5. Enzyme-free optical glucose sensors

Among the different optical transduction systems, fluorescence and SPR based glucose detection systems attracted much interest. In the last decade, fluorescence-based sensors technology has progressively evolved as a promising alternative to electrochemistry for the detection of glucose (Moschou et al., 2004). Fluorescence-based optical sensors use variable frequencies of light to establish the interaction of the fluorescent nanoparticles or semiconductors with glucose molecules in a concentration-dependent fashion (Mello et al., 2019). The operation principle of the fluorescence sensors is based on various strategies, including quenching, ratiometric, resonance energy transfer (RET), and photoinduced electron transfer (PET) (Mello et al., 2019). Mai et al. developed a vertically aligned ZnO nanotube (NT) modified circuit board substrate by a one-step hydrothermal method (Fig. 4a). The sensor could detect glucose concentration based on the photoluminescence (PL) quenching of ZnO NTs. Generally, upon illumination of ZnONTs, using UV light, the photoexcited electrons in the conduction band of ZnO NTs are recombined radiatively with the emission of photon energies. In the presence of glucose molecules, ZnONTs, and UV light act as a catalyst to oxidize the glucose molecules, which induces fluorescence quenching and reduction of fluorescence intensity. The decrease of the intensity is directly proportional to the glucose concentration over the range between 0.1 and 15 mM and a LOD of 70 µM (Mai et al., 2019). Shen et al. prepared fluorescent carbon dots, functionalized with boronic acid groups, by hydrothermal carbonization of phenylboronic acid. These nanomaterials were used for the non-enzymatic detection of glucose, using UV light as the excitation source (Fig. 4b). The boronic acid functional groups act as binding sites for glucose, via a covalent bond. The attached glucose molecules induce fluorescence quenching of carbon dots emission, which can be utilized for the detection of glucose. The dynamic range found was 9-900 µM and LOD of 1.5 µM (Shen and Xia, 2014). To widen the linear range within the clinically relevant range of glucose, Wang et al. incorporated carbon dots into the glucose -imprinted poly(*N*-isopropylacrylamide-acrylamide-vinylphenylboronic acid) [poly(NIPAM-AAm-VPBA)] copolymer microgels. These systems allowed a continuous fluorescent detection method of glucose (Fig. 4c). The hydroxyl/carboxyl groups functionalized carbon dots can easily form complexes with AAm co-monomers via hydrogen bonding, which can be easily immobilized into the poly(NIPAM-AAm-VPBA) microgels during polymerization. The resulting glucose-poly(NIPAM-AAm-VPBA) hybrid microgels are capable of swelling and shrinking reversibly with the variation of glucose concentration, and induce the quenching of fluorescence intensity of the embedded carbon dots. The variation of the fluorescence intensity of the carbon dots in the hybrid microgels is directly related to the concentration of glucose, over the clinically relevant range of 0–30 mM and at physiological pH (Wang et al., 2015).

The general performance of the above glucose sensors is very good in terms of linearity, accuracy and LOD. However, their practical application as wearable or implantable devices is still questionable, due to the application of hazardous UV light as the excitation light source.

Considering the practical application of optical sensors for the development of wearable or implantable devices, SPR based sensors are much advantageous due to the fact that they use visible light sources. In addition, SPR based sensors are promising for the non-invasive or minimally invasive detection of glucose without the damage or partial

Table 1
Analytical performance, solution/pH, and the detection method of reported non enzymatic electrochemical glucose sensors functioned at physiological conditions.

