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Review

Review on synthesis of ferrocene-based redox polymers and derivatives and their application in glucose sensing

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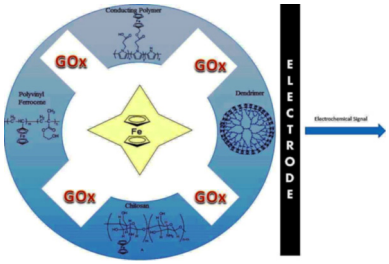
HIGHLIGHTS

- Synthesis and analytical performance of ferrocene as redox mediators were discussed.
- Key features are their stability and excellent redox properties.
- Applications of ferrocene-based polymers in other biosensors were briefly mentioned.
- Challenges in this field and future trend were discussed.

GRAPHICAL ABSTRACT



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ABSTRACT

The interest in glucose biosensors persisted over many years and persistent efforts have been made to develop long term stable glucose biosensors with precision, smart analytical performance, good linearity and resistance to communal interferences. In this regard, ferrocene-based polymers and derivatives (FBPDs) for the development of glucose biosensor (GBs) as redox mediators have acquired utmost attention of the scientists, especially in the second generation biosensors, as a large number of innovative molecules have been synthesized. Most of the FBPDs are considered as active components in the development of GBs, due to their ease of modification, biocompatibility, stability, large surface area, good electrical conductivity and especially excellent redox properties. This review provides a brief description of synthesis, analytical performance and glucose sensing application of ferrocene-based dendrimers, polythiophenes, polypyrroles, polyethylenimine, chitosan and carbon nano tubes (CNTs). Moreover, the analytical performance of ferrocene-based glucose biosensors (FBGBs) is summarized and the problems associated with the construction of GBs and the future trends are discussed.

Contents

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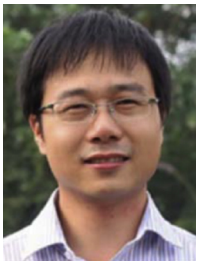

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1. Introduction

Diabetes mellitus, a disorder in glucose regulation accompanied by the increase of glucose concentration in the blood, has become one of the leading health fears worldwide. With prompt increase in diabetic patient worldwide, diabetes is anticipated up to 366 million by 2030 [1,2]. The careful and precise checking of blood glucose level greatly reduces the threat of diabetes mellitus [3]. Thus, diagnosis and monitoring need a stringent checking of blood glucose level. Subsequently, millions of diabetic patients check their level of glucose in blood every day, which makes glucose an important daily used analyte. Electrochemical biosensors including amperometric, potentiometric, impedimetric or conductometric are commonly based on sensing [4–6]. Due to easily available commercial devices, enzymatic amperometric glucose biosensors were studied extensively from the last five decades, in which amperometric sensors (AS) work by the electrons exchange between biological organization and electrode [7,8]. Commonly, the amount of glucose depends on the interactions among glucose-1-dehydrogenase, hexokinase or glucose oxidase (GOx) enzymes [9,10]. GOx is atypical enzyme for biosensors owing to its impartial high selectivity for glucose and resistance for temperature extremes, ionic strength, and pH, thus permitting less rigorous environment during built-up process [11,12]. Clark and Lyons reported biosensors which gained considerable attention in which GOx thin layer was entangled on oxygen electrode by a semi-permeable membrane [13]. The maximum numbers of initial GBs are built on the amperometric assessment of hydrogen peroxide (H_2O_2) formation or oxygen (O_2) used during enzymatic oxidation of glucose by GOx [14].

As discussed above, the concentration of glucose was monitored indirectly by checking O_2 spent by GOx during the enzyme catalysis. Additional developments on this plan directed to the progress of the first useful glucose biosensors (GBs), which can measure the produced amount of H_2O_2 [15]. However, the measurement of H_2O_2 by a commonly used platinum electrode needs a high potential (~0.6 V vs Ag/AgCl) which culminate to the risk of interference with ascorbic acid and uric acid electroactive moieties present inside the blood models [16]. In 1980s "second generation" glucose biosensors were developed. These sensors used minor and synthetic electron transfer mediators, instead of O_2 as electron acceptors as a mean of transporting electrons amongst enzyme active sites and electrode surface. Mediators ($Med_{ox./red.}$), tiny molecules of low redox potential can transport electrons between enzyme and electrode. The general scheme for the sensing mechanism is given as follows [17]:

$$\text{Glucose} + \text{GOx (FAD)} \rightarrow \text{GOx (FADH}_2\text{)} + \text{Glucolactone}$$

$$\text{GOx (FADH}_2\text{)} + 2\text{Med}_{ox.} \rightarrow \text{GOx (FAD)} + 2\text{H}^+ + 2\text{Med}_{red.}$$

$$2\text{Med}_{red.} \rightarrow 2\text{Med}_{ox.} + 2\text{e}^- \text{ (at electrode surface)}$$

Numerous electron mediators, such as tetracyanoquinodimethane (TCNQ), ferricyanide, quinines, tetrathialfulvalene (TTF), methyl viologen, methylene blue, thionine and ferrocene, have been cast off to increase performance of sensor [18,19]. Among all these mediators, ferrocene was found to be more suitable and fit to all benchmarks for a good mediator, as it does not respond with O_2, independent of pH, stable in oxidized as well as reduced forms, shows reversible electron transfer kinetics and responds fast when interacted with the enzyme [19]. FBPDs remained commonly considered electron transporting mediators between GOx and electrodes [18,20]. The function of electrode is to detect the quantity of electrons transferred, and this electrons transfer is comparative to the amount of glucose present in the blood [21].

