



Optical glucose biosensor built-in disposable strips and wearable electronic devices

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ABSTRACT

On-demand screening, real-time monitoring and rapid diagnosis of ubiquitous diseases, such as diabetes, at early stages are indispensable in personalised treatment. Emerging impacts of nano/microscale materials on optical and portable biosensor strips and devices have become increasingly important in the remarkable development of sensitive visualisation (i.e. visible inspection by the human eye) assays, low-cost analyses and personalised home testing of patients with diabetes. With the increasing public attention regarding the self-monitoring of diabetes, the development of visual readout, easy-to-use and wearable biosensors has gained considerable interest. Our comprehensive review bridges the practical assessment gap between optical bio-visualisation assays, disposable test strips, sensor array designs and full integration into flexible skin-based or contact lens devices with the on-site wireless signal transmission of glucose detection in physiological fluids. To date, the fully modulated integration of nano/microscale optical biosensors into wearable electronic devices, such as smartphones, is critical to prolong periods of indoor and outdoor clinical diagnostics. Focus should be given to the improvements of invasive, wireless and portable sensing technologies to improve the applicability and reliability of screen display, continuous monitoring, dynamic data visualisation, online acquisition and self and in-home healthcare management of patients with diabetes.

1. Introduction

Real-time and remote monitoring systems of metabolites, such as glucose, in human body fluids are revolutionising personalised treatment to meet the needs of patients with diabetes (Haxha and Jhoja, 2016; Kassal et al., 2018; Elsherif et al., 2018a; Jernel et al., 2019; Wang and Lee, 2015; Yum et al., 2013; Kim et al., 2018a; Kim et al., 2019; Emran et al., 2020a; Khairy et al.). A wide range of glucose biosensors based on electrochemical, optical, thermometric, piezoelectric and magnetic signalling transductions was used for the dynamic detection and tracking of glucose levels (Wang and Lee, 2015; Emran et al., 2020a). Optical glucose biosensors offer accurate detection, visualisation with the naked eye, real-time monitoring and high-frequency estimation without demanding sophisticated processes (Haxha and Jhoja, 2016; Kassal et al., 2018; Elsherif et al., 2018a; Jernel et al., 2019; Wang and Lee, 2015; Yum et al., 2013). Visual gadgets are next-generation tools that offer effective patient monitoring for remote diagnostic testing of patients with diabetes. Over the past few years,

considerable interests and growth have been associated with the development of sensors that can offer simple, cost-effective and real-time detection of endogenous chemicals and biological active species (Kim et al., 2018a; Kim et al., 2019; Emran et al., 2020a; Khairy et al.; Lee et al., 2018a; El-Safty et al., 2015; Emran et al., 2019; Strakos et al., 2019; Emran et al., 2018a; Akhtar et al., 2017). Optical glucose biosensors have demonstrated a massive potential in the early diagnosis and accurate monitoring of diabetes (Haxha and Jhoja, 2016; Kassal et al., 2018; Elsherif et al., 2018a; Jernel et al., 2019; Wang and Lee, 2015; Yum et al., 2013).

As reported by the American Diabetes Association (ADA) in 2017, more than 425 million adults were diagnosed with diabetes. This number is expected to increase to 629 million by 2045 (Emran et al., 2018b; Cho et al., 2018; Murfitt et al., 2018; Markwalter et al., 2019; Ruder et al., 2018; Koye et al., 2018; Chen et al., 2018a). For instance, 30.2 million Americans suffer from diabetes and its devastating consequences (Emran et al., 2018b). Abnormal glucose concentration levels in blood lead to chronic metabolic diseases, such as diabetes. Multiple

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pathogenic processes, including autoimmune destruction in the pancreas beta-cells, exacerbate diabetes. This β -cell metabolic behaviour causes insulin deficiency and abnormality, enabling insulin resistance along the target tissues (Quinault et al., 2016). Moreover, diabetes can be classified into four categories: (i) diabetes associated with β -cell destruction which causes absolute insulin deficiency; (ii) diabetes associated with progressive abnormalities in insulin secretion; (iii) diabetes associated with use of chemicals or drugs, genetic defects in insulin action and β -cell function, and exogenous pancreatic disease; and (iv) gestational diabetes (Quinault et al., 2016). Indispensable diabetes and high blood sugar levels cause an imbalance in insulin secretion and its function, or even both. In addition, long-term, chronic hyperglycaemia contributes to the dysfunction and failure of various organs, especially the kidneys, eyes, heart, nerves and blood vessels. In the long period, insufficient glycaemic control in patients with diabetes results in serious and chronic diseases, including kidney failure and neurological problems. Neurological disorders lead to foot ulcers and amputations, dysfunction of vital organs, such as the digestive, urinary, reproductive and cardiovascular organs, sight loss due to retinal injury and sexual dysfunction (He et al., 2020; Cai et al., 2021; Xue et al., 2020; American Diabetes Association, 2010).

At a risk level, diabetics also develop atherosclerosis and peripheral cardiovascular diseases (CVDs). CVD is a dangerous and chronic disease associated with diabetes (Cai et al., 2021; Xue et al., 2020; American Diabetes Association, 2010). It is the main cause of deaths in patients with diabetes (Tuttle et al., 2021). High blood pressure is commonly associated with diabetic and cardiovascular diseases. Peripheral arterial and vascular diseases are associated with reduced blood flow to the extremities, stomach and kidneys as a result of narrowed blood vessels. This behaviour may cause intermittent claudication and decrease the blood flow to the affected limb, leading to amputation (Miguel et al., 2015; Chawla et al., 2016). In addition, several oral diseases, such as gum disease, cavities, tooth erosion, taste disorders, salivary dysfunction and oral cancer, and mucosa diseases are major problems associated with diabetes (Borgnakke, 2019; Skamagas et al., 2008). Retinal injury in diabetes is the most common microvascular complication which substantially increases the rate of blindness annually (Kubo et al., 2014). Clinical nephropathy without a urinary tract infection is a relatively late event in patients with diabetes. Patients with nephropathy/diabetes are always needed for kidney transplant or chronic haemodialysis (Chen et al., 2018b; Rodionov et al., 2019; Deng et al., 2018). Therefore, a control over diabetes would effectively reduce the exacerbation of chronic diseases and the mortality rate. To date, simple, effective sensing protocols and easy-to-use techniques are urgently needed to screen and monitor diabetes.

New technology-based sensing techniques, data acquisition tools and personalised medicine devices are needed for the precise and rapid monitoring of patients with diabetes worldwide. This review highlights the visualisation assays and advances in optical biosensor designs and device-integrated smartphones to help drive the scientific developments in the personalised monitoring of glucose levels in human body fluids. Realising a truly personalised approach to diabetic care requires effective advances in nano- and micro-metric disposable test strips and in remote sensing technology to usher the early discovery and on-demand treatment of diabetes.

In visualisation sensing methods, optical glucose-responsive biosensors allow the strong readout signalling and transduction of a wide range of light visualisation properties, such as photon absorption, diffraction, reflectance, transmittance, fluorescence, polarisation, frequency, scattering and refraction (Zhou et al., 2019; Asrami et al., 2017; Sabu et al., 2019; Rachim and Chung, 2019; Steiner et al., 2011; Chen et al., 2019a; Yu et al., 2019a; Shrivastava et al., 2020; Yang and Gao, 2019; Malhotra and Ali, 2018; Li et al., 2020). The optical monitoring or readout mechanism of diabetic biosensors is mainly based on the equipped transduction units that enable the conversion of light photons to electrically digital signals for analysing and tracking glucose levels. A

wide range of optical detection techniques, including surface-enhanced Raman spectroscopy (SERS), absorptiometry or reflectometry, chemiluminescence (CL) and fluorescence- and surface plasmon resonance (SPR), are central to the accurate and precise monitoring of blood glucose levels (Skamagas et al., 2008; Kubo et al., 2014; Chen et al., 2018b; Rodionov et al., 2019; Deng et al., 2018; Zhou et al., 2019). To date, most reported visualisation assays allow the real-time, accurate and cost-effective monitoring of glucose levels in physiological fluid samples with fast response and high sensitivity and selectivity (Haxha and Jhoja, 2016; Kassal et al., 2018; Elsherif et al., 2018a; Jernelov et al., 2019; Wang and Lee, 2015; Yum et al., 2013; Kim et al., 2018a; Kim et al., 2019; Emran et al., 2020a; Khairy et al., Elshehy). Among all visualisation methods, bio-visualisation assay was formulated as result of the configuration of glucose biosensor entities in fully harmonised sensing systems, including robust design, biological sampling, readout data analysis and acquisition system (Shrivastava et al., 2020; Yang and Gao, 2019; Malhotra and Ali, 2018; Li et al., 2020). Progress in the development of visually integrated devices and reliable visualisation assays for on-demand screen display, longitudinal continuous monitoring and dynamic and online data acquisition signals for personal monitoring of diabetes must be considered (Steiner et al., 2011; Chen et al., 2019a; Yu et al., 2019a; Shrivastava et al., 2020; Yang and Gao, 2019; Malhotra and Ali, 2018; Li et al., 2020; Sanchis et al., 2017; Soni et al., 2018).

Self-testing readout strips and patches for continuous monitoring and multiple daily analyses of glucose concentration in the epidermal or interstitial fluids at the tip of optical biosensors have become assessable and configurable (Shrivastava et al., 2020; Cho et al., 2017; Erenas et al., 2019; Akhtar et al., 2015; Soni and Jha, 2015; Soylemez et al., 2019; Santana-Jiménez et al., 2018). Disposable test strip biosensing technology offers simple, cost-effective and point-of-care analyses, short home and personal testing and on-time diagnosis of diabetes. Challenges remain for the development of disposable enzyme-based microfluidic devices and paper-test strips in terms of multiplex capabilities, single stability with interferences and continuous calibrations compared with the traditional paper-test strip sampling. In addition, the miniature reading device and the wireless signal transmission into smartphones represent a new generation of point-of-care diabetic diagnosis for rapid home testing with accurate display of blood glucose levels, graphic curves, tendencies and status (Shrivastava et al., 2020).

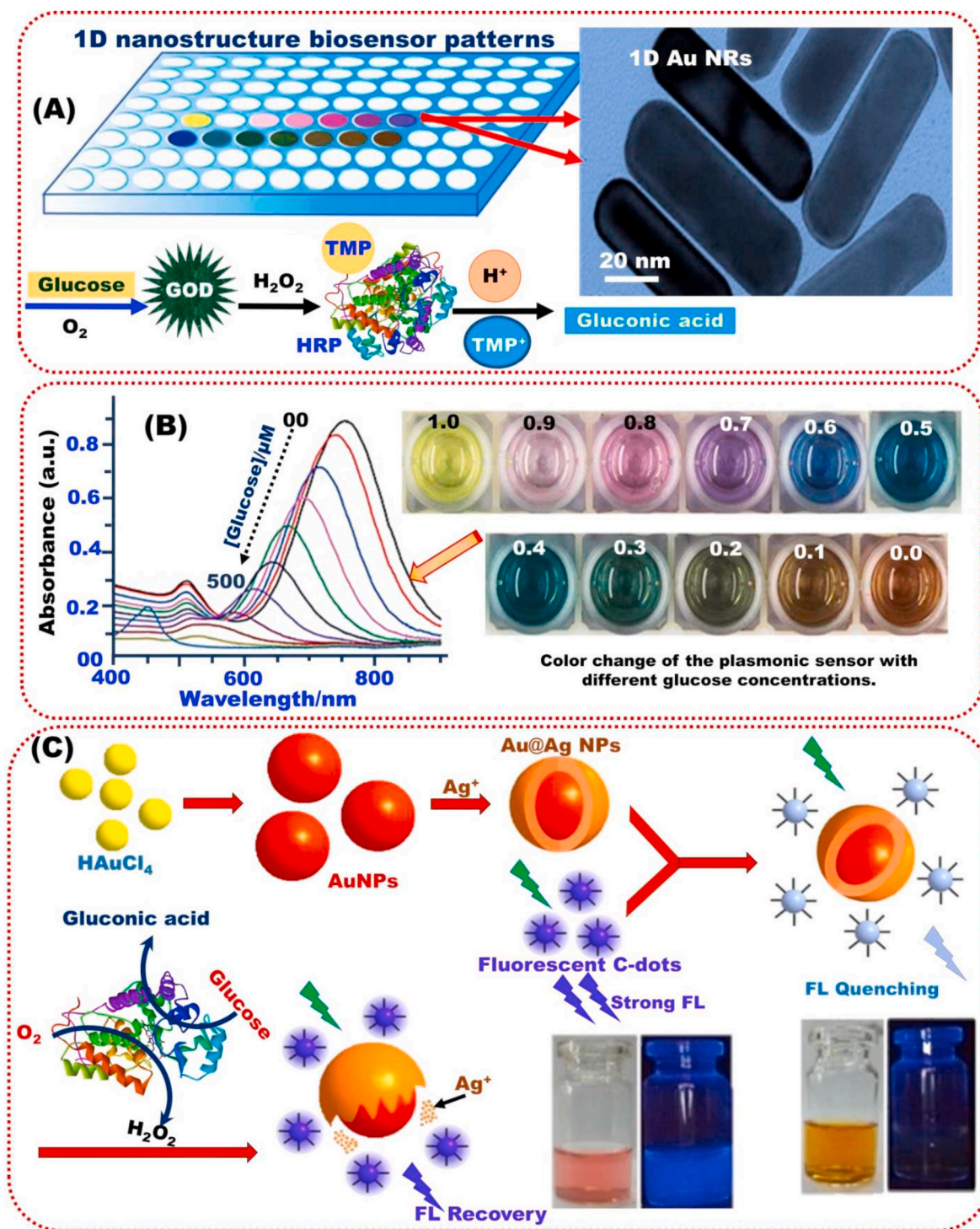
The extraordinary advances in mobile and interoperable devices, wireless capability and the Internet have led to wearable sensing technologies that enable the personalised therapeutics and diagnostics of diseases (Haxha and Jhoja, 2016; Kassal et al., 2018; Elsherif et al., 2018a; Jernelov et al., 2019; Wang and Lee, 2015; Yum et al., 2013; Kim et al., 2018a; Kim et al., 2019; Emran et al., 2020a; Khairy et al., Elshehy; Lee et al., 2018a). With regards to the personalised self-testing of glucose in the medical device industry, the disposable and wearable optical sensors for patients with diabetes are important (Gao et al., 2016). Reliable nano/microscale optical biosensor gadgets offer automatic and small-volume sampling, low-operating power energy and compact analytical tools (Shrivastava et al., 2020; Yang and Gao, 2019; Gao et al., 2016; Rodin et al., 2019). The ADA reported that diabetes is difficult to diagnose at the early stage. This diagnostic limitation can be minimised through the potential design of nanoscale glucose sensors and its precise integration into sizable and compact device modalities that can be implantable with the human body. Therefore, the integration of flexible skin-based or contact lens devices with on-site wireless signal transmission into smartphones is central to develop enhanced sensor gadgets. Challenges remain in the nano/micro fabrication of flexible, stretchable, portable, self-powered and optical biosensor electronics to personalise diagnosis and treatment. In addition, the scalable and optical electronic devices in the commercial market are still vital concerns. Wearable device challenges that should be considered include the actual and cheap cost, comfortable, repeatable analysis, easy-to-read without supplying power, biocompatible and harmless to humans (Kim et al.,

2018a; Kim et al., 2019; Emran et al., 2020a; Khairy et al., Elshehy; Lee et al., 2018a).

2. Bio-visualised signalling mechanism for non-invasive glucose analysis

Continuous glucose monitoring (CGM) in blood sugar or other body fluids (interstitial fluids, saliva, sweat and tears) enables ultrahigh

sensitivity and selectivity and fast response time. The glucose oxidase (GOD) enzymes which react specifically to glucose are immobilised into the active signalling layers developed along the biosensor filter paper strips and platform-based devices to monitor responsive glucose binding at wide-range levels (Shrivastava et al., 2020; Yang and Gao, 2019; Malhotra and Ali, 2018; Li et al., 2020; Sanchis et al., 2017; Soni et al., 2018; Cho et al., 2017; Erenas et al., 2019; Akhtar et al., 2015; Soni and Jha, 2015; Soylemez et al., 2019; Santana-Jiménez et al., 2018). The



Scheme 1. Schematic design of the colorimetric plasmonic biosensors patterns for visual glucose detection (A, B). (Malhotra and Ali, 2018) Copyright 2016, reproduced after permission from Nature Publishing Group (NPG). The colorimetric and fluorescent visualisation assays of glucose based on the potential Au@AgNPs/GOD/CDs core-shell biosensors (C). (Sanchis et al., 2017) Copyright 2018, reproduced after permission from Elsevier.

detection of glucose concentrations in biological fluids depends on the mechanistic binding events and the relevant signal generation of glucose analyte-oxidising enzymes. Glucose-responsive enzyme binding events can be transduced with changes in their intrinsic (i) light (optical) characteristics, such as photon absorption, polarisation, reflectance and fluorescence or (ii) electrochemical properties (Jernelv et al., 2019; Wang and Lee, 2015; Yum et al., 2013; Kim et al., 2018a; Kim et al., 2019; Emran et al., 2020a; Khairy et al., Elshehy).

Glucose-oxidative biosensors can be configured by using enzymes such as GOD or other specific enzymes such as glucose-1-dehydrogenase (GDH) and hexokinase. (Khairy et al., Elshehy; Steiner et al., 2011). A number of mechanisms for enzymatic glucose monitoring can be mainly described in three strategies. Firstly, GOD signal screening can be detected as a function of the consumed O_2 concentration to form H_2O_2 . The dissolved O_2 molecules or the generated H_2O_2 can be electrochemically or optically detected to determine glucose concentration. GDH-based enzyme sensor systems can bind coenzymes such as flavin adenine dinucleotide or pyrroloquinoline quinone nicotinamide adenine dinucleotide phosphate. Dehydrogenase GDH-glucose biosensors do not depend on O_2 concentration. Secondly, electron GOD mediator systems allow GOD to interact with small (redox) mediators, such as ferricyanide or ferrocene compounds, which enable electron transfer along detector surface devices. Thirdly, specific GOD structures which usually enable direct electron exchange between surface design and the specified enzyme were used for signalling GOD responses (Steiner et al., 2011).

