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Advanced biosensors for glucose and insulin

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder lasting for the lifetime of a person. Glucose and insulin are the main indicators in the monitoring and control of this disease. Most often, various laboratory tests are used in the diagnosis and control of diabetes. Among them, the estimation of blood glucose concentration is one of the main diagnostic criteria. Proper control of the blood glucose level can delay, and to a greater extent, prevent complications. Thus, blood glucose monitoring is a requisite tool in the management of diabetes mellitus. Insulin plays a major role in glucose metabolism and its determination is of great value in the diagnosis and control of diabetes. An uncountable number of biosensors have been developed based on various mechanisms which will make sure a continuous glucose as well as insulin monitoring. Biosensors became the most sophisticated tool for the detection of glucose and insulin and they are of different types. Enzymatic, non-enzymatic, electrochemical, optical, non-invasive, and continuous monitoring biosensors are discussed in this review. In recent years, there is progress towards the development of nanobiosensors using various nanomaterials. Here, we have reviewed the fabrication, modification, and recent approaches associated with insulin and glucose biosensors for the treatment of diabetes.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder lasting for the lifetime of a person. Prevalence of diabetes mellitus continues to increase, leading to a higher rate of morbidity and mortality in developed societies. Most often, glucometers and glycohemoglobin test kits are used in the diagnosis and monitoring of the disease. Immense research has been carried out for the development of new approaches for the diagnosis of this disease (Khadilkar et al., 2013). Various laboratory tests are used in the diagnosis and control of diabetes. Among them, an estimation of blood glucose concentration is one of the main diagnostic criteria. Proper control of the blood glucose level can delay, and to a greater extent can prevent complications. Blood glucose monitoring is a requisite tool in the management of diabetes mellitus. Increased market size and huge demand for the tests pave new approaches to the development of biosensors (Vigneshvar et al., 2016). In order to monitor the blood glucose level, a series of biosensors have been developed. The implementation of microsystem technologies has made considerable advancement in the development of biosensors (Scheller et al., 2001).

A biosensor includes three fundamental parts as shown in Fig. 1; sensitive recognition element, signal transducer element, and data evaluation component. Recognition component can be biological elements like enzymes, antibodies, receptors, nucleic acid or biomimetic components (Frew and Hill, 1987). Recent research is concentrated on the employment of artificial receptors as a recognition element (Moreno-Bondi, 2012). The signal transducer converts the recognizable event into detectable and readable signal whereas electronic systems mainly constitute the data evaluation component (Sanghera et al., 2016; Scheller et al., 2001). The mechanism of working involves the

Abbreviations: GO, Glucose oxidase; H_2O_2, Hydrogen peroxide; MoS_2, Molybdenum disulfide; QD, Quantum dot; FAD, Flavinadenonucleotide; $NiFe_2O_4$, Nickel ferrite; NCNFs, Nitrogen-doped carbon nanofibers; ZnO, Zinc oxide; PEDOT, poly(3,4-ethylenedioxythiophene); HRP, Horseradish peroxidase; Au-BC, Gold nanoparticles–bacterial cellulose; MWCNT, multi walled carbon nanotube; TiO_2, Titanium dioxide; EDC, 1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide; NHS, N-hydroxysuccinimide; SWCNT, single-walledcarbon nanotubes; BSA, Bovine serum albumin; CNT NEs, carbon nanotube nanoelectrodes; APTES, 3-aminopropyl-triethoxysilane; GCEs, glassy carbon electrodes; SGGT, solution gated graphene transistors; PCBMA, poly(carboxybetaine methacrylate); LRET, luminescence resonance energy transfer system; ECL, electrochemiluminescent; PBCD, Pb(II)-beta-cyclodextrin; CRS NPs, Chitosan/$Ru(bpy)_3^{2+}$/silica nanoparticles; ILPR, insulin-linked polymorphic region; CD, circular dichroism; C/$NiFe_2O_4$NPs, chitosan/$NiFe_2O_4$ nanoparticles; EIS, electrochemical impedance spectroscopy; CPE, Carbon paste electrode; TTF–TCNQ, Tetrathiafulvalene–tetracyanoquinodimethane; PB, Prussian blue; PW, Prussian white; CdTe, Cadmium telluride; InN, Indium nitride; AgNW, Silver nanowire

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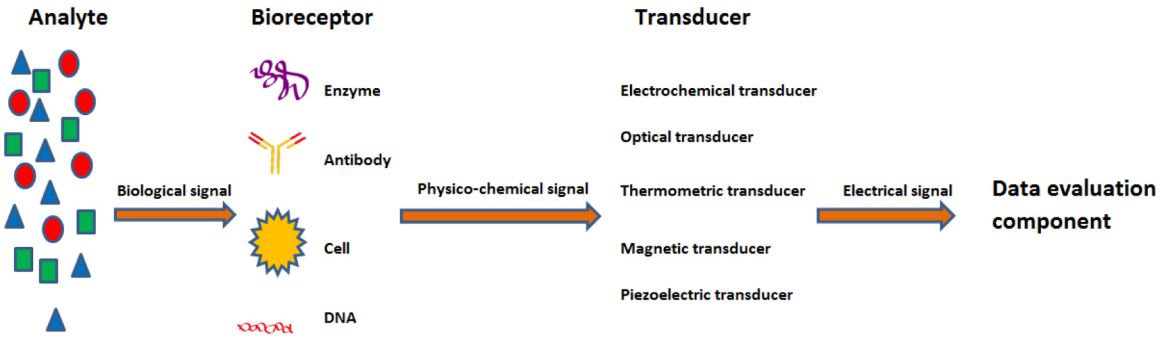

Fig. 1. Various components and working of a biosensor.

measurement of electrical response when the biological material combines with the transducer. The different types of transducers include electrochemical, optical, thermometric, piezoelectric, and magnetic (Hall, 1992). In certain cases, the analyte is changed to a product having the probability to associate with the release of heat, oxygen, and electrons (Malhotra et al., 2017).

Biosensors for diabetes mellitus work on the principle of determination of analytes like glucose and insulin which are the main indicators in the monitoring of the disease. The specificity of the catalytic or affinity biosensor depends on the binding reaction. With the help of a catalytic sensor, change in concentration of a component can be determined whereas with affinity biosensor the binding event is monitored (Turner et al., 1999). A biosensor is an analytical device promising a better communication of our bodies with and response to our environments resulting in the improvement of the healthcare of patients by early diagnosis and treatment of the disease (Sanghera et al., 2016). Biosensor device determines the analyte concentration with the help of physicochemical detector making it user-friendly. The biosensor is defined as a self-contained incorporated device which gives precise quantitative or semi-quantitative analytical data using a biological recognition element (Thévenot et al., 2001).

A wide number of techniques have been devised for the development of biosensors. The coupling of biosensors with high-affinity biomolecules results in the determination of a large number of analytes like glucose and insulin. The review focuses on the different type of biosensors used for insulin and glucose detection mainly to target or identify a disease (Fig. 2). The dynamic attributes such as selectivity, reproducibility, sensitivity, stability, and linearity contribute a crucial part in the development of a biosensor (Bhalla et al., 2016).

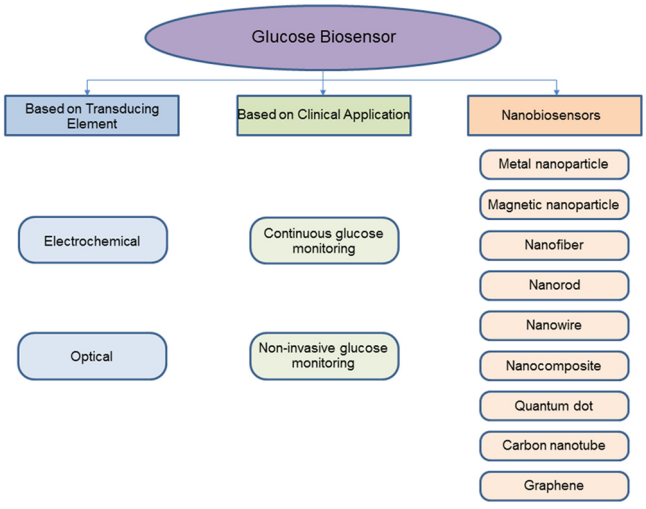

Fig. 2. Classification of glucose biosensors.

2. Biosensors for glucose

Earlier, the testing of the blood glucose level was a tedious process. The evolution of biosensors has made the estimation of blood glucose level much reliable and easy, overcoming the limitations encountered with blood glucose level testing. Real-time control of glucose transport is important in understanding the advance of diabetes. Although many techniques like radio labeling are developed, they are confined by the complication of the measurement, demand for bulky equipment, destruction of the sample and low temporal or spatial resolution. As a result, the development of various biosensors waves a new path to the diagnostic and possible treatment of diabetes (Taguchi et al., 2014).

The first enzyme-based electrode to measure the blood glucose level was proposed by Clark and Lyons (1962). Accordingly the advancement in the science and technology the category of enzyme-based glucose biosensors categorized to first, second, and third generation biosensors (Yoo and Lee, 2010). Likewise, there is a number of detection techniques involved in the detection of glucose; electrochemical, optical and nano-technology based biosensors (Pisoschi, 2012). In 1965, the first colorimetric biosensor was developed based on colorimetric detection of hydrogen peroxide liberated by oxidation of glucose by glucose oxidase (GO) followed by first functional electrochemical biosensor by Updike and Hicks in 1967 (Updike and Hicks, 1967). The usage of thermal transducers in enzymatic biosensors came during 1974–75 (Mosbach and Danielsson, 1974). Since then various biomolecules are used as receptor elements. Thus, various classification has been devised based on the types of biomolecule and transducer (Mehrotra, 2016).

Commercially, the glucose biosensor market is predominated by finger prick type blood glucose sensor. They provide fast response over a dynamic sensing range. They pose limitations like invasive procedure and the need for replacement after some time (Hovorka et al., 2013). Unfortunately, lack of precision and delay in time possess major challenges in the development of a biosensor. Other *ex vivo* glucose biosensor uses a multiplexing path which carries out multianalyte determination on a diagnostic point of view (Taguchi et al., 2014). An artificial endocrine artificial pancreas with a needle-type glucose sensor has been developed for glycaemic control in ambulatory patients. Such a system act as a wearable closed loop control system which calculates the glucose infusion rate (Thabit and Hovorka, 2012).

2.1. Classification of glucose biosensors based on transducing element

2.1.1. Electrochemical glucose biosensors

Commonly used electrochemical biosensors are based on the detection of the electrochemical signal by a detection system when the electrochemical species such as electrons are utilized or produced in a biointeraction process (Wang, 2008). They are mainly run in turbid media with comparable sensitivity. Based on the detector mechanism, electrochemical biosensors are classified into potentiometric, amperometric or conductometric (Chaubey and Malhotra, 2002). The variation in charge density at the surface of the electrode can be measured by

potentiometric sensors. The exchange of electrons between a biological system and electrode liberates current which is measured by amperometric biosensors. Conductometric senses the change in ionic conductance between a pair of metal electrodes (Rakhi et al., 2016). Reagentless glucose analysis can be carried out by the coupling of an immobilized enzyme system with an electrochemical sensor. Thereby, miniaturization and simplification of the system are done (Chen et al., 2017).

Electrochemically reduced conjugated cinnamic acid diazonium salt acts as an immobilization matrix for glucose biosensor. The immobilization of GO in glassy carbon electrode with the help of a redox mediator lead to the fabrication of a biosensor in presence of a redox mediator. The glassy carbon electrode (GCE) can be modified with the cinnamic acid group for the attachment of other biochemical agents (Yang et al., 2003). However, the chemical adsorption of enzyme on to pyrrole film can also lead to the fabrication of a glucose biosensor (Cho et al., 1996). When the miniaturization of the biosensor is essential, the attachment of the enzyme to self-assembled monolayers is utilized. An electrochemical glucose biosensor can be fabricated with a gold electrode comprising self-assembled oligophenylethynylenethiol monolayer and GO. The oligophenylethynylenethiol act as a crosslinker for the immobilization of the GO onto the gold electrode (Jung et al., 2009).

Basically, the glucose level is determined based on the interaction between one of the three enzymes; hexokinase, glucose oxidase (GO), and glucose-1-dehydrogenase. Certain characteristics like high selectivity, low price, and ability to withstand high pH, temperature, and ionic strength make GO a standard enzyme for biosensors (Niraj et al., 2012). Majority of the biosensors are electrical with different detection capacity in response to analyzed matrices from blood to intestinal fluids (Scognamiglio, 2013). The enzyme electrode proposed by Clark and Lyons in 1962 depends on the immobilization of GO over an oxygen electrode, wherein the oxygen consumption is monitored by an enzyme-catalyzed reaction (Clark and Lyons, 1962) :

$$\text{glucose} + O_2 \xrightarrow{GO} \text{gluconic acid} + H_2O_2$$

Clark's original works dealt with the transformation of an electroinactive substrate to an electroactive product using one or more enzymes. The interference effect is eliminated by using two electrodes and measuring the differential current. Later, in 1973, an enzyme electrode with good precision and accuracy was developed for determining the blood glucose based on amperometric tracking of the released hydrogen peroxide (H_2O_2) (Guilbault and Lubrano, 1973):

$$H_2O_2 \rightarrow O_2 + 2H^+ + 2e^-$$

Amperometric biosensing of glucose can also be carried out with glucose dehydrogenase instead of GO. However, the fabrication of such type biosensor requires an NAD^+ source and a redox mediator to decrease the excess voltage needed for the oxidation of NADH product (Wang, 2008; Zhang et al., 2015a, 2015b, 2015c). An amperometric enzyme electrode using substituted ferricinium ion as a mediator of electron transfer between the immobilized enzyme and graphite electrode is used for the analysis of glucose (Cass et al., 1984).