Working Electrode	Linear range (mM)	LOD (μM)	Electrolyte/pH	Method	Working potential(V)	Ref.
Pt nanoflower/GO	0.002–20.3	2	PBS/7.4	CA	+ 0.47	Wu et al. (2013)
Cu nanowires-MOFs-GO	0.02–26.6	7	PBS/7.4	CA	+0.3	Zang et al. (2018)
Pt/MWCNT	0.0–20	1.10	PBS/7.4	CA	+ 0.55	Rathod et al. (2010)
Au nanocoral	0.05–30	10	PBS/7.4	CA	−0.1	Cheng et al. (2010)
PtAu/C	0.0–10	2	PBS/7.4	CA	+0.35	Singh et al. (2010)
Au thin films	0.01–100	10	PBS/7.4	SWV	−0.3 to 0.7	Gougis et al. (2014)
Pt_2Pb alloy	0.0–10	–	PBS/7.0	Amp.	−0.15	Sun et al. (2001)
3D Cu@Cu_2O Aerogels	0.1–10	54	PBS/7.0	CA	+0.6	Gao et al. (2019)
Graphene/CuO	5.0–14	5	PBS/7.4	CA	−0.05	Foroughi et al. (2018)
Au/Pt–black	1.0–40	23	PBS/7.4	CA	+0.12	Gao et al. (2019)
Au NP/GONR	0.0005–10	5.0	PBS/7.0	CA	+0.2	Ismail et al. (2014)
Pd@Pt CINPs	1.0–8.5	0.82	PBS/7.4	CA	−0.1	Wu et al. (2019)
Pt_3Ru NP/GCE	0.0005–10	0.3	PBS/7.4	CA	+0.05	Yang et al. (2016)
PtRu/MWCNT/IL	0.2–15	50	PBS/7.4	CA	−0.1	Xiao et al. (2009)
PtNi/graphene	up to 35	10	PBS/7.4	CA	−0.35	Gao et al. (2011)
PtPb nanoparticles/MWCNTs	up to 11	7	PBS/7.4	CA	−0.15	Cui et al. (2007)
PtAu/MWCNTs	up to 24.44	10	PBS/7.4	CA	+0.3	Ryu et al. (2010)
Pt nano cluster/graphene	1.0–25	30	PBS/7.4	CA	+0.05	Chang et al. (2015)
Co@Pt	1.0–30	300	PBS/7.4	CA	−0.05	Mei et al. (2015b)
Pt NP/Carbon nano cubes	0.05–10	20	PBS/-	CA	−0.3	Gao et al. (2017)
Nano porous Pt	1.0–10	800	PBS/7.4	CA	+0.4	Weremfo et al. (2017)
3D honeycomb like nano porous Au	0.02–17.3	200	PBS/7.4	CA	+0.35	He et al. (2019)
TiO_2-Au	0.05–3	45	PBS/-	CV	−0.8 to 1.2	Grochowska et al. (2019)
PtNPs/BSA-rGO	0.02–7.5	2	PBS/7.4	CA	+0.5	Wu et al. (2018)
Mesoporous Pt	0.0–10	9.6	PBS/7.4	Amp.	+0.45	Park et al. (2003)
Pt@CNOs	2.0–28	90	PBS/7.4	Amp.	+0.45	Mohapatra et al. (2018)
(Pd core/Pt shell)–graphene	1.0–23	5	PBS/7.4	Amp.	+0.1	Zhang et al. (2013)
PtPd/rGO	0.1–22	2	PBS/7.4	Amp.	0	Li et al. (2014)

Notes: CA = Chronoamperometric; SWV = Square Wave Voltammetry; CNOs = Carbon nano-onions; rGO = Reduced graphene oxide; MWCNT = Multi wall carbon nanotubes; CINPs = Concave island nanoparticels, GONR = graphene oxide nanoribbons; BSA = Bovine serum albumin.

damage of the host medium (Elsherif et al., 2018a).

SPR detection method is based on the principle of oscillation of electrons at the metals and dielectric interface, which can detect the concentration of glucose via the variation of the local refractive index before and after the binding of glucose molecules (Damborský et al., 2016; Wang and Fan, 2016). Yuan et al. developed a highly sensitive SPR glucose sensor using a mixed-self-assembled monolayer (SAM) modified Au coated optical fibers (Fig. 4d and e). Glucose can easily interact, with enhanced sensitivity, with the p-mercaptophenylboronic acid and 2-aminoethanethiol SAM molecules onto the Au coated optical fibers. To increase the selectivity of glucose detection, a signal amplification tag, p-mercaptophenylboronic acid and 2-aminoethanethiol SAM molecules modified AuNPs were used to prepare a sandwich structure. This sandwich-type sensor resulted in the red shifting of SPR wavelength with the increase of the concentration of glucose. The dynamic range was 0.01–30 mM and LOD of 80 nm (Yuan et al., 2018). Lobry et al. developed a similar fiber-optic based SPR-assisted tilted--fiber Bragg gratings (TFBGs) sensor (Fig. 4f) (Lobry et al., 2019). Firstly, Au was coated onto the TFBGs, then a thin layer of poly(dopamine) intermediate layer was deposited by polymerization processes. The quinone functional groups in the poly(dopamine) allowed the binding of glucose captured protein, concanavalin A (Con A). This fiber optic-based sensor induces a shifting of the wavelength upon the binding of glucose. This displayed a linear dependence on concentration over the range between 1 μM and 0.1 mM and a LOD of 0.1 μM.

Table 2 summarizes the analytical performance of the reported non-enzymatic glucose sensors based on different other optical methods in conjunction with fluorescence and SPR methods. Even though the general analytical performance of the above described optical sensors is good and are promising for industrial and hospital applications, the point-of-care detection of glucose is still limited due to the high cost of the detection tools. Therefore, the development of optical wearable cost-effective sensors that can monitor the glucose concentration continuously in biological fluids is still an open issue.