2.1. Self-testing fluorescence-based biosensor strips

Fluorescent, non-invasive glucose sensors have several advantages, including high sensitivity and specificity, low cost and simple analysis (Malekzad et al., 2018; Wang et al., 2018; Majdinasab et al., 2019; Khansili et al., 2018; Patra et al., 2016; Israr-Qadir et al., 2017). The development of the sensitive fluorescence and absorption colour signals of biosensors highly depends on changes in the morphology, surface topographies and architectonic geometrics of nanomaterial platforms. In this section, we report on the leverage of nano/microscale architectures in terms of configurations, dimensions and orientation structures in the fabrication of diverse ranges of fluorescence sensing assays, selective signalling outputs and distinctive biosensor models and test strips of glucose analytics.

Simple self-testing glucose patterns of fluorescence-based biosensors can be developed by noble metal (Au and Ag) nanoparticles (NPs) oriented geometrically with 1D nanostructures and 2D nanoprisms (Scheme 1) (Lin et al., 2016; Zhang et al., 2017a; Liu et al., 2018; Radhakumary and Sreenivasan, 2011; Xia et al., 2013; Wang et al., 2016). For example, 1D nanostructure plasmonic biosensor pattern etching of Au nanorods (NRs) produces different colors using enzymatic reactions of the H_2O_2 -enzyme horseradish peroxidase (HRP) substrate of 3,3',5,5'-tetramethylbenzidine (TMB) system. The H_2O_2 species produced from the glucose catalytic reaction of GOD using architectonic AuNRs enable visual detection assays in the dynamic range of 0.1–1.0 mM (Scheme 1 A–C) (Lin et al., 2016; Zhang et al., 2017a). Nanotectonic Au@Ag core-shell NPs and carbon dots (CDs) offer fluorescent visualisation assays of glucose levels in physiological fluids. The visual glucose detection is based on changes in fluorescence colour (Scheme 1 D) (Liu et al., 2018). Fluorescent biosensors allow the wide-range and ultra-sensitive detection (i.e. 2.0–400 μ M) of glucose levels with a low limit of detection (LOD) of 670 nM. The sensitive glucose assays indicate the leverage of 1D and 2D NPs in the fabrication of optical biosensors (Lin et al., 2016; Zhang et al., 2017a; Liu et al., 2018; Radhakumary and Sreenivasan, 2011; Xia et al., 2013; Wang et al., 2016).

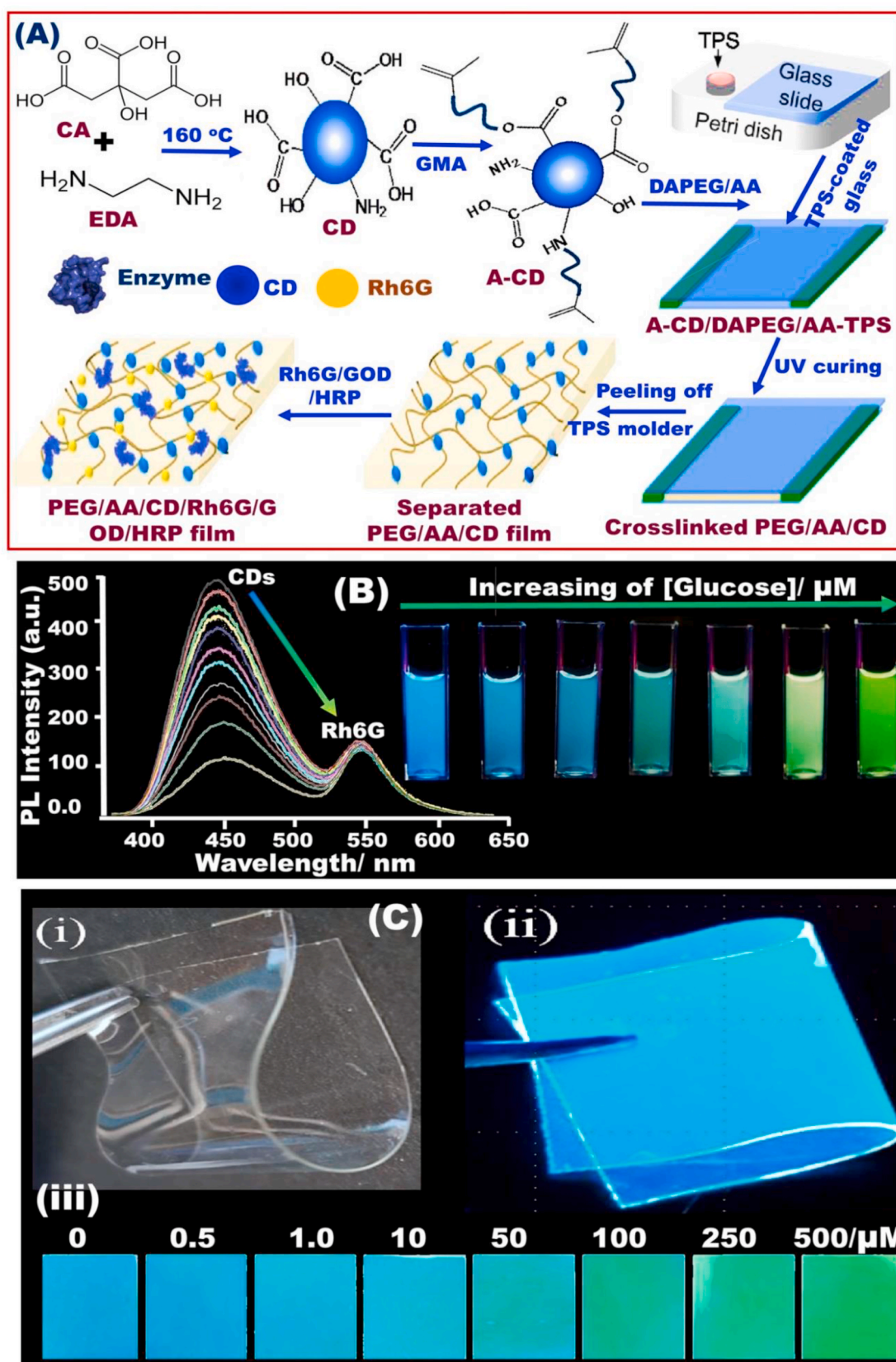
Park et al. reported the controlled fabrication of optical, bendable biosensor films to explore the promising potentials of nano/microscale bio-sensory molecular buildings in flexible, portable biosensor-film strip designs (Scheme 2) (Wang et al., 2016). For instance, active platform material-modified film strips can be fabricated using CDs which are

decorated by a range of molecular building blocks. Firstly, the CD surfaces were modified by glycidyl methyl methacrylate molecules and acrylic groups and then by diacrylated poly(ethylene glycol)/acrylic acid (AA) (DAPEG) mixture, respectively. Secondly, CD/DAPEG/AA composite structures were embedded between two glassy substrates to fabricate flexible film layers. The bottom of the glassy substrate was covered by trichloro(1H,1H,2H,2H-perfluorooctyl)silane to simplify the removal of the CD-modified film from the platform substrate (Scheme 2A). Thirdly, the active signalling sites including rhodamine 6 G (Rh6 G)/GOD/HRP mixtures were immobilised into the CD-modified film to form portable glucose biosensor films. Changes in fluorescence signals and colour intensity enable visual glucose detection with a wide dynamic range of 0.1–500 μ M and sensitive quantification with a low LOD of 0.04 μ M in blood (Scheme 2B) (Cho and Park, 2019). Moreover, the immobilisation of CD/Rh6 G/GOD/HRP into an AA/diacrylated polyethylene glycol mixture enables the fabrication of flexible, stretchable biosensor hydrogel films for sensitive glucose detection (Scheme 2C) (Cho and Park, 2019).

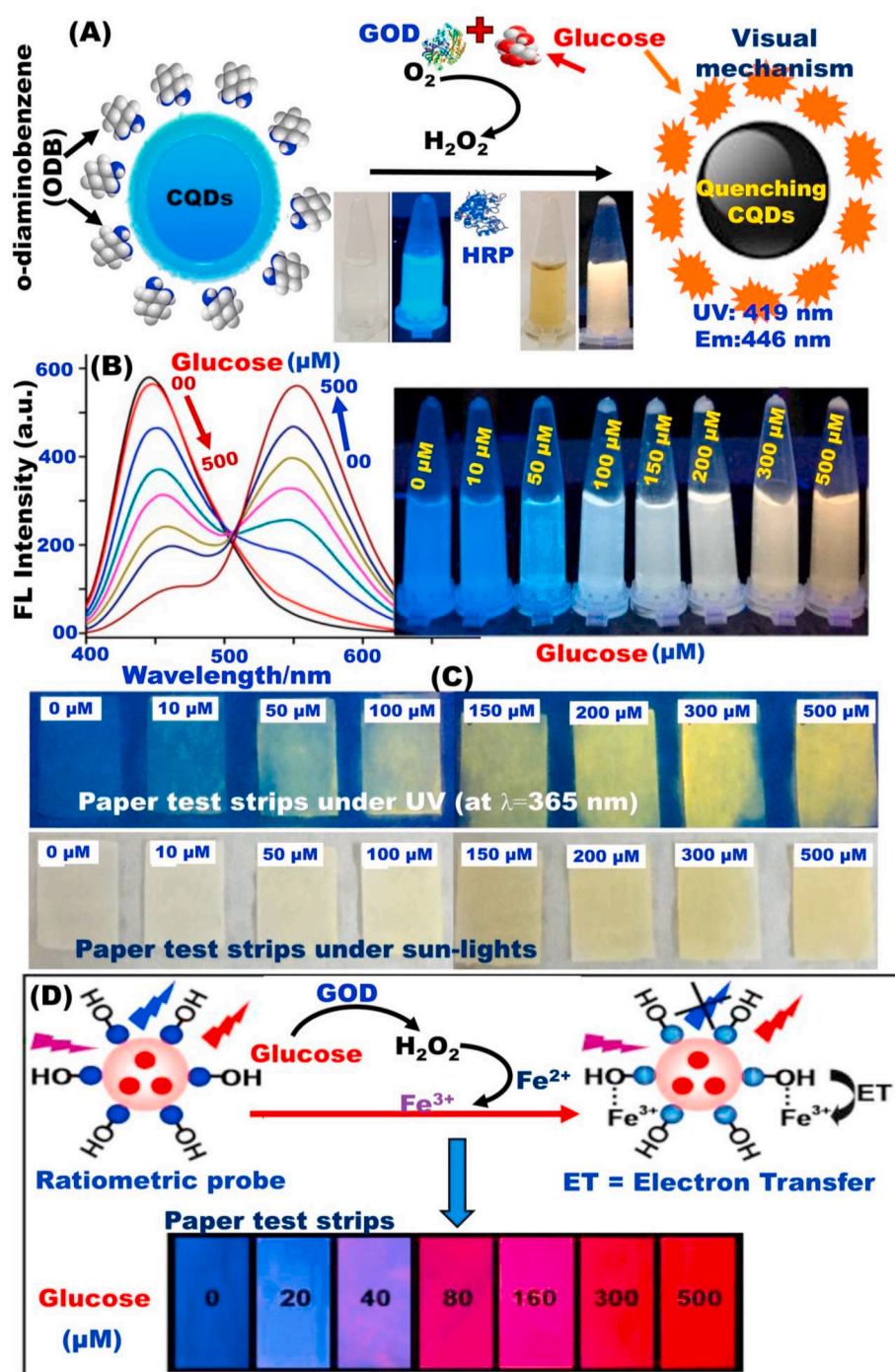
Nano-dimensional QD-immobilised paper films are important to develop test strips for visible detection assays of low-concentration (μ M) glucose analytics (Scheme 3) (Zhai et al., 2019; Huang et al., 2016a). Optical biosensor-induced visible light for glucose detection was reported by using an effective biosensing system fabricated by the immobilisation of *o*-diaminobenzene (ODB)/GOD into carbon quantum dots (CQDs) (Zhai et al., 2019). The ODB/GOD/CQD biosensor paper test was used for the colorimetric detection and fluorescence quenching of CQDs to monitor glucose levels. These portable paper test strips enable the linear biosensing visualisation assay of blood glucose (Scheme 3A–C) (Wang et al., 2018). Paper test strip-based fluorescent biosensor films were further developed through the surface decoration strategy of red QDs with silica NP surfaces (Huang et al., 2016a). The biosensing paper test strips enable the linear and visual detection ranges of glucose concentrations (Scheme 3 D) (Huang et al., 2016a).

Portable paper test strip-based fluorescent biosensor designs using nanoscale materials provide a suitable platform for the early-stage detection of glucose via precise sensing, visual fluorescence signals and continuous analysis of glucose levels (Shehab et al., 2017; Bayat and Saievar-Iranizad, 2017; Chang et al., 2018). Graphene quantum dots (GQDs) were used as decent detection probe candidates for the fabrication of optical biosensor strips. QD-modified strips offer unique properties, including extraordinary photoluminance, low toxicity, disposability and outstanding photochemical aspects. Nanoscale QD (7–10 nm)-modified phenylboronic acid (PBA) probes were used for optical glucose detection in the range of 4–40 mM and LOD of 3.0 mM (Shehab et al., 2017; Bayat and Saievar-Iranizad, 2017). Aggregation-induced emission (AIE) fluorogens were used to control the fabrication of portable, paper-based fluorescent biosensor strips (Scheme 4) (Chang et al., 2018). The AIE fluorogens were formulated through the reaction between L-cysteine and maleimide-functionalised tetraphenylethene (TPE-M) to produce TPE-M-L with high emitting properties in aggregated states. The visual mechanism is based on the existence of H_2O_2 that enables the quenching of fluorescence strength as a function of glucose concentration (Scheme 4B–D). GOD-immobilised AIE-based TPE-M-L fluorogen biosensors allow the sensitive and selective detection of glucose up to 50 nM in concentration. For the fabrication of portable, fluorescent biosensor strips, AIE-based TPE-M-L fluorogen/GOD components were embedded into paper substrate to realise the on-site detection of glucose from physiological samples (Scheme 4B–D).

Disposable paper-, glass- and polymeric resins-based biosensor tests can be fabricated by embedding nanoscale active detectors into solid surface materials. Such disposable biosensor strips enable the fabrication of simple and sensitive visualisation and detection methods of glucose in real human samples (Gao et al., 2018; Wang et al., 2009; Su et al., 2018). Nano-MnO₂-phenol formaldehyde resin composite was used as a quencher for turn-on fluorescence glucose detectors with high



Scheme 2. Representative fabrication steps of DAPEG/AA/CD/Rh6 G/GOD/HRP biosensor film strips (A). Quantitative visualisation assays based on photoluminance (PL) and fluorescence images at different glucose concentrations in the range of 0–500 μM (B). (C) Original (i) and photo-induced (ii) images under exposure of UV light (at $\lambda = 365\text{ nm}$) for the flexible, portable biosensor film strips based (DAPEG/A-CD/AA/Rh6 G/GOD/HRP) composites. Fluorescent visualisation assays of test film strips with addition of glucose concentration in the range of 0–500 μM (Cho and Park, 2019) Copyright 2019, reproduced after permission from Elsevier.

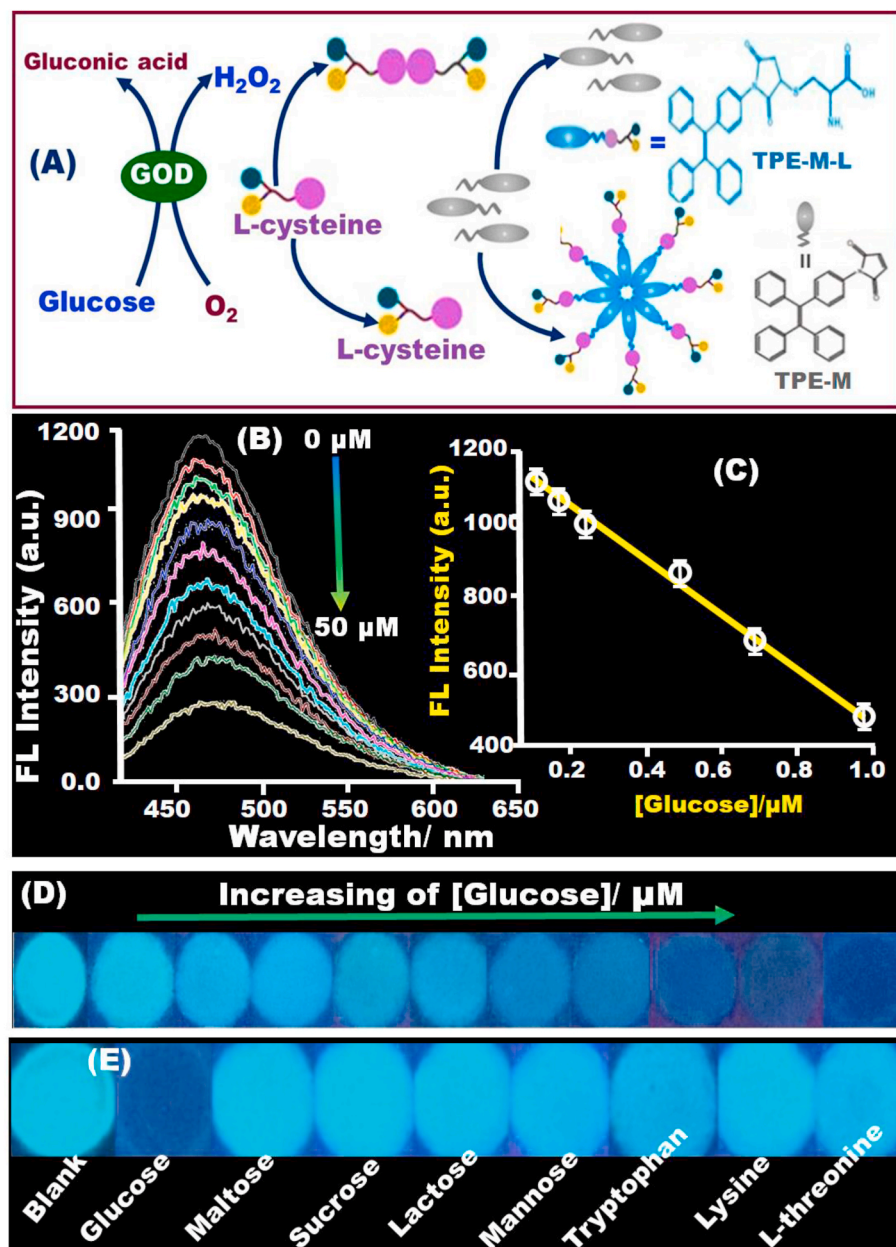


Scheme 3. (A) Schematic design of optical biosensor-induced visible light for quantitative analysis and visual detection of glucose. (B) The fluorescence-dependence spectra and the corresponding colour changes of glucose concentrations in the dynamic range of 0–500 μM. (C) Photo-induced biosensors based paper test strips under exposure of UV light (at $\lambda = 365$ nm). (Zhai et al., 2019) Copyright 2019, reproduced after permission from Multidisciplinary Digital Publishing Institute (MDPI). (D) Fluorescent paper test strips for visual quantification of blood glucose. The silica NPs embedded active sites of blue CDs and red QDs for formation of the biosensor strips. The Fe(III) ion-mediator affected the glucose oxidation process by GOD. (Huang et al., 2016a) Copyright 2016, reproduced after permission from Elsevier.

sensitivity and selectivity in human blood (Scheme 5 A) (Gao et al., 2018). Building blocks of multilayer films based on glass substrates enable the fabrication of portable glucose biosensors (Huang et al., 2016a). The precise microscale biosensor patterns of active composite layers have been built with three significant consequences of (i) green-emitted CdTe/CdS QDs, (ii) red-fluorescent Pt-porphyrin O₂ sensors and (iii) GOD (Scheme 5 B) (Wang et al., 2009). Portable paper test strips of glucose were used with ratiometric fluorescent biosensors (Su et al., 2018). The biosensor strip surfaces were activated by using blue fluorescent graphene oxide (FGO), bovine serum albumin (BSA) and red fluorescent Au-nanostructure for significant singling of glucose levels. The resultant BSA–Au/FGO biosensor paper strips were utilised for visual glucose detection in human serum in the range of 1–10 mM with

LOD of 0.16 mM (Scheme 5 C) (Su et al., 2018).