The connection between the redox enzymes and electrodes can be enhanced using biologically active or synthetic carriers known as mediators. The mediators are capable of eliciting reversible electrochemistry promoting the oxidation and reduction reactions at the active site of the enzyme. The artificial electron donor or acceptor molecules are known as electron transfer mediators. Various trials have been conducted to reoxidize the resulting reduced enzyme. However, mediated enzyme electrodes are less prone to interfering substances due to low electrode potential (Chaubey and Malhotra, 2002).

2.1.1.1. Enzymatic glucose biosensor

2.1.1.1.1. First generation glucose biosensor. The first generation glucose biosensor works on the principle of the use of oxygen as co-substrate and also on the formation and liberation of H_2O_2 (Pauls et al., 2016). The electrochemical immobilization of enzyme in electrosynthesized non-conducting polymeric membrane leads to the development of first-generation glucose biosensor (Centonze et al., 1997). When miniature devices are used, the measurement of peroxide formation is simpler. One of the major limitations encountered in the amperometric measurement of H_2O_2 is the requirement of a high operating potential needed for the high selectivity as well as for the reduction in the interference due to endogenous species. Therefore, a similar estimation is usually carried out on a platinum electrode. In addition to it, the presence of dissolved oxygen in biological fluids leads to fluctuation (Scognamiglio, 2013; Wang, 2008; Zhang et al., 2015a, 2015b, 2015c).

The sensitivity of a first generation glucose biosensor is tested based on fibrinogen precoating to carbon paste electrode (CPE). The plasmatic protein is adsorbed on the CPE by two different mechanisms. In one case, the GO is adsorbed prior to fibrinogen and in the latter case, the fibrinogen is adsorbed prior to GO. The fibrinogen-coated surface exhibits comparable linearity and sensitivity (Longchamp et al., 1998). A highly sensitive electrochemical biosensor is fabricated by the immobilization of copper microparticles and GO into a carbon paste matrix. Copper exhibits high electrocatalytic activity towards the reduction of enzymatically generated H_2O_2 (Rodrıguez and Rivas, 2001).

A highly stable glucose biosensor can be fabricated by utilizing polystyrene latex bead as an immobilizing matrix for GO. The H_2O_2 liberated by the enzyme is detected by the biosensor by amperometry. The sensor is stable and is applicable to a wide range of pH (Koopal and Nolte, 1994). Here, Prussian blue is considered to be a better electrocatalyst than H_2O_2. A first generation amperometric glucose biosensor was fabricated by glucose oxidase immobilization on Prussian blue modified electrode coated with a Nafion layer. The application of low potential reduces the influence of reductants (Kayakin et al., 1995). A novel design of glucose biosensor based on metal dispersed carbon paste electrode exhibits remarkable selectivity, high stability, low oxygen interference and good performance (Liu and Wang, 2001).

Redox interferences

The amperometric determination of H_2O_2 should be carried out at a potential where the coexisting species are electroactive. Several methods have been devised to reduce the interference of electroactive species on the glucose electrode. One useful approach is a selective coating which reduces the interference on the electrode surface. Distinctive polymers, multilayers and mixed layers with variable transport properties in view of its attributes are utilized to lessen the impedance (Malitesta et al., 1990; Zhang et al., 1994). The normally used coatings include size exclusion cellulose acetate films, Nafion ionomers, and hydrophobic alkanethiol or lipid layers (Moussy et al., 1994; Sternberg et al., 2015). The usage of overlaid multilayers offers extra benefits since it possesses the property of different films.

Another way to accomplish high selectivity includes the particular electro catalytic location of liberated hydrogen peroxide. This can be accomplished by tuning the operating potential to the ideal region. Highly discriminatory biosensing of glucose can likewise be accomplished by utilization of metalized carbon; for example, rhodium or ruthenium on carbon. Extra enhancements can be accomplished by this preferential catalytic activity with a discriminative layer; for example, by scattering rhodium particles inside a Nafion film. The low potential selective of the GO generated H_2O_2 is conceivable by conjugation with compounds that catalyze peroxide development like horseradish peroxidase (Guilbault and Lubrano, 1973).

Oxygen interference

Since oxidase based device relies on the utilization of oxygen as the physiological electron acceptor, they are more prone to the variations resulting from the changes in the oxygen tension and the stoichiometric restriction of oxygen. This restriction can be overcome by enhancing oxygen/glucose permeability ratio with the help of mass transport limiting films (Gough et al., 1985; Reach and Wilson, 1992). The

oxygen limitation of glucose biosensors can be dealt with the use of oxygen-rich carbon paste enzyme electrode like fluorocarbon pasting liquid (Kel-F oil) (Wang and Lu, 1998). The oxygen demand can be circumvented by replacing GO with glucose dehydrogenase which does not need an oxygen cofactor (D'Costa et al., 1986).

2.1.1.1.2. Second generation glucose biosensor. The second-generation biosensors can overcome the limitation encountered by the first-generation biosensor. They replace oxygen with redox mediators which transfer an electron from enzyme to the working electrode surface. The formed reduced mediator is further oxidized at the electrode giving the amperometric signal and finally reconstructing the oxidized form of the mediator (Scheller et al., 1991). Various electron mediators used to improve the sensor performance include ferrocene, ferrocyanide, quinine, methylene blue, thionine, etc (Niraj et al., 2012).

The electrical connection between the redox surface of the enzyme and electrode can be improved by enzyme wiring with redox polymer. The redox polymer permeates and attaches with the enzyme to frame a three-dimensional network that binds to the surface. The folding reduces the distance between redox and FAD centers. The resulting three-dimensional network results in fast response and high current outputs. Another method that facilitates the electron transfer includes chemical modification of glucose oxidase with electron relay groups. An enzyme reconstitution process results in efficient electrical communication (Wang, 2008; Zhang et al., 2015a, 2015b, 2015c).

The second generation biosensor is considered to be a modification of carbon paste/ GO. In addition, this biosensor consists of an artificial mediator which transfers electrons between the FAD center and the surface leading to a current that depends on glucose concentration. For an electrical contact with the enzyme GO, various diffusional electron mediators are used. The low potential decreases the effect of interfering species. For the effective functionalization of the system, the mediator should possess the ability to react promptly to the reduced enzyme minimizing the interaction with oxygen. The application of mediators reduces the enzyme progressive degeneration due to a high potential. A novel second generation biosensor comprising of GOX and electron mediators in carbon paste electrode using the chrono-impedance technique as a transduction method has been used for the determination of glucose (Mayorga et al., 2011).

2.1.1.1.3. Third generation glucose biosensor. A third-generation biosensor works on the principle of direct transfer of electrons between enzyme and electrodes in the absence of mediators and is reagentless. In this type, the electrodes can directly perform electron transfer based on charge transfer complex (Niraj et al., 2012). High selectivity is achieved due to very low operating potential. One of the main advantages associated with third generation biosensor is the absence of mediators. Use of conducting organic salt electrodes based on charge transfer complexes lead a way to the development of amperometric glucose biosensors. A stable charge transfer complex electrode for the fabrication of third generation biosensor is prepared wherein an organic charge transfer complex is grown at the surface of an electroconductive film. The enzyme is directly oxidized at the crystal surface due to the favorable orientation of the enzyme at charge transfer complex and glucose concentration is determined with sensor (Khan et al., 1996). Third generation biosensor based on the electron transfer of protein is developed (Zhang and Li, 2004).

A reagentless third generation glucose biosensor can be fabricated by the wiring of the template enzyme GO with graphene nanoribbons. This facilitates the electron transfer between coenzyme and the electrode. The steps involved in the fabrication of such type of biosensor are isolation of the apo-enzyme from co-enzyme, preparation of graphene nanoribbons by oxidative unzipping of multi-walled carbon nanotubes, immobilization of the graphene nanoribbon onto a carbon electrode, covalent interaction of the coenzyme to the nanoribbon, recombination of the apoenzyme with covalently bound FAD to the holoenzyme, and finally stabilization of the bio-layer with thin membrane of Nafion. This biosensor finds the main application in the determination of glucose in human serum (Mehmeti et al., 2017). A mediator free third generation glucose biosensor fabricated by the immobilization of GO on boron-doped diamond electrode elicit a fast amperometric response to glucose (Wu and Qu, 2006).

The organic conducting polypyrrole act as an environment for the immobilization of GO (Czajka et al., 1992). A porous membrane can be synthesized by the utilization of latex particle and agarose gels. The development of a sensor independent of oxygen concentration takes place by electrochemical attachment of the polypyrrole onto the porous membrane. The basic principle involved here is the direct electron transfer from the redox enzyme to the conducting polymer due to the strong adsorption of glucose oxidase and the morphology of the internal conducting polymer surface (Czajka et al., 1992). This amperometric determination of glucose takes place in a continuous mode (Koopal et al., 1992). Chronoamperometric determination of glucose sensor based conducting polypyrrole microtubule has a long sensor lifetime (Koopal et al., 1993).

Direct amperometric determination of glucose can be carried out fabrication of a third generation biosensor based on conducting screen printing ink. The carbon prints comprising the electrodes act as a substrate for the sensor. Carbon ink consists of a redox enzyme and conducting polymer which communicates with each other (Koopal et al., 1994). Recently, a third generation glucose biosensor was fabricated using graphene polyethyleneimine-gold nanoparticle hybrid. The enzyme is immobilized on the hybrid with the help of glutaraldehyde which acts as a cross-linking agent. The sensor exhibits a sensitivity of about 9.3 $\mu A\ mM^{-1}\ cm^{-2}$ (Rafighi et al., 2016). Similarly, a simple amperometric determination of glucose can be carried out with PVC/tetrathiafulvalene–tetracyanoquinodimethane (TTF–TCNQ) composite electrode. TTF–TCNQ acts as the redox mediator as well as the conducting phase. The sensor helps in the determination of glucose as well as ascorbic acid (Cano et al., 2008). Another novel structured third generation biosensor is fabricated by the in-situ limited electrodeposition of gold nanocubes on a thiol graphene film. The uniform distribution and regular nanostructure of the biosensor result in an ultrasensitive glucose detection with high sensitivity and selectivity (Chu et al., 2015). A disposable reagentless glucose biosensor based on immobilization of GO on tetrathiafulvalene-tetracyanoquinodimethane conducting salt onto an overoxidized polypyrrole film has been fabricated. The salts crystal grows on the non-conducting film and emerges like a tree structure. The direct re-oxidation of the enzyme at the surface of the crystal helps in sensing glucose. The interference-free sensor exhibits remarkable sensitivity and selectivity (Palmisano et al., 2002). A strong edible electrochemical biosensor for glucose detection in the gastrointestinal fluids has been developed. This pH-sensitive glucose biosensor is made possible with olive oil and activated charcoal and this can act as a protective coating for the glucose oxidase enzyme embedded, from the strongly acidic environment around. This glucose sensor based on edible carbon paste is having a pH sensitive enteric coating to get a predetermined activation in specific pH at desired times (Ruiz-Valdepeñas Montiel et al., 2018).

2.1.1.2. Non-enzymatic glucose biosensor. To account for the limitations offered by enzymatic glucose biosensor, non-enzymatic glucose biosensor was developed. The non-enzymatic biosensors improve the reliability by the elimination of drift. The output signal is decreased in proportion to the glucose concentration which further depends on enzymatic degradation and loss of activity (Hussain et al., 2011; Jiang and Zhang, 2010; Yang et al., 2011). These sensors work by the oxidation of glucose using metal oxide catalyst like gold nanoparticle (Hussain et al., 2011). However, this amperometric detection requires an applied voltage, battery, and reading device making it less convenient for the patients. In addition, it is less accepted due to its large size. Another method in non-enzymatic approach involves the binding of glucose to the sensor which finally gives a fluorescence

(Pickup et al., 2005) or volumetric output (Scognamiglio, 2013). Recent studies have shown that a fluorescence-based sensor provides a reliable output. The various glucose binding moieties include natural molecules like concanavalin-A, synthetic molecules like phenyboronic acid, and polyacrylamide based molecular imprinted hydrogel (Yang et al., 2011).

A non-enzymatic electrochemical biosensor fabrication has been reported by modification of the electrode with palladium nanoparticles (PdNPs)-functioned graphene (Nafion–graphene). Such electrode shows high electrochemical activity for the electrocatalytic oxidation in alkaline medium. This biosensor quantifies glucose over a linear range from 10 μM to 5 mM with a detection limit of 1 μM and shows good reproducibility and stability (Lu et al., 2011). Similarly, a non-enzymatic biosensor based on cupric oxide nanoparticles modified multiwalled carbon nanotube array electrode was fabricated. The electrochemical characteristics of the biosensor were then further analyzed by cyclic voltammetry and chronoamperometry. The sensor shows a linear response of 0.10 mM glucose with a detection limit of 0.2 μM (Jiang and Zhang, 2010).

2.1.2. Optical biosensor

Glucose can be sensed based on the optical properties of the intrinsically fluorescent compound, their co-enzymes or co-substrates. This class of biosensors results in optical changes in their spectral properties upon the binding of the enzyme. Changes in the fluorescence intensity occur to the protein part of the enzyme upon binding with glucose but no change occurs in the absorption spectra for the protein part of the enzyme (Lakowicz, 2006). Coenzymes also cause changes in the absorption and luminescence upon interaction with glucose. Moreover, glucose concentration can also be determined by measuring the consumption of oxygen upon the interaction of the enzyme with the help of probes (Steiner et al., 2011). Several detectors have been enlisted to detect the glucose in fluorescence sensors. This includes the lectin concanavalin-A, enzymes, bacterial glucose-binding protein, and boronic acid derivatives. The principle behind is the measurement of fluorescence resonance energy transfer between a fluorescent donor and an acceptor either within a protein which results in glucose-induced changes in conformation or changes in intrinsic fluorescence of enzymes and extrinsic fluorophores (Pickup et al., 2005).