6. Wearable electrochemical and optical glucose sensors

Wearable devices are the upgraded versions for non-invasive detection of human disease at early stages (Bandodkar and Wang, 2014). For diabetic patients, online glucose monitoring is very important, and with the existing devices, it is always painful, invasive, and difficult to carry out for patients (Elsherif et al., 2018b; Xiao et al., 2019). Wearable devices are the perfect replacement of existing detection systems due to easiness of integration into the body in the form of wearable clothes, watch lenses, and rings for continuous measurements of glucose in tears, sweat, and saliva (Kim et al., 2018). This section summarized recent developments of wearable electrochemical and optical glucose sensors that could operate at physiological pH conditions.

Considering the practical applicability, wearable electrochemical sensors are advantageous over wearable optical sensors. This is due to their predisposition to miniaturization and the requirements of low operational voltages, generating from biochemical reactions or external sources. Toi et al. reported a very sensitive, wrinkled, stretchable, nanohybrid fiber (WSNF) based electrochemical sensor for the continuous monitoring of glucose from body sweat (Fig. 5a) (Toi et al., 2019). The WSNF was prepared by partially covering reduced graphene oxide (rGO)/polyurethane composite with Au nanowrinkles. The synergistic effect of the high percentage of oxygen functionalities in rGO and the Au nanowrinkles promote the dehydrogenation of glucose in the oxidation reaction, due to the numerous $Au(OH)_{ads}$ active sites. Using this device, a LOD of 500 nM was obtained. This stretchable and patch type non-enzymatic system is promising, as it involves a simple fabrication route, while it can be integrated into cloths or body accessories for continuous monitoring of glucose from body sweat. Lee et al. demonstrated a patch-shaped, enzyme-free, and painless continuous glucose monitoring device based on a micro-needle array with Pt black sensing electrode layer (Fig. 5b). This Pt sensing electrode-based microneedle was fabricated onto a stainless-steel electrode with the integration of Ag/AgCl as the counter/reference electrode. This minimally invasive wearable electrochemical sensor is able of detecting glucose with sensitivity and LOD of 1.62 μA/mM and 50 μM, respectively (Lee et al.,