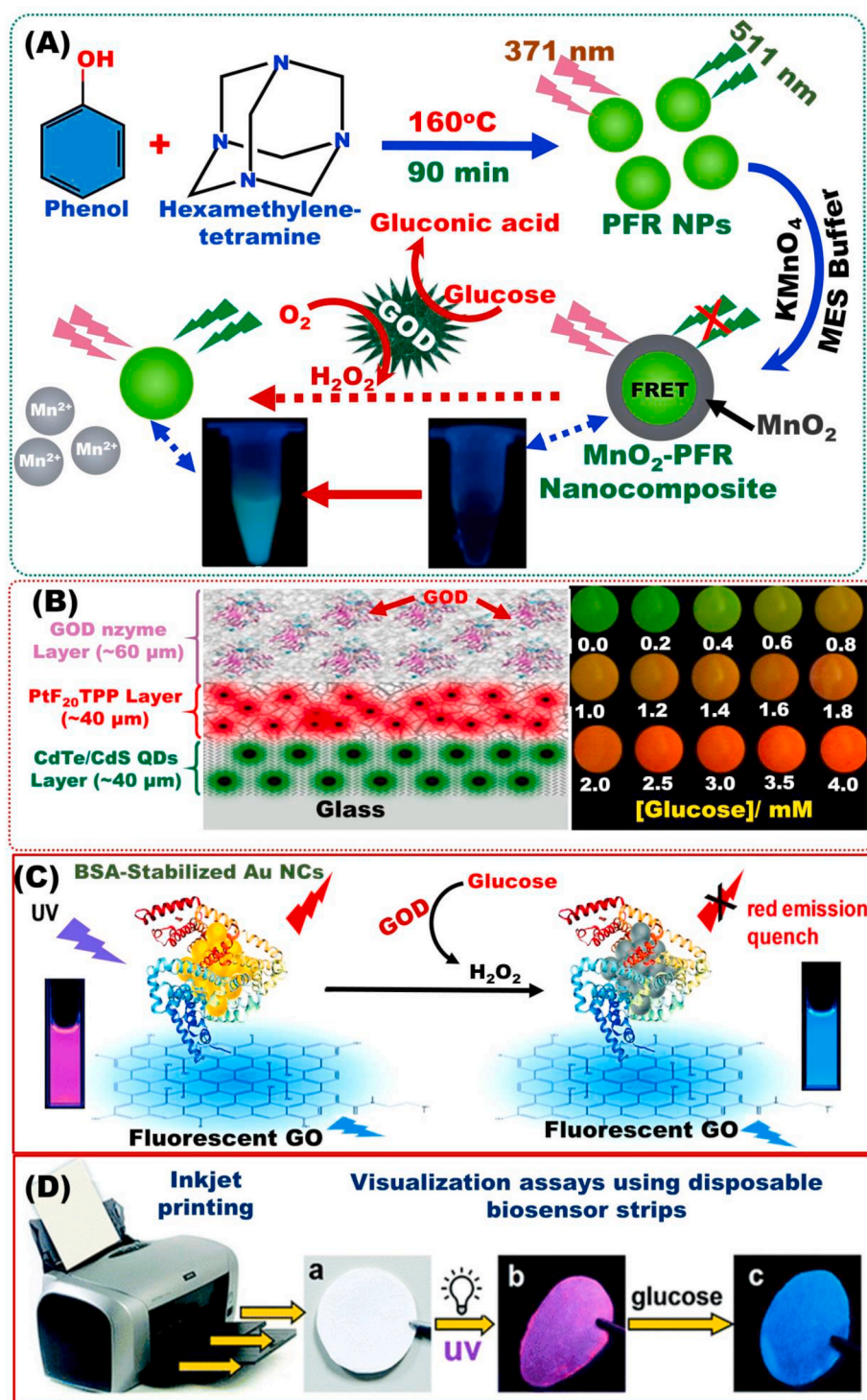
Functional nanocomposite biosensor architecture, including CeO₂, ZnS and Co₃O₄-chromogens or CuO nanoneedle-modified GQDs, have played a significant role in the development of magnetic and visible light biosensors. Nanoscale active material-based biosensors provide visual colorimetric sensing assays with the following features: (i) low-cost, colorimetric and sensitive glucose assays with low LOD (~nM level) and (ii) real-time detection of glucose levels in actual samples (Ding et al., 2017; Zhang et al., 2014, 2017b; Lin et al., 2015; Su et al., 2012, 2015; Lu et al., 2015; Zhao et al., 2015; Peng and Weng, 2017; Liu et al., 2014, 2017a, 2017b; Chen et al., 2018c). Morphology-controlled structures were used to fabricate fluorescent, colorimetric, magnetic glucose biosensors with superior surface photon sanitisation and



Scheme 4. (A–D) Portable paper test strips based fluorescent biosensor designs of glucose. (A) Mechanistic bio-sensing of glucose, (B,C) quantitative analysis in terms of fluorescence-concentration dependent spectra, and the corresponding calibration, (D) selective visualisation assays under exposure of UV light (at $\lambda = 365$ nm). The changes of fluorescence images with interferences were detected by using portable, paper-based fluorescent biosensor strips. (Chang et al., 2018) Copyright 2018, reproduced after permission from Elsevier.

intrinsic catalytic activity toward GOD and TMB (peroxidase substrate) (Su et al., 2012, 2015; Zhang et al., 2014; Lu et al., 2015; Zhao et al., 2015; Peng and Weng, 2017; Liu et al., 2014, 2017a, 2017b; Chen et al., 2018c; Guo et al., 2018). For instance, nanomaterial-based magnetic-NPs and photo-induced MoS_2 /GO surfaces provide indoor and outdoor bio-visualisation assays of glucose. Indoor biosensing visualisation assays of glucose levels in physiological fluids were developed by embedding sodium dodecyl sulphate into MoS_2 nanostructures (Zhao et al., 2015), and a range of magnetic-NPs (MNPs), such as $NiFe_2O_4$ MNPs, $ZnFe_2O_4$ MNPs, Prussian blue NPs (PB NPs) and Janus $\gamma-Fe_2O_3/SiO_2$ NPs (Su et al., 2012, 2015; Zhang et al., 2014; Lu et al., 2015; Zhao et al., 2015). Such MNPs exhibit peroxidase-like nanozyme functionalities, enabling glucose colorimetric biosensing in urine samples up to 0.03 μM (Su et al., 2012, 2015; Zhang et al., 2014; Lu et al., 2015; Zhao et al., 2015). Outdoor glucose colorimetric biosensing assays were developed using MoS_2 -modified-GO (MoS_2 /GO) platforms. MoS_2 /GO nanocomposite biosensor architecture enables significant photocatalytic peroxidase-like activity (Peng and Weng, 2017).

Portable hydrogel biosensor strip-based periodically photonic crystal architecture was configured into a photonic sensor visualisation system. A coating of self-assembled polystyrene NPs using 4-boronobenzaldehyde-functionalised poly(vinyl alcohol) hydrogel forms highly ordered mono-layered colloidal crystals. Unique mono-layered scales were used to fabricate 2D glucose-sensitive photonic crystals for the visual detection of glucose in the range of 0–20 mM in physiological blood and tear samples (Chen et al., 2018d). Despite the sensitivity and selectivity of nano/microscale glucose biosensors, the challenges in the configurations of these nanoscale sensing designs into portable, easy-to-use devices in daily routine monitoring and household applications remain sobering (Chen et al., 2019b). Considering the combination of optical sensing assays in one-screen shot records, exceptional ingenuity, easy-to-use and portable or wearable devices can be developed for the remote care of diabetes.



Scheme 5. (A–D) Polymeric resins-, glass- and paper-based test strips for biosensing assays of glucose concentrations in physiological samples. (A) Mechanistic formation of nano-MnO₂-phenol formaldehyde resin (PFR) composite detector and its visualisation assays. (Gao et al., 2018) Copyright 2018, reproduced after permission from Elsevier. (Huang et al., 2016a) Building blocks of multilayer films based biosensors and variable visualisation sensing assays of glucose. (Wang et al., 2009) Copyright 2009, reproduced after permission from Elsevier. (C, D) Fabrication and visual detection mechanism of glucose of disposable biosensor paper strips. (Su et al., 2018) Copyright 2018, reproduced after permission from RSC (Royal Society of Chemistry).

2.2. Portable CL glucose biosensor systems

The integral CL glucose response assays are based on light emission in detectable ranges (i.e. from visible to near-infrared regions) because of probe-to-glucose biochemical reactions and binding events (Guo et al., 2013; Chen et al., 2017a; Zhang et al., 2019a; Yang et al., 2019; Yu et al., 2016; Li et al., 2017a). Along with optical biosensors, CL signals have low emission background that eschews light scattering noise. CL biosensors have shorter lifetimes than fluorescence-based biosensors because of the exhaustion, peregrination and collapse of reagents. One of the main advantages of CL biosensors is the CL red-out signals that are

usually associated with chemical reaction changes. The indicative biosensor signalling can be assigned to the real identification and quantitative determination of glucose levels (Yu et al., 2016). Currently, the development of various CL biosensor systems with highly sensitive and selective CL glucose sensing assays has recently attracted increasing interest. Convincing evidence of efficient and dynamic CL systems in terms of superior LOD and wide linearity ranges can be achieved with the precise building of CL device patterns associated with nano/micro-scale architectonic platforms, appropriate reaction conditions and reagents, and potential immobilisation of probes (Guo et al., 2013; Chen et al., 2017a; Zhang et al., 2019a; Yang et al., 2019; Yu et al.,

2016; Li et al., 2017a, 2018a).

The CL building blocks of device patterns via surface functionalisation and interior decoration of nanostructured platforms, such as GO sheets, porous metal oxide frameworks (MOFs), hollow silica microspheres (HSMs) and well-defined NPs, improve CL biosensing signals (Peng and Weng, 2017; Liu et al., 2014, 2017a, 2017b; Chen et al., 2018c; Guo et al., 2018). The surface interfaces, voids and spaces of sensor carriers provide multi-diffusible pathways, suitable pocket accommodation of active reagents and analytic targets for sensitive CL assays. The surface activity of nanoscale bio-sensory molecular buildings boosts the luminol CL signals during the binding with glucose. A good example of the influence of CL nanofabrication biosensors is that the incorporation of HRP/GOD-luminol into GO platform enables the ultra-sensitive and wide-range detection of glucose (i.e. 5.0 nM–5.0 mM) with LOD of 1.2 nM (Li et al., 2018a). In addition, the fabrication of large-surface-area CL hybrid biosensors enhances CL glucose detection. The CL MOF-235/ β -CD and MIL-53(Fe) MOF hybrid sensors with large surface coverage show great catalytic activity for luminol–H₂O₂ systems and low LOD up to sub-nanomolar (nM) level of glucose in real samples (Mao et al., 2018; Yi et al., 2016). Nanopore sensing platforms have a distinct effectiveness for CL glucose signalling (Yu et al., 2010). For instance, the inner modification of the porosity of multi-functional HSMs by the rhodanine derivative KMnO₄–HCl–H₂O₂ instead of luminol/HRP/H₂O₂ produces a low LOD of 0.8 μ M (Yu et al., 2010). The nanoscale features are clearly evidenced in the fabrication of CL glucose sensing systems based on dendritic Au–Ag bimetallic NPs (Yu and He, 2015). The addition of copper NPs (Cu-NPs) into chitosan-coated Au/Ag NPs/GOD systems enhances enzymatic and CL reaction kinetics and empowers the sensitivity and accuracy of glucose detection in the range of 1.0 μ M–7.5 mM, with LOD of 0.4 μ M (Chaichi and Alijanpour, 2014).

Towards the development of portable CL sensor systems, ultra-cheap cloth-based glucose test strip CL biosensors (CCGTSSs) were designed and patterned using wax screen-printing for glucose detection (Li et al., 2017b). CL glucose detection can be achieved through high-performance enzymatic oxidation to produce H₂O₂ species, which are consumed in luminol HRP-catalysed oxidation. The CL-CCGTSS approach offers sensitive CL signalling of glucose level by the addition of a *p*-iodophenol probe. The linearity detection range and LOD of glucose using CCGTS CL-based sensor strips are 0.1–100 and 0.0948 mM, respectively. Other examples are based on the multifunctional surface dressing of glassy carbon electrode (GCE) film electrode by the active CL nanostructures, enabling the formation of sensitive electro-chemiluminescence (ECL) signals during glucose detection (Tian et al., 2017; Zhong et al., 2014). The formulation of GOD/chitosan/nano-GQD or chitosan-Au@GOD nanospheres along the GCE-electrode films displays ECL behaviour with a wide glucose concentration range of 1.0 mM–120 μ M and ultra-low LOD of 0.3 μ M. Observational studies offered convincing evidence of the dynamic function of nanoscale device platforms in well-defined CL biosensors with fast response via inter-diffusivity, high enzyme loading onto surface coverage, low-concentration detection and real-time monitoring of glucose.

2.3. Visual testing based on SPR biosensors

Optical SPR sensing assays are based on signalling changes in physical and optical refraction properties in response to specifically selective glucose binding with biosensor strips or devices (Luo et al., 2016; Masson, 2017; Zhang et al., 2017c; Nootchanat et al., 2019; Liu et al., 2020; Li et al., 2015a, 2015b; Paliwal et al., 2016; Wang et al., 2011; Wu et al., 2012). Challenges remain in the fabrication of SPR glucose biosensor patterns. However, the optimisation of biosensor designs and the choice of plasmonic substrate-based architectonics are key components to deploy practical SPR sensors. For instance, the nano-/microscale fabrication-wise chipsets of compact SPR sensor patterns and devices offer applicable and perspective tools for the low-cost and

early-stage detection of diseases, such as diabetes (Luo et al., 2016; Masson, 2017; Zhang et al., 2017c; Nootchanat et al., 2019; Liu et al., 2020).

Li et al. (2015a) used a layer-by-layer building block to modify Au-film SPR surface sensor strips through random arrangements of borate polymers, such as poly (acrylamide-ran-3-acrylamidophenylboronic acid) (PAA-ran-PAAPBA). The number of building block layers influences the stability functions of SPR sensing methods in terms of recyclability and reproducibility. The active-surface SPR sensor can effectively capture glucose from extracellular fluid samples with the detection range of 1–1000 mg dL^{−1}. Moreover, PAA-ran-PAAPBA polymer was used to modify a fibre optic SPR (FO-SPR) for non-consumption glucose (Li et al., 2015b). The building blocks of FO-SPR sensor composites are based on self-assembled PAA-ran-PAAPBA layers. The FO-SPR sensing system displays accurate glucose analysis, particularly at low concentration levels in real samples, such as blood, where the glucose can be measured in the range of 1–300 mg dL^{−1}.

The functionalisation of noble metal NPs into SPR surface platforms is important for the sensitive signalling of optical glucose biosensors (Paliwal et al., 2016; Wang et al., 2011; Wu et al., 2012). The sensory building of GOD/ZnO/Au bilayered film strips exhibits highly sensitive SPR-based detection at low glucose levels (~0–300 mg dL^{−1}) in phosphate buffer saline (PBS) compared with GOD/ZnO film-based biosensors (Paliwal et al., 2016). Selective glucose biosensor patterns were constructed using imprinted hydrogel or microgel polymer membranes (Wang et al., 2011; Wu et al., 2012). Membrane sensor fabrication was carried out by embedding glucose phosphate barium salt in interior crosslinking copolymer gel systems. The in situ embedding of nanoscale-sized Au and Ag geometry in the vicinity of molecularly fabricated hydrogel or microgel polymer matrix networks allows the fast, naked-eye and sensitive detection of glucose in human physiological samples and artificial tear fluids (Wang et al., 2011; Wu et al., 2012).