Electrical interaction between redox enzymes electrode supports is key factor in constructing an enzyme based biosensors [22,23]. Nevertheless, shielding of the redox active sites by the protein shells blocks uninterrupted electron transmission between the enzyme and unchanged electrode [24].

Redox mediators can be possibly used to detect glucose at low potentials with greater sensitivity and accuracy in the blood glucose levels. Fig. 1 [25] shows general working mechanism in detail for ferrocene-based mediators (Fc-MET) on the electrode surface for signal generation mechanism. In this mechanism, the enzyme implicates in the redox reaction by means of the substrate and then reoxidised by Fc-MET, which consecutively is restored. The mediators circulate constantly between the enzyme as well as electrode, which ascribed to its cycle between oxidised and reduced states, creating catalytic current, accordingly. For procurement of an efficient electron-transfer biosensing system, redox mediators are added to a polymeric material pasted on an electrode surface considered as a smart technique [26,27]. Since FBPDs are frequently employed as mediators to transport electrons among oxidoreductases and electrodes [19,28,29].

Therefore, FBPDs are extensively cast off in the building and development of glucose biosensors. In 1984, ferrocene derivatives as GOx mediators were stated [18] and up to now, more than 9000 articles related to FBGBs are reported. Such enormous contribution of ferrocene in the development of glucose biosensors clearly highlights its importance. Numeral of glucose sensor related articles have kept an increasing drift from 3000 to 9000 over the last 10 years [30], but to the best of our knowledge, no review article is available so far which summarizes FBPDs for application in glucose sensing. The purpose of this review is to offer an outline about the synthesis of FBPDs for their application in glucose biosensors.

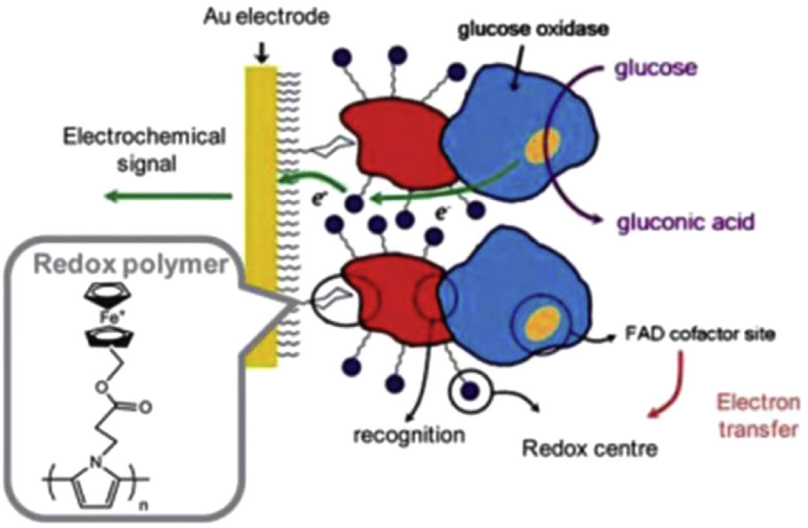


Fig. 1. Signal generation mechanism of glucose electrochemical GBs, reprinted with the permission of Ref. [25].

2. Synthesis of ferrocene-based polymers and derivatives

In 1951 ferrocene (Fc) was discovered [31,32] and its exact structure was explicated by Wilkinson et al. [33]. The similarity of its reactivity to benzene motivated the scientists to name this new iron sandwiched compound as ferrocene [33]. The structure disclosure of Fc was a breakthrough in the realm of chemistry, and steered to the birth of recent organometallic chemistry. Ferrocene rapidly attracted thoughtfulness of the scientist and technical communities on expenses of its charming chemistry. Researchers started to develop synthetic approaches using ferrocene derivatives, and discovered their uses in extensive array of scientific zones. From 1984 to till now numerous categories of ferrocenyl compounds have been produced and assessed for their glucose sensing applications. The following section of this review describes the synthesis of FBPDs that have been elucidated for glucose sensing application.