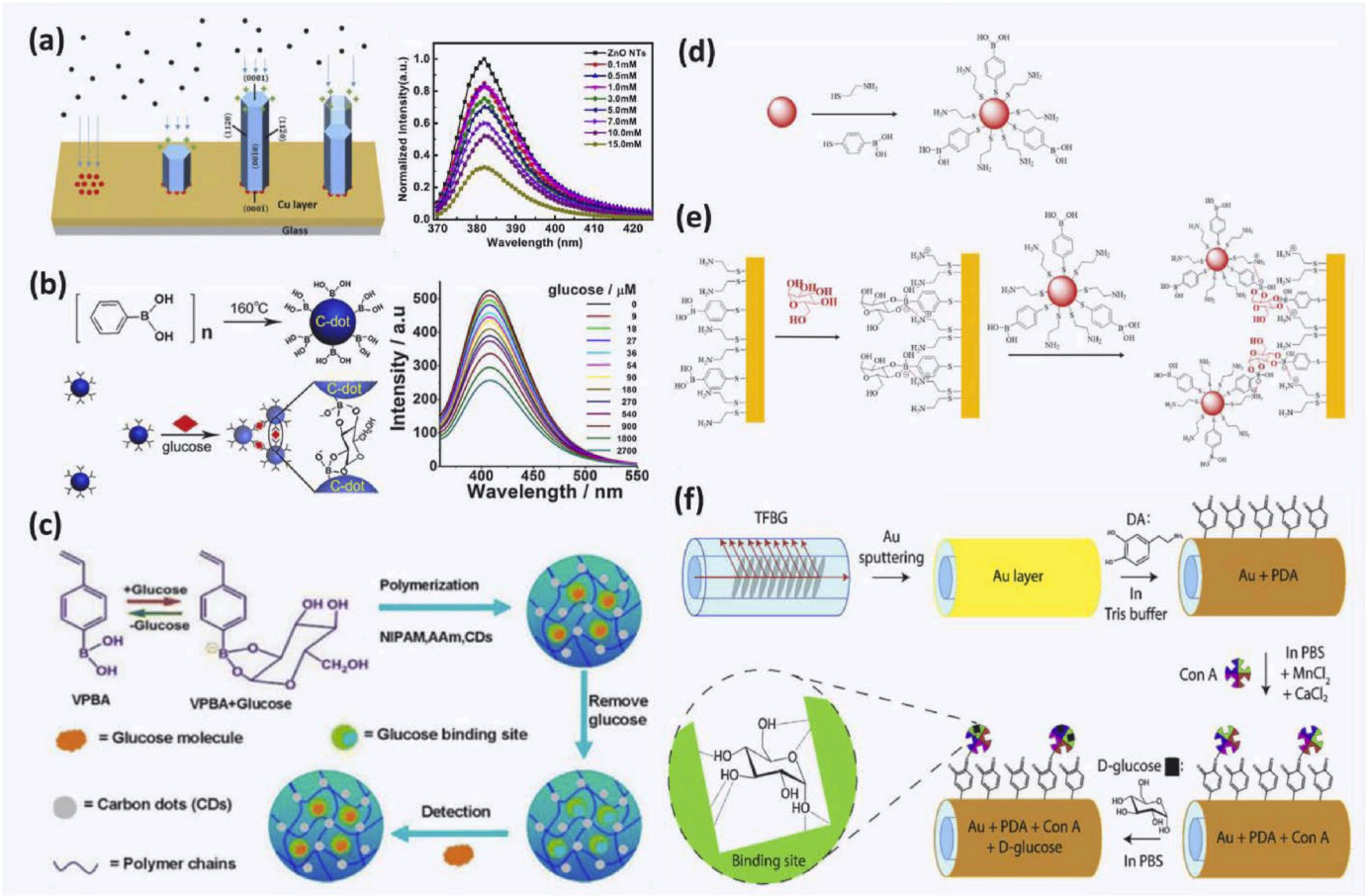

Fig. 4. *(a) Schematic illustration of the seedless growth of ZnO NTs and the corresponding fluorescence signals for glucose detection (Reproduced with permission from Ref.* (Mai et al., 2019). *(b) Scheme of the synthesis of boronic acid functionalized carbon dots, attachment of glucose, and the corresponding fluorescence signals for glucose detection (Reproduced with permission from Ref.* (Shen and Xia, 2014). *(c) Scheme of the synthesis of glucose embedded poly(NIPAM-AAm-VPBA)-carbon dots hybrid microgels for specific glucose-binding (Reproduced with permission from Ref. (*Wang et al., 2015).(d) and (e) *Reaction scheme of the synthesis of Au NPs/p-mercaptophenyl boronic acid and 2-aminoethanethiol and glucose recognition by Au NPs/p-mercaptophenyl boronic acid and 2-aminoethanethiol sandwich structures (Reproduced with permission from Ref.* (Yuan et al., 2018). *(f) Scheme of fabrication and sensing principles of glucose detection based on SPR-TFBG biosensor (Reproduced with permission from Ref (*Lobry et al., 2019).

2016). Hong et al. developed a disposable sweat-based glucose-sensing strip integrated into a wearable smart band (Fig. 5c) (Hong et al., 2018). This integrated system is capable of measuring the concentration of glucose in sweat electrochemically while monitoring other important signs of body function such as heart rate, and blood O_2 saturation level. The sensor consists of three carbon-based working electrodes and two Ag/AgCl reference electrodes for multiple sensing. A hydro-chromic layer of magnesium is used for the accumulation of sweat. With the application of a potential pre-stabilization step, the sensor can successfully monitor the pre-/post-exercise glucose concentration in sweat.

Some other wearable electrochemical sensors reported recently in the literature for non-enzymatic detection of glucose at physiological conditions from different body fluids are summarized in Table 3.

Optical transduction based wearable glucose sensors have been less investigated, possibly due to the difficulty in their miniaturization. Furthermore, a wearable optical sensor requires complex fabrication processes, while readout needs the use of costly optical fibers mounted on rotating stages, and spectrophotometers coupled to a computer. Therefore, wearable optical sensors of glucose are not mass-produced or commercialized for point-of-care testing. Recently, Elsherif et al. reported breakthrough research by developing a contact lens-based wearable sensor for continuous monitoring of glucose by using a smartphone (Fig. 5d and e) (Elsherif et al., 2018a,b). A photonic microstructure with the periodicity of 1.6 μm was printed on a phenylboronic acid-functionalized hydrogel film for selective detection of glucose. With the addition and binding of a glucose molecule with the phenylboronic acid functional groups, the volume of the hydrogel film expand and causes the variation of periodicity constant value. This results in the change in Bragg's diffraction and the resultant reflected power of the first-order diffraction was measured using a smartphone application with a very good correlation between the glucose concentration (0-50 mM) and periodicity constant. This commercial contact lens integrated sensor is promising for real-time monitoring of glucose at point-of-care settings. In another report, the same research groups introduced densely packed concavities in hydrogel film with phenylboronic acid-functionalization (Elsherif et al., 2018a). In addition, an optical diffuser was added to the phenylboronic acid-based recognition motif. This diffuser layer is able of transmitting and reflecting the incoming light into a measurable signal. Upon the binding of glucose molecules with the phenylboronic acid functional groups, the variation of the intensity of transmitted light was measured to determine the concentration of glucose in a concentration range from 0 to 100 mM.