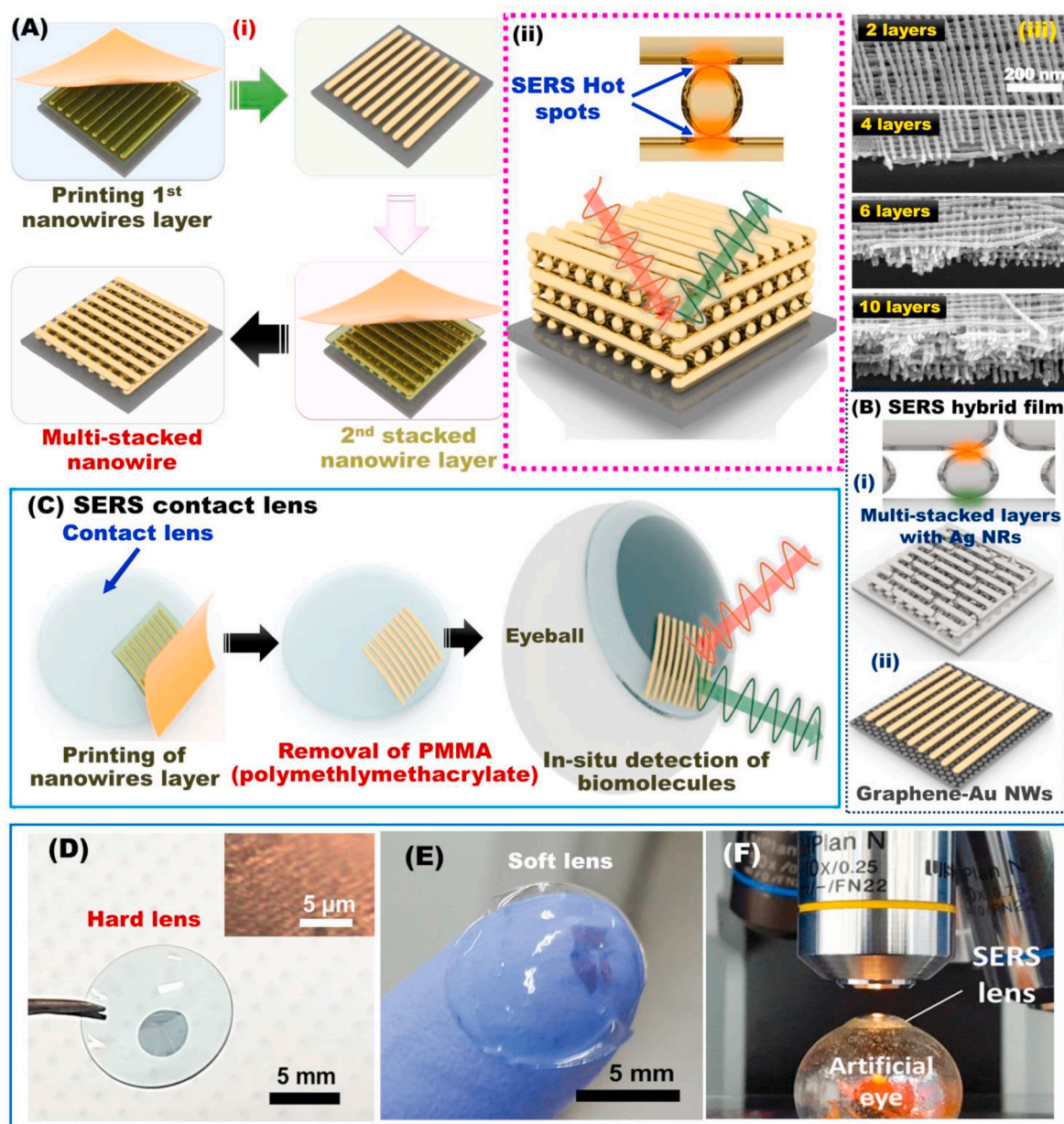
Together, the realisation of the quantifiable SPR visualisation analysis of glucose levels in blood and interstitial fluids with miniature, accurate and stable biosensors becomes factual for the real-time monitoring of patients with diabetes.

2.4. Molecular SERS building block biosensor strips

SERS is a methodological approach that enhances the dispersion of Raman scattering signals during the signalling of active targeted species. SERS biosensor patterns generate exclusive vibrational marks within the binding of small-molecule targets, such as glucose, even in ultra-trace levels. The surface enhancement of SERS biosensor platforms is usually associated with its incorporation by highly active catalytic noble and precious metal NPs (i.e. Ag, Au and Pt) and colloidal NPs (Yuan et al., 2018; Wang et al., 2017; Kong et al., 2013, 2014; Yang et al., 2018; Yonzon et al., 2004; Sooraj et al., 2018; Botta et al., 2018; Al-Ogaidi et al., 2014; Chen et al., 2017b; Gupta et al., 2013; Li et al., 2016).

Molecular SERS building block strip-based biosensor patterns with highly sensitive signal transduction were designed by the self-assembly of 4-mercaptophenyl-boronic acid (4-MPBA) into 10–20 nm Ag@Au NP-functionalised GO nanocomposite surfaces (Kong et al., 2014). The immobilisation of GOD into the modified MPBA-Ag@Au NPs-GO nanocomposite biosensor facilitates glucose detection with the dynamic range of 2–6 mM and LOD of 330 μ M (Gupta et al., 2013). For the compact fabrication of SERS biosensing strips onto hard substrates, the coating of Ag and Au film structures onto nano-Si wafer was built to enhance SERS glucose signalling and transduction. The potential Ag/Au-modified Si-wafer design produces sharp-edged nanogaps, which enhance the SERS performance for in vitro glucose detection (Dinish et al., 2011).

Recently, non-invasive glucose tear sensing and screening assays of diabetes patients have been controlled by using optical SERS contact lens biosensors (Scheme 6A–F) (Jeong et al., 2016). Nanotransfer



Scheme 6. (A–F) Fabrication of plasmonic nanostructure devices based SERS-based contact lens for glucose detection. (A) Different stages to design 3D cross-point plasmonic nanostructures (3D-CPN) (i, ii), and the top-down and cross-section scanning electron microscopy (SEM) images of the designed stacked Au NWs or Ag NRs at different numbers of layers (iii). (B) Multi-layered building blocks of hybrid SERS structures based on AgNRs-on-Ag film and AuNWs-on-graphene. (C) Simple designed of the contact SERS lens through printing Ag NRs on commercial contact lenses through transfer printing. (D–F) Image objects represented the fabricated SERS contact lens (hard) (D), printed Ag NRs on a soft contact lens fabricated using hydrogel (E), and hybrid SERS AgNRs structures connected to artificial glass eye (F). (Jeong et al., 2016) Copyright 2016, reproduced after permission from Wiley-VCH.

printing techniques enable the design of multi-layered building blocks of longitudinally stacked Au nanowires (NWs) or Ag NRs onto metal or graphene films. The unique order, axially-directional plasmon coupling and dense arrays of hybrid architecture-on-film intensify the SERS signalling of contact lens nanodevices (Scheme 6). The flexible hydrogel platform of soft contact lens nano-array devices can be built by embedding the longitudinal stacked metal-NWs into a single-layered film of polymethylmethacrylate replica. In addition, the polyimide (PI) adhesive film associated onto a Si substrate can be used as a platform for nanotransfer printing (Scheme 6A–F). The flexible SERS contact lens nanodevice provides long-term signal stability and ultra-sensitive detection of trace-concentration glucose tears (Scheme 6 B–E).

Overall, the functional tailoring of nanomaterial-based molecular biosensors featuring architectural geometrics, topographic

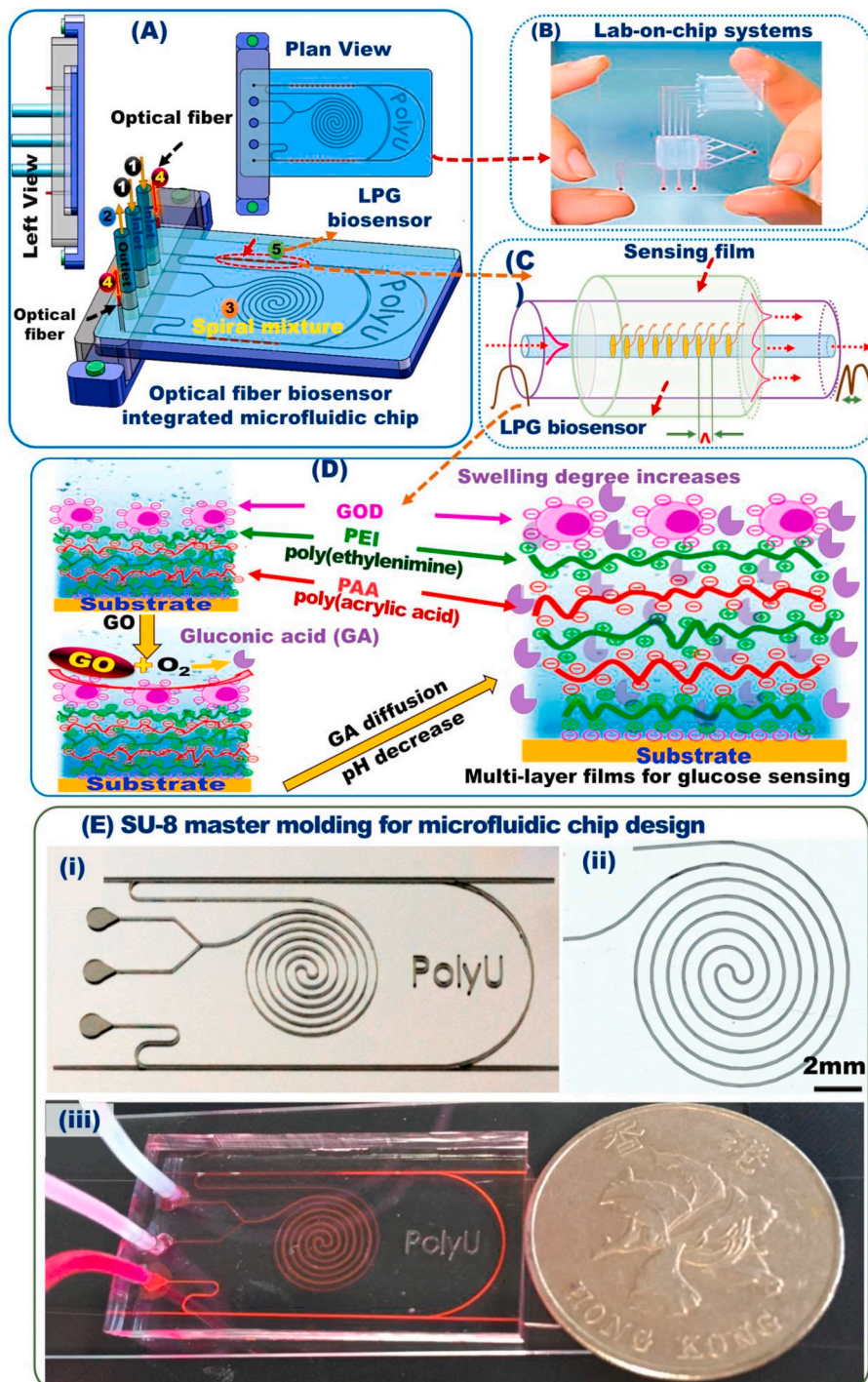
configurations and morphologic structures into nano-pattern SERS biosensor assemblies is a critical issue in the monitoring of diabetes. The nano-SERS surfaces integrated into fluidic pattern arrays potentially lead to unique electron stream movements and flow dynamics during glucose-to-site binding for ultra-high sensitivity SERS signal processing. The stability of nano-SERS patterns within integrated wireless transduction and battery devices can simplify the remote monitoring of patients with diabetes.

2.5. Disposable fibre optic micro/biosensor strips

Optical fibre-based nano/microscale sensors are ideal technical platforms for the rapid and reliable analysis of low-frequency signals of glucose in different environments and physiological fluids (Chen et al.,

2018e; Jiang et al., 2018; Shukla et al., 2017; M-et al., 2014). Compact hybrid fibre optode microsensor membranes or strips feature remote detection susceptibility, multiplexed possibility, electromagnetic interference inviolability, long distance sensing, low-cost analysis and personalised home test of diabetes. Optical fibre probe biosensor membrane strips can be used with the SPR, CL, fluorescence and phosphorescence techniques or with the coupling fibre modes (Shukla et al., 2017; M-et al., 2014; Li et al., 2018b; Khan et al., 2018). To date, the precise fabrication of nano/microscale optical fibre probes provides a key for miniaturisation of nanostructured biosensors into submicron-size and disposable mobile strips (Shrivastava et al., 2020; Yang and Gao, 2019; Malhotra and Ali, 2018; Li et al., 2020; Sanchis et al., 2017).

A wide range of fibre optic glucose biosensor strips in μm -miniaturised size can be fabricated by surface functionalisation of low-cost platforms, such as various polymers, agarose microbeads and optical fibre matrices, including U-shaped fibre and tilted-angle or long-period fibre grating probes. The fibre surface functionality with active multi-components, such as fluorophore or chromogenic signalling indicators, NPs, QDs, charge-transfer complexes, proteins and cellulose acetate can be controlled through long-term grafting, silanisation, immobilisation and layer-by-layer deposition methodologies (Chen et al., 2018e; Jiang et al., 2018; Shukla et al., 2017; M-et al., 2014; Li et al., 2018b; Khan et al., 2018; Yuan et al., 2017; Huang et al., 2016b; Yu et al., 2019b; Pahurkar et al., 2015; Schoolaert et al., 2017; Saxl et al., 2011; Zhang

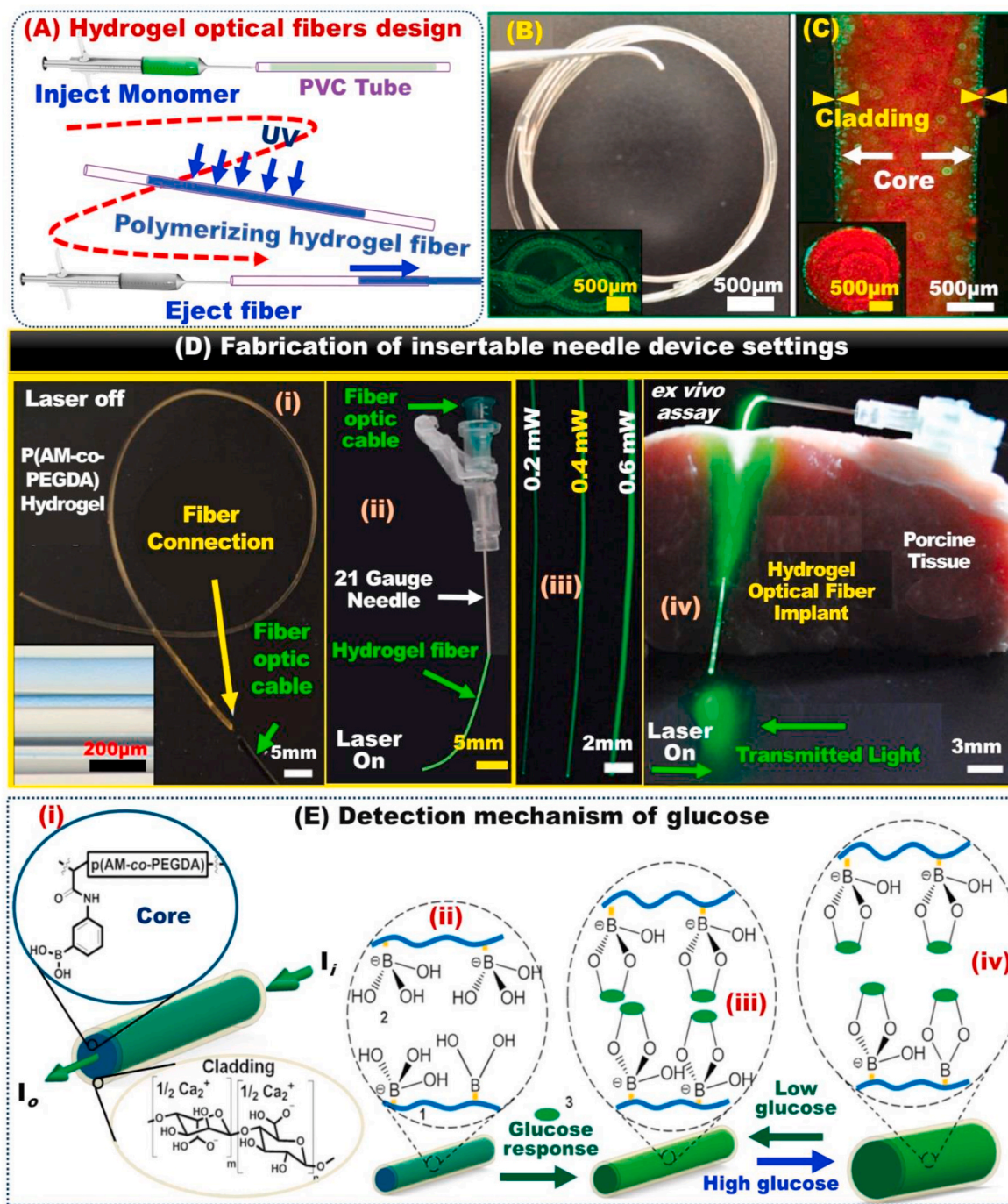


Scheme 7. Control fabrication of portable opto-fluidic biosensor devices for ultra-sensitive detection of glucose concentration ($\sim 10^{-9}$ M). (A, C & D) The specific design of the optical fiber biosensor integrated microfluidic chip. In such fabrication, a GOD hybrid sensing film is deposited on the side surface of long-period grating (LPG). The multilayer layer-by-layer self-assembly sensing film can be fabricated by using poly (ethylenimine) (PEI) and poly (acrylic acid) (PAA) substrates. (B) Real image of the microfluidic lab-on-chip system. (E) Portable design objects of the microfluidic chip based on SU-8 master substrate molding. (Yin et al., 2016) Copyright 2016, reproduced after permission from The Optical Society (OSA).

et al., 2018a; Badmos et al., 2017; Tiangco et al., 2017). The modulation of GOD onto these hybrid microscale sensor optodes led to the ultra-sensitive monitoring of glucose concentration under specific physiological conditions. An alternative route to determine transdermal glucose from adults or neonates was created by using proteins capable of specifically binding to glucose instead of GDO, enabling the fabrication of portable and accurate optical fibre biosensors (Tiangco et al., 2017). In general, these portable/disposable biosensors based on nano-/micro-fibrous membrane strips offer easy visualisation assays of glucose

with fast response time (in order of seconds), remote operation, wide detection ranges and low LOD at micromolar to sub-picomolar levels (Shukla et al., 2017; M-et al., 2014; Li et al., 2018b; Khan et al., 2018; Yuan et al., 2017; Huang et al., 2016b; Yu et al., 2019b; Pahurkar et al., 2015; Schoolaert et al., 2017; Saxl et al., 2011).