2.1. Ferrocene-based polypyrroles and polythiophenes

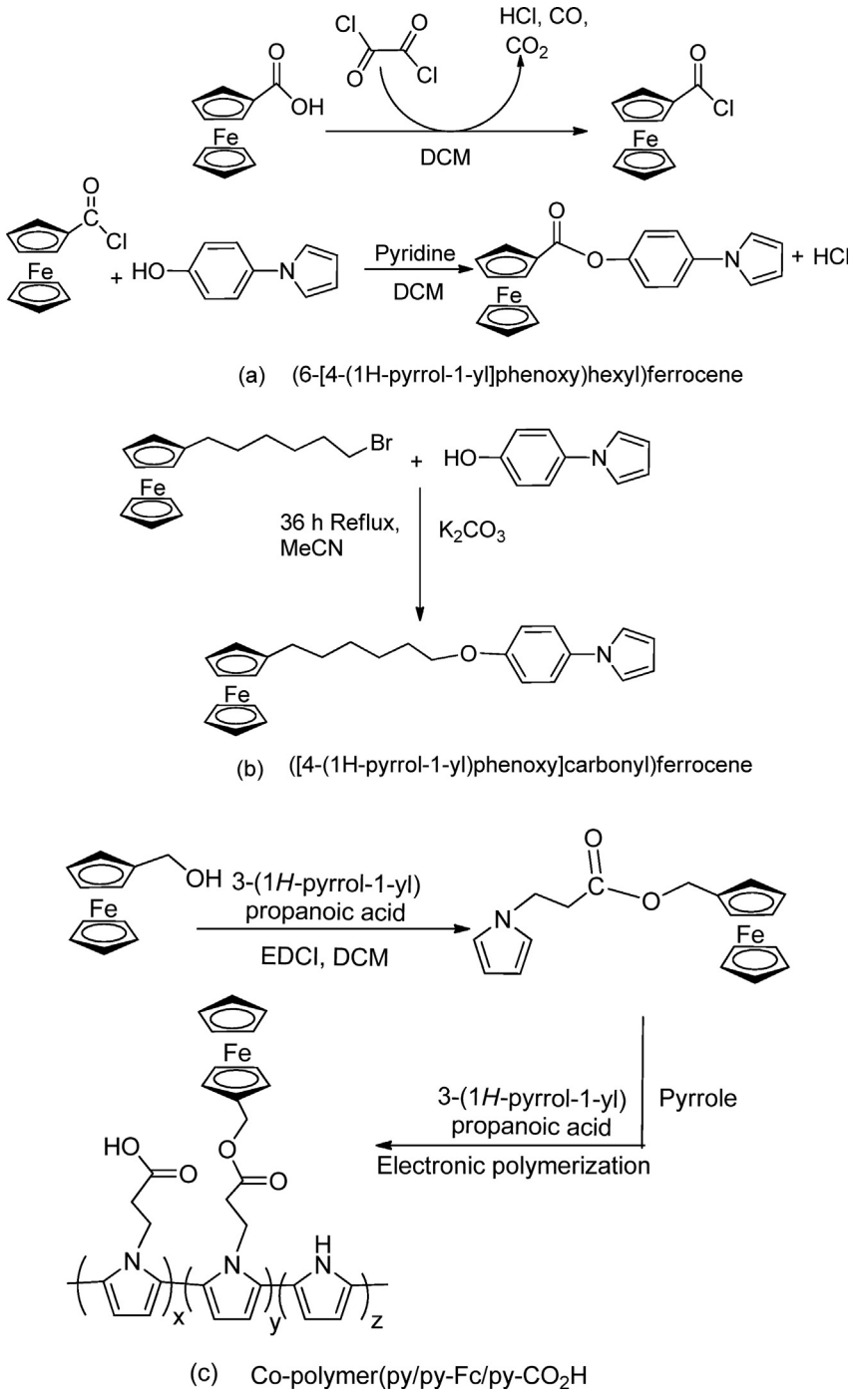
The improvement of several conjugated polymers in the past few decades has steered to processable materials with stimulating electronic and optical properties [34–36]. Among conjugated polymers polypyrroles [37], polythiophenes [38] and substituted polythiophenes (PTs) [39] have attracted much attention, while ferrocene-substituted thiophene and terthiophene were pronounced as possible biosensor compounds [12]. Ferrocene-based pyrrole for better electronic communication in glucose sensing [40] and electrochemical copolymerization of thiophene-3-acetic acid, thiophene and dicyclopentadienyl iron-1, 4-dienylmethyl-2-(thiophen-3-yl) acetate, in the form of films for fabricating GOx-immobilized electrodes [17] have been reported. The formation of dynamic active redox species inside polymer films unlocks potentials for the design mode of electronic communication between electrode surfaces and immobilized enzymes [41].

Functionalized polypyrrole dendrimers combined electronic conductivity of the conducting polymer with the redox properties of ferrocene to mediate electron transfer reactions and improved sensing behavior. Palomera et al. reported the synthesis of mediator-less co-polymer (electrochemical biosensor) of pyrrole and ferrocenecarboxylate modified pyrrole by electropolymerization method [42].

Functionalized polypyrrole materials are easy to deposit from non-aqueous electrolytes and have potential applications in electronic or sensor devices. Senel reported the synthesis of copolymer (ferrocene branched polypyrrole) by condensation between ferrocene ethanol, 3-(1H-pyrrol-1-yl) propanoic acid, ferrocene-pyrrole and 3-(1H-pyrrol-1-yl) propanoic acid [43]. Furthermore, Soon et al. reported the synthesis of ferrocene-based pyrrole derivatives with differing spacer linkages by coupling reactions (Scheme 1) [44]. With the use of ferrocene-based pyrrole derivatives, it was found that film growth using potential sweeping was the most suitable for adherent film formation with well-defined redox electrochemistry and surface confined behavior. Moreover, advantageous feature of these functionalized polypyrrole materials were easy to deposit from non-aqueous electrolytes and have potential applications in electronic or sensor devices.

2.2. Ferrocene-based cyclodextrin

Cyclodextrins (CDs) are well-known for insertion complexes formation in aqueous media by a great variety of hydrophobic organic molecules [45]. FBPDs have been used for strong inclusion complexes formation with CDs in electrochemistry [46–49] with enhanced solubility, bioavailability and electrostability [50]. Fc derivatives with different solubility and charges have been established in the application of electrochemistry [18], but use of hazardous chemicals during preparation made these methods complicated. This problem can be solved by forming inclusion complexes of Fc with cyclodextrins (CDs). Several studies were reported about Fc with CDs to enhance the addition's solubility [51,52], but the limited solubility of host CDs curtails the application of Fc in aqueous media. Therefore, a highly water soluble host is a primal factor to extensive aqueous phase applications of Fc. Facile strategies using partial oxidation of β-CD were designed for preparation of water-soluble β-CD derivatives [53]. The breaking of the intramolecular hydrogen bonding network can efficiently increase the solubility of carbonyl-β-cyclodextrin. However, the more positive cavity of β-CD (20 mV) than Fc hindered the electron transfer between Fc and electrode surface, but incorporation of CNTs overcomes the hindrance problem by elevation of electron transfer between Fc-CD complex and electrode surface [54]. Casas-Solvas et al. reported on synthesis of Fc–bis (β-CD) and Fc–β-CD