A novel optical biosensor based on Prussian blue (PB) has been developed. The unique feature of PB electrode is that it possesses the ability to detect the H_2O_2. The PB helps in the evaluation of pH over a physiological range and plays a role as an optical transducer in pH based biosensor (Guo et al., 1999; Koncki and Wolfbeis, 1999). Moreover, it also helps in the detection of redox species which causes reduction of PB film to Prussian white (PW). The film can be regenerated by the introduction of the sensing film into a flow injection system. It has been seen that the redox-sensitive PB/PW film system can be effectively used as a transducer platform for optical biosensors. Modification of the reduced film with GO acts as an optical biosensor (Lenarczuk et al., 2001). Entrapment of GO within xerogel results in the development of an optical biosensor. This sensor exhibits extended storage stability and is mainly used for the determination of glucose in urine samples (Wu and Choi, 2004). Moreover, a novel optical fiber biosensor based on electrochemiluminescence is developed. Here, the enzyme GO is immobilized on the surface of GCE by sol-gel technique. This sensor exhibits good selectivity and stability with a detection limit of 26 μM. The sensor elicits the ability to determine the glucose in soft drinks (Zhu et al., 2002).

The glucose concentration can be determined directly in the blood with a reagentless reversible biosensor. This biosensor works on the principle of intrinsic spectroscopic properties of peroxidase fabricated by the entrapment of GO and peroxidase on a polyacrylamide gel matrix. In glucose determination, the blood is diluted with water and fed into the sensor with the cleaning of samples in between. Here the biosensor works in a continuous mode offering better sensitivity and reproducibility (Sanz et al., 2007). The concentration of glucose in the human blood can be analyzed with optical fiber grating with a wavelength in proportion to the absorbance of the glucose content of blood serum (Goes et al., 1998).

Optical biosensor helps in monitoring variation in glucose flux and their related chemical pathways. Glucose level can be monitored optically by a reported organic-inorganic hybrid microgel with high selectivity and sensitivity at the concentration normally seen in blood and tear fluid (Alexeev et al., 2004). Here, the microgel acts as a glucose indicator. This imprinted microgel is made up of small silver nanoparticles closely immobilized in a glucose-imprinted boronate derived gel network of poly(N-isopropylacrylamide-acrylamide-vinylphenylboronic acid) (poly(NIPAM-AAm-VPBA)), such that the silver nanoparticle is in close proximity to each other allowing glucose responsive gel actuated tunable plasmon coupling. The color shift of microgel dispersion enables to determine the glucose level without any instrumental aid. The surface plasmon responses are free of significant interference, enabling monitoring of glucose at a concentration range of 0.1–20 mM (Wu et al., 2012).

A quick and highly sensitive optical biosensor could be fabricated by the immobilization of GOx on polystyrene optical fibrous membrane prepared by the electrospinning process, which is shown in Fig. 3. Doped iridium complex in presence of UV irradiation resulted in enhanced luminescence at 405 nm. The various factors responsible for high sensitivity and response are high surface area to volume of the porous membrane, biocatalyst reaction occurring on the fiber surface and the energy transfer between dissolved oxygen and porous membrane. The reported sensor elicits a detection limit of 1.0×10^{-10} M with a response time of less than 1 s (Zhou et al., 2013). A blue to green ratiometric fluorescent color change developed determines the glucose concentration in a ratiometric fluorescent glucose biosensor which is based on carbon dots and rhodamine 6G (Cho and Park, 2019).

There is an emerging need in the development of an inexpensive and non-invasive biosensor having the ability to detect glucose in micro concentration in other biofluids. Molybdenum disulfide (MoS_2) with unique atomic structure helps in the intercalation of metal atoms and ions, but the poor intrinsic solubility results in an inadequate performance in the electrochemical device. This problem can be avoided with the use of a conductive additive like silver which improves the electrochemical performance. The porous structure of silver nanoparticle and large surface area of MoS_2 enable accelerated electron transfer resulting in high sensitivity of the biosensor. This biosensor possesses excellent sensitivity (9044.6 μA mM^{-1} cm^{-2}), low detection limit (0.03 μM), the appropriate linear range of 0.1–1000 μM, and high selectivity (Anderson et al., 2017).

2.2. Classification of glucose biosensors based on clinical application

2.2.1. Continuous glucose monitoring biosensors

Although self-testing has a great advantage, it is limited by the requirement of a high number of testing during a time period. Tighter continuous monitoring of glycaemic control helps to get a valid response (Henry, 1998). For the fabrication of such a type of biosensor, various factors like biocompatibility, miniaturization, long-term stability of enzyme and transducer, oxygen deficit, in vivo calibration, safety, and convenience have to be considered. The size and shape of biosensor should be such that it causes less discomfort. In addition, the sensor environment also contributes an important role in the long term stability of biosensor (Wang, 2001).

Currently, two types of systems are in use for continuous monitoring of subcutaneous and blood glucose levels. However, the application of continuous blood glucose monitoring is limited due to certain limitations like the risk of thromboembolism and surface contamination of electrode by proteins (Niraj et al., 2012).

2.2.1.1. Implantable glucose biosensor. An implantable glucose biosensor is a current approach for the continuous monitoring of glucose with long-

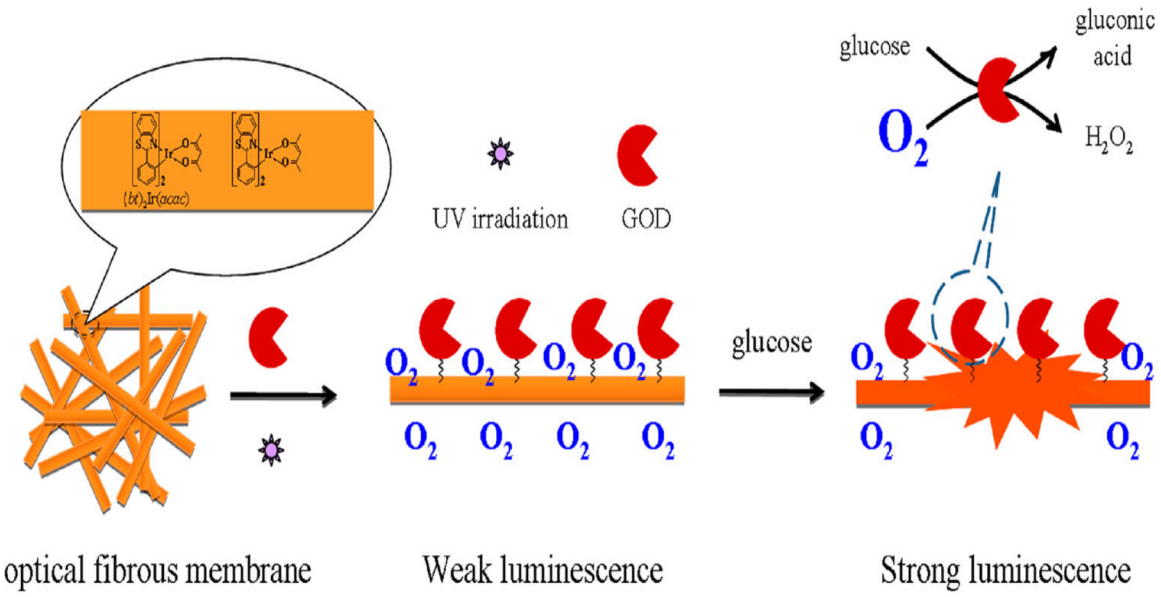

Fig. 3. Schematic illustration of sensitive optical biosensor based on immobilization of glucose oxidase on polystyrene optical fibrous membrane. "Reprinted with permission from (Zhou et al., 2013),. Copyright (2013) American Chemical Society.".

term stability. Glucose reacts with molecular oxygen can undergo oxidation in presence of GO to form gluconolactone and H_2O_2. The increase in H_2O_2 concentration and a decrease in oxygen concentration is directly proportional to the glucose concentration which can be detected electrochemically. For oxygen detection, the amperometric signal obtained as a result of the electrochemical reduction of oxygen on catalytic (platinum) electrode is utilized. When the mass transfer of oxygen and glucose is the limiting step, a linear dependence of amperometric signal can be attained for substrate concentration, which can be accomplished by the use of oxygen permeable and glucose diffusive membrane (Atanasov and Wilkins, 1994).

Generally, an amperometric biosensor consists of an oxygen selective electrode and a glucose oxidase enzyme bioreactor for measuring oxygen. The movement of other components from physiological fluids to the working electrode surface can be restricted by application of a hydrophobic oxygen permeable membrane which separates the above two parts resulting in less interference. For an implantable glucose biosensor, long-term operational stability is a major hurdle. The lifetime of the implantable biosensor should be long to avoid the problems (Atanasov and Wilkins, 1994). Enzyme deactivation process limits the lifetime of a biosensor, which could be avoided by enzyme immobilization, thus increasing the stability (Tse and Gough, 1987).

Another approach to expanding the biosensor lifetime can be achieved by in situ sensor reviving supplementation of the immobilized compound with a fresh enzyme (Xie and Wilkins, 1991). The GO enzyme is immobilized on fine ultra-low-temperature isotropic carbon powder, which is then maintained in a fluid suspension. The development of the biosensor with new compound suspension infused through a septum, without sensor dismantling is challenging. This idea encourages reviving the embedded sensor without surgical expulsion from the patient (Atanasov and Wilkins, 1994).

An implantable glucose sensor with GO immobilized on fine graphite powder was fabricated. The graphite enzyme in a fluid state can be recharged when the enzyme activity decreases resulting in the improvement in the lifetime of the detector. The electrode is constructed using a hydrophobic membrane having high permeability to assure that required oxygen is available and a platinum electrode for hydrogen peroxide detection. The electrode has a wide range for determining glucose concentration from 20 to 300 mg dL^{-1}. This fabrication possesses a short response time over 4 months with a high current output signal with minimal noise (Xie and Wilkins, 1991). Advanced minimally invasive PAMAM-functionalized smart microgels offer a glucose sensitive platform. They emit a fluorescence signal upon recognition of glucose by transdermal transmission (Chen et al., 2017). Photoluminescent materials such as semiconductor quantum dots (QD) are used as sensing material because of size-tunable optical properties (Rosenthal et al., 2011). Combining photoelectrochemical QD sensors with certain enzymes allow indirect measurement of glucose (Schubert et al., 2010). Recently, a smartphone based continuous monitoring biosensor is reported (Elsherif et al., 2018).

2.2.2. *Non-invasive glucose monitoring systems*

Non-invasive glucose monitoring systems have gained significant interest among glucose biosensors. The limitations of the continuous monitoring system were overcome by use of noninvasive glucose monitoring systems. A developed wearable glucose monitor measures electro-osmotically the extracted glucose within a clinically acceptable range. The metal oxide gas sensor is a noninvasive method to determine glucose concentration by measuring the concentration of gas present in the exhaled air. Generally, human beings inhale oxygen and expire carbon dioxide. However, in the case of diabetic patients in addition to carbon dioxide, they also expire certain amounts of volatile organic solvents like acetone. The exhaled air containing any volatile organic solvent is introduced into the input chamber where a sensor detection system is present. Any variation is recorded in the form of voltage or resistance into the output. The utilized metal oxide sensors work on the principle of difference in conductivity in presence of oxidizing and reducing agents. The output increases in response to the nature and concentration of the volatile organic solvent (Yadav and Manjhi, 2014).

A flexible three-dimensional electrochemical glucose biosensor is possible for continuous glucose monitoring from human tears. Sensitivity enhancement is one of the important factor need to be considered in the detection of glucose in tear fluids. This problem can be solved by increasing the electrode surface area by three dimensional micropatterning of the electrode. Immobilization of GO on to this three-dimensional electrode gives a fast response and good repeatability over low glucose concentration (Patel et al., 2011). The implementation of non-invasive electrochemical epidermal glucose monitoring systems can offer continuous and real-time glucose sensing and also enables patient self-monitoring. Moreover, such systems are a future promise to diabetes management (Kim et al., 2018; Wang, 2008; Zhang et al., 2015a, 2015b, 2015c).

2.3. Nanobiosensors: types of glucose biosensors based on nanoparticle used

Nanotechnology provides a path for the development of improved biosensors with defined and tailored characteristics. Glucose sensing molecules can be classified into three major groups which are used to engineer nanoparticle-based biosensor. They are GO, glucose binding proteins, and glucose–binding small molecules (Veiseh et al., 2014). Nanoparticles, used as transducers, coupled with glucose detecting molecule lead to the development of a new type of biosensors with merits like more patient-friendly, rapid measurement, and improved precision characteristics.

The characteristics of nanomaterials like high surface to volume ratio imparts unique properties and exhibits easy absorption, thus improving the sensor performance (Luo et al., 2006; Taguchi et al., 2014). It is observed that the rate of electron transfer decreases in response to an increase in distance between the enzyme and electrode. Consequently, the small size of the nanoparticles decreases the distance when compared with bulk materials (Murphy, 2006). Specificity, selectivity, reproducibility, and reliability can be improved by the functionalization of nanomaterial. Nanotechnology, which permits to lessen dimensions at the nano-size range improves the overall performance of the biological components with the use of new nanomaterials (Scognamiglio, 2013). The suitable nanostructures of a detection system for a biosensor include metal nanoparticles, magnetic nanobeads, quantum dots, nanotubes, nanowires, nanorods, nanofibres, nanocomposites, nanofilms, nanopolymers, and nanoplates due to their unique physical, chemical, mechanical, magnetic, and optical properties (Zhang et al., 2009).

2.3.1. Metal nanoparticle-based biosensors

The metal nanoparticle as biosensing element shows a lower limit of detection. GO enzyme is utilized to monitor blood glucose. But for the enzyme to be active, it has to come in contact with flavin adenine dinucleotide (FAD) which is embedded in a protective protein shell. Therefore, to promote the effective interaction between the active site and electrode, functionalization of FAD with gold nanoparticle is employed. Immobilization of enzyme on gold nanoparticles prevents leakage due to its strong adsorption and results in increased stability. In the process of electrochemical decomposition, a biocomposite film comprising of chitosan, gold nanoparticles, and glucose oxidase is electrochemically deposited on the gold electrode. The study reports revealed that high stability to glucose is exhibited by biosensor made with gold nanoparticles (Liu et al., 2005).