The ultimate target of research and development is the commercialization of the products for practical applications. Obviously, based on the advancement of current sensor technologies, electrochemical wearable glucose sensors are more realistic than optical wearable glucose sensors for a real use with low-cost, point-of-care testing, and short response time characteristics. Accordingly, several electrochemical wearable glucose devices together with a few optical wearable glucose devices are already commercialized or in the early stage of

Table 2
Analytical performance, measurement method, and solution type of reported non-enzymatic optical glucose sensors functioned at physiological conditions.

Measurement methods	Linear range (mM)	Solution/pH	Ref.
Fluorescence	0.05–0.5	Human tears/8.0	Badugu et al. (2004)
Fluorescence	up to 100	Aqueous solution/7.4	Cordes et al. (2006)
Fluorescence	0.0–30	PBS/7.4	Cordes et al. (2005)
Fluorescence	2.5–20	PBS/7.4	Cordes et al. (2007)
Fluorescence	0.4–150	PBS/7.4	Wang et al. (2012)
Fluorescence	0.009–0.9	Human serum/ 7.4	Shen and Xia (2014)
Fluorescence	0.1–15	Human blood serum/7.0	Mai et al. (2019)
Fluorescence	1–30	Human blood serum/-	Krishna and Shanti (2016)
Fluorescence	1–200	PBS/7.4	Zhang et al. (2014b)
Fluorescence	0–30	PBS/7.4	Wang et al. (2015)
SPR	1.0–40	Tears, blood, and urine/7.4	Aslan et al. (2004)
SPR	0.1–20	Tear fluid/7.38	Wu et al. (2012)
SPR	1–300	Human blood/-	Li et al. (2015)
SPR	0.01–30	Physiological blood level/-	Yuan et al. (2018)
SPR	0.001–10	PBS/7.4	Lobry et al. (2019)
Transmittance and reflectance	0.0–20	PBS/7.4	Elsherif et al. (2019)
Diffraction	0.0–100	PBS/7.4	Lee et al. (2004)
Diffraction	0.1–10	Artificial tear fluid/9.0	Xue et al. (2014)
Diffraction	0.0–11	PBS/7.4	Kabilan et al. (2005)
Diffraction	1.0–200	PBS/7.4	Bajgrowicz-Cieslak et al. (2017)
Diffraction	3–33	Blood plasma/7.4	Worsley et al. (2007)
FT-NIRS	–	Water/ intralipid/-	Yatim et al. (2014)

commercialization, as summarized in Table 4. Most of them showed promising results and made a huge contribution to the industries and sensor market. Of them, few devices are withdrawn from the market due to the lack of accuracy, precision, and reliability.

7. Challenges and future prospects

7.1. Electrochemical sensors

Although enzyme-based electrochemical glucose sensors are widely used in diabetes management at the clinical level, an ideal electrochemical glucose sensor is expected to be free of enzyme and should work at physiological conditions. This consideration stems from the problems related to the enzyme degradation due to external environmental factors (Kim et al., 2018), which induce unreliable readings of glucose concentration (Zang et al., 2018). Thanks to the advances of nanoscience and nanotechnology, which paved the way for developing novel organic or inorganic nanomaterials for the direct catalytic oxidation of glucose, it has been possible to get rid of the use of enzymes for the construction of sensors for the detection of glucose concentration with high accuracy. However, most of the nanomaterials employed for the above goals cannot be used directly in biological fluids, and require time-consuming and expensive pre-/post conditioning of the real samples and cannot catalyze the oxidation of glucose at physiological pH. Although some novel Pt- and Au-nanostructures can successfully catalyze the oxidation of glucose at physiological pH, they are-costly and suffer from poisoning effect due to adsorbed intermediates of the glucose oxidation process (Cash and Clark, 2010).

It is challenging to develop novel nanomaterials other than Pt and Au, which can oxidize glucose non-enzymatically at physiological conditions with high selectivity and sensitivity. One of the possible solutions could be the development of highly catalytic organic and inorganic composite type materials such as MOF, MAF, and two-dimensional MXene (Bolotsky et al., 2019; Xu et al., 2018).

7.2. Optical sensors

Optical devices for glucose sensing are based on a variety of spectroscopic techniques (Jernelv et al., 2019). Although optical transduction systems are costly and difficult to miniaturize, relevant analytical methodologies are considered to be more specific, over other methods, for the quantification of glucose in diabetes management (Gonzales et al., 2019). In particular, SPR based glucose sensors can work on local refractive index changes upon metal nanostructures or functionalized metal nanostructures that interact with glucose molecules. To this purpose, Au nanostructures are most commonly used. However, the binding of glucose to the Au-functionalized nanostructures could easily lead the aggregation of Au, which induces a detectable shifting of SPR signals and decreases the accuracy of glucose detection (Aslan et al., 2004). Furthermore, Au is expensive, and it suffers from the poisoning effects from adsorbed intermediates at physiological pH. Thus, the future direction of SPR based glucose sensors could be the development of Au nanostructures with capping agents, where capping agents can simultaneously act as glucose binding sites and minimize the aggregation of Au nanostructures.