Scheme 1. Synthesis of (a) (6-[4-(1H-pyrrol-1-yl]phenoxy) hexyl) ferrocene [44], (b) ([4-(1H-pyrrol-1-yl) phenoxy] carbonyl) ferrocene [42] and (c) pyrrole co-polymer (py/py-Fc/py-CO_2H) [43].

conjugatesusing click chemistry by azido Fc derivatives and β-CD monopropargylated at O_2. These two conjugates containing Fc core with one β-CD unit linked by its secondary face to one or both of the cyclopentadienyl rings [45]. Tan et al. also synthesized Fc–β-CD based supramolecular hydrogel and achieved good glucose response after immobilizing GOx [55].

2.3. Ferrocene-based polyethylenimine

Lan's group reported on the synthesis of linear polyethyleneimine (LPEI) and branched polyethyleneimine (BPEI) based ferrocene redox polymers, that can be simply modified to produce facile mediator carriers and enzyme owing to greater concentration of primary amino groups on BPEI. Another important feature they have stated about BPEI is the elastic nature of its backbone playing a vital role for facile electron transport between enzyme and electrode [56]. Schmidtke's group also reported LPEI and BPEI based Fc redox polymers accomplished of electrically interactive redox centers of enzymes and explained multiwave redox behavior of redox polymer films which is dependent upon electrolyte, pH and cross-linking degree [57].

Wang et al. synthesized branched polyethylenimine attached with ferrocene (BPEI-Fc) by simple coupling of ferrocenecarboxaldehyde to BPEI (Fig. 2) [58].

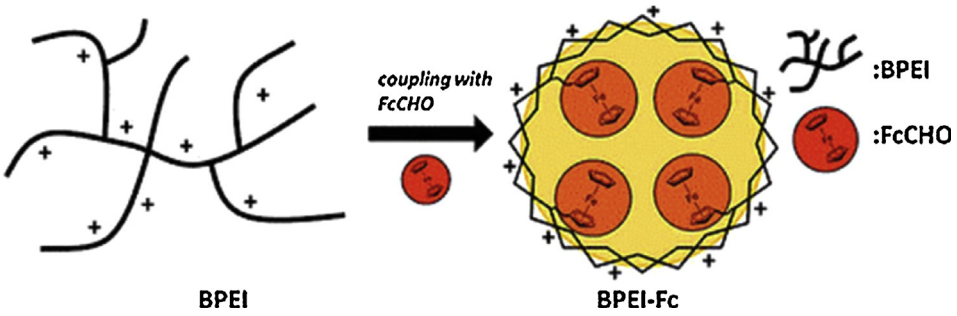


Fig. 2. The formation of the BPEI-Fc, reprinted with the permission of Ref. [58].

2.4. Ferrocene-based dendrimers

Dendrimers are distinct functionalized macromolecules with extremely branched design, created by continues reaction sequences. These materials have gained substantial attention in the past few years due to their lightening-like patterns present in the macromolecules, controllable peripheral functionality, controllable microenvironment around the dendritic core and other valued properties which make them favorable for a range of applications [59,60]. High molecular weight ferrocenyl silicon dendrimers with ferrocenyl units at the margin of long elastic branches containing silicon (Scheme 2) as 1–4 dendritic molecules were synthesized by the multi electron-transfer redox reactions [61] and a biosensor application was studied [62]. Increased mediating ability was observed from the dendrimers in which ferrocenyl units were attached to the dendritic framework through two methylene chain. Patently flexibility, as a function of the chain size and spaces between ferrocenes [63–69], is a major factor in helping transfer the electrons from reduced enzyme due to slight energy obstacle, which leads to more efficient communication between dendritic systems and enzyme molecules.

Dendrimers bearing long organosilicon branches possesses good sensitivity and can function efficiently at small, applied potential as compared to fewer branched dendrimers. Siloxane based copolymer comprising suspended dendritic segments with electronically connected to ferrocenyl moieties was reported for development of GOx-based biosensors immobilized onto ferrocene-modified electrodes [70]. Deriu et al. reported (G4-PAMAM) which was functionalized chemically by Fc chained groups [71]. Further development in application of dendrimers biosensors was reported as electrocatalytical properties of polymethylferrocenyl dendrimers [72,73].

Recently, instead of covalent attachment of ferrocene onto electrode surface, a dendritic network was developed [74] and new redox active ferrocene-based PAMAM dendrimers were produced, for the creation of amperometric biosensor to enhance binding affinity of primary amines on dendrimer surfaces. Synthetic strategy of these dendrimers includes preliminary Michael reaction of ferrocene-based amine with methyl methacrylate (MMA) tailed by amidation of the resultant esters by addition of ethylenediamine to produce dendrimers. The dendrimers consisting of ferrocene at the sideline were cast off through covalent binding with coupling agent to alter artificial redox protein implanted gold electrode and later GOx was covalently immobilized on the pre-modified gold electrode [74].

2.5. Ferrocene-based polyvinylferrocene

Modified electrodes comprising of Fc-based polymer films, for instance polyvinylferrocene, have gained considerable attention in rapid heterogeneous electron-transfer rates. Electrochemical deposition of PVF on carbon electrode as a mediator was reported by Nguyen and Luong [75]. Further Kuramoto et al. [76] and Kuramoto and Shishido [77] reported thermally responsive and electroactive polymers by using redox properties of PVF with other thermo responsive monomers like NIPAM. Reported polymer was synthesized via radical polymerization and tested as polymeric mediator for glucose biosensing materials [78]. Topçu Sulak et al. reported the preparation of gold deposited PVF films as promising candidate for glucose sensing, having inordinate sensitivity and current density with broader linear range [8]. Afterwards, composites of CNTs with PVF were synthesized as molecular wires [5]. A hydrophilic copolymer, (poly(VFc-co-HEMA), was prepared by using conventional radical copolymerization [79].