In another study, glucose biosensor was fabricated by the covalent attachment of GO to a gold nanoparticle monolayer modified gold electrode. The presence of gold nanoparticle on biosensing interface improves the electron transfer between analyte and electrode surface based on cyclic voltammetry and electrochemical impendence investigations. The sensor provides good reproducibility over a concentration range of $2.0 \times 10^{-5} - 5.7 \times 10^{-3}$ M with a sensitivity of 8.8 μA mM^{-1} cm^{-2} and with a detection limit of 8.2 μM with stability for 30 days (Zhang et al., 2005).

Studies on the nature of GO immobilized on graphite rod modified with gold nanoparticle and the impact of amperometric glucose sensor on both the presence and absence of gold nanoparticles are reported. These studies report an increase in rate mediated electron transfer for an electrode with gold nanoparticles. The sensor shows a linear response to glucose concentration from 0.1 to 10 mmol L^{-1} with a detection limit within 0.1 and 0.08 mmol L^{-1} and stability for 19.5 days (German et al., 2010).

2.3.2. Magnetic nanoparticle-based biosensors

Magnetic nanoparticles as immobilizing carriers are a current area of research. Biocompatibility, low toxicity, and excellent superparamagnetic property of magnetic nanoparticles make them gifted nanostructures in the area of the biosensing. In the preparation of a reported biosensor, a nanocomposite film on the indium tin oxide glass plate is fabricated by dispersion of ferric oxide nanoparticle in chitosan solution. GO is further immobilized on the film by physical adsorption. This nanocomposite bioelectrode shows a response time of 5 s with the linearity of 10–400 $mgdL^{-1}$ of glucose and sensitivity of 9.3 μA/($mgdLcm^2$) with a shelf life of 8 weeks under cool conditions (Kaushik et al., 2008).

Biosensing application of nickel ferrite ($NiFe_2O_4$) has been evaluated with the help of glucose biosensor. A new biosensor was developed by the immobilization GO in chitosan/$NiFe_2O_4$ nanoparticles (C/$NiFe_2O_4$NPs) film. The electrode modified with the C/$NiFe_2O_4$NPs/GO revealed an exemplary electrocatalytic response to the oxidation of glucose when ferrocene carboxylic acid was used as an artificial redox mediator. The response was further studied by cyclic voltammetry The biosensor detects glucose with a linear range of 1×10^{-4}–2.0×10^{-2} $molL^{-1}$ (Luo et al., 2010).

2.3.3. Nanofiber-based glucose sensors

Nanofibers along with other conducting nanomaterials exhibit good sensor performance due to their distinct electronic, magnetic and optical properties. Carbon nanomaterials are easily functionalizable, biocompatible, conductive, and possess large surface area which plays a significant role in sensor application. In the case of carbon nanofibers, which are cylindrical nanostructures with graphene layers arranged as stacked cones, the whole surface area can be activated. They can act as an immobilization matrix for biomolecules as well as transducers, thus playing a dual role. Studies have shown that carbon nanotube-based biosensors have high sensitivity, and improved operational and storage stability. The sensor is fabricated by the direct immobilization of the enzyme onto the surface of carbon nanofibers (Vamvakaki et al., 2006). Additionally, electrochemical amperometric bienzymatic glucose biosensor can be fabricated by co-immobilization of horseradish peroxidase and GO on vertically aligned carbon nanofibers which can detect low concentrations of glucose (0.4 μM) (Islam et al., 2011).

Nitrogen-doped carbon nanofibers (NCNFs) having highly flexible structure can be used for electrode modification. Their electron microscopic images (SEM, TEM, HR-TEM) are given in Fig. 4. Electrochemical measurements have shown that NCNFs have a large surface area and electron transfer in relation to carbon nanofibers. Glucose biosensor based on GO/NCNFs shows high stability (Liu et al., 2014). Practically, the electrospun nanofibers based glucose sensor plays a great role in sensor applications due to an increased lifetime. A fusion of electrospun nanofibers and integrated nanomaterials resulted in excellent sensor fabrications. Limited studies are related to the screening of toxic feature of electrospun nanofibers and this exemplifies the need for further research in this aspect (Senthamizhan et al., 2016).

Electrospinning and further calcination steps result in the formation of Co_3O_4nanofiber. A non-enzymatic biosensor for glucose detection in alkaline solution is possible by the application of Co_3O_4 nanofibers. These biosensors show a sensitivity of 36.25 μA mM^{-1} cm^{-2} with a detection limit of 0.97 μM and a response time of less than 7 s (Ding et al., 2010). A highly sensitive amperometric glucose biosensor with good anti-interference ability has been fabricated with zinc oxide (ZnO) nanofiber was developed. Sensor development takes by the immobilization of GO by a single nanofibre on a gold electrode with a sensitivity of 70.2 μAcm^{-2} mM^{-1} and response time of less than 4 s. The sensor exhibits a linear range of 0.25–19 mM with a low limit of detection (LOD) of 1 μM (Ahmad et al., 2010). Nanofibers of poly(vinyl pyrrolidone)/zinc acetate composite prepared by electrospinning technique followed by high-temperature calcination results in the formation of zinc oxide nanofibres with diameters in the range of 350–195 nm were obtained. A single NF on a gold electrode is functionalized with glucose oxidase by physical adsorption. biosensor revealed high and reproducible sensitivity of 70.2 μA cm^{-2} mM^{-1} within a response time of less than 4 s Fig. 5 represents the cyclic voltammograms of the electrode and biosensor towards glucose solution (Ahmad et al., 2010).

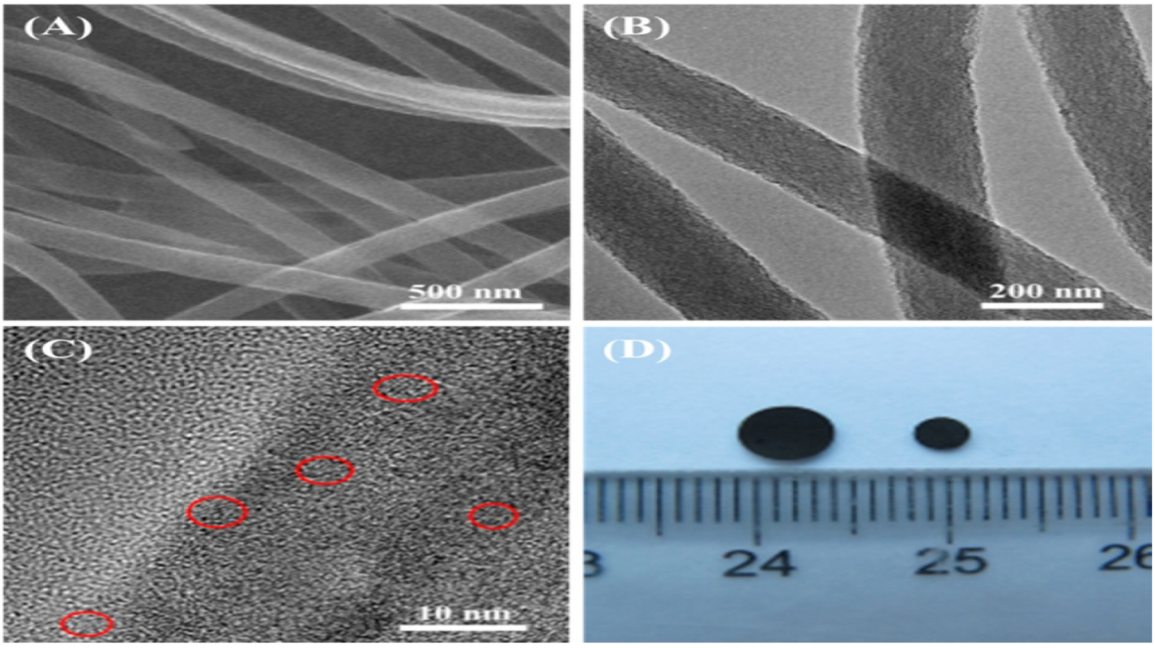

Fig. 4. Characteristic images of nitrogen-doped carbon nanofibers (NCNFs) film a] SEM image b] TEM image c] HRTEM d] Photograph of disc-shaped film. "Reprinted with permission from (Liu et al., 2014). Copyright (2014) American Chemical Society.".

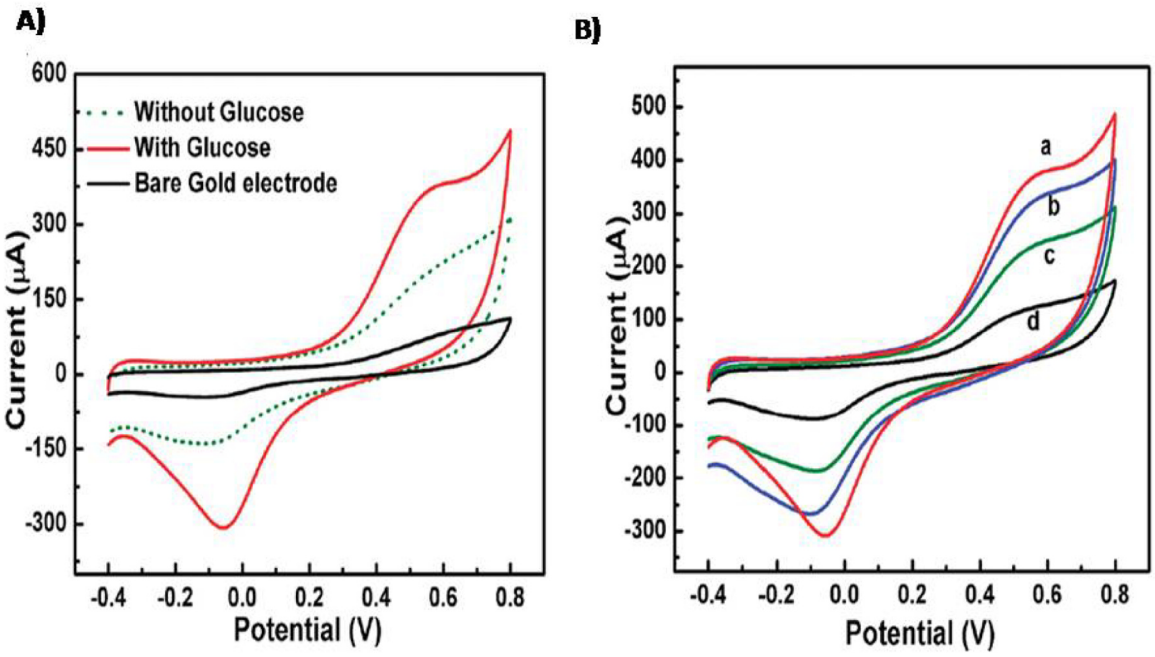

Fig. 5. A) Cyclic voltammograms of the bare and modified gold electrode without and with 100 μM glucose in pH 7.0 Phosphate buffer solution. (B) Cyclic voltammograms of the biosensor in Phosphate buffer solution containing 100 μM glucose at a scan rate of (a) 100 mV, (b) 80, (c) 50, and (d) 20 mV s^{-1}. "Reprinted with permission from (Ahmad et al., 2010). Copyright (2010) American Chemical Society".

A new methodology for the electro-deposition of poly (3,4-ethylenedioxythiophene) (PEDOT) nanofibers includes the combination of a soft template acting as a surfactant and an ionic liquid which acts as a non-surfactant. A modified electrode is fabricated by electrochemical deposition of palladium nanoparticle and immobilization of glucose oxidase into nanofibrous PEDOT which is free from electroactive interference. The sensor displays a sensitivity of 1.6 mA M^{-1} cm^{-2} over a concentration range of 0.5–30 mM (Santhosh et al., 2009). Sensitive detection of glucose can be carried out by GO–graphene–chitosan nanocomposite film. The fabricated biosensor shows linearity from 0.08 mM to 12 mM glucose with a detection limit of 0.02 mM and high sensitivity of 37.93 μA mM^{-1} cm^{-2} (Kang et al., 2009). Gold nanoparticles–bacterial cellulose nanofibers (Au-BC) nanocomposite as a platform for amperometric determination of glucose is also possible. For this purpose, two enzymes, GO and horseradish peroxidase (HRP) are immobilized in Au-BC nanocomposite modified glassy carbon electrode. This biosensor can determine the glucose level in blood samples over a linear range of 10–400 mM with a detection limit of 2.3 μM (Wang et al., 2010).

2.3.4. Nanorod based biosensors

Zinc oxide (ZnO), a compatible material, has a high affinity to operate with the oxygen species rendering it a potential material for

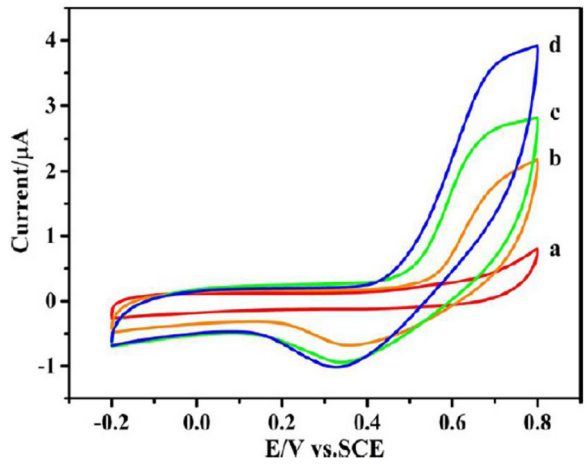

Fig. 6. Cyclic voltammogram curves of the a) electrode in Phosphate buffer saline containing 0.2 mM glucose b) proposed biosensor in phosphate buffered saline containing 0 mM glucose (c) 0.1 mM glucose (d) 0.2 mM glucose. "Reprinted with permission from (Han et al., 2016). Copyright (2016) American Chemical Society.".

electrochemical sensor fabrication (Zhao et al., 2010a, 2010b). ZnO nanorods as an electrochemical biosensor is an economical, authentic, fast, and harmless approach (Bhattacharya et al., 2012; Kong et al., 2009). The mechanism of action relies on an electrochemical reaction between ZnO nanorods and glucose, an electroactive molecule in the blood. Later the signal is read out as an electrical current (Umar et al., 2006; Wei et al., 2010).