Portable optofluidic and flexible hydrogel biosensors can also offer easy-to-handle, low-cost and disposable glucose strips (Yin et al., 2016; Yetisen et al., 2017). The synergistic assembly of photonic fibres and microfluidics enabled the fabrication of portable lab-on-a-chip devices



Scheme 8. (A) Schematic design illustrate the production of hydrogel optical fibers through injection of monomer into a mold tube of poly(vinyl chloride) (PVC). (B) Photographic images of flexible design of the hydrogel core treated with Ca alginate hydrogel cladding. (C) A fluorescent image of the optical hydrogel fiber based on p(AM-co-PEGDA) (Poly (acrylamide-co-poly(ethylene glycol) diacrylate)) core (red) and Ca alginate cladding (green). (D) The fabrication of insertable needle device setting for porcine tissue via consequence steps of (i) the coupling of p(AM-co-PEGDA) hydrogel fibers to fiber optic cables, (ii-iii) the integration into a hypodermic needles (ii) at different light intensities (iii), and (iv) the processing sets of the insertable devices into porcine tissue. (E) Quantitative detection mechanism of glucose using the hydrogel optical fibers as a function of output light intensity (I_i/I_o). (Yetisen et al., 2017) Copyright 2017, reproduced after permission from Wiley-VCH.

(Scheme 7) (Yin et al., 2016). Meanwhile, the flexible hydrogel optical fibres enabled the fabrication of insertable needle device settings on porcine tissue (Scheme 8) (Yetisen et al., 2017). Optic fibre device patterns were built by the functionalisation of polymeric-layered films and then GOD and PBA along the fibre optics of long-period grating and flexible hydrogels, respectively (Yin et al., 2016; Yetisen et al., 2017). Such fibre optofluidic and hydrogel needle devices enabled changes in refractive index and light transmission properties during the binding with glucose. Results indicated that the integration of optical fibre biosensors into a portable microfluidic chipset leads to the quick and ultra-sensitive determination of ultra-trace glucose levels (Scheme 7) (Yin et al., 2016). The optical visualisation pattern of flexible hydrogel fibres is controlled by embedding the red and green fluorescent beads to the inner core and the outer cladding (Scheme 8C) (Yetisen et al., 2017). The flexible optical hydrogel fibre was modified to mimic thin hypodermic needles as insertable and implantable devices for the easy-handling and label-free optical sensing of glucose levels (Scheme 8D) (Shukla et al., 2017).

With the progress of wearable/implantable optical fibre glucose sensors, smartphone-incorporated flexible and optic hydrogel fibre biosensors were designed to enable easy-to-read output signals of responsive and selective glucose physiological samples. In this regard, thin light-transmitting, biocompatible, optical glucose fibres were fabricated by imprinting hydrogel with asymmetric micro-lens array, which is significantly connected to a multimedia silica fibre tip during the photo-polymerisation of its surface topographies (Scheme 9A,B) (Elsherif et al., 2019). The readable signal output of biocompatible fibre glucose optodes was developed and monitored on the screen display of smartphones, thereby allowing well-controlled optical power assessment assays. This sensory glucose device provides continuous glucose visualisation assays for the on-time monitoring, fast response and sensitive and selective detection of glucose in physiological fluids (Scheme 9) (Elsherif et al., 2019).

In the view of close proximity of influence of optical fibre probes, the facile and practical readout approach of combined nano-/micro-fibrous devices can offer excellent linearity response, ultra-high sensitivity and selectivity of physiological glucose fluids. The hybrid fabrication of compact optoelectronic nano/microsystems improves the application of nano-/micro-fibrous biosensors. Intensive efforts are needed to fabricate wearable and implantable fibre optode electronics for improving instantaneous and on-time monitoring, and glucose-sensitive visualisation assays.

3. Nano/microscale engineering hybrid strip and device modulations

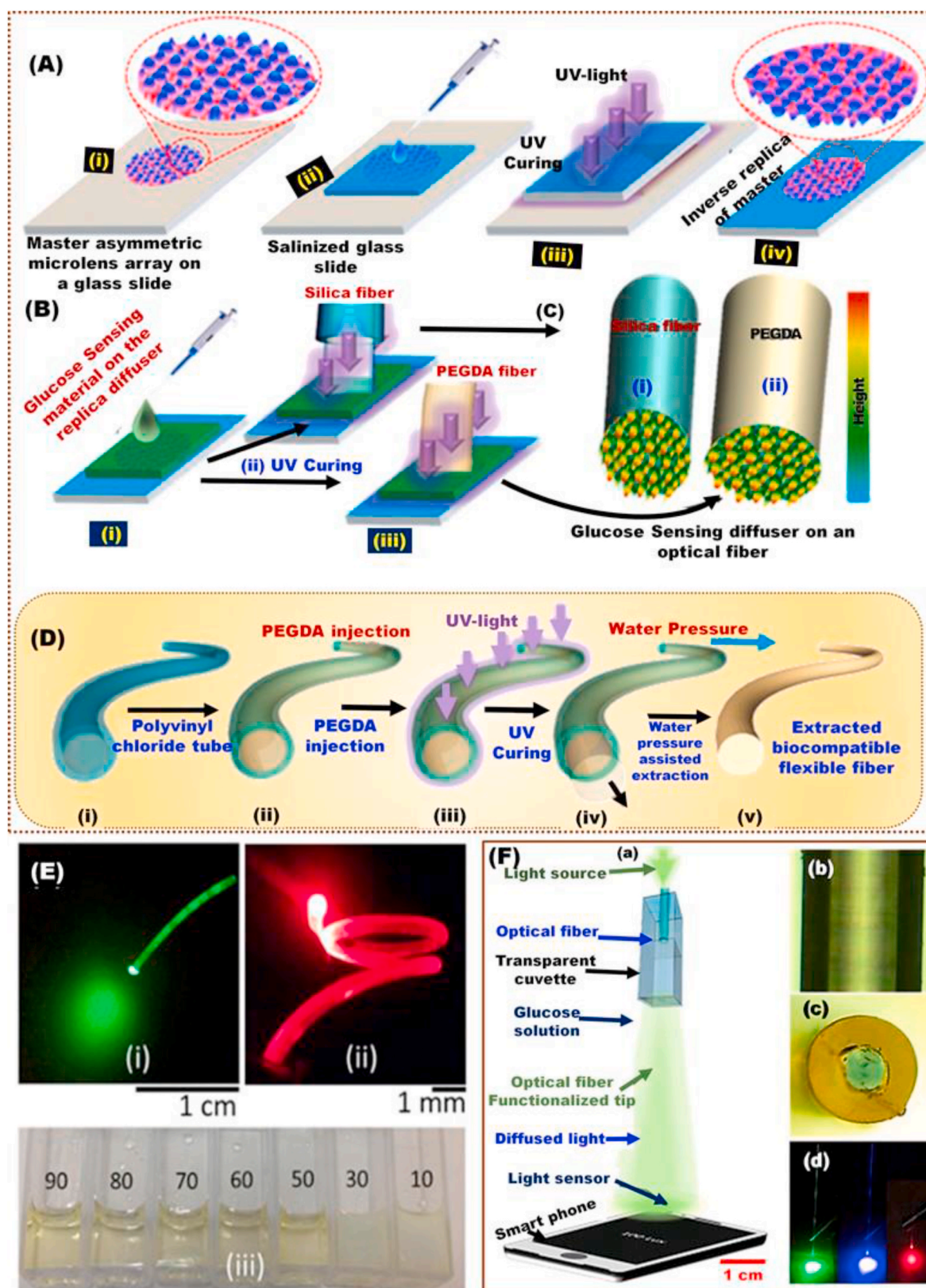
In consideration of the importance of hybrid nano/microscale biosensors in CGM, the integration of hybrid biosensors with unique geometry, morphologic configuration, electronic mobility, multi-directional orientations and surface topographic interfaces into disposable/wearable devices is substantial to improve optical readout signalling and selective and sensitive reliability assays (Table 1) [(Malekzad et al., 2018; Wang et al., 2009, 2011, 2016, 2017, 2018; Majdinasab et al., 2019; Khansili et al., 2018; Patra et al., 2016; Israr-Qadir et al., 2017; Willander et al., 2014; Zhu et al., 2016; Lin et al., 2015, 2016; Zhang et al., 2014, 2017a, 2017b, 2017c, 2019a; Liu et al., 2014, 2017a, 2017b, 2018, 2020; Radhakumary and Sreenivasan, 2011; Xia et al., 2013; Cho and Park, 2019; Zhai et al., 2019; Huang et al., 2016a; Shehab et al., 2017; Bayat and Saievar-Iranizad, 2017; Chang et al., 2018; Gao et al., 2018; Su et al., 2012, 2015, 2018; Ding et al., 2017; Lu et al., 2015; Zhao et al., 2015; Peng and Weng, 2017; Chen et al., 2017a, 2018c, 2018d, 2019b; Guo et al., 2013, 2018; Yang et al., 2018, 2019; Yu et al., 2010, 2016; Li et al., 2015a, 2015b, 2017a, 2017b, 2018a; Mao et al., 2018; Yi et al., 2016; Yu and He, 2015; Chaichi and Alijanpour, 2014; Tian et al., 2017; Zhong et al., 2014; Luo et al., 2016; Masson, 2017; Nootchanat et al., 2019; Paliwal et al., 2016; Wu et al., 2012; Yuan et al.,

2018; Kong et al., 2013; Yonzon et al., 2004; Sooraj et al., 2018; Botta et al., 2018; Al-Ogaidi et al., 2014), (Chen et al., 2017b; Kong et al., 2014; Gupta et al., 2013; Li et al., 2016; Dinish et al., 2011; Jeong et al., 2016; Chen et al., 2018e; Jiang et al., 2018; Shukla et al., 2017; M-et al., 2014; Li et al., 2018b; Khan et al., 2018; Yuan et al., 2017; Huang et al., 2016b; Yu et al., 2019b; Pahurkar et al., 2015; Schoolaert et al., 2017; Saxl et al., 2011; Zhang et al., 2018a; Badmos et al., 2017; Tiangco et al., 2017; Yin et al., 2016; Yetisen et al., 2017; Elsherif et al., 2019)]. Table 1 lists the effects of surface embedding and decoration by nanoscale composite materials into sensory design ingredients. Nano/microscale molecular structures enable the construction of nano-patterned and multifunctional biosensor strips or devices (Jeong et al., 2016; El-Safty and Shenashen, 2020a; Emran et al., 2018c; Dervisevic et al., 2020; Nag et al., 2017). As a result, simultaneous detection stimuli and excellent sensing performance significantly improve in terms of the ultra-high sensitivity, selectivity and reliability of real-time visualisation assays. The optical nano/microscale-based biosensors demonstrate great potential in light visualisation monitoring and dynamic and detectable signal transduction. The signalling performance of detectable light visualisation can be used as indicators to evaluate the optical biosensor sensitivity, selectivity, repeatability and time response of glucose levels in physiological fluids (Table 1).

To date, non-invasive nano/microscale sensor designs featuring super-efficient, high-quality and reliable and periodic analysis are of interest for disposable sensing strip/membrane platforms. However, a real, full-package implantation in all-printed wearable biosensing systems is still questionable (Shrivastava et al., 2020; Yang and Gao, 2019; Malhotra and Ali, 2018; Li et al., 2020; Sanchis et al., 2017). The emerging impacts of active nano/microscale materials into optical and portable biosensor arrays provide promising prospects for direct bio-visualisation sensing systems, on-demand screening and self-testing home analysis. Wireless smart devices should respond to personalised medicine to use the wearable sensing technology for applicable and precise point-of-care analysis. Therefore, the integration of smart nanoscale materials into flexible skin-based wristbands and watches or contact lens biosensor array devices may offer biosensor designs with precise and personalised characteristics;

- (i) multi-diffusive nanoscale channels and vast transport gates afford continuous flow kinetics without fouling or obstructing of body fluids, and rapid molecular/physiological rate analysis (El-Safty and Shenashen, 2020a; Emran et al., 2018c; Dervisevic et al., 2020; Nag et al., 2017),
- (ii) multi-dimensional and -directional alignments around longitudinal and lateral axes enable effectively wearable and implantable nano/microscale array systems,
- (iii) dense and facile electron/charge transfer surface scales provide in situ signalling stability and ultra-high sensitivity and selectivity with broad linear detection range and
- (iv) atomic-scale and high-index exposure surfaces would help to fabricate a particular form of compact nano-sized devices with instantaneous data acquisition and accurate signal transmission.

For the future designation of personalised healthcare, fully configured wearable biosensor systems must be developed urgently using hybrid nanomaterials for the on-time visual screening, regulatory point-of-use monitoring, extremely low-cost and rapid diagnosis of diabetes at early stages (Dervisevic et al., 2020). For personal self-testing, the signal analysis can be transferred wirelessly to a read-out electronic devices or smartphones. On the screen display, the glucose levels can be monitored digitally or graphically according to the individual preferences and needs of each patient with diabetes.



Scheme 9. Step-by-step fabrication sets for controlling the design of flexible, biocompatible fiber optodes for continuous glucose monitoring (A–E). Smartphone-integrated fiber optics and the experimental sets used for glucose detection (F). (Elsherif et al., 2019) Copyright 2019, reproduced after permission from Elsevier.

Table 1

Influence of surface embedding of the nano/microscale composite materials into sensory design buildings on optical monitoring, dynamic transduction signals, and precision detection of glucose using various visualisation techniques.

Material-based biosensor strips	Signaling Techniques	Detection range/ μ M	LOD/ μ M	Ref.
Au@Ag NPs and carbon dots (CDs)	Fluorescent-based biosensor strips	2.0–400	0.67	Soylemez et al. (2019)
DAPEG/AA/A-CD/Rh6G/GOD/HRP film		0.1–500 (aqueous)	0.04	Malekzad et al. (2018)
o-diaminobenzene/GOD/carbon quantum dots		0.5–500 (Film)	0.08	
red QDs/silica NPs		10–200	1.15	Wang et al. (2018)
GQDs (7–10 nm)		0–500		Majdinasab et al. (2019)
AIE (TPE-M-L)/aqueous		4–40 mM	3.0 mM	Khansili et al. (2018)
TPE-M-L/paper			0.05	Israr-Qadir et al. (2017)
Nano-MnO ₂ -PFR composite		5–1000	1.5	Israr-Qadir et al. (2017)
CdTe/CdS QDs/red-fluorescent Pt-porphyrin/GOD		0–3000		Willander et al. (2014)
FGO/Au-nanocluster/BSA.		1–10 mM	160	Zhu et al. (2016)
GQDs/CuO nanocomposite	CL glucose biosensor systems	SDS–MoS ₂ NPs	0.59	Lin et al. (2016)
H ₂ TCPP–ZnS nanocomposites		5–500		Liu et al. (2018)
H ₂ TCPP–Co ₃ O ₄ nanocomposites		1–10	0.86	Shehab et al. (2017)
Ag nanoprisms and GOD		0.2–100	0.2	Chang et al. (2018)
Graphene quantum dots (GQDs)		0.2–120 pM	0.3 pM	Zhang et al. (2017a)
Iodophenol blue		0.1–30	0.06	Gao et al. (2016)
CCGTs- p-iodophenol		100–100000	94.8	Chen et al. (2018c)
HRP/GOD-luminol-GO		0.005–5000	0.0012	Lu et al. (2015)
MOF-235/ β -CD hybrid		0–10	0.01	Chen et al. (2018d)
luminol–H ₂ O ₂ –MIL-53(Fe) MOF		0.1–10	0.05	Peng and Weng (2017)
Au-shell@GOD-GCE	Visual-testing based on SPR biosensor patterns	1000–4300	0.3	Liu et al. (2017a)
Au–Ag bimetallic NPs		1–1000	0.4	Liu et al. (2017b)
Chitosan-induced Au/Ag alloy NPs		1–7500	0.4	Guo et al. (2013)
HSMs/rhodanine derivative-KMnO ₄ -HCl-H ₂ O ₂		7.72–25400	0.8	Chen et al. (2018c)
PAA-ran-PAAPBA		55.5–55500		Guo et al. (2018)
PAA-ran-PAAPBA/FO-SPR		55.5–16650		Liu et al. (2014)
GOD/ZnO/Au bilayered		0–16650		Li et al. (2018a)
AuNPs hydrogel membrane			111.01	Mao et al. (2018)
AgNPs/poly(NIPAM-AAm-VPBA)		1–20000		Yi et al. (2016)
Au nanostar@SiO ₂ /GOD	SERS building-block biosensor strips	25–25000	16	Yu et al. (2010)
Au@Ag NRs-(4-CPBA)		2000–6000	330	Yu and He (2015)

Table 1 (continued)

Material-based biosensor strips	Signaling Techniques	Detection range/ μ M	LOD/ μ M	Ref.
GOD/MPBA-Ag@Au NPs-GO				Li et al. (2015b)
GO-AuNR		100–100000		Paliwal et al. (2016)
Glucose binding protein (GBP)-immobilised agarose beads	fiber optic micro/biosensor strips	4.0–20	2.0	Chen et al. (2018e)
Cu(II)-doped polyaniline		50–200 mg/dL	0.2 mg/dL	Kong et al. (2013)
Tilted fiber Bragg grating (TFBG)-SPR structure		0.12 dB/mM	0.5 dB/mM	Dinish et al. (2011)
GODs onto SiO ₂ NPs and polyacrylamide gel).		0–80 mg/dL	0.14 nm	Botta et al. (2018)
Enzyme-functionalised long-period fiber grating		0.1–3.2 mg/ml	7.12 nm/mg/ml	Jeong et al. (2016)

4. Wearable glucose biosensor-integrated smartphones

4.1. Key advances of wearable and mobile biosensors

To date, easy-to-use, flexible and wearable electronic devices are urgently needed for daily glucose monitoring from body fluids (interstitial fluids, saliva, sweat and tears). Patients with diabetes suffer from long-term illness management in terms of longitudinal and continuous daily monitoring and screening display for maintaining the blood glucose in standard levels. The key health risks associated with surgical insulin therapy of diabetes are related to injection pain, pressure from blood collection and frequent insulin shots (Dervisevic et al., 2020; Nag et al., 2017; Cappon et al., 2017). Wearable and mobile glucose biosensors are required to provide the reliable point-of-care (POC) and medical healthcare monitoring of diabetes. In this regard, skin-safely soft, painless and flexible biosensors are potentially effective for patients with diabetes. The promising wearable devices are recognized to offer convenient handling and sampling without pain or harm to the human body. Ideal wearable systems to the individual needs and preferences should not cause skin/or eye irritation and laminate conformably, as comfortable as possible, on the human epidermis without malfunction in the sampling collection of sufficient and quantitative amount of physiological fluids. On this point, the integration of implantable array systems with microfluidic channels can quickly build and shape a regulatory access of the collective body fluids along the way of daily activities. Real-time CGM analysis of accessible glucose concentrations in physiological sweat and tear samples can be monitored via signal transductions of biosensors. CGM is conducted via a miniature readout detector or analyser, which should be held with accurate location and liable intensity onto the contact lens or on the patient's skin via flexible, adhesive bandage. The internal integration systems of self-powered components and data processing circuitry into the wearable biosensors transmit wirelessly the simultaneous signal detection of glucose into mobile devices, such as tablets and smartphones.