Large scale production of copolymer of acrylamide (AAM), vinylferrocene (VFc) and 2-(diethylamino) ethyl methacrylate (DEAMA) by free-radical polymerization was reported by Liu et al. [4]. In this copolymer AAM formed principal hydrophilic polymer backbone, VFc worked as mediator moiety, and DEAMA confided the operating capability of in vitro solubility as well as incorporating positive charges which could be attributed to the negative charges of enzyme when the solution is beyond the enzyme isoelectric point.

Continuing in chronological order, Dursun et al. also reported the synthesis of VFc based copolymer with glycidyl methacrylate and methylthienyl methacrylate monomers by free radical technique [80]. The copolymer was covalently attached via epoxy groups with enzyme due to vicinity of enzyme, mediator and electrode.

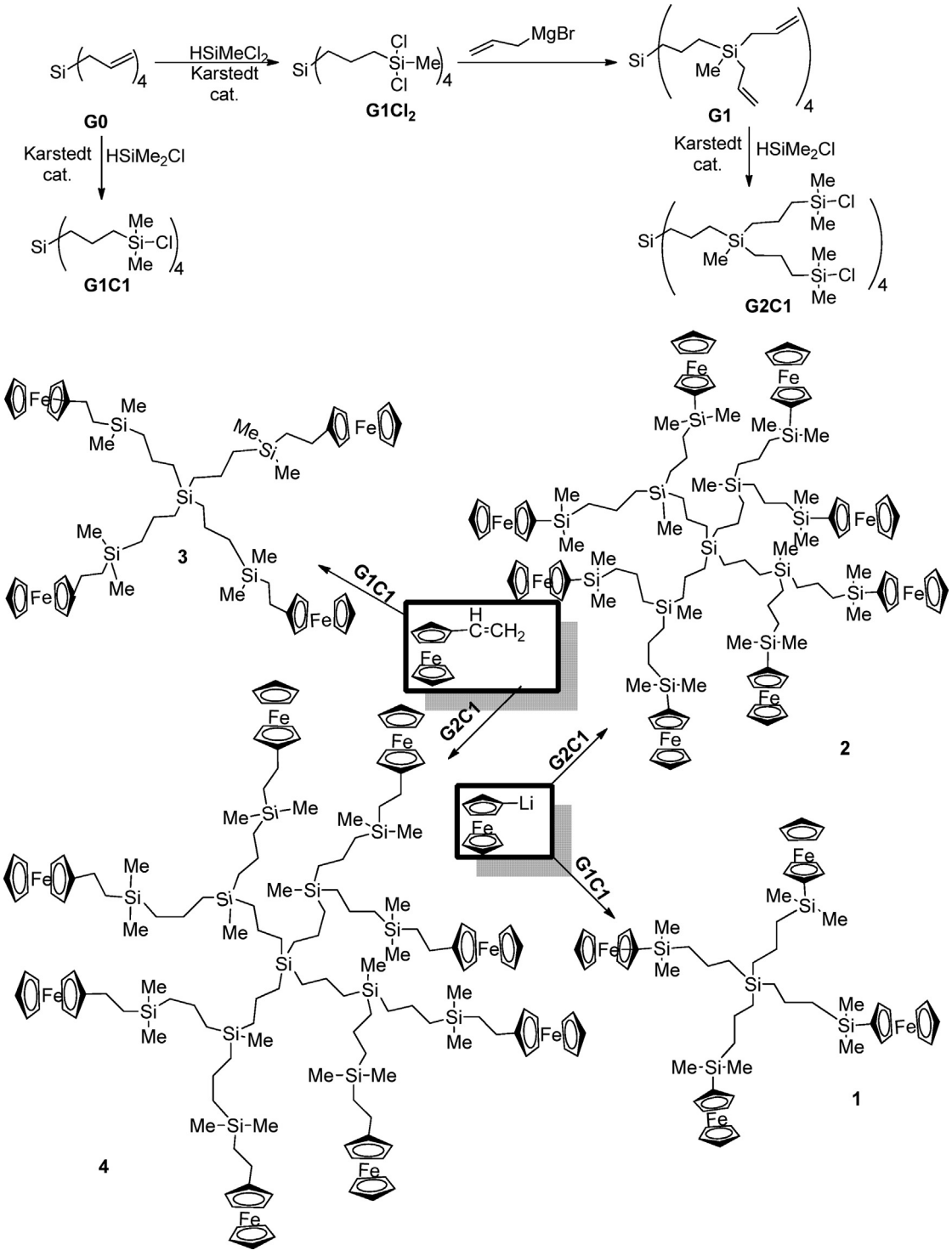
Several cross-linkable ferrocenyl redox polymers with aqueous solubility were synthesized and studied as electron transfer mediators in biosensors. These redox polymers bear carboxylic acid or amine moieties in the side chains which allows facile cross-linking with enzymes, proteins, antigens and antibodies [81].