A newly developed electrochemical sensor works on the principle ZnO nanorods and a sol-gel technique. It offers advantages like cost-effectiveness, accuracy, fast response, and high sensitivity. ZnO nanorods can be synthesized by an easy, cheap and low growth temperature chemical method known as hydrothermal growth. The behavior of the fabricated sensor can be evaluated by aspect ratio which is the ratio between the length of grown ZnO nanorods and their diameter. The growth time and temperature regulate the length of synthesized ZnO nanorods (Fulati et al., 2010). Another important factor is the synthesis of a growth solution. The final shape of the nanorod is affected by the homogeneity of growth solution (Marie et al., 2015). An electrochemical sensor was fabricated with indium tin oxide glass substrate coated with a titanium layer act as a working electrode while platinum act as a reference electrode. The enzyme leakage and stability of the working electrode can be greatly increased by spin coating with a thin membrane of Nafion. The spin coating on the top of the working electrode by GO has a high affinity for ZnO nanorods to absorb the GO. The biosensor produces a sensitivity of 10.9111 mA mM^{-1} cm^2 with a response time of 3 s (Marie et al., 2015).

Recently, a nonenzymatic fluorescent biosensor based on zinc oxide is developed. This sensor works based on the detection of glucose concentration directly immobilized on ZnO nanorods through photoluminescent quenching of ZnO under UV irradiation. Here, the glucose is decomposed into H_2O_2 and gluconic acid. The sensor shows linearity over the range of 1–20 mM with a sensitivity of 2.3% mM (Mai et al., 2017).

2.3.5. Nanowire-based biosensors

The electron transfer between the enzyme and electrode can be enhanced by incorporating enzyme activity in the nanomaterial. Enzymatic glucose sensor based on ZnO nanowires electrochemically deposited on an Au coated polyester substrate is fabricated. By a simple physical adsorption method, glucose oxidase was immobilized on zinc oxide nanowires. The sensor shows a high sensitivity of 19.5 μAmM^{-1} cm^{-2} with a detection limit of less than 5 s (Pradhan et al., 2010). A new sensor system involves immobilization of glucose oxidase on a cross-linking matrix of bovine serum albumin on a platinum electrode. The system was further altered by gold nanoparticle decorated platinum nanowires (GNPs-Pb NWs). A good electrochemical performance of this biosensor, optimized by chronoamperometry and voltammetry, is due to the combined response of Pb nanowires and gold nanoparticle. The biosensor exhibits a sensitivity of 135.5 μAmM^{-1} cm^{-2} with a detection limit of 2 μM and a response time of less than 5 s. This biosensor exhibits long term stability and good anti-interference (Wang et al., 2009).

A silver nanowire (AgNW) and chitosan-glucose oxidase film-based amperometric glucose biosensor has been developed with excellent selectivity, high response, and stability. Moreover, this biosensor is having the potential to be used for the serum detection of glucose. The AgNWs facilitates an enhanced electron transfer between the electrode surface and the enzyme immobilized (Wang et al., 2013). Manganese oxide nanowires having unique characteristics of electron transfer, genetically engineered M13 phages can be used as a template for precise nucleation and growth of manganese oxide crystals. The morphology of nanowires can be modified by surface charge of phage mutants. Manganese oxide crystals were uniformly distributed on the surface of negatively charged tetraglutamate-fused phage. the novel M13-templated manganese oxide nanowires exhibited high electrocatalytic activity at neutral pH. The proposed biosensor exhibited a low limit of detection and god interassay (Han et al., 2016). Fig. 6 represents the cyclic voltammogram response of the biosensor in response to glucose.

2.3.6. Nanocomposite based biosensors

Apart from single nanostructures, nanocomposites involving different nanomaterials like nanotubes, nanofilms, and nanowires are extensively used in sensor fabrication. A glucose biosensor fabricated based on electrodeposition of palladium nanoparticle and GO onto Nafion solubilized carbon nanotube retains the biocatalytic ability and carries out efficient oxidation and reduction of liberated H_2O_2. This fabrication results in increased storage time decreased interference and performance. In addition, this sensor has a linear response up to 12 mM with a detection limit of 0.15 mM (Lim et al., 2005). An amperometric biosensor can be developed by the immobilization of GO on to a gold and platinum nanoparticle modified CNT electrode exhibiting good electrocatalytic activity and rapid response to glucose. The electrode could be coated with Nafion to avoid loss of GO and to eliminate interference (Chu et al., 2007). A biosensor on MWCNT-Nafion-GOD nanobiocomposite films with a sensitivity of 330 nA/mM, a linear range of 2 mM, a detection limit of 4 μM, and a response time of < 3 s is also possible (Tsai et al., 2005).

A well applicable non-enzymatic glucose biosensor in alkaline media with Cu nanoclusters electrochemically deposited on multi-walled carbon nanotube (MWCNT) modified glassy carbon electrode can detect glucose in real blood serum samples with good reproducibility and stability. This sensor is able to detect glucose within a linear range 7.0×10^{-7} to 3.5×10^{-3} M with a high sensitivity of 17.76 μAmM^{-1} and a low detection limit of 2.1×10^{-7} M, and fast response within 5 s (Kang et al., 2007). An inexpensive and disposable glucose biosensor with titanium dioxide (TiO_2)–cellulose hybrid nanocomposites which are further immobilized with GO by physical adsorption have a linear response in the range of 1–10 mM (Maniruzzaman et al., 2012). Recently, a novel electrochemical glucose biosensor based on immobilization of glucose oxidase on graphene/AuNPs/chitosan composites film is reported. This sensor shows a linear response from 0.2 to 4.0 with a high sensitivity of 99.5 μAmM^{-1} cm^{-2} (Shan et al., 2010). A bionanocomposite film consisting of glucose oxidase/Pt/functional graphene sheets/chitosan (GOD/Pt/FGS/chitosan) for glucose determination is also in pipeline (Wu et al., 2009).

A metal protein nanocomposite such as platinum-bovine serum albumin nanocomposite synthesized by a green method having great electrocatalytic activity has been used as electrochemical sensing

matrix for glucose determination. The bioactivity of glucose oxidase and excellent catalytic performance of inner platinum particles lead to an improved electrocatalytic activity toward oxygen reduction. The developed biosensor exhibits high selectivity and satisfactory storage stability. This sensing method proved to be a good application in real serum samples (Hu et al., 2014).

2.3.7. Quantum dots based biosensor

The unique electronic and photophysical properties like broad absorption, narrow emission and high quantum yield of semiconductor quantum nanoparticles attracted great interest in biosensor studies. An economical and disposable modified electrode can be developed by the electrodeposition of hybrid quantum dot (QD) onto pencil graphite electrode surface followed by immobilization of glucose dehydrogenase onto the QD modified electrode (Luo et al., 2010; Willner et al., 2007; Yue et al., 2013). The modified electrode finds wide application in the photoelectron chemical determination of glucose on flow injection analysis system. This biosensor exhibits good selectivity, sensitivity, and repeatability, and real samples can be easily detected. It possesses other advantages like a fast response, simple design, easy integration and portable sensor system (Ma and Su, 2011). The fabrication of photochemical biosensors mainly involves three steps which include immobilization of QD into an electrode, illumination of the electrode surface and finally generation of photocurrent based on the analyte in supporting electrolyte. Illumination of the QD modified electrode surface causes the photoexcitation of semiconductor QDs (Ertek et al., 2016).

Various QD ligand systems find application as glucose biosensing elements (Saran et al., 2011). Bioconjugated fluorescent quantum dots improve fluorescence detection by increasing the lifetime. Significant fluorescence emission is shown by Mn-doped ZnS quantum dot (Fig. 7). Conjugation of glucose oxidase with Mn-doped ZnS quantum dots with EDC-NHS coupling by use of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS) results in the fabrication of a biosensor with the improved enzymatic process. The sensor possesses a detection limit of 3 μM (Wu et al., 2010). Recently, a glucose biosensor is fabricated based on the multilayer films of cadmium telluride (CdTe) QDs and GO, and using the layer-by-layer assembly technique. When the film comes in contact with glucose solution, quenching of the photoluminescence of QDs in the film takes place. These are due to the reaction between enzyme-catalyzed reaction products and GO leading to surface defects on QDs. The quenching rate is directly proportional to the concentration of glucose. Satisfactory reproducibility is obtained using the biosensor (Li et al., 2009).

Fig. 8 shows a phenylboronic salt (PBS) functionalized GQD designed for glucose detection. Addition of PBS to graphene quantum dots leads to fluorescence enhancement, and in the presence of glucose, PBS covalently binds with glucose to form a new PBS-glucose complex, it leads to fluorescence quenching, (Shehab et al., 2016).

A highly sensitive and potentiometric glucose biosensor can be fabricated using functionalized indium nitride (InN) QDs. The unique properties of InN QDs like high surface charge density and robust surface properties make it a promising approach towards biosensing applications. The biochemical functionalization of InN QDs is achieved through physical adsorption of GO. The enzyme coated InN QDs can detect the electrochemical response with high sensitivity. Moreover, the sensor elicits a fast response of less than 2 s with good stability and negligible interference (Alvi et al., 2012). A highly sensitive electrochemiluminescence glucose biosensor is fabricated based on the immobilization of QDs and graphene QDs exhibit a detection limit of 0.3 pmol L^{-1} (Tian et al., 2017).

2.3.8. Carbon nanotube-based biosensors

Carbon nanotubes (CNTs), owing to its excellent electrical properties, is useful in the fabrication of biosensors (Wang and Musameh,

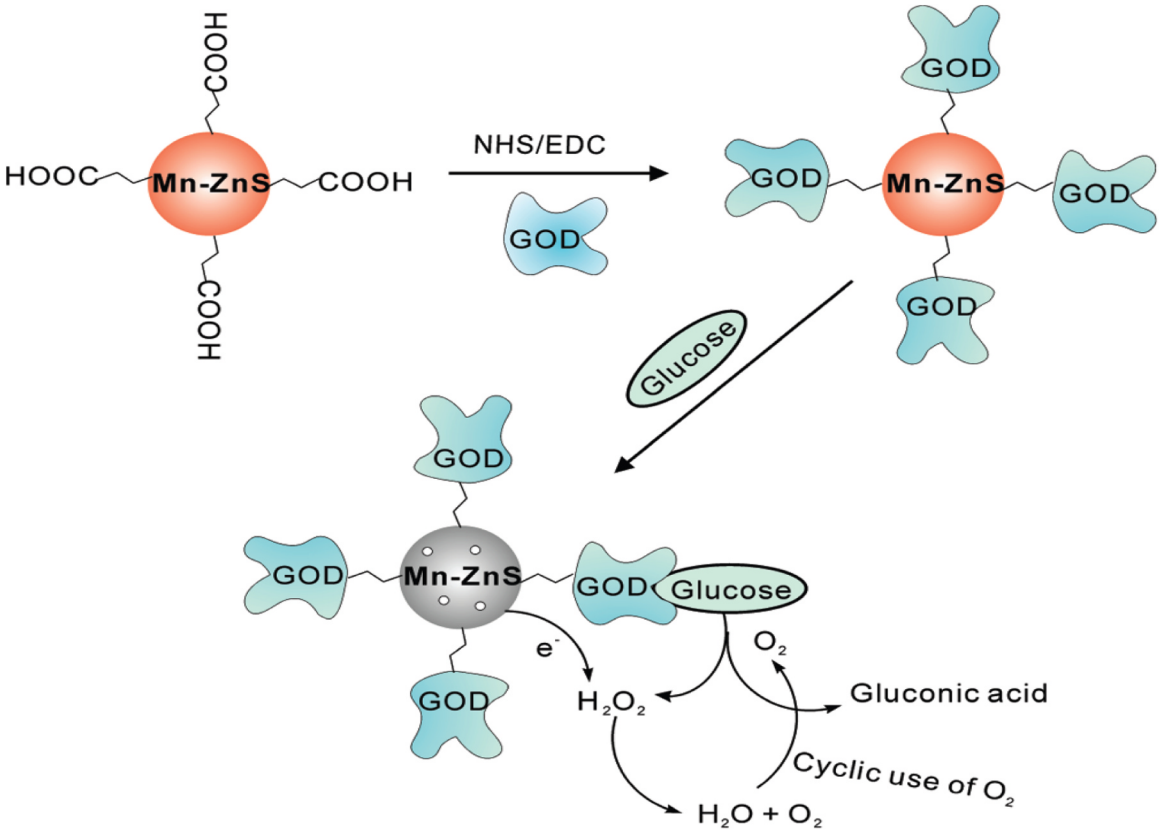

Fig. 7. Schematic representation of GOD-Mn-Doped ZnS QD-Bioconjugate for Glucose Sensing. "Reprinted with permission from (Wu et al., 2010). Copyright (2010) American Chemical Society.".

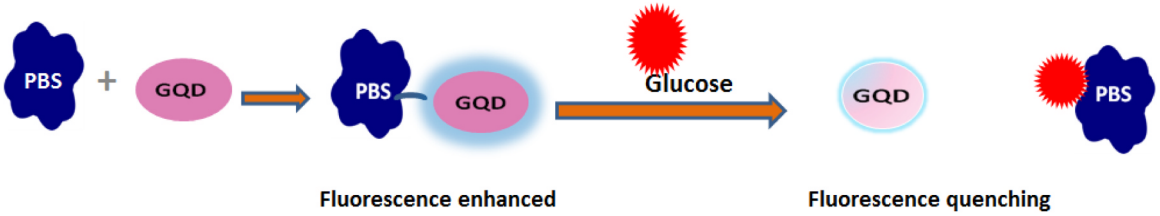

Fig. 8. Schematic representation fluorescent quenching of GQD-PBS complex in the presence of glucose.