Considering fluoresce-based sensors, for their functioning, a fluorescence label is required. The commonly used exogenous fluorescent markers are based on organic dyes and semiconductor quantum dots, which, however, can exhibit photobleaching and toxicity effects, respectively. In addition, fluorescence-based glucose sensors display low stability and lifetimes (Damborský et al., 2016; Mello et al., 2019), and suffer from problems related to the variation in the illumination/excitation wavelengths that cause underestimation of glucose concentration. Thus, one of the future directions of the fluorescence-based glucose sensors could be the development of novel nanomaterials, dyes, and quantum dots with long fluorescence lifetime, while ensuring biocompatibility.

7.3. Wearable sensors

Recently, wearable sensor technologies have attracted growing interests for continuous monitoring of glucose during work, school, and offices. These systems are suited for non-invasive or minimally invasive measurements, without the need for painful finger strips (Toi et al., 2019). In addition, they allow measurements to be performed in body sweat, tears, and saliva. These devices are mostly made by using flexible materials and substrates and therefore fit conveniently with, for instance, human skin or eyes (Bandodkar and Wang, 2014). However, some on them, specifically those developed for glucose monitoring in sweat and tears, lack of a good correlation with the blood sugar level. For example, the normal level of glucose in the blood is about 50 and 100 times higher than in tears and sweat, respectively. Furthermore, the glucose level in tears and sweat changes unpredictably every day or time (Bandodkar and Wang, 2014; Gonzales et al., 2019). Wearable devices also present long-term stability problems, which limit their practical use at the clinical level (Gonzales et al., 2019). For instance, contact lens glucose sensors, which allow performing easy measurements of glucose in tears, can work properly up to 24 h (Gonzales et al., 2019). To develop very stable and reliable wearable glucose sensors, to be used in various biological fluids during daily life (sport, walk, etc.), apart from long term stability, they require also relating their responses with the variation of other parameters, such as temperature, pH and humidity. Though the development of wearable glucose sensors is just beginning, a significant number of wearable glucose sensors is already commercialized (Table 4). Some of them were withdrawn from the market or retracted after FDA approval due to the lack of accuracy and safety. Thus, a large-scale study, research, and clinical trials are required to assess the reliability and accuracy of these wearable glucose sensors before they