2.6. Ferrocene-based chitosan derivatives

The aldehyde group of ferrocene can simply react with the NH_2 group of chitosan (CHIT) via a schiff base and succeeding reduction by $NaCNBH_3$ (Scheme 3A) [82]. CHIT-Fc/GOD film electrodes are very sensitive in the electroanalysis of glucose, but due to the hydrophobic nature of the ferrocenyls, the amount of redox active sites in this polymer is restricted. This problem was overcome by functionalized polysiloxane with chitosan composite of ferrocene (Scheme 3B) in which uniform dispersal of Fc in chitosan matrix and the stability between hydrophilic/hydrophobic properties of nanocomposite made smooth mass-transporting redox film and showed greater transport rate in aqueous condition [83].

3. Applications of ferrocene-based polymers and derivatives in glucose sensing

FBPDs, excellent electron transfer mediators, are broadly used in the development of intermediated amperometric biosensors,



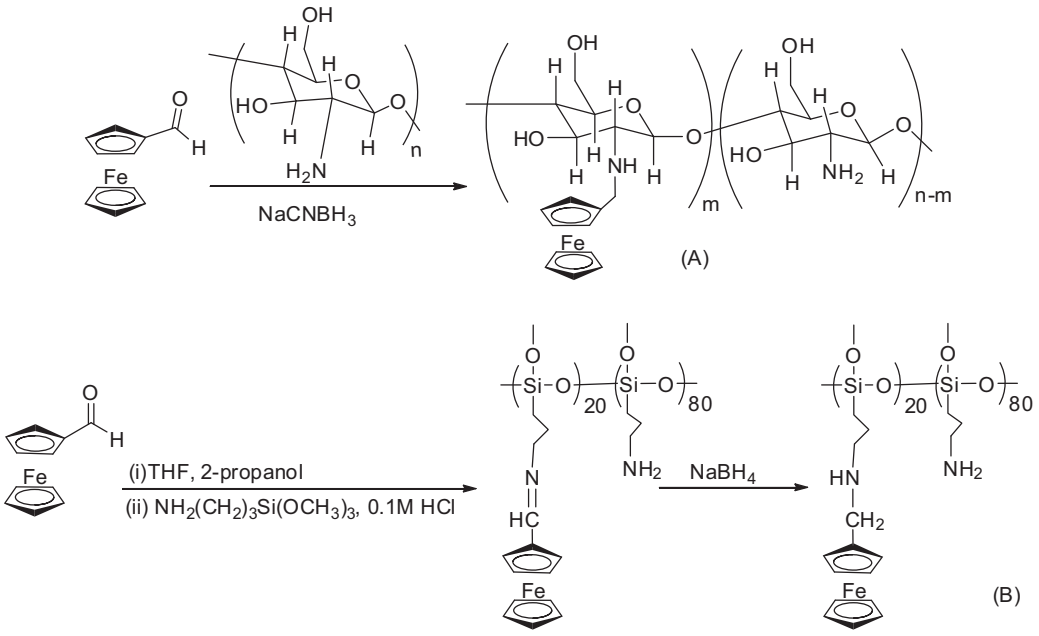
Scheme 2. Synthesis of ferrocene-containing dendrimers using organosilicon dendritic units [62].

especially in the second generation GBs. Applications of FBPDs in glucose sensing are discussed in the following section.

3.1. Ferrocene-based dendrimers

The deposition of functionalized dendrimers without loss of material on numerous electrode surfaces by layer formation showed great mechanical stability. Furthermore, their large surface area and extremely branched structure makes it an appropriate candidate for biosensors fabrication and enzyme immobilization [36,37].

Architectural properties and grouping of dendritic molecules organized via electronic communication among metal centers and properties of polysiloxane, for example, chemical stability and low toxicity, is encouraging approach for monitoring physical and redox properties of hybrid molecules. PAMAM dendrimers with Fc group, at middle point, were used. These were covalently attached with coupling agent, changed pre-modified (with mercapto propionic acid) gold electrode (Fig. 3). Efficient enzyme immobilization can be achieved from ferrocene-based PAMAM dendrimers, accompanied by high enzyme loading, decreased



Scheme 3. Synthesis of ferrocene-based chitosan (A) [82] and polysiloxane derivative (B) [83].

working potential, enzyme stability and increased electrode lifetime [74].

3.2. Ferrocene-based cyclodextrin

Practical use of natural cyclodextrin (α, β, and γ cyclodextrins) is limited due to poor aqueous solubility, particularly that of β-CD. Improved aqueous solubility of ferrocene makes it an ideal addition for hydrophobic holes of cyclodextrin (CD) in aqueous media. An Fc-carbonyl-β-CD inclusion complex was prepared by highly soluble carbonyl-β-CD in which Fc was contained within the hole of carbonyl-β-CD [53]. The CNT incorporation in Fc-carbonyl-β-CD inclusion complex boosted electron transfer between electrode surface and FcCD complex to construct an amperometric glucose biosensor [84]. Molecular size selective glucose sensor was also prepared from thiolated α-CD in which glucose molecules fit right into the template molecules and competed well with the electrochemically active compound for insertion complex formation [85].

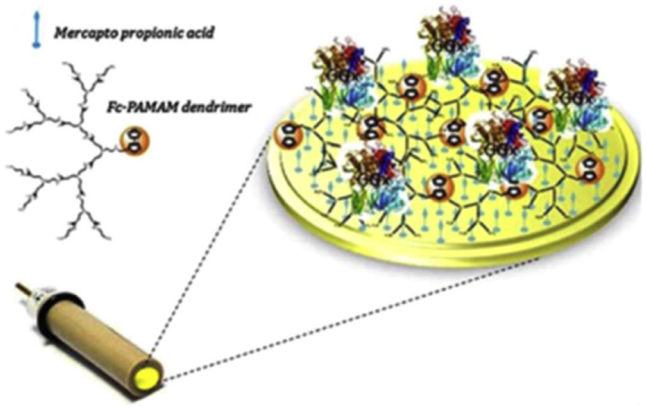


Fig. 3. Schematization of PAMAM dendrimer on the surface of GOx-immobilized gold electrode, reprinted with the permission of Ref. [74].