2003). Generally, carbon nanotubes are divided into two types; single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). SWCNT is fabricated by rolling single graphite sheet into tube whereas multi-walled carbon nanotube consists of several layers of concentrically arranged graphite sheets. Since MWCNTs have excellent electrical conductivities, their use is preferred to SWCNT. A real-time monitoring needle-like glucose biosensor with favorable stability based on carbon nanotubes is feasible. Such a biosensor can be fabricated by packing a combination of MWCNT, graphite powder, and glucose oxidase freeze-dried powder in a glass capillary. The resultant output can be determined electrochemically by amperometry in presence of glucose and H_2O_2. The sensor has detection of down to 20 mM with significant sensitivity and stability (Jia et al., 2008).

A biosensor fabricated with nanomaterials such as carbon nanotubes decorated with platinum nanospheres improves the electrochemical performance by improving the glucose sensitivity amperometrically. Carbon nanotubes are prepared in situ by microwave plasma chemical vapor deposition was used in a reported biosensor. The intensity of peak observed from this biosensor for an immobilized electrode with bovine serum albumin is much higher when compared to CNT electrode alone and the schematic representation is given in Fig. 9. The biosensor has a linear sensitivity of 1 μM to 0.75 mM with a detection limit of 380 nM. The molar sensitivity of the detector is high with 70 μA mM^{-1}/cm^2 and a response time of 8 s (Claussen et al., 2010).

Amperometric CNT/GO-based biosensors can be fabricated with a Nafion, a perfluorosulfonate polymer having the ability to solubilize CNT. Nafion, due to its unique properties, is widely used in the fabrication of biosensors and in the modification of electrode surface (Fan and Harrison, 1992; Fortier et al., 1992). Thus, CNT/Nafion/GO-coated electrodes, along with electrocatalytic detection ability of H_2O_2, promise a great role in the detection of glucose. In addition to it, this combination offers added merits like increased coupling effect of CNT towards hydrogen peroxide and NADH with the antifouling effect of Nafion (Wang et al., 2003). Improved sensitivity to biosensor is shown by deposition of platinum nanoparticles onto CNT/GO electrode

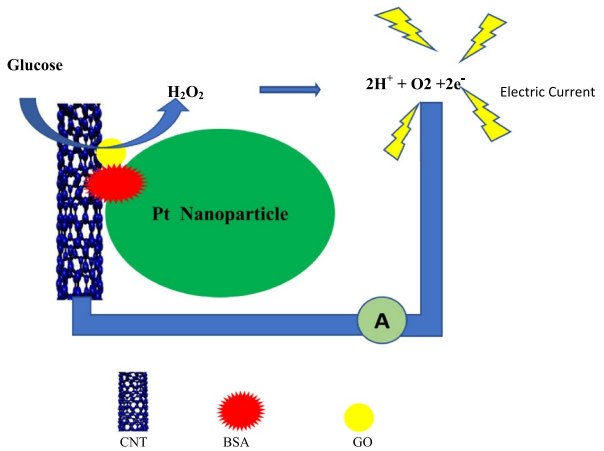

Fig. 9. Schematic representation of CNT/Pt nanoparticle immobilized with BSA and GO; and amperometric detection of glucose.

resulting in a detection limit of 0.5 μM glucose and a response time of 3 s (Hrapovic et al., 2004).

A biocomposite prepared by mixing of the GO with CNT and packed into a 21 gauge needle and can be utilized for amperometric determination of glucose. The latter microsensor has high selectivity and sensitivity with linearity up to 40 mM glucose (Wang and Musameh, 2003). Similarly, a highly sensitive and selective glucose response could be received using CNT paste enzyme electrode. A linear response up to 30 mM glucose with a detection limit of 0.6 mM is reported (Punbusayakul, 2012). Fig. 10 shows biosensor fabricated with carbon nanotube nanoelectrodes (CNT NEs) that can analyze glucose in presence of common interfering compounds. Immobilization of GO on CNT NEs takes place by carbodiimide chemistry where amide linkage is formed by the amino acid and carboxylic acid. The enzymatic reaction of GO on glucose and oxygen of CNT NEs leads to a catalytic reduction of H_2O_2 liberated, which finally detects the glucose with the linear response of 30 mM with a detection limit of 0.6 mM (Lin et al., 2004).

Additionally, graphene and MWCNT based electrochemical glucose biosensors are fabricated employing GO by a facile procedure. In a reported procedure, graphene and MWCNTs were dissolved in 0.25% 3-aminopropyltriethoxysilane (APTES) and drop-casted on 1% KOH-pretreated glassy carbon electrodes (GCEs). The EDC (1-ethyl-(3-dimethylaminopropyl) carbodiimide)-activated GO was then bound covalently to the graphene- or MWCNT-modified GCE. This biosensor demonstrated a linear response in the range of 1.4–27.9 mM. Moreover, direct electron transfer was seen for MWCNT based biosensor (Zheng et al., 2013).

Displacement-based chemiresistive biosensor consisting of single-walled carbon nanotubes is also reported. This type of biosensor

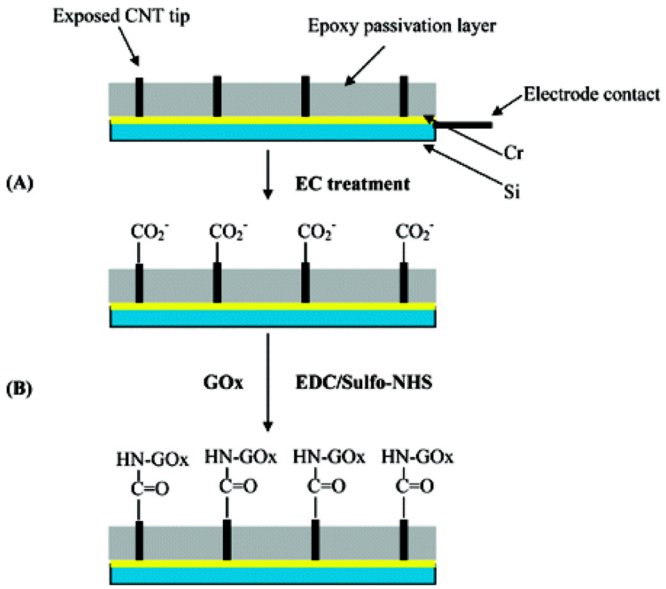

Fig. 10. Schematic representation of the fabrication of CNT nanoelectrode ensembles showing electrochemical treatment for functionalization and coupling with the enzyme. "Reprinted with permission from (Lin et al., 2004). Copyright (2004) American Chemical Society.".

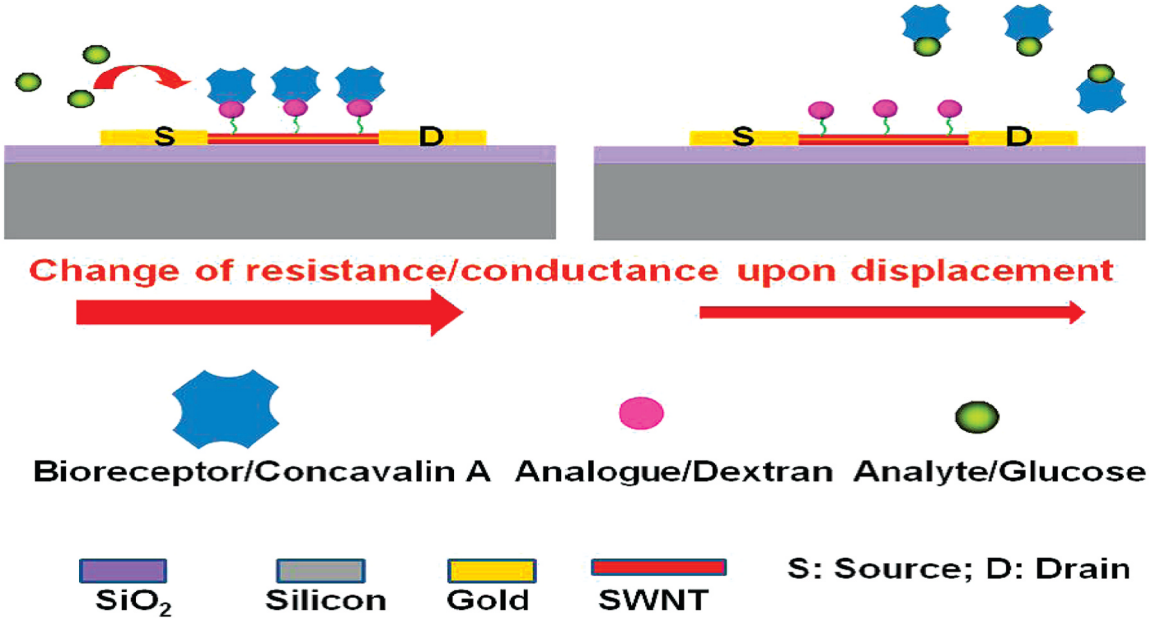

Fig. 11. Schematic representation of a displacement-based chemiresistive biosensor. "Reprinted with permission from (Cella et al., 2010). Copyright (2010) American Chemical Society.".

provides a highly sensitive and selective identification of small weakly charged or uncharged molecules like glucose. Here, detection of glucose is based on the displacement of a plant lectin-like concanavalin-A, bound to a polysaccharide dextran immobilized on SWCNT (Fig. 11). This system offers the advantage of enzyme-free glucose biosensor with picomolar sensitivity (Cella et al., 2010).

2.3.9. Graphene associated biosensors

Graphene gained an increasing attraction in the scientific and technological field in the last few years. The unique properties such as low cost, high surface area, ease of processing, and safety offer potential advantages. Functionalized graphene sheets, made by reduction of graphene oxide exhibiting sufficient structural defects and functional groups, show superior performance in electrochemical applications. In particular, the fast electron transfer property for some enzymes and excellent electrocatalytic ability to some biomolecules (hydrogen peroxide, NADH, and dopamine) of graphene makes it useful for enzyme-based biosensor (Shao et al., 2010). The high electron transferring ability of graphene causes high electron density over a wide energy range due to its distinct electronic structure (McCreery, 2008).

Among the graphene-based biosensors, solution gated graphene transistors (SGGTs) have acquired a great role in the real-time, high throughput and highly sensitive glucose detection (Yan et al., 2014). Detection of glucose level less than 0.1 mM can be done by biosensor based on SGGTs by modifying the graphene layers with GO enzyme (Huang et al., 2010). Later, an SGGT glucose sensor with GO immobilized on graphene channel having a detection limit in the range of 3.3–10.9 mM was proposed (Kwak et al., 2012). Recently, a new type of sensor based on graphene solution gated transistors (Fig. 12) was studied (Wang, 2008; Zhang et al., 2015a, 2015b, 2015c). The basic mechanism includes GO catalyzed the oxidation of glucose which generates H_2O_2 near the gate electrodes and oxidation of H_2O_2 which finally regulates the gate voltages. The method gives noninvasive glucose detection in human body fluids with detection limit less than 0.5 mM (Yamaguchi et al., 1998). Moreover, as a potentiometric transducer, the sensitivity of the system depends on transconductance (Khodagholy et al., 2013).

Table 2 concludes sensitivity and assay time of various nanobiosensors.

3. Biosensors for insulin

Insulin is a polypeptide hormone composed of 51 amino acid residues; chain A with 21 amino acid residues and chain B with 30 amino

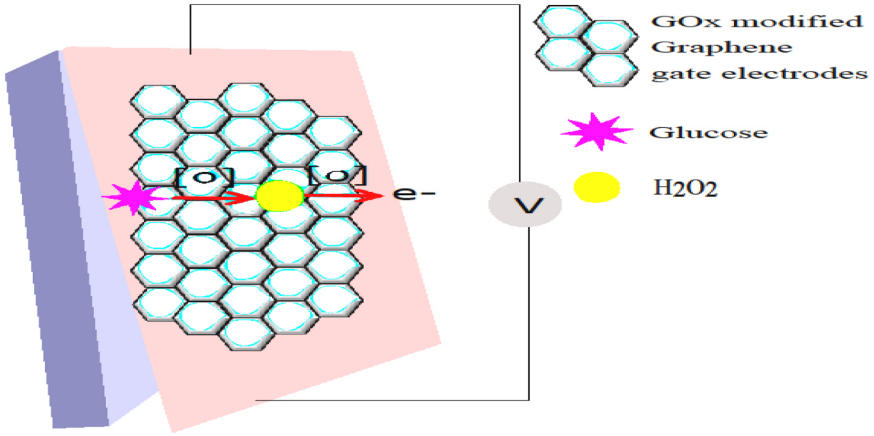

Fig. 12. Diagrammatic representation of SGGT glucose biosensor and the glucose oxidase catalyzed oxidation of glucose.

acid residues joined together by a disulfide linkage. Insulin plays a major role in glucose metabolism. The determination of insulin is of great value in the diagnosis of diabetes. Various methods have been devised for the detection of insulin, most of which are insensitive and laborious. Currently, the methods employed for the determination of insulin include bioassays, immunoassays, chromatography, surface plasma resonance (Frasconi et al., 2010), electrochemistry (Wang and Li, 2009), and flow injection analysis (Taghdisi et al., 2015). Despite the advancement and research in the fabrication of glucose biosensors, the progress in the development of insulin biosensors is still backward.

However, despite the high sensitivity offered by the biosensor, it offers certain demerits like labor intensiveness and long optimization curves. A low concentration of biomolecules can be determined by an array of the microfabricated biosensors (Wu et al., 2001). Recently it has been proved that fluorescence-based triple helix molecular switch containing target aptamer sequence results in a sensitive and rapid determination of insulin. The sensors show a low limit of detection and high selectivity (Taghdisi et al., 2015).