4.2. Configured workability of wearable biosensor electronics

A sweat-based glucose tracking is of interest as an alternative sensing method to alleviate the difficulty associated with blood glucose testing. Wearable, electronic devices are important developments for accurate tracking of glucose level in sweat (Lee et al., 2017a; Patra et al., 2018). The strategic leverage of sweat-based glucose tracking affords a real sensory system for painless and efficient glucose analysis in terms of

sample collection, real-time sensor accuracy and monitoring rate. In specific, the sweat glucose assay provides a simple, economical method to monitor glucose level because of the proliferation of sweat glands in the body. Sweat samples provide an accurate reflection of the blood glucose level in the human body (Lee et al., 2017a; Patra et al., 2018; Heikenfeld, 2016a; Bariya et al., 2018). For instance, the eccrine and apocrine sweat on the skin can be used to determine the glucose level as a diabetic disease marker. Wearable sweat sensors are expected to improve the future healthcare of patients with diabetes (Heikenfeld, 2016a; Bariya et al., 2018).

The advances in a wide range of printing and manufacturing fields allowed the prototype all-printed wearable devices such as teeth- or skin-tattoos, contact lenses, wristbands and watches to be designed with key-mechanic workability features; (i) transparent, mechanical, biocompatible properties similar to human-targeted body surfaces in ways that ultimately meet the individual lifestyle preferences; (ii) low-sample volume with rapid detection rate to avoid the sample biodegradation and time-lag effects that ultimately affect the calibration changes and low correlation coefficients between the collective sample concentration and its real venous blood level and to eliminate any interferences associated with non-delivery samples; and (iii) a regulatory signal readout to be monitored precisely and effectively for CGM patches with a comprehensible fashion of data transmission to avoid multiple recalibrations in a short working time (Ma et al., 2019; Chen et al., 2020a). In situ stability and working lifetime of the implantable or wearable glucose biosensors depend on the comprehensible ways of implantation of device platforms to be well-defined configuration with human contact interfaces, enabling convenient handling with no tissue disruption, biocompatibility and anti-fouling properties for painless sample collections (Lee et al., 2017b). The in situ sensing components used for the effective signalling and transmission of sensor glucose devices can be appropriately composed of well-oriented means, such as (i) microfluidic channels, (ii) electronic circuits to allow communication with a wired network protocol or external wireless to transfer results and analysis and (iii) digitalised data readout units (Gao et al., 2019; Chen et al., 2020b; Vaddiraju et al., 2010; Carlson et al., 2012; ChenFeng et al., 2013; Huang et al., 2016c). Most of these wearable sensor designs were built to improve adequate reliability, virtual price, continuous measurements and precise sampling correlations between the collected glucose analytics from sweat and blood samples. Reliable glucose testing and consistent measurements of wearable biosensors are also affected by environmental parameters, such as temperature change, humidity, pH, skin pollution, sensitivity and external anomalies of the human body (Shokrehodaei and Quinones, 2020; Sezen et al., 2016; Amay-Bandodkar et al., 2014). In most wearable sensor designs, simple workability and accurate CGM remain challenging. An interesting design based on a tattoo-like sensor was fabricated under certain conditions to improve its sensing reliability and accuracy of sweat glucose measurements (Lee et al., 2016, 2018b). Recent studies have proposed applicable sensor designs which were built with integral compatibility between ultra-thin and stretchy pads using soft and flexible materials. The integrity of materials allows an effective skin contact device to improve sweat absorption/collection and perform convenient and continuous sampling even under mechanical deformation. Applicable sweat sensors, such as multi-modal temperature, humidity and pH sensors, can be used for accurate sweat glucose monitoring in real time through multiple corrections and calibrations of signals (Kim et al., 2018a; Lee et al., 2016). Indeed, powering sweat-based glucose tracking devices are still problematic because of the precision and stability of CGM measurements.

4.3. Biosensing optimisations of wearable electronics

For highly integrated wearable biosensor electronics, rapid developments of seamless wireless digital systems for data processing, signal transmission and long-distance workability using Wi-Fi network

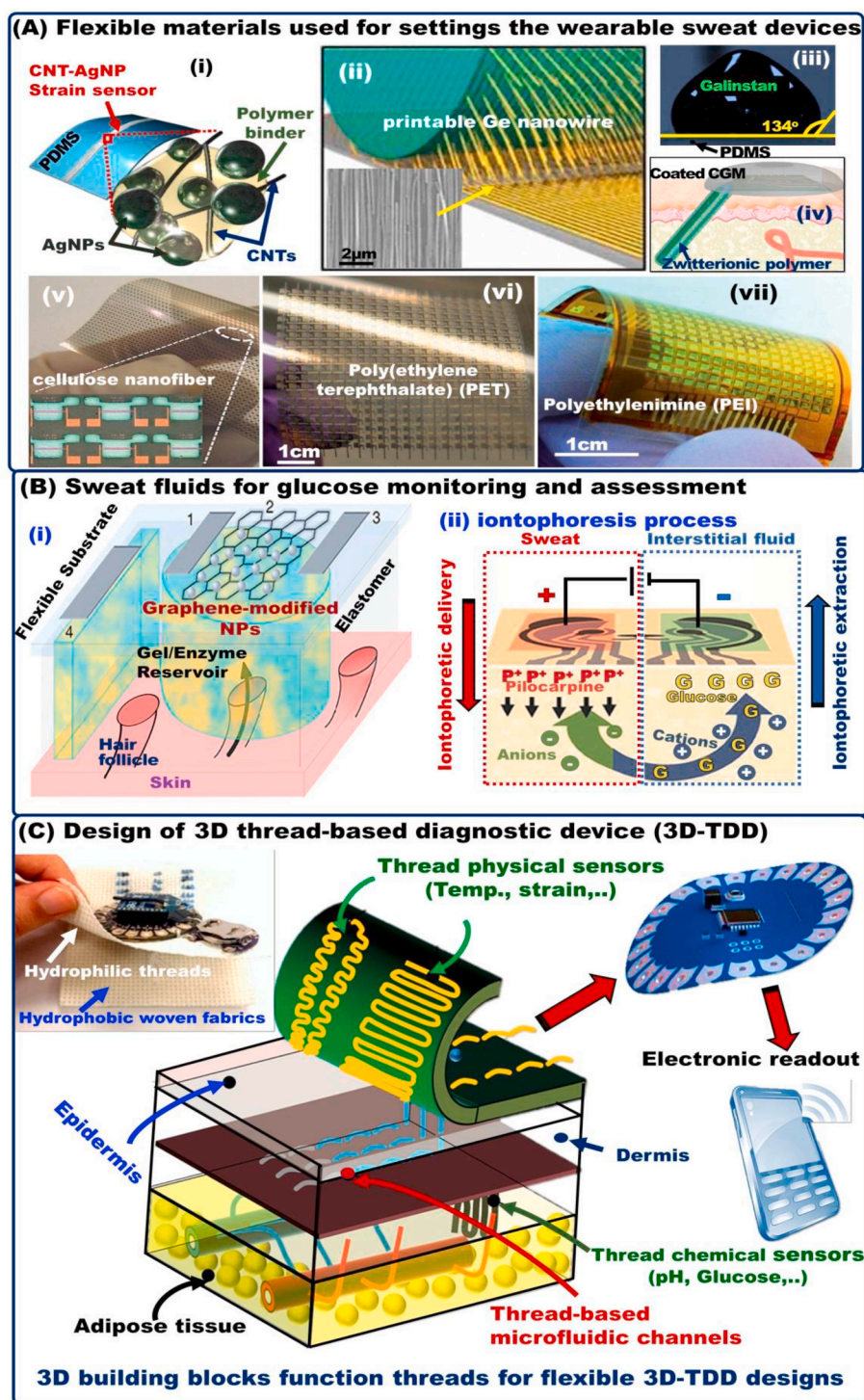
protocol are substantial. Highly efficient and flexible electronics, ultra-sensitive and selective analysis systems and circuitry devices with autonomous self-power operation, signal conditioning, processing and transmission should be tailored to meet the stringent demands for personalised medicine of diabetes. The integrated wireless circuit systems require stable power sources without influence on the easy-of-use devices in accurate glucose analysis and signal data transmission. Therefore, ultra-low power-based wearable electronics with miniaturised circuits are the route to achieve self-power operation devices for the invasive, longitudinal monitoring of patients with diabetes (Lee et al., 2017b; Gao et al., 2019; Chen et al., 2020b). Furthermore, full manufacturing processes and optimisations of wearable sensor systems should be integrated with soft, ultra-lightweight, flexible or stretchable and biocompatible materials. Wearable medical devices provided evidence for future opportunities to achieve real-life diabetic management, regular and continuous monitoring healthcare initiatives and appropriate assessment of insulin administration and drug delivery methods.

5. Fabrication and transduction mechanism of wearable biosensors

The fabric components for flexible device electronics were configured with bendable, stretchable, self-healing, lightweight, translucent, mechanically stable and harmless-to-human materials. The fabrication of wearable biosensors and systems was built-in with three essential key ingredients (Gao et al., 2019; Chen et al., 2020b).

The first key component is the configured substrate as the basic support for the low-cost building of wearable sweat or contact lens devices. The soft substrate materials are mainly composed of a number of bendable polymers which have a high degree of mechanical stabilities, such as polyethyleneterephthalate, polyvinyl alcohol (PVA), PI, polyethylenimine, polydimethylsiloxane (PDMS), polyvinyl chloride, cellulose acetate and others (Scheme 10A). These integrating substrate supports are characterised by high flexibility/stretchability/bendability, low thermal resistivity and highly selective porosity for oxygen permeability, high conductivity, biocompatibility, comfortability and strong mechanical stability (Chen et al., 2020b; Vaddiraju et al., 2010; Carlson et al., 2012; ChenFeng et al., 2013; Huang et al., 2016c; Shokrehodaei and Quinones, 2020; Sezen et al., 2016; AmayBandodkar et al., 2014; Lee et al., 2016, 2018b; Nery et al., 2016; Burleson et al., 2014; Gonzales et al., 2019; Sonner et al., 2015; Heikenfeld, 2016b). For the mechanistic capillary performance, the skin-contact layer substrates should be fabricated by using porous sponge films to make the capture, throughput rate and retention of collected sweat samples facile and rapid. As recently reported, a number of micro-porous materials including silicone sponge, cellulose paper, hydrogel-type polymers, PVA sponge, polyurethane sponge and recycled cellulose sponge have been used to design an effective sweat uptake or gather (reservoir) layer (Gao et al., 2019; Chen et al., 2020b; Vaddiraju et al., 2010).

The second key component is the fabrication of actively modified printing layer that is composed of active binding materials or electrically responsive compounds. The sweat uptake at a reservoir was transferred to the active central binding sites via microfluidic channels, enabling a direct glucose-responsive signalling. This active sensing layer was fabricated from human-safe materials, such as porous/hybrid nano/microscale. The active, ultra-thin film materials should have high transparency and conductivity to improve the accurate detection of low signal noise ratio (Lee et al., 2016; Shokrehodaei and Quinones, 2020). The active layer transduction signals depend on the physicochemical, optical and electrochemical characteristics of applied materials, enabling sensitive changes in their light and photon density, electron/hole mobility and vibrational frequency during the target binding (Scheme 10B,C). Organic-inorganic nano/microscale materials oriented with morphologic and geometric hierarchy are critical in the building blocks of actively designed layers. The unique nano/microscale structure features of flexibility, mechanical strength, high conductivity and



Scheme 10. (A) Unique materials with mechanical and geometrical features used to construct the substrate layer settings for wearable sensor devices. (i) A group of low-cost supports such as (i) CNT-AgNP composite films patterned on a PDMS substrate, (ii) printable Ge nanowire, and (iii) Galinstan on oxygen plasma-treated PDMS, (iv) Schematic object of wearable biosensor devices using flexible substrates based a zwitterionic polymer-coated devices, (v) cellulose nanofiber, (vi) PET, and (vii) PEI. [(Ma et al., 2019), (Chen et al., 2020b), (Takei et al., 2014), (Ota et al., 2014), (Xie et al., 2018), (Kim et al., 2018b)] Copyright 2019, 2020, 2014, 2017, 2018, and 2018, reproduced after permission from RSC, NPG, National Academy of Sciences (NAS), Wiley-VCH, NPG and Wiley-VCH. (B) Mechanistic sweat extraction, collection and sensing by building biosensor devices. (i) Wearable devices based graphene-platform for selective sweat or interstitial fluid (ISF) extraction, and (ii) tattoo-like epidermal biosensor systems for noninvasive CGM in sweat or ISF. (Kim et al., 2018b) Copyright 2018, reproduced after permission from Wiley-VCH. (C) A 3D design control of the thread toolkit sensor into microfluidic channels for fabrication of TDD devices. These TDD devices enabled simple colorimetric display the glucose concentration and pH value using smartphone. (Mostafalu et al., 2016) Copyright 2016, reproduced after permission from NPG.

stability, ultra-lightweight, outstanding physicochemical, optical and electrochemical properties are characteristics of a strong candidate for wearable electronic patches (Gao et al., 2019). The active layers were designed using various materials, such as graphene, carbon nanotubes (CNTs), semiconducting crystalline nanowires, Au-doped graphene and AgNP-modified CNT nanocomposites (Gao et al., 2019; KimZhao et al., 2009; Chen et al., 2016; TakahashiTakei et al., 2010; Takei et al., 2014). These active layer materials should be implemented along the sensor device pattern without changes in the central site ability for glucose-responsive binding impacts. Therefore, the modifiers such as surfactants and (3-aminopropyl)triethoxysilane/poly-L-lysine were used

to facilitate the homogenous assembly single-walled-CNT inks onto the substrate surface without aggregation (Scheme 10 A) (Kiriya et al., 2014).

The third key component is the formulation of interface layer bites to keep the active layer on or inside the substrate supports. Given their unique flexibility, elasticity and conductivity, the liquid metals such as gallium alloys (gallium indium and galinstan) materials can serve as congruously coverage supports on various interface layer surfaces (Daeneke et al., 2018; Ota et al., 2014; Gao et al., 2017). Furthermore, zwitterionic polymers with anti-inflammatory properties were used to fabricate the layer interface coating. Such zwitterionic polymers have

been utilised to improve the accuracy, lifetime and sensing performance of CGM without multiple re-calibrations in a short working lifetime (Scheme 10A) (Xie et al., 2018).

Overall, diverse nano- and micro-materials with different sizes, shapes and surface functionalities were used as potential components in the design of flexible device layouts and chipsets (Scheme 10). For instance, applicable sensor array platforms based on hydrophilic hydrogel polymers were applied on harmless, soft and mechanically stable and flexible devices. Several studies introduced diverse types of popular composite or hybrid materials which feature long-term and biocompatible skin-, epidermis-, or human-friendly microelectronics and facile electron/charge transfer surfaces to provide conformal full-package wearable systems (Kim et al., 2018b; Mostafalu et al., 2016; Lim et al., 2020). Prospective and applicable nano- and micro-materials used into wearable sensing layouts are still required to provide unique skin devices with the following multifunctional keys and smart workability features:

- (i) to protect the epidermis from burning after multi-sensing assays at active sampling layers;
- (ii) to inhibit any skin inflammatory or toxicity due to the potential pH changes or non-preferable sample leakage during analysis;
- (iii) to provide facile yet efficient glucose collection without inter-sampling interferences;
- (iv) to create a built-in system with contentious sample diffusion;
- (v) to suppress the wearable device layout deformation or defects (i.e. cracks or damages) from mechanical strains, including bending, twisting and stretching, during multiple analyses;
- (vi) to offer biocompatible and toxicological CGM systems in both sensing assays of in vitro and in vivo analyses; and
- (vii) to help stabilise the dynamic device linearity in terms of gauge signalling and sensing accuracy under applied condition strains, such as high humidity and temperature, and photo- and biodegradation.

6. Epidermal fluid-integrated skin-like glucose biosensors

Alternative glucose sources in the epidermal fluids, such as interstitial fluid (ISF) and sweat or perspiration, were used to determine the physiological status of blood sugar levels through non-invasive CGM systems. Sweat and ISF samples extracted into or across the skin epidermis surface via iontophoretic (IP) sweat-stimuli drug delivery and reverse iontophoretic (R-IP) ISF extraction, see Scheme 10B (Kim et al., 2018b). R-IP processing offers a gateway of small quantity of non-invasive ISF sampling for glucose analysis. The R-IP glucose extraction can effectively occur via stimuli insertion of ultra-low electric current that penetrates the skin cuticle under applied IP skin electrodes. Under this process, the electro-migration of sodium ions in body fluids ultimately led to the electro-osmotic transport of glucose in ISF toward the actively layered biosensor arrays for direct off-body thread-based analysis (Kim et al., 2016, 2018b; Mostafalu et al., 2016; Lim et al., 2020). The scale variations in collective glucose concentration-based sweat or ISF fluids depend on the difference in sampling methods, physical and metabolic activities such as exercise, uptake foods or meals with glycaemic index, thermal heating and stress. Likely to epidermal ISF or blood contents, the chemical ingredients of natural and artificial sweat sampling formulates include minerals (with Na^+ , K^+ , Cl^- , Ca^{2+} and trace- Mg^{2+} ions), glycaemic metabolites, lactic acids, harmonic proteins and peptides (Chen et al., 2018b). Epidermal wearable electronic systems with skin-based biosensors were used for non-invasive glucose analysis from stimuli-induced sweat sampling (Scheme 10 B, C) (Chen et al., 2016, 2017c, 2020a, 2020b; Lee et al., 2016, 2017b, 2018b; Gao et al., 2017, 2019; Vaddiraju et al., 2010; Carlson et al., 2012; ChenFeng et al., 2013; Huang et al., 2016c; Shokrehodaei and Quinones, 2020; Sezen et al., 2016; AmayBandodkar et al., 2014; Nery et al., 2016; Burlinson et al., 2014; Gonzales et al., 2019; Sonner et al.,

2015; Heikenfeld, 2016b; KimZhao et al., 2009; TakahashiTakei et al., 2010; Takei et al., 2014; Kiriya et al., 2014; Daeneke et al., 2018; Ota et al., 2014; Xie et al., 2018; Kim et al., 2016, 2018b; Mostafalu et al., 2016; Lim et al., 2020; Wang et al., 2013).