3.3. Ferrocene-based polypyrroles

Conducting polymers were frequently used in amperometric enzyme electrodes to enhance the electron transportation reaction between electrode and enzyme via branched conducting network [41,44,86]. Covalent functionalization of conducting polymers is a key factor, as it averts the mediator leakage by attachment of the ferrocene-based mediators on top of polymeric films. Leakage problem from the electrode surface was solved by the introduction of covalent connection of enzyme through peptide linkage and excellent biosensing property of ferrocene-functionalized polypyrrole derivatives was reported on [43]. Ferrocene-based pyrroles in copolymer increases redox properties and consequently perform in virtual reversibility with promising electron transfer and better electrochemical sign for electrochemical biosensors [42]. The use of alcohol in polymeric matrix plays a productive role by avoiding mass transport (which effects as interfering in the polymerization kinetics and leads to the effective immobilization of both, the enzyme and ferrocene, in very thin electroactive films) and improves biosensor's response time [87].

3.4. Ferrocene-based polyvinylferrocene

The vinyl monomers due to hydrophilic properties are compatible with the enzyme and can be used as physical communication sites. Hydrophilicity of vinyl monomers also allows functional groups to relate easily on the surface of the electrode. Vinylferrocene (VFc), a fairly efficient mediator for oxidases [88] has been reported to undergo free radical polymerization [18] to form polyvinylferrocene (PVF) [75,88,89]. Co-polymerization of vinylferrocene with a suitable water-soluble polymer makes ferrocenyl materials readily soluble in water. But the free radical polymerization of VFc is atypical due to direct participation of the Fc during the radical polymerization reactions of VFc in benzene [90,91]. FBPDs leaching from biosensors effects in deterioration of sensor performance and offers insight into potential safety questions when applied to health care products [6]. However, leakage problems were reduced by synthesis of water-soluble polymeric mediator via free-radical copolymerization of acrylamide (AAM), 2-(diethylamino)ethyl methacrylate

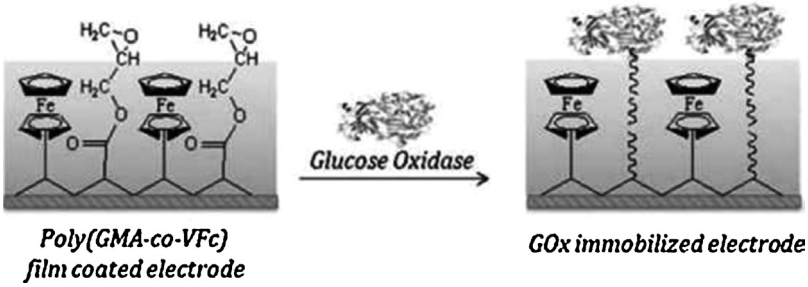


Fig. 4. Immobilization of enzyme onto a polyGMA-co-VFc film electrode, reprinted with permission of Ref. [92].

(DEAMA) and VFc [4,81]. The electrochemical polymerization of VFc on MWCNT carbon-modified electrodes was studied and used to detect glucose in diluted laked horse blood [5].

PVF has inimitable properties as an immobilizing intermediate for GOD enzyme and also as a catalyst for H_2O_2 oxidation for the improvement of sensitive, simple, cheap and stable enzyme electrodes. In comparison with PVF based GOD electrode, the PVF–Au–GOD electrode has greater current density and sensitivity with broader linear response due to presence of Au particles. Moreover, a series of poly(glycidyl methacrylate-co-vinylferrocene) redox copolymers were synthesized by using free radical polymerization to improve immobilization of GOx (Fig. 4) [92].

3.5. Ferrocene-based polythiophenes

The most important application of ferrocene-based polythiophenes in glucose sensing is in offering a solution to the leaching problem of enzyme electrode by covalent attachment. Ferrocene-based thiophene and terthiophene compounds in which a conjugated linker provides communication at the molecular level between the polythiophene support and the Fc group [12].

Abasiyanik and Senel reported electrochemical copolymerization of thiophene-3-acetic acid, thiophene and dicyclopentadienyl iron-1, 4-dienylmethyl-2-(thiophen-3-yl) acetate as films. GOx was covalently immobilized on copolymer films/polythiophene derivatives surfaces through amide linkages designed by the COOH group's condensation (Fig. 5) [17].