3.1. Label-free insulin detection

Current methodologies of protein assaying are hampered by the slow, complicated and fallible laboratory methods. A profound amount of biological markers are present in biological fluid even at low concentration, the evolution of a label-free method will enhance the future demand for the revelation of insulin in blood serum (Luo et al., 2013). Label-free nanosensors serve great potential in point of care diagnosis. Thus, it improves the real-time, ultrasensitive detection of multiple biomarkers in biological fluids. Label-free assays further offer advantages of decreased cost, decreased sample preparation time and potential reactions of chemical labeling. However, the presence of biofouling, non-specific binding, and the use of purified buffer reduces the significance of the biosensor (Stern et al., 2010).

Electrical assays offer a cheap and extremely sensitive multiplexed means of protein detection (Kimmel et al., 2012). Moreover, when tested in a reagentless manner, the assays are affected by the effect of specific signals when used to detect a target in the biological fluid. The problem can be overcome by the development of an insulin biosensor based on chemisorbed zwitterionic polymer support and a novel reagentless sensing technique based on phase monitoring electrochemical impedance spectroscopy (EIS) (Luo et al., 2013).

A sensitive method for the detection of insulin with a negligible nonspecific response by the construction of surface assembled and chemisorbed poly(carboxybetaine methacrylate) (PCBMA) polymer wherein the sensing signal is produced by the phase offset between the input voltage and output current. Zwitterionic polymers like PCBMA act as antifouling materials. EIS modality for analysis utilizes the application of a sinusoidal voltage which measures the associated current. The detection of protein takes place on the principle of formation of the double layer by the immersion of modified metal electrode in the electrolyte. The distraction of double layer and impendence characteristics occurs by any binding event that takes place at the surface. In order to overcome the problem of the nonspecific signal, use of a non-Faradic EIS will be helpful, wherein a low potential is enforced to the receptive electrode and a non-redox probe is added to the solution (Luo et al., 2013).

The fabrication of EIS based biosensor takes place in the following steps. A cysteamine adsorbed layer modified gold cathode is covalently altered with carboxyl-containing CBMA monomers with the help of EDC-NHS coupling. The connected monomers are then photopolymerized with arrangement stage monomers to frame a chemisorbed zwitterionic PCBMA polymer interface. This interface demonstrates fantastic stability. Finally, hostile to insulin antibodies, are the coupling of amides to the copious carboxyl gatherings of PCBMA, framing an antifouling responsive interface specific for insulin (Luo et al., 2013).

An ultrasensitive label-free electrochemical biosensor able to detect a picomolar concentration of insulin in blood serum is also available. The changes associated with binding of material to the electrode surface can be determined by electrochemical impendence spectroscopy. The level of polypeptide mediates the confinement of glucose to blood. Moreover, this facile impedimetric biosensor offers high selectivity and linearity (Xu et al., 2013). Recently, a label-free silicon-based optical biosensor containing antibody and an aptamer receptor motif has been fabricated for the determination of insulin. Antibodies possess a unique ability to bind target molecules. Moreover, they are mainly used as bioreceptors. Despite, they acquire certain advantages, there are certain limitations of high cost, large size, and instability. A promising alternative is an aptamer, which is a single-stranded DNA or RNA folded into specific conformation to imitate the function of an antibody (Mairal et al., 2008; Song et al., 2008). In the fabrication of this type of biosensor, the bioreactors covalently adhere to a thermally hydrosilylated surface through amide coupling. Incorporation of the PEG moieties makes the unreacted surface area stable and of low fouling effect. The insulin detection is finally carried out by interferometric reflectance spectroscopy which is comparatively superior in performance compared to other optical biosensing techniques. The capability of the aptamer modified surface to detect the presence of insulin secreted from the islets of a human donor upon stimulation of glucose was also evaluated. The study shows a good response to insulin detection (Chhasatia et al., 2017; Zhou et al., 2014).

3.2. Sandwich-type electrochemiluminescent (ECL) biosensors

A luminescence resonance energy transfer system (LRET) requires a good overlap between the donors and the acceptors. The three types of LRET, based on the luminescent type of donors are fluorescence resonance energy transfer (Shi et al., 2006), chemiluminescence resonance energy transfer (Wang, 2008; Zhang et al., 2015a, 2015b, 2015c), and bioluminescence resonance energy transfer (Zhao et al., 2010a, 2010b) plays a significant role in biomedical applications. An electrochemiluminescent (ECL) biosensor has been fabricated based on a novel ECL-RET strategy. In this strategy, carboxyl poly (9,9-dioctyfluorenyl-2,7-diyl) dots utilized as ECL donor and 3,4,9,10-perylenetetracarboxylic acid exploited as ECL acceptor and hydrogen peroxide as the co-reactant. The ECL donor and ECL acceptor were separately labeled with primary antibody and secondary antibody forming a sensing interface to the analyte target, insulin. The fabricated sensor exhibits excellent stability and sensitivity (Zhang et al., 2018).

Recently, a novel sandwich-type ECL biosensor with a linear response range of 0.1 pg mL^{-1} to 10.0 ng mL^{-1} and limit of detection 0.042 pg mL^{-1} having excellent stability and good specificity has been fabricated based on ECL resonance energy transfer from donor to acceptor. The metal-organic framework shows great potential insensing probe and catalysis. The unique properties of cyclodextrin include coordination ability, biocompatibility, and water solubility. Henceforth, the cyclodextrin-based metal organic framework can show great application biological sensing field; but the ECL emission behavior is less investigated. It is shown that Pb(II)-beta-cyclodextrin (PBCD) has fine ECL emission and sudden reducing capacity to $AuCl^{4-}$. Au nanoparticles-doped PBCCD metal-organic

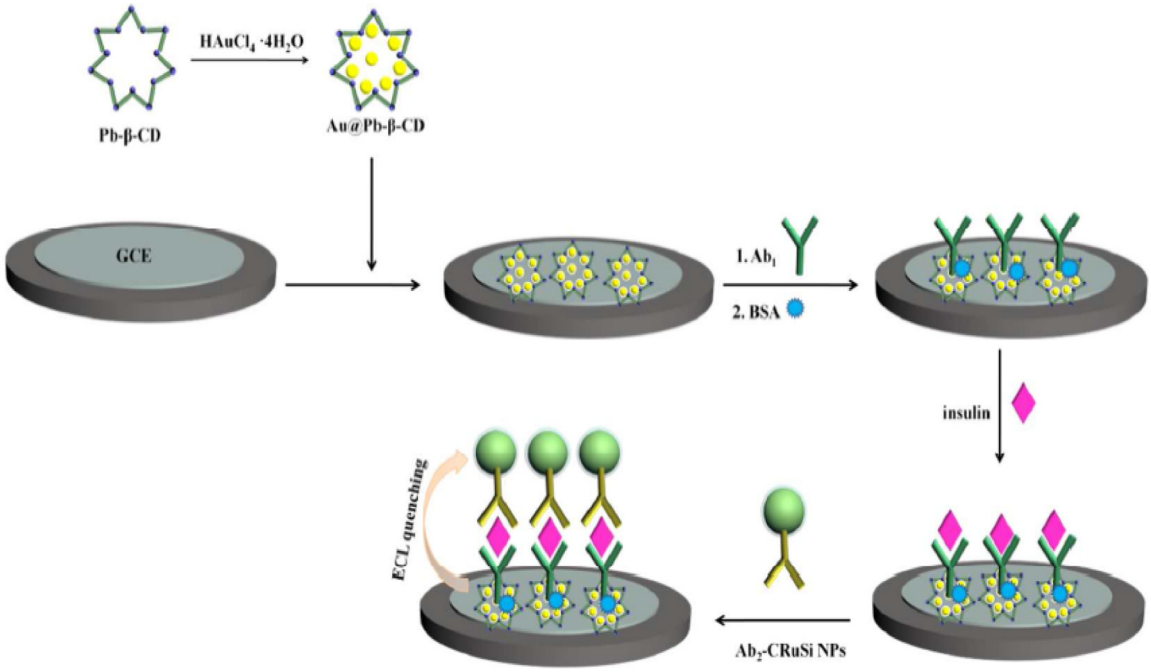

Fig. 13. Schematic illustration of the fabrication process of the immunosensor. "Reprinted with permission from (Ma et al., 2016). Copyright (2016) American Chemical Society.".

framework is exploited as ECL donor which is essential in the fabrication of an immunosensor (Ma et al., 2016).

Traditional luminescent reagent, $Ru(bpy)_3^{2+}$ has a few merits, like high emanation effectiveness, synthetic idleness, and great biocompatibility in ECL bioanalytical system. Chitosan/$Ru(bpy)_3^{2+}$/silica nanoparticles (CRS NPs) with steady ECL signals can be detected utilizing an ordinary emulsion method. The amino gatherings on chitosan empower the simple labeling of recognition antibodies with CRS NPs. Insulin can be delivered inside the body at a consistent extent to expel overabundant glucose from the blood and can be utilized therapeutically to treat a few types of diabetes mellitus. Consequently, building up another quick and delicate technique for the detection of insulin is exceptionally necessary. Recent studies proposed a RET procedure for recognition of insulin in view of the vitality exchange from Au@PBCD (ECL contributor) to CRS NPs (ECL acceptor). Au@PBCCD was kept on a terminal surface to immobilize essential counteracting agent (Ab1) through Au adsorbing proteins, framing a detecting surface to insulin antigen as shown in Fig. 13. At the point when the created immunosensor was concealed with insulin antigen arrangement and CRS NPs named optional counteracting agent (Ab_2-CRS NPs) arrangement in this manner, a momentous ECL reaction is acquired for quantitative recognition of insulin (Ma et al., 2016).

3.3. Aptamer-based electrochemical biosensors

The electrochemical aptamer-based sensor offers sensitivity and selectivity essential for clinical and medical diagnostics. DNA or RNA modified redox labeled aptamer is used as a biosensing probe capable of binding with great affinity to the target. The aptamer probe is immobilized on a gold electrode surface through alkanethiol ether and is enclosed in a self-assembled monolayer. The target binding triggers conformational or dynamic change is reflected as a change in redox current. Utilization of a 28-base DNA segment of the insulin-linked polymorphic region (ILPR), a natural aptamer can selectively capture insulin. ILPR, a stretch of tandem repeats which bind with high affinity to insulin is located on the upstream coding region of the insulin gene. In-1T, a sensor construct is associated with internal thymine present in the sequence (Gerasimov et al., 2013).

G-quadruplex is formed by two or more tandem repeats of IPLR (Williamson, 1994). The ILPR G-quadruplex partition mutually between the parallel and antiparallel conformations both of which offers high stability at room temperature (Xiao et al., 2009). In the polymorphism studies of ILPR, high affinity for insulin is observed for antiparallel conformation. A problem associated with designing of a biosensor is the potential loss of high-affinity conformation when conjugated with the label and linker (Schonhoft et al., 2010).

To integrate a solution probe sequence for application in surface-based electrochemical biosensing it is necessary to study the DNA modification effect which can be carried out by circular dichroism (CD) spectroscopy. Studies report that the sequence property to bind to the target is altered by the presence or absence of certain cations that play a great role in the formation of G-quadruplex. The effect can be studied by observing the CD spectrum of each probe in Na^+ buffer and K^+ buffer. Both parallel and antiparallel conformations are highly stable, with the kinetic limitation of transition between these two forms at room temperature. The secondary structure of DNA is denatured by heating to 95 °C. The probe assumes conformations favored in experimental condition on cooling (Gerasimov et al., 2013).

The results obtained from studies show that the parallel G-quadruplex conformation in IPLR sequence is stabilized by K^+ buffer. In the absence of K^+, the antiparallel conformation is more stable, as proved by the increase in CD spectrum intensity at 295 nm for the In-IT sequence. The CD spectral analysis reports the fact that probe architecture occupies a major role in the extent of structural switching (Gerasimov

Table 1
Comparison of various biosensors for glucose and insulin.