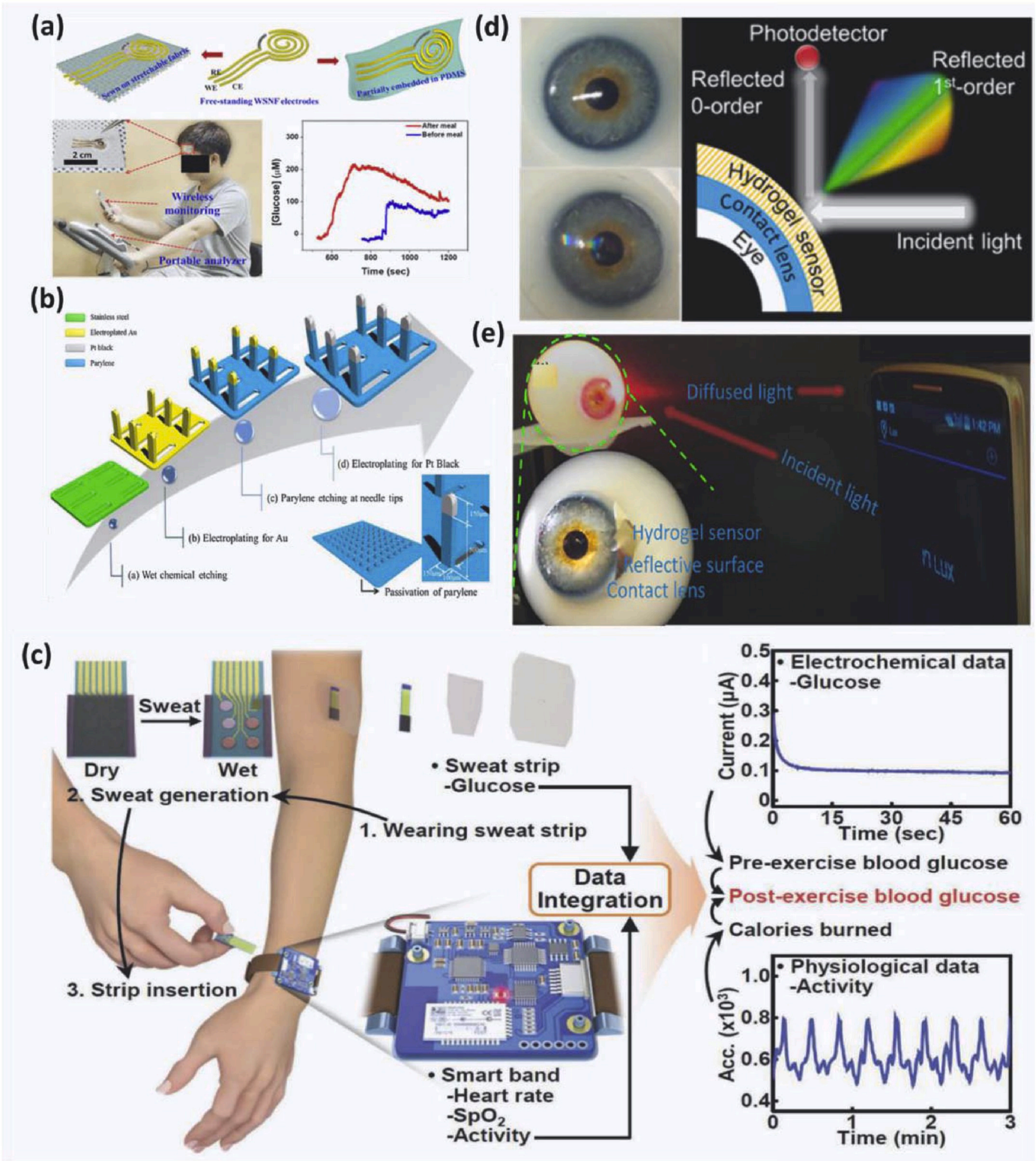

Fig. 5. *(a) Schematic illustration of the fabrication of free-standing WSNF electrodes, WSNF based wearable sensor attached to the forehead of a human body, and the corresponding glucose signal in sweat before and after meals (Reproduced with permission from Ref.* (Toi et al., 2019)*). (b) Fabrication steps of 3D micro-needle array-based patch type glucose sensor (Reproduced with permission from Ref.* (Lee et al., 2016)*). (c) Schematic illustration of the wearable sweat based disposable strip for glucose detection using a wearable smart band together with the electrochemical and physiological data (Reproduced with permission from Ref.* (Hong et al., 2018)*). (d)* and *(e) Photographic image of an artificial eye with the attached hydrogel-based optical contact lens glucose sensor together with the detection mechanism of sensor (Reproduced with permission from Ref* (Elsherif et al., 2018b) *and* (Elsherif et al., 2018a).

Table 3
Properties and analytical performance of reported non-enzymatic wearable electrochemical and optical glucose sensors functioned at physiological conditions.

Transduction type	Platform	Recognition Element	Solution/pH	Linear range (mM)	Ref.
Electrochemical/Amp.	Stainless steel	Nanoporous Pt	Blood/7.4	0.0–30	Yoon et al. (2018)
Electrochemical/Amp.	$CoWO_4$/Polyaniline CNTs/ PET	CNT-AuNs	Skin sweat/-	0.0–0.3	Yun Oh et al., 2018
Electrochemical/Amp.	Elastomeric fibers/PDMS	rGO/PU-Au	Skin sweat/7.4	0.001–1	Toi et al. (2019)
Electrochemical/Amp.	PDMS	Nanoporus Au	Skin sweat/7.0	0.01–1	Bae et al. (2019)
Electrochemical/ Voltammetry	Ti foil	TiND/Au /Nafion	PBS/-	0.01–12.80	Olejnik et al. (2020)
Electrochemical/ Voltammetry	PET	Pd@ZIF-67	Skin sweat/7.4	0.01–1	Zhu et al. (2019)
Electrochemical/CA	Screen printable stretchable ink	Pt-decorated graphite	PBS/7.0	0.0–82	Abellán-Llobregat et al. (2017)
Electrochemical/Amp.	Rubber fiber	Cu-CNTs composites	PBS/-	0.05–5	Jiang et al. (2018)
Electrochemical/Amp.	Graphene paper	PtAu/MnO_2	PBS/7.4	0.1–30	Xiao et al. (2013)
Electrochemical/Amp.	Cu foil	CuO NWA/Cu	–	Up to 2.05	Huang et al. (2015)
Electrochemical/Amp.	PET	CuO nano wires	Tears & saliva/-	0.0–12	Bell et al. (2017)
Electrochemical/Amp.	Graphene paper	3D graphene/CNT/PtAu	PBS/7.4	0.1–11.6	He et al. (2016)
Electrochemical/CA	PET	Glucose sensitive hydrogel	Skin/-	0.0–0.1	Emaminejad et al. (2017)
Optical/Diffraction	Hydrogel	Polystyrene CCA in 4-BBA-modified PVA hydrogel	Tears/-	0–50	Ruan et al. (2017)
Optical/Diffraction	Hydrogel	Boronic acid derivatives	Tears/-	Up to 0.1	Alexeev et al. (2004)
Optical/Diffraction	PBA–PVA complexes hydrogels	PBA–Tris–PVA PCCA based contact lens	Tear and PBS/7.4	0.0–50	Zhang et al. (2014a)
Optical/Fluorescent/ Diffraction	–	Boronic acid-containing fluorophores	Tear and PBS/7.4	0.05–0.5	Badugu et al. (2004)
Optical/Fluorescent/ Diffraction	Hydrogel film	Phenyl boronic acid	Tear/-	0.0–50	Elsherif et al. (2019)
Optical/Raman	Fiber-optic probe	–	Human skin/-	–	Peng et al. (2017)
Optical/OCT	Super luminescent diode	photodiode	Pigs and Rabbit skin/-	3–30	Larin et al. (2003)