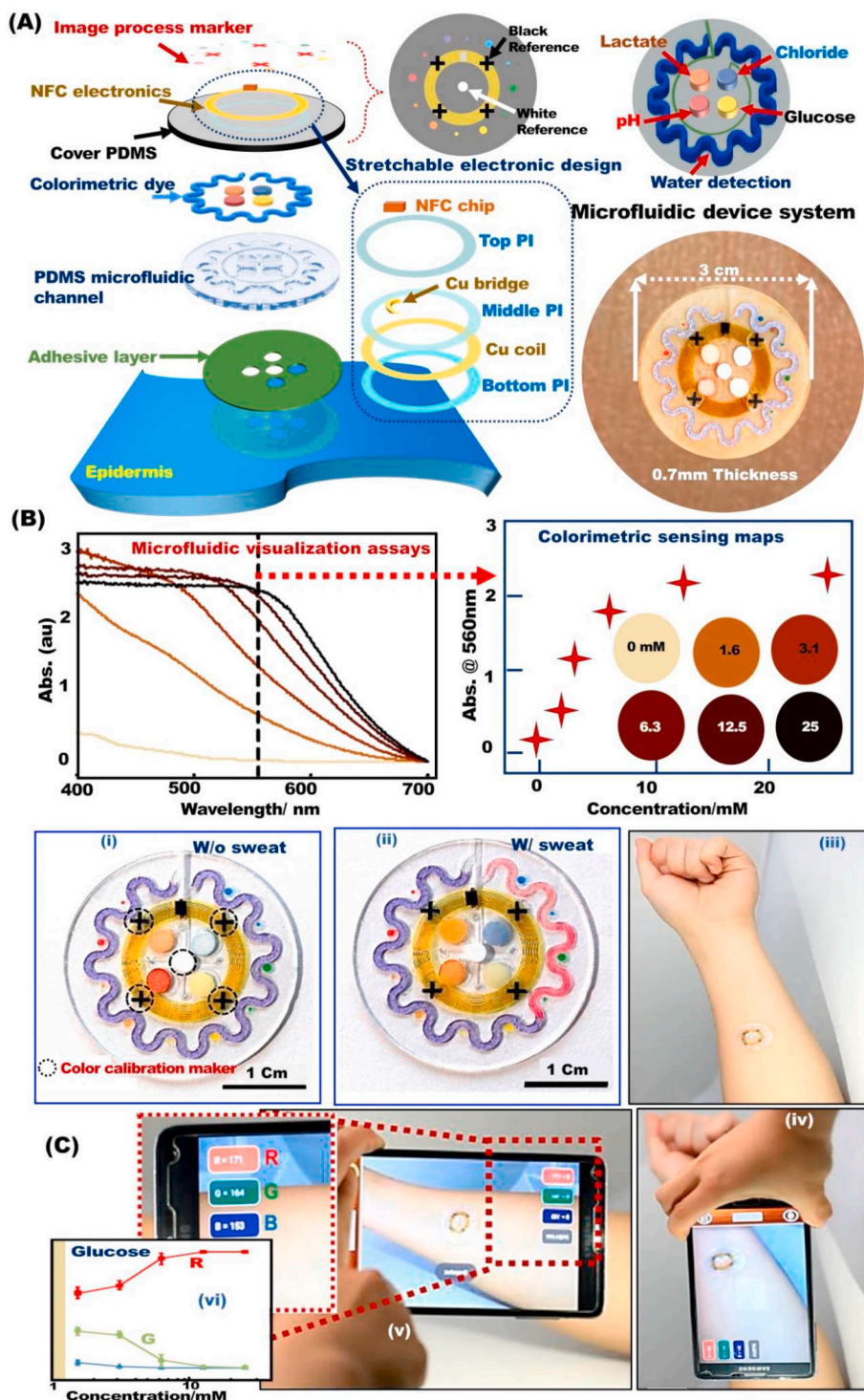
7. Optical skin-friendly wearable devices for sweat glucose biosensing

Optical skin-based soft and stretchable biosensor patches or devices are adhesive and close to the epidermal human surfaces to collect the sweat physiological fluids for glucose monitoring and assessment. The direct visualisation and optical signal readout (i.e. visible changes in range of the human eye) of glucose level in collected sweat samples provide powerful, flexible and easy-to-use portable biosensor design for patients with diabetes. Furthermore, optical and visual tools increase the threshold of glucose estimations and caution indicators (Patra et al., 2018). The colorimetric detection assay was applied in the quantitative and qualitative estimation of sweat glucose by using simple and personal wearable devices, but the in situ data accuracy and reliable processing for signal transmission requires further development for visual health monitoring compared with electrochemical wearable electronics (Patra et al., 2018; Heikenfeld, 2016a; Bariya et al., 2018; Ma et al., 2019). In this context, we outline the adaptability fabrication protocol of optical biosensor designs, visualisation mechanism and building of electronic skin-sweat devices for the wireless monitoring of sweat glucose level.

7.1. Microfluidic chipset based wearable devices for colorimetric glucose in sweat

The soft and flexible skin-like wearable devices based microfluidic channels connected to colorimetric microchamber systems for simple and reliable sensing of glucose level in sweat (Koh et al., 2016; Xiao et al., 2019; Bandodkar et al., 2019a). The skin-mountable microfluidic devices of glucose analysis in epidermal sweat were embedded by chromogenic bioreceptor reagents for selective, sensitive and naked-eye sensing feasibility.

Fully integrated assemblies of soft microfluidic devices and micro-chambers for the colorimetric sensing of glucose sweat sample were designed, as shown in Scheme 11 (Koh et al., 2016). Koh et al. reported the step-by-step layout fabrications of wearable biosensor electronics with full processing of (i) glucose sweat collection rates and volumes, (ii) colorimetric assay chambers and (iii) wireless transmission system. Skin medical-grade acrylic adhesive films were used to extract and capture the fluid sweat flow sensitively via open micromachinery under natural pressure (~ 70 kPa). The sweat samples were collected through capillary microchannel-connected reservoirs (approximately with a volume of ~ 120 mL/h per cm^2) and mixed chromogenic-responsive agent for in situ chemical analysis (Koh et al., 2016). Soft lithography patterns were used in the microfluidic chip devices for specific sweat-collection design and to examine glucose levels. The dimensional, microfluidic systems (with 3 cm diameter and 0.7 mm thickness) are composed of a 500 μm PDMS layer platform. The near-field communication (NFC) chip connected with magnetic antenna can be used for signalling readout data transmission via wireless (Scheme 11A). Stretchable electronic design offers a soft engineering of microfluidic devices with high elasticity and enables the direct readout of signals via wireless data transmission. Microfluidic sweat-based glucose visualisation and sensing systems were built to transfer the normal colorimetric sensing maps of glucose concentration (Scheme 11B) to real-time tracking using wireless data transmission. Quantitative colorimetric sensing assays of glucose in sweat samples were developed inside the serpentine microchannel by a colorant indicator fabricated by the incorporation of anhydrous CoCl_2 within polyhydroxyethylmethacrylate hydrogel. The glucose concentration can be monitored through the formation of enzymatic glucose oxidase reaction. A sensitive, visual detection assay of glucose concentration in sweat was developed with LOD of 200 μM . The conversion and

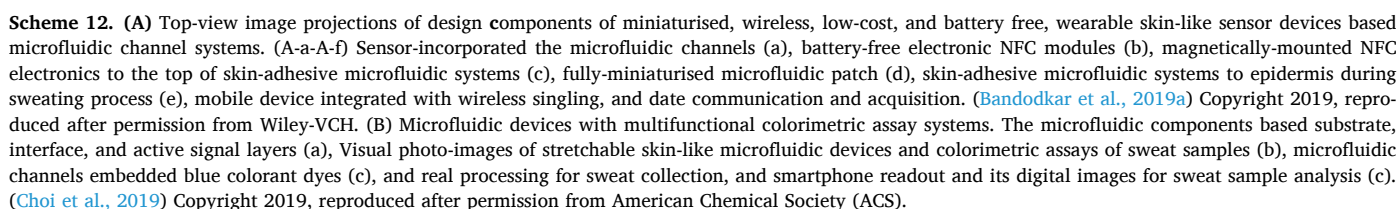


Scheme 11. (A) Schematic design for optical microfluidic biosensor devices using an integrated near-field communication (NFC) system for glucose screening in sweat. Top view (left), the step-by-step design of surface fabrication of the NFC electronics sensor embedded microfluidic channels. (A-right-top): Top-view designs of the colorimetric sensing process of analytic targets in sweat. (A-right-bottom): The visual image of the designed microfluidic device as a tattoo on skin. (B) Simple colorimetric detection tests of glucose in sweat using ultraviolet (UV)-visible spectroscopy and the calibration curves (insert is the colour map images of glucose concentrations). (C-i-iii) A wearable sensory patch of microfluidic sweat devices for noninvasive glucose visualisation assays with or without artificial sweat. (C-iv-v) Real time detection of multiple targets in sweat samples including glucose using NFC system integrated with the smartphone software for image capture and analysis of colorimetric sensor. (C-vi) quantitative detection of glucose appears as a relationship to the standard calibration curves. (Koh et al., 2016) Copyright 2016, reproduced after permission from AAAS (i.e., American Association for the Advancement of Science).

readout of the optical colour signals to digital analysis systems are associated with portable smartphone devices. The image capture processing and software analysis provides the precise assessment of glucose level in sweat samples (Scheme 11 C) (Koh et al., 2016).

Motivated by powerful biofuel cell functions, Rogger et al. (Bandedkar et al., 2019a) designed miniaturised, wireless, low-cost, battery-free, wearable sensors. In-depth layout fabrications, the network systems of chrono-sampling microfluidic channels were implanted with electrochemical and colorimetric sensor assays for multimodal sweat analyses of pH and of lactate, glucose and chloride concentrations and simultaneous quantitation of sweat rate/loss. The stretchable

skin-interfaced platforms were lithographically patterned with the isolated chambers and ratcheted channels to avoid the flow-through mixing along the multiple analytic analyses. The skin-based biofuel cell electronics enabled self-powered energy (power density of $\sim 1.2 \text{ mWcm}^{-2}$) from lactate in epidermal fluids (Scheme 12A). In addition, the capillary bursting valves connected to individual microreservoirs and inter-connecting microchannels are well-oriented through the patches to help time-sequential collection changes in specific capture sampling from sweat compositions and to assure the single and accurate sensing assay without cross-sampling interferences. For the cheap manufacture of wearable electronics, the top surface of skin-adhesive microfluidic



smartphone digital images or by electronic wireless system via NFC modules by using the smartphone. Likely to this device layout, the biocompatible, soft skin-integrated microfluidic networks enable the accuracy and reliability of multiple colorimetric assays of sweat reagents (chloride, glucose and lactate) and sweat pH and dermal temperature under lighting conditions (Scheme 12B) (Choi et al., 2019). The precise

analysis of sweat glucose in high comprehensive correlation with its physiological state and level in blood over long-period monitoring indicates the potential fabrication of non-invasive wearable biosensors for the reliable, in situ tracking of glucose levels in blood.

7.2. Challenges of optical skin-like biosensors

Optical sweat-based glucose detection devices, wireless transmitting signals and digital readouts by smartphones have attracted considerable interest in the potential visualisation of glucose detection and real-time monitoring of patients with diabetes. Similar to most skin-based soft and flexible biosensors, the optical biosensor design provides real-time, easy-to-use, accurate and cost-effective sensing assays of glucose levels in sweat test fluids. However, non-invasive CGM systems using optical or electrochemical sweat glucose biosensors have the following shortcomings: (i) pre-concentration, continuous collection, time-lag and sufficient access of body sweat fluids; (ii) low-cost device-based substrate supports enabled the fabrication of disposable test strips; (iii) in situ calibration and blood-sweat correlation of glucose level in body fluids; (iv) sweat sensor accuracy, sensitivity and readout stability for personal measurements by publics; and (v) on-site circuit loops integrated with multiplex sensing signals or systems for simultaneous wireless data transmission. Subsequently, improvements are essential for optical sweat biosensing verification assays, portable lightweight device structures and wireless digital systems for integral signal processing and simultaneous transmission (Chung et al., 2019; Cappon et al., 2019; Bandodkar et al., 2019b; Zhang et al., 2019b; Bozzola et al., 2017).

8. Optical, wearable contact lens glucose biosensors

8.1. Tear glucose sampling

Non-invasively diagnosed glucose levels in tear fluids have recently become a method of interest to bring wearable electronics in the precisely CGM of patients with diabetes. The eye is considered as central and direct gate to a range of functional human organs. The tear fluid composition has low complexity and interference concentrations compared with other body fluids. Therefore, tear sample can serve as a unique diagnosis assay for systematic diseases (Tseng et al., 2018). Similar to physiological sweat glucose, the tear fluids obtained from human eyes can offer an alternative quantification to glucose level in blood with slightly amenable correlation coefficients according to the artificial collection methods, physical/chemical stimulations and natural accumulations. Although, the tear fluid collection showed tedious glucose sampling in terms of low volume sampling, lag time, weak correlation with blood and time consuming, but successful designs of flexible contact lens biosensors covering the corneal surface of the eye can use a small volumetric quantity to maximise signal measurements (Chen et al., 2020b; Daeneke et al., 2018). The glucose level in the tear fluid is usually used to identify the stage and progress of diabetes and then enable an accurate direction of therapeutics (Khairy et al., Elshehy; Shrivastava et al., 2020; Kim et al., 2017). Indeed, the integral analysis of wearable contact lens sensors is based on the precise collection of the tear fluid and its components. Several studies indicated that the measurable range of glucose levels in tear is 0–9.1 mM/L (164 mg/dL) (Bozzola et al., 2017; Tseng et al., 2018; Kim et al., 2017; Lane et al., 2006; Glucose-Sensing Contact Lens Development on Hold). The difference in tear glucose concentrations may be due to the different techniques used to collect tear samples (Lane et al., 2006). Nevertheless, contact lens sensors are capable of reliable glucose measurements, but the device manufacture has the following limitations (Yang and Gao, 2019):

- (i) poor vision as a result of lens transparency, which can be improved in lens design by using a particular form and type of nanostructure materials;
- (ii) eye discomfort and irritation due to the high-temperature environment surrounding the contact lenses;
- (iii) the wireless reading distance close to the eye, which is impractical for long-term continuous monitoring; and
- (iv) an unpleasant emotion caused by possible damage to the cornea as a result of side effects, such as bacterial keratitis, peripheral contact lens ulcers and inflammatory complications (Yang and Gao, 2019).

Along with the experimental sets of contact lens sensors, undergoing features related to the consistent measurements of glucose sampling levels include (i) lower glucose level in the eye than in the blood or physiological fluids, (ii) evaporation of tears, (iii) interference with other substances which substantially affect the accuracy of reading signals and (iv) continuous movements in different directions (Glucose-Sensing Contact Lens Development on Hold). The successful CGM is reported via wearable lens designs, but intensive addressing of the precision and the consistent correlation of glucose levels between tear and blood samples remains a challenge (Cha et al., 2014; Kownacka et al., 2018). As a result, Verily Life Sciences (i.e. Alphabet INC., Google's health-focused sister company) built a contact lens sensor using teardrops to track glucose levels as an alternative to traditional lancing devices (Alphabet stops its project to create a glucose-measuring contact lens for diabetes patients, 2018). However, Verily/Google was recently paused this smart contact-lens sensing program due to the difficulty of its CGM management system. However, intensive studies based on tear glucose monitoring were conducted to assume its future feasibility as a clinical tool for glucose detection (Aihara et al., 2018). For example, Aihara et al. (2018) found a significant correlation between tear glucose level and blood glucose level ($P < 0.001$) throughout a set of monitoring experiments by using 10 non-diabetics and 20 diabetic subjects. Several tear CGM systems were built on the basis of accurate correlation of glucose levels between tear and blood (with R and P factors of 0.50–0.9745 and 0.01–0.05, respectively) (Baca et al., 2007; Daum and Hill, 1982; Yan et al., 2011; Lane et al., 2009). A recent study has also reported a feasible glucose monitoring system which uses glycubumin (GA) from the tear of patients with diabetes as a biomarker with significant correlation ($P < 0.001$) (Aihara et al., 2020). However, tear glucose sensors still need to be optimised in terms of CGM stability under multiple usages, reliable tear testing in real samples and convenience.