Type of biosensor	Detection mechanism	Advantages	Disadvantages	Example	Reference
Glucose biosensors					
Electrochemical glucose biosensor	Detection of electrochemical signals produced during biointeractions	High selectivity, low price, ability to withstand high pH, temperature, and ionic strength	Oxygen interference, redox interference ein 1st generation glucose biosensor	GO immobilised on polystyrene latex bead	Rakhi et al. (2016)
Non- enzymatic glucose biosensor	Oxidation of glucose using metal oxide catalyst	Eliminated drift,	Less accepted due to large size	Cupric oxide nanoparticle modified MWNT array electrode	Jiang and Zhang (2010)
Optical biosensor	Measures optical property (Especially fluorescence)	Reproducibility, sensitivity, selectivity	Fabrication is limited to optical materials	Optical biosensor based on FT-IR spectroscopy	Saiki et al. (2007)
Implantable continuous glucose monitoring biosensors	Electrochemical detection	Continuos monitoring gives valid response, long term stability,	Enzyme deactivation process limits the lifetime	Implantable glucose sensor with GO immobilized on fine graphite powder	Atanasov and Wilkins (1994)
Non-invasive glucose monitoring systems	Measuring the concentration of gas present in the exhaled air.	Real time glucose sensing, Non-invasive, self monitoring by patients	Low sensitivity	Metal oxide gas sensor	Yadav and Manjhi (2014)
Metal NP based nanobiosensor	Electrochemical detection	High stability, good reproducibility	Reproducibility, toxicity effect of metal core	Immobilization of GO on gold nanoparticle monolayer modified gold electrode.	Zhang et al. (2005)
Magnetic NP based nanobiosensor	Redox reaction	Biocompatibility, low toxicity, and excellent super paramagnetic property of magnetic nanoparticles	Need surface modification, difficulty in synthesis.	GO immobilized on C/ $NiFe_2O_4$NPs	Kaushik et al. (2008)
Nanofiber based nanobiosensor	Electrochemical amperometric detection	Easily functionalizable, biocompatible, conductive, and possess large surface area.	Toxic feature of electrospun nanofibers	Nitrogen-doped carbon nanofiber	Vamvakaki et al. (2006)
Nanorod based nanobiosensor	Electrochemical detection	ZnO nano rod have high affinity towards oxygen species, cost effective, authentic, accuracy,reproducibility, fast response, harmless, easy fabrication, sensitivity.	Poor stability, fabrication difficulty.	ZnO nano rod based nanobiosensor	Bhattacharya et al. (2012); Kong et al. (2009)
Nanowire based nanobiosensor	Electrochemical detection	high sensitivity of 19.5 $\mu AmM^{-1}\,cm^{-2}$ with a detection limit of less than 5 s, long term stability and good anti-interference.	Analytical signal intensity is too low.	ZnO nanowire	Wang et al. (2009)
Nano composite based nanobiosensor	Electrochemical detection	Increased storage time, decreased interference, response within 3 s, good reproducibility and stability	Complex synthetic procedure.	MWCNT-Nafion-GOD nanobiocomposite films	Lim et al. (2005)
Quantum dot based nanobiosensor	Photoluminescene	Superior luminescent property, simple design, high surface charge density, fast response of less than 2 s, good sensitivity, selectivity, repeatability, negligible interference, portable sensor system, easy integration, good stability.	Toxic elements like Cd cause cytotoxicity	Mn-doped ZnS QD	Ma and Su (2011)
Carbon nanotube based nanobiosensor	Electrochemical detection	Enzyme free glucose biosensor, detect with picomolar sensitivity, high selectivity, sensitivity.	Non-functionalized CNT show toxicity to cells, Integration of CNT into biosensing electrode is challenging.	CNT/Nafion/GO	Punbusayakul (2012)
Graphene associated nanobiosensor	Electrochemical detection	Ease of processing, safety, low cost, high surface area, high electron transfer rate, water soluble, biocompatible, exhibits more surface functional groups.	Reproducibility is difficult, well controlled synthesis and processing of graphene is a great challenge.	solution gated graphene transistors	Shao et al. (2010)
Insulin biosensors					
Label-free insulin detection	Label free detection of insulin	Decreased cost and sample time preparation	Instabilty, Non-specific bounding	Label-free silicon-based optical biosensor	Mairal et al. (2008)
Sandwich-type electrochemiluminescent biosensor	Luminescence resonance energy transfer	Sensitivity, selectivity and stability	Fabrication is limited to luminescent materials	Au@PBCD- CRS NP biosensor	Ma et al. (2016)
Aptamer based electrochemical biosensor	An aptamer having affinity to insulin used as biosensing probe, and is immobilised on an electrode. Presence of insulin changes redox current	High specificity	Potential loss of high affinity conformation when conjugated with label & linker	ILPR aptamer based insulin sensor	Gerasimov et al. (2013)

Table 2
Characteristics of some glucose and insulin biosensors.

Type of sensor	Sensitivity	Assay time	Reference
Biosensors for glucose			
Biosensor based on transducing element			
Enzymatic glucose biosensor (Electrochemical)	9.3 μA mM^{-1} cm^{-2}	–	Rafighi et al. (2016)
Non-enzymatic glucose biosensor (Electrochemical)	2596 μA mM^{-1} cm^{-2}	1 s	Jiang and Zhang (2010)
Optical biosensor	9044.6 μA mM^{-1} cm^{-2}	–	Anderson et al. (2017)
Biosensor based on clinical application			
Continuous glucose monitoring biosensors	12 nm mM^{-1}	1 s	Elsherif et al. (2018)
Non-invasive glucose monitoring systems	26.6 μA/mM-cm^2	–	Wang (2008); Zhang et al. (2015a, 2015b, 2015c)
Nanobiosensors			
Magnetic nanocomposite based sensor of ferric oxide NP in chitosan on inidium tin oxide glass plate	9.3 μA/(mgdLcm^2)	5 s	Kaushik et al. (2008)
ZnO nanorod based sensor	10.9111 mA mM^{-1} cm^2	3 s	Marie et al. (2015)
ZnO nanowire sensor	19.5 μAmM^{-1} cm^{-2}	< 5 s	Pradhan et al. (2010)
Gold nanoparticle decorated platinum nanowire sensor	135.5 μAmM^{-1} cm^{-2}	< 5 s	Wang et al. (2009)
MWCNT-Nafion-GOD nano biocomposite film based sensor	330 nA/mM	< 3 s	Tsai et al. (2005)
MWCNT modified glassy carbon electrode sensor	17.76 μAmM^{-1}	< 5 s	Kang et al. (2007)
Graphene/AuNPs/chitosan	99.5 μAmM^{-1} cm^{-2}	–	Shan et al. (2010)
CNT/Pt nanoparticle immobilised with BSA sensor	70 μA mM^{-1}/cm^2	8 s	Claussen et al. (2010)
Biosensors for insulin			
Label-free insulin detection	LOD = 42.6 fM	–	Luo et al. (2013)
Sandwich-type electrochemiluminescent biosensor	LOD = 0.042 pg mL^{-1}	–	Ma et al. (2016)
Aptamer-based electrochemical biosensor	LOD = 0.27nmolL^{-1}	–	Ensafi et al. (2017)

et al., 2013). Development of G-quadruplex is fast, but the conformational change between the parallel and antiparallel conformation is slow and is modulated by the unfolding step (Wang and Patel, 1992). In-IT sensor has high sensitivity, good selectivity, stability, and more importantly, sensor reproducibility sensor.

Earlier it was seen that binding to insulin results in the full formation of G-quadruplex at room temperature. CD spectral analysis is done to determine the binding-induced conformational change of probe in presence of insulin. The essential rule is that in the event that a test is weakened in half, the so formed CD peaks display half the intensity observed in the CD spectrum of the undiluted test. Insulin binding aptamer IGA3 can form anti-parallel G-quadruplex having the ability to bind with hemin and can exhibit peroxidase activity. The IGA3 was then immobilized on to the gold electrode. The peroxidase action of IGA3 immobilized hemin complex was further analyzed by cyclic voltammetry, where the cathodic current decreases in response to binding to insulin (Kubo and Eguchi, 2015). Recently, a poly-ortho-phenylenediamine substrate decorated with gold nanoparticles and then with single-stranded DNA aptamer immobilized on the surface of a pencil graphite electrode facilitated the effective determination of insulin in plasma and urine (Ensafi et al., 2017).

A comparison of various biosensors for glucose and insulin reviewed in previous sections is given in Table 1. Meanwhile, Table 2 provides the characteristics of some glucose and insulin biosensors in terms of sensitivity/LOD and assay time. Additionally, Table 3 presents a summary of very recent reports on glucose and insulin biosensors.

4. Conclusion and future prospects

Over the last 40 years, there has been tremendous progress in the development of biosensors. Enhancement and improvement in glucose detection are carried out by modification of the electrode surface. Highly sensitive aptamer-based insulin biosensors have been developed. Label-free detection of insulin at picomolar concentration is helpful in the determination of insulin and offer many advantages. The regulation of the sensing device has been possible at the molecular level with the application of nanotechnology.

Studies are still progressing for the development of improved biosensors for glucose and insulin. From a manufacturing point of view, the sensor should be cheap and capable of mass production. Furthermore, the biological components should be stable in operation and storage. Finally, all components should be integrated into a single system which ensures ease of use. Development needs to be carried out in the fabrication of handheld diagnostic tools having the ability to analyze multiple components and to monitor other components in addition to glucose. In addition, efforts need to be provided in the field of nanotechnology and microfluidic technology for the development of biosensor with advanced characteristics in an automated fashion. They would enable the routine check at home easier as well as for the identification of abnormalities at an early stage.

Despite the tremendous improvement in the advancement of an accurate and reliable glucose monitoring system, many challenges need to be overcome to develop an accurate system in the real world application. Likewise, there is an increased need in the development of insulin biosensor which detects insulin in physiological range without complex process. Technical improvement in glucose biosensor, continuous assessment and training lay users should be achieved. Most of the methods are less accurate compared to that used in central laboratories. Calibration of the device and quality control should be carried out to meet good performance. Moreover, the commercialization of the biosensor is at its lowest point. System integration is one of the most critical challenges in biosensor technology. If all the challenges are met, the movement of biosensor from the research field to the clinical area can be achieved. The biosensors thus could offer a promising area of research in the future years. Moreover, the precise and convenient monitoring and control of diabetes mellitus can be a reality in the near future.

Table 3
Recent reports on glucose and insulin biosensors.

Sl. No.	Biosensor	Features	Reference
Glucose			
1	Carbon-dot-based ratiometric fluorescence glucose biosensor	LOD = 30 nM	Cho and Park (2019)
2	Laser-scribed carbon paper substrate based non-enzymatic glucose biosensor	Sensitivity = 3626.6 μA mM^{-1} cm^{-2} LOD= 30 nM	Hou et al. (2019)
3	Bio-derived nitrogen-doped carbon sheets wrapped titanium dioxide nanoparticles based glucose biosensor	LOD= 13 nM	Atchudan et al. (2019)
4	Nitrogen-doped graphene based glucose biosensor	LOD = 14.52 Mm Sensitivity = 774.23 Ma mM^{-1} cm^{-2}	Rahsepar et al. (2019)
5	Palladium nickel/activated carbon nanocomposites based glucose biosensor	LOD = 0.014 Mm Sensitivity = 90 mA mM^{-1} cm^{-2}	Koskun et al. (2018)
6	Polyaniline nanorods based glucose biosensor	Sensitivity = 486 μAmM^{-1} cm^{-2} LOD = 4 μM	Palsaniya et al. (2019)
7	Metal wire networks functionalized with nickel alkanethiolate based glucose biosensor	Sensitivity = 675.97 μAmM^{-1} cm^{-2} LOD = 2.2 μM	Urgunde et al. (2018)
8	Layered double hydroxide combined with carbon nanomaterial composites glucose biosensor	Sensitivity = 2.6 A M^{-1} cm^{-2} LOD = 0.6 μM	Gualandi et al. (2019)
9	Poly(3,4-ethylenedioxythiophene) nanofiber based glucose biosensor	Sensitivity = 272.58 μmM^{-1} cm^{-2} LOD = 67.8 μM	Cetin and Camurlu (2018)
10	Manganese dioxide nanoparticles decorated on graphene nanoribbons based glucose biosensor	LOD = 0.05 mmol/l Sensitivity = 56.32 μA/mmol cm^2	Vukojević et al. (2018)
11	Cadmium sulfide quantum dots based glucose biosensor	LOD = 31 μM	Ngamdee and Ngeontae (2018)
12	Lutetium bis-phthalocyanine incorporated silica-polyaniline based glucose biosensor	LOD = 0.1 mM sensitivity = 38.53 μA mM^{-1} cm^{-2}	Al-Sagur et al. (2018)
13	Mucin and carbon nanotube-based biosensor	Sensitivity = 0.44 ± 0.01 mA M^{-1}	Comba et al. (2018)
14	Titanium carbide–carbon nanofibers based glucose biosensor	LOD = 3.7 μM	Guo et al. (2018)
15	DVD-laser scribed graphene substrate based glucose biosensor	Sensitivity = 1.518 mA mM^{-1} cm^{-2} LOD = 0.35 μM	Lin et al. (2018)
16	$Nico_2o_4$ nanoneedle-decorated electrospun carbon nanofiber nanohybrids based glucose biosensor	LOD = 1.5 μM Sensitivity= 1947.2 μA mM^{-1} cm^{-2}	Liu et al. (2018)
17	Nio quantum dots modified zno nanorods based glucose biosensor	Sensitivity = 13.14 μA cm^{-2} mM^{-1}	Jung et al. (2018)
18	Graphene oxide/silver coated polymer cladding silica fiber based glucose biosensor	Sensitivity = 0.4985 nm/(μg/mL) LOD = 0.04 μg/mL	Wang et al. (2018)
19	Porous $nite_2$ nanosheet array based glucose biosensor	LOD = 0.12 μM Sensitivity = 5146 mA mM^{-1} cm^{-2}	Li et al. (2018b)
20	Ag@ZIF-67 nanocomposite based glucose biosensor	Sensitivity = 0.379 μA μM^{-1} cm^{-2} LOD = 0.66 μM	Meng et al. (2018)
21	3D graphene aerogels decorated with Ni_3N nanoparticles based glucose biosensor	LOD = 0.1–7645.3 Mm Sensitivity = 905.6 μA mM^{-1} cm^{-2}	Yin et al. (2018)
22	Carbon nano-onions based glucose biosensor	Sensitivity = 21.6 μA mM^{-1} cm^{-2}	Mohapatra et al. (2018)
23	Ag@tio_2 core shell nanostructure based glucose biosensor	Sensitivity= 1968.72 μA m M^{-1} cm^{-2} LOD = 0.19 μM	Dayakar et al. (2018)
24	$Ni(OH)_2$ @PEDOT-rgo nanocomposite based glucose biosensor	LOD= 0.6 μM Sensitivity = 346 μA mM^{-1} cm^{-2}	Sheng et al. (2018)
25	Hydrothermally grown zinc oxide nanorods based glucose biosensor	Sensitivity = 48.75 μA mM^{-1}	Ridhuan et al. (2018)
Insulin			
1	Photoelectrochemical immunosensor for insulin detection	LOD = 0.03 pg mL^{-1}	Wang et al. (2018)
2	Molecularly imprinted polymer based quartz crystal microbalance sensor	LOD= 0.00158 ng/mL LOQ = 0.0198 ng/mL	Kartal et al. (2019)
3	Zinc silicate spheres-palladium nanoparticles based insulin immunosensor	LOD = 0.25 fg mL^{-1}	Li et al. (2018b)

CRediT authorship contribution statement

Chinnu Sabu: Conceptualization, Writing- Original draft preparation, Writing- Reviewing and Editing. **T. K. Henna:** Writing- Original draft preparation, Writing- Reviewing and Editing. **V. R. Raphey:** Writing- Original draft preparation, Writing- Reviewing and Editing. **K. P. Nivitha:** Writing- Original draft preparation, Writing- Reviewing and Editing. **K. Pramod:** Conceptualization, Writing- Original draft preparation, Writing- Reviewing and Editing, Supervision.

Declaration of interests

None.

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