3.6. Ferrocene-based chitosan, carbon nanotubes and polyethylenimine

Chitosan (CS), the second most abundant polysaccharide after cellulose [93], is a biocompatible biopolymer consisting of *N*-acetyl-D-glucosamine and D-glucosamine units connected in a β (1 → 4) manner [21]. CS is synthesized by a partial deacetylation of chitin and possesses distinctive physico-chemical characteristics such as biocompatibility, adhesion capability, excellent membrane forming capability, high mechanical strength and water permeability, non-toxicity and simplicity toward chemical modifications [21,94]. For sensors fabrication, CS has been broadly studied as an immobilization material due to such a unique blend of properties [22–24] but very low electron transfer efficiency has limited its application. To overwhelm this limitation, ferrocene-based redox mediators were covalent connected to the biopolymer [27,95]. Ferrocene (Fc) and its derivatives among several redox polymers have excellent properties such as oxidation/reduction stability at low potential, pH-independent, fast electron transfer, rapid responses to electroactive substances that make them commonly used class of mediators for chemically modified electrodes growth [19,28,29]. Fc covalent linkage to CS can also reduce the principal problem of low-molecular-weight mediators leakage [10]. Furthermore, Fc groups enhance electron transfer process between electrode surface and immobilized biocatalyst which can lead to more sensitive and stable biosensors. Primarily, to increase GOx based biosensor's performance, operative immobilization of GOx in a biocompatible surroundings and presence of species which can enhance electron transfer between electrode and enzyme are strongly essential [96]. The approach of developing CS–Fc conjugate not only inhibits the Fc mediator from leakage, but also affords a favorable microenvironment to maintain the biocompatibility of CS. Therefore, it can be a promising candidate for the development of novel biosensors and bioelectrochemical devices [26,82,83,97]. In electrochemical biosensors CS–Fc mixtures as a functionalized matrix is also used in immobilize various enzymes such as laccase, GOx, horseradish peroxidase (HRP) [98–100]. Chitosan composite of ferrocene with functionalized polysiloxane showed greater transport rate in aqueous condition, probably due to high hydrophilic character of chitosan composite [83]. Three dimensional nanocomposites film of chitosan covalently bonded to ferrocene due to its insoluble behavior at

Fig. 5. Illustration of immobilization of enzyme by amine group on Th/Th–COOH/Th–Fc film electrode, reprinted with the permission of Ref. [17].

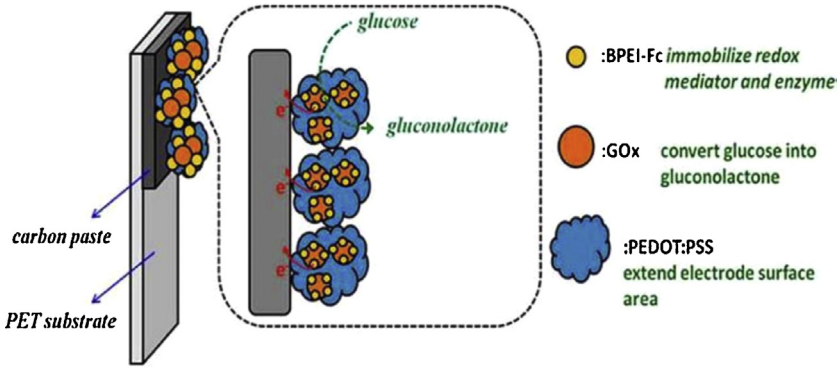


Fig. 6. Mechanism of glucose immobilization of ferrocene-based PEI and polymer on electrode surface, reprinted with the permission of Ref. [58].

high pH (greater than 6.3) was deposited with negatively charged (Au NPs) onto the electrode surface. In addition, GOx was immobilized on the CS–Fc/Au NPs chains due to strong interaction between amino group of the enzyme and Au NPs [95].

Chuang et al. reported on ferrocene based branched polyethylimine as a medium for facile electron transfer due to high concentration of amino acids and its flexible chain [56]. A multiple redox behaviors and electron deficient coefficient of PEI was found to be 40 times greater than other ferrocene based polymers [57]. Recently redox nanobeads of branched polyethylenimine were incorporated with other polymers to enhance the charge transfer and catalyze GOx more efficiently (Fig. 6) [58]. The electrochemistry of CNTs similarity in electronic properties with metals, high electroactive surface and stability makes them an important area of research for ferrocene-based glucose biosensors [10,101–103].

Ferrocenyl-functionalised SWNTs within an amphiphilic polypyrrole matrix coupled to glucose oxidase for the detection of glucose were then discussed and it was suggested that ferrocenyl-functionalised SWNTs afford preferential directions for the electrical wiring of the enzyme, likely via the aligned ferrocenyl groups, thus illustrating the potentialities of redox-active CNTs for the elaboration of mediated biosensor [101].

Covalent grafting with CNTs onto film was attained through electroreduction of salt which was followed by post-functionalization with an activated ester derivative of Fc (Fig. 7) [104]. The covalent derivatization of multi-walled CNTs with ferrocene moieties unlike the π-stacking one gives a stable and steadfast glucose sensor electrode material while the incorporation of CNT onto GOx with the help of Nafion for stability, enhanced the electrical signal. FMCA (ferrocene monocarboxylic acid) is also used as a mediator due to metal organic framework which can increase sensitivity and selectivity of sensor, and can reduce interference throughout the recognition of the desired species [105].

Qiu's group described amperometric GBs by entrapping GOD in a novel chitosan composite doped with ferrocene monocarboxylic acid-modified 3-(aminopropyl) triethoxy-silane enwrapping carbon nanotubes (FMC-AMWNTs). These FMC-AMWNTs composite films can be protracted to immobilize various enzymes in addition to biomolecules, which can greatly facilitate the progress of biosensors and various bioelectrochemical devices [100].

MWNTs-Fc/CS composite contains large surface area, good conductivity and good mechanical stability, which prevented leakage of mediator and provided a well-matched microenvironment for the activity maintains of the immobilized mediator and enzyme. As biosensors, PEI or BPEI are mainly used with both SWNTs and MWNTs as a method to scatter CNTs [106–109] and/or link biological molecules such as antibodies [110,111], enzymes [106,107,109] or DNA [109] to the nanotubes and, more notably, in glucose sensors [106,107,109]. Furthermore, the manifestation of SWNTs in thick films permits more Fc redox centers to become available (Fig. 8) [112]. To improve the solubility of CNTs in aqueous