Notes: TiND/Au= Au dimpled titanium heterostructures; PBA = phenylboronic acid; PVA= Poly (vinyl alcohol); PCCA = polymerized crystalline colloidal array; PET= Polyethylene terephthalate; NWA= Nanowire array; PDMS = Polydimethylsiloxane.

Table 4
Summary of commercialized non-enzymatic electrochemical and optical wearable glucose sensors functioned at physiological conditions.

Company, product	Sample	Wearable platform	Transduction type	Approval stage	Website
GlucoWatch, Cygnus Inc.	ISF	Watch Type	Electrochemical	FDA approved but retracted	–
Freestyle Libre, Abbot	ISF	Patch	Electrochemical	FDA approved	https://www.freestylelibre.us/
Dexcom G6 CGM, Dexcom	ISF	Patch	Electrochemical	FDA approved	https://www.dexcom.com/
NovioSense tear glucose sensor, Noviosense	Tear	–	Electrochemical	Successful in phase-II clinical trails	–
Smart contact lens, google and Novartis	Tear	Contact lens	Electrochemical	Project is on hold, last update 2018	https://verily.com/projects/sensors/smart-lens-program/
Pendra®	–	–	Electrochemical	Withdrawn	–
Glucoband®	–	Wrist band	Electrochemical	Withdrawn	–
GlucoTrack	–	Ear clip	Ultrasonic, electromagnetic and Thermal	FDA approved	http://www.glucotrack.com/
BioMkr, Prediktor Medical	Blood	Wrist strap	NIRS	Under clinical testing	https://www.prediktormedical.com/
Glucowise	–	Portable Hand used	Wave transmission spectroscopy	FDA approved	http://glucowise.com/
Eversense® (*Senseonics*)	–	Patch	Fluorescence	FDA approved	https://www.senseonics.com/
HELO Extense (World global Network)	–	Finger ring	NIRS	–	https://website.worldgn.com/heloextense/
Combo glucometer (*Conga Medical)*	–	Finger ring	NIRS	FDA approved	https://medaval.ie/device/cnoga-combo-glucometer/
Eversense, Sensonics	–	–	Fluorescence	FDA approved	https://www.eversensediabetes.com/
Touch Track Pro	–	–	NIRS	Withdrawn	–
C8 Medisensors	–	–	Raman	Withdrawn	–

Note: ISF = interstitial fluid.

are sale on the market.

8. Conclusions

Herein, we have summarized recent developments of enzyme-less electrochemical and optical glucose sensors, including wearable devices, able to work under physiological conditions. In particular, the review highlights the current advances, challenges, and future perspectives of electrochemical, optical, and wearable glucose sensors to be employed directly in body fluids.

Considering the electrochemically-based non-enzymatic sensors, it appears that Pt and Au nanostructures, or their alloy/composite-modified electrodes, provide responses that are characterized by good sensitivity, low detection limits, and wide linear ranges. However, for clinical applications, it is desirable developing non-invasive or minimally invasive wearable and implantable type devices.

As for the most widely investigated SPR and fluorescence-based optical glucose sensors, the use of Au nanostructures and exogenous fluorescence markers, respectively, can lead to various drawbacks. In fact, Au nanostructures can aggregate and this induces unreliable SPR signals upon varying the glucose concentration. On the other hand, most of the exogenous fluorophores employed in fluorescence-based sensors exhibit a photobleaching effect, which leads to a short lifetime of the sensors. In addition, it appears challenging to integrate these transduction systems in miniaturized, wearable, and implantable type devices.

Therefore, in general, in both electrochemical and optical transduction systems, further development of novel materials, methodologies and technologies are required to achieve the goal of producing enzyme-free devices for the detection of glucose directly in the body fluids, as well as to allow their integration into wearable, reliable, and low-cost with long-term stability devices.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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