8.2. Wearable contact lens biosensors

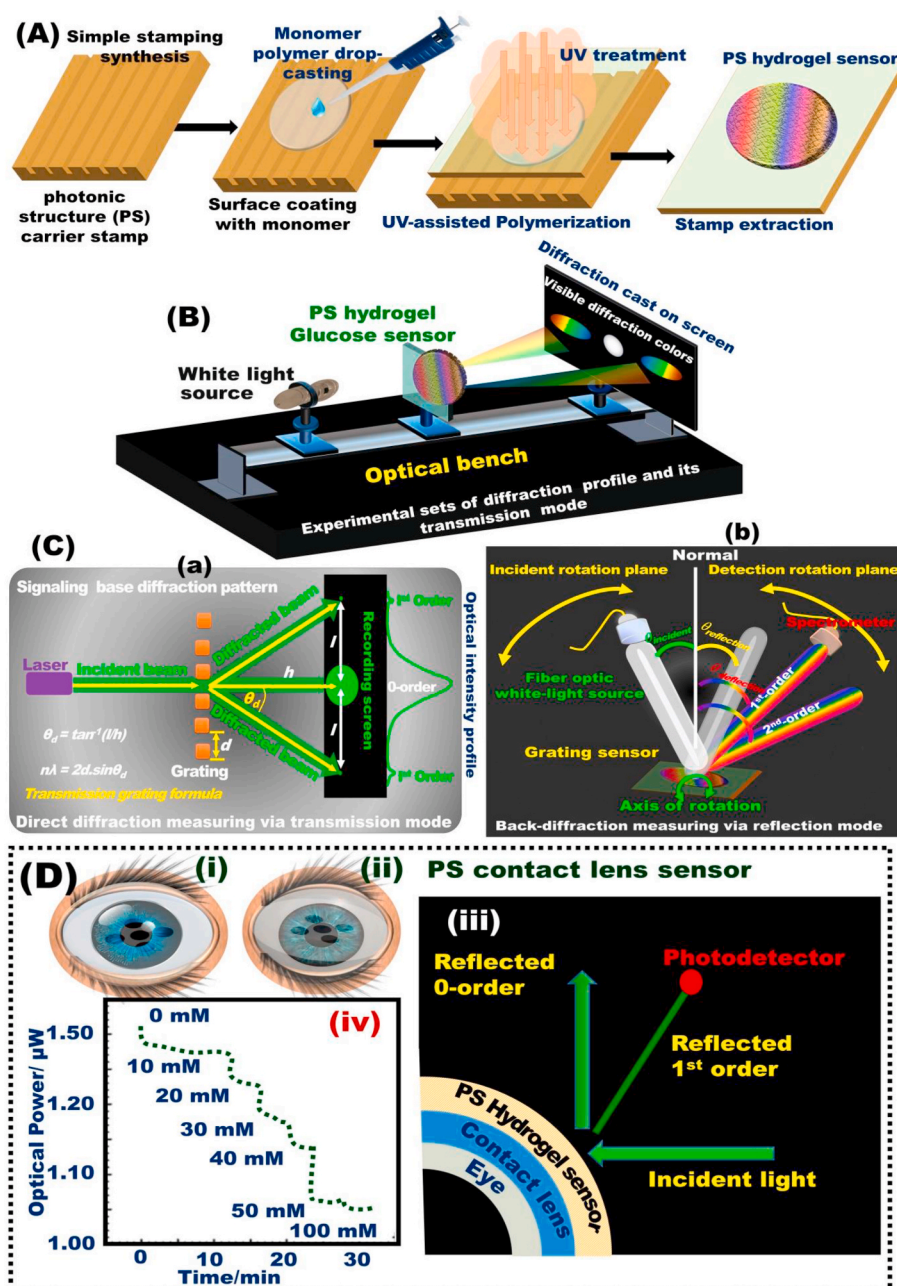
An in-depth perception, wearable contact lens biosensor using tear glucose fluids offers a non-invasive monitoring of diabetic patients at home, leading to potential POC diagnostics. Collaboration between Google and Novartis produced a new brand of portable contact lens electrochemical glucose sensor for monitoring of diabetes, but its commercial prototype device technology still suffers challenges (Senior, 2014). For personal healthcare information, the advances of remote communication technology led to develop wireless smart contact lenses, enabling remote and real-time analysis of diabetes. Recently, Keum et al. have reported wireless multifunctional smart electrochemical contact lenses for (i) in vivo diabetic diagnosis and CGM in live rabbit eyes using GOD-based hydrogel biosensors and (ii) in vitro and in vivo therapeutic systems of diabetic retinopathy. The smart device features remotely controllable and readable signals using powerful wireless energy and data-transfer management systems for diagnostics and therapeutics of diabetes (Keum et al., 2020). As next-generation bio-marketing medical devices in on-demand diagnosis and medication, wearable device-based contact lens or sweat sensors feature reliability associated with the electronic miniaturisation, circuitry system, small size and transparent antenna, wireless transmission, external power source system,

stretchability or bendability of constituents, high cost and complicated analysis and safety vigilance issues (Khairy et al., Elshehy; Shrivastava et al., 2020; Chen et al., 2020b; Tseng et al., 2018). Along with these advanced contact lens biosensors, we discussed recent developments of optical wearable modules of glucose in tear fluids. Optical contact lens biosensors provide non-invasive CGM assays with easy-to-read, biocompatible, non-toxic and battery-free and portable patches for visible tracking of patients with diabetes.

8.3. Optical wearable contact lens biosensors

Optical, user-friendly contact lens biosensors were built to detect the tear glucose level with high sensitivity, selectivity and reproducibility. Wireless tear biosensing systems, including wearable, reusable and non-invasive optical contact lens biosensors, have recently become of interest for diabetes diagnostics (Elsherif et al., 2018b; Yetisen et al., 2014; Emran et al., 2020b).

Elsherif et al. (Kim et al., 2018b) developed optical microscale device-based contact lens glucose sensors for quantitative visualisation assays and POC settings. Microfluidic device visualisation is technically based on the function of periodically ordered photonic structure (PS)-based biosensor building blocks for identification and visible colour tracking of glucose samples. For instance, one-step, fast (5 min) synthesis which includes coating, polymerisation, imprinting PS film, functionalisation of active surface and then attachment to contact lens protocols can control the fabrication of PS contact lens glucose sensors (Scheme 13) (Elsherif et al., 2018b). In general, the PS hydrogel sensor is firstly fabricated by the formation of imprinted PS hydrogel film. As shown in Scheme 10A, consequence steps for free-standing manufacture of PS hydrogel glucose detector are achieved via a simple stamping protocol. The imprinted PS process of hydrogel matrix was developed through the modification of photonic stamp of the PS master by a well-ordered monolayer monomer polymer. A hydrogel film was grown under UV polymerisation followed by extraction of the PS master for the



Scheme 13. (A) Fabrication of 1D photonic microstructure (PS) sensor was controlled through stamping procedures. (B) Design of the experimental settings of PS hydrogel glucose sensor on the optical bench for identification and visible tracking the glucose sample, as evidenced from the transmitted diffraction patterns. (C-a-b) The glucose signaling based on the diffraction measurements in transmission and reflection modes, respectively. The diffraction patterns were recorded by exposure of monochrome light to the PS hydrogel sensor under controlling the humidity conditions. The changes in the angle and zero/1st order d-spacing of optical diffraction profiles can be detected by visible colors (see formation of rainbow on screen). (C) (i-iv) The PS hydrogel sensor integrated commercial contact lenses for fabrication of wearable, optical glucose sensors. (C-i-iii) Photo-image of the PS hydrogel contact lens to artificial and modeling eye objects. (C-iv) Simple readout, visible determination of the 1st order diffraction based on reflection mode signaling as a function of glucose concentration. (Elsherif et al., 2018b) Copyright 2019, fully re-designed according to the published work at ACS.

replica of the potential PS hydrogel sensor. Then, the incorporation of a PS hydrogel film layer with non-enzyme phenylboronic acid (PBA) provides strong binding with glucose and leads to (i) reversible glucose-to-boronate complex formation in PBS solution and (ii) PS hydrogel swelling. Glucose quantitation can be performed by recording the optical diffraction patterns of the PS hydrogel sensor as a result of the transmission and reflection signalling modes. The read-out sensing principle is based on the glucose concentrations, which significantly affect the swelling/shrinking of the PS hydrogel sensor. The reversible changes in the PS sensor matrix swelling increase the volumetric thickness and periodicity constant of PS sensor films (Elsherif et al., 2018b; Yetisen et al., 2014). The increase in periodicity constant decreases the angle and zero/1st order d-spacing of Bragg peak diffraction profiles according to the glucose-to-boronate binding. The wearable PS hydrogel sensor into contact lens enables suitable response time (in the order of minutes) and visual glucose linearity in the range of 0–50 mM. Furthermore, the integration of sensor lenses into smartphone device readouts allows non-invasive, short-response detection of glucose within 3 s as a route of diagnostic test at home (Scheme 10D) (Kim et al., 2018b). However, the long-term calibration of wearable contact lens PS hydrogel biosensors is required for clinical diabetic practices (Yetisen et al., 2014).

Considerable sensing optimisation is necessary for sensory devices to offer on-time, personalised monitoring and continuous measurements of glucose and other biomolecules in a swift response (Emran et al., 2018d, 2020b, 2021a, 2021b; Akhtar et al., 2016). Lin et al. reported on visualisation assays of tear glucose level by using portable contact lens sensors for optical and non-invasive diagnostic monitoring (Lin et al., 2018). The fabrication of this contact lens sensor is based on the functional modification of poly-hydroxyethylmethacrylate (poly-HEMA) with PBA. The glucose signal readouts of non-enzymatic PBA-modified poly-HEMA contact lens sensors can be monitored by a real-time image processing program incorporated into a smartphone. The detector red LED light-emitting diode device, in principle, changes the intensity of red light with the changes in the volumetric thickness of the swelled PBA-based poly-HEMA contact lens sensor. The visual set of the diabetic sensing assay is carried out with addition of various tear glucose concentrations (0.1–0.6 mM range) in PBS solutions. As a result of the reversible glucose-to-boronate binding, swelling/shrinking in contact lens sensor thickness simultaneously changes the red LDE light that can be detected and analysed by Sony IMX230 photosensitive image software in a smartphone (Lin et al., 2018). These optical contact lens biosensors offer a simple, visible monitoring of tear glucose, but the integrated wireless digital system based on processing of sensor data acquisition and sensitive transmitting signals in smartphones or over long-distances still have stringent constraints.

8.4. Remarkable devices for optical tear glucose biosensors

The recent advancements in optical sensor-based contact lens materials, particularly soft hydrogel lenses-integrated microfluidic chips, provide evidence of simple fabrication, easy-to-use and biocompatible non-enzyme smart polymers. In terms of wearable electronics, optical contact lens sensors may have potential to be fully integrated into portable point-of-care medical devices. As reported in some studies, optical contact lens sensors were not constructed with integrated circuit chipsets, rigid interconnects and external/circumferential power sources to avoid the complicated structures and the distortion of eyelid or even cornea with long-term usage, but their usage in real applicability is still questionable. Regarding sampling collection, the glucose concentrations in tears vary because of irritation or emotion; such phenomenon should be considered to ensure the absence of associated interferences or stimulated environments (Keum et al., 2020).

After close inspection of the significant development of contact lens biosensors, further improvements in reliable fabrications for electronic miniaturisation, signalling and transmission are needed to develop these

smart contact lens sensors into on-time point-of-care diagnosis tools. Moreover, visual, soft sensory contact lens allows lab-scale reliability analysis of glucose levels in tears. In turn, contact lens sensors should feature low cost, transparency and comfort, and safety and user friendliness to promote their commercial use (Gu et al., 2019).

9. Market overview of electronic glucose devices for diabetes

The current situation of chronic diabetes suggests the urgent need for modern CGM systems to provide personalised and effective healthcare to millions of patients with diabetes. The growth rate of the global market and the latest CGM technology developments have increased. To date, several CGM systems were developed by using flexible, wearable electronic devices to measure glucose levels in the interstitial fluid or blood. Along with these devices, an accurate transmission of the analytical information could be achieved by using a transmitter. In addition, the displaying screen device is essential to improve the reliable CGM of diabetes (El-Safty and Shenashen, 2020a, 2020b; Seshadri et al., 2019). According to CGM market demands, a number of companies have lucrative opportunities for manufacturing wearable and portable glucose devices.

Blood glucose test is usually performed by pricking a patient's finger for blood sample collection onto a disposable test strip (Scheme 14A) (Bruen et al., 2017; <http://technologyinscienc>, 2015; <https://www.onetouch.com/>). The sensor layout is generally composed of layers of electrodes, separators and enzymes frozen in a small package. Recent developments of strip sensor designs are focused in the following: (i) compact size, (ii) auto-sampling collection, (iii) small amount of blood sample and (iv) accurate diabetic examination to reduce disease complications and mortality. Regular collection of blood samples for analysis causes discomfort, pain and stress to patients with diabetes. Virtual developments of portable and sensitive sensors which enable an alternative glucose sampling collection from biological fluids (i.e. sweat, tear and saliva) are an important issue for future healthcare concerns of patients with diabetes to enhance their quality of life.

In this context, the GlucoWatch®G2™ biographer developed a non-invasive glucose analysis with high sensitivity for patients with diabetes (Scheme 14B) [(Tierney et al., 2001; <https://medaval.ie/device>). The mechanistic glucose detection by using the GlucoWatch®G2™ biographer was based on glucose extraction through intact skin via reverse iontophoresis. In addition, the GlucoWatch®G2™ device can provide real-time glucose readings every 20 min for 12 h. This device has three major parts: (i) glucose sensor platform, (ii) transmitter (parts (i) and (ii) are connected to the skin by a patch) and (iii) monitoring screen. The sensor device converts the information data of glucose level in the interstitial fluids into electronic signals, and then the transmitter transfers to the readable monitor at a specific period. Moreover, the iPro2 device controls the screaming, reading and storing of glucose level every 5 min for 6 days (Scheme 14C) (Welsh et al., 2012; <https://www.mesm.com/prod>). This device features water resistance, light weight and compact size. However, the applications of the iPro2 device are limited by the difficult direct reading of data by patients. Along with the utilization of the iPro2 device, the reading-out process can be obtained using a special software.

To provide real-time data analysis and fast response feedback to patients, the Dexcom G4 PLATINUM Professional device was designed for a personal, CGM system and facile decision-making related to diabetes management (Scheme 14D) (<https://www.diabetesnet.c>). The Dexcom G4 PLATINUM device is calibrated twice daily by using the patient's fingerprint and offers glucose concentration levels every 5 min for 7 days. Data can be downloaded using the Dexcom CLARITY web-based software for simple reading of data by individuals. Furthermore, the FreeStyle Libre device (Abbott Diabetes Care Inc., Alameda, CA, USA) was formulated with auto-calibration (i.e. no need of personal calibration) for direct monitoring of diabetes (Scheme 14E) (Schier-enbeck et al., 2017). This FreeStyle Libre device, composed of a small



Scheme 14. The schematic design shows an overview of CGM's current commercial devices for CGM including (A) a glucometer for blood glucose sensor [Yetisen et al., 2014], (Emran et al., 2020b)] Copyright © 2018–2020 LifeScan IP Holdings, LLC. (a) Commercial Products and (b) the composition of a test strip; (B) GlucoWatch® biographer [Tierney et al., 2001]] Copyright © 2001 Elsevier Science B.V.; (C) iPro2 sensing system contains monitor and docking station [(<https://www.mesm.com/prod/>)] Copyright©N avantor®; (D) Dexcom G4® PLATINUM (<https://www.diabetesnet.c>) Copyright © <https://www.diabetesnet.com/>; (E) FreeStyle Libre continuous glucose monitor [(Schierenbeck et al., 2017)] Copyright © 2016 Diabetes Technology Society; (F) the Eversense System [(<https://global.eversensed>)], and (G) the Medtronic 670G device (<https://www.diabetesdaily>, 2018) Copyright © 2005–2021 Thrivable Inc. All rights reserved.

sensor (about 2 cm in diameter) placed under the upper arm skin, detects glucose level every 15 min for 14 days. However, FreeStyle Libre is not systematically permitted to be used for children under the age of 18, pregnant women and dialysis patients. The Eversense XL System was designed to provide simple and reliable CGM up to 180 days. In this sensor design, implantable, removable and rechargeable smart transmitter, and compatible smartphone app are correlated for accurate and on-time analyses (Scheme 14F) (<https://global.eversensed>). The Medtronic 670G device is used for CGM analysis and for delivery of diabetes-related products. This device affords great possibility to regulate the delivery of normal insulin rate every 5 min under automatic control mode (Scheme 14G) (<https://www.diabetesdaily>, 2018). The quality of these electronic devices for CGM is undisputable, but novel developments of nano-electronic devices with compact size, low-cost analysis and on-time and accurate data acquisition are still demanded to improve public healthcare and to reduce mortality (Quinault et al., 2016; van den Berghe et al., 2001).

10. Conclusion and future outlook

With the increasing public demands of early detection and self-monitoring of diabetes, the development of visual, easy-to-use and wearable sensor electronics, physiological fluid sampling, readout data analysis and acquisition has gained considerable interest. Our comprehensive review bridges the practical assessment gap between optical bio-

visualisation assays, disposable test strips, sensor array designs and the full integration into flexible skin-based or contact lens devices with on-site wireless signal transmission.

In-depth study, this review sheds insight into the recent, considerable growth associated with the development of nano/microscale architecture-based optical biosensor strips and devices for simple, cost-effective visualisation and real-time detection of glucose. The emerging impacts of active nano/microscale materials into optical and portable biosensor arrays have promising prospects for direct bio-visualisation sensing systems and their integrations into flexible skin-based or contact lens biosensor array devices. To date, nano/microscale architecture sensor designs featuring high efficiency, high quality and reliability and periodicity have attracted attention for disposable test strips and wearable biosensing technology. For future personalised healthcare, development of a wearable biosensor-integrated smartphone for the on-time visual screening, point-of-use monitoring and rapid diagnosis of diabetes at early stages is urgently needed.

Growing developments of optical whispering gallery mode (WGM)-incorporated plasmonic nanostructures have been recently reported (Kang et al., 2017; Frustaci and Vollmer, 2019; Zhang et al., 2018b). Sensing device systems are based on the integration leverage of hybrid confining plasmonic-photonic biosensors for strong signalling and detection of single molecules, such as glucose. Hybrid WGM biosensors have shown promise to be technologically relevant for sensitive visualisation, selective signalling and precise identification assays of glucose

levels in physiological fluid samples. To improve the promising prospects of WGM-hybrid biosensors, a molecularly selective device with low-cost analysis, reliable and rapid measurements, dynamic signal processing and multimodal sensing integrations into wearable medical devices is necessary. Therefore, the future challenges and directions should integrate the multifunctional WGM hybrid plasmonic-photon-colorimetric readouts into mechanically flexible skin-based wearable sensors for the in situ analysis of body physiological fluids. Such developments of wearable optical-WGM multi-sensor array settings are expected to offer low-cost, ultra-high sensitivity, smart portability and wirelessly detectable transmission with higher sensitivity compared with the single WGM sensing array.

The advances of the wearable sensing technology open insights of easy-to-use, portable and optical glucose biosensors for suppressing the health risks associated with the surgical insulin therapy of diabetes. Nano/micro physiological biosensor chipsets with circuits that have high electronic transmittance, robust structural stabilities, readable output signalling and visible tracking without power consumption are of particular interest for the synthesis of wearable electronic devices. Optical skin or contact lens biosensors have become an important tool in real-time health indication of patients with diabetes. Accordingly, a series of flexible and wearable devices based on nano/microscale biomolecular sensor technology is vital for reliable healthcare information and non-invasive monitoring. Fully modulated integrations of optical, physiological biosensors into electronic device modalities, such as smartphones, are substantial to meet the demands of rapid visualisation readout analysis, real life-self-powered monitoring and early detection of diabetes. Development of continuous, applicable and dynamic visualisation readouts and battery-free wireless systems for online data acquisition and transmission is a key challenge for the large-scale manufacture and commercialisation of wearable medical sensors for patients with diabetes.

Improvement of clinical settings and full integration of skin-safely soft, transparent and stretchable nanoscale materials on wearable medical devices for wireless signal detection and accurate modulation into smartphones are urgently needed to improve the self-care management of patients with diabetes. For prolonged periods of indoor and outdoor clinical diagnostics, a substantial management of optical wearable skin-based or contact lens sensors is needed to control the continuous and self-monitoring of and provide appropriate treatment for patients with diabetes.

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 review article.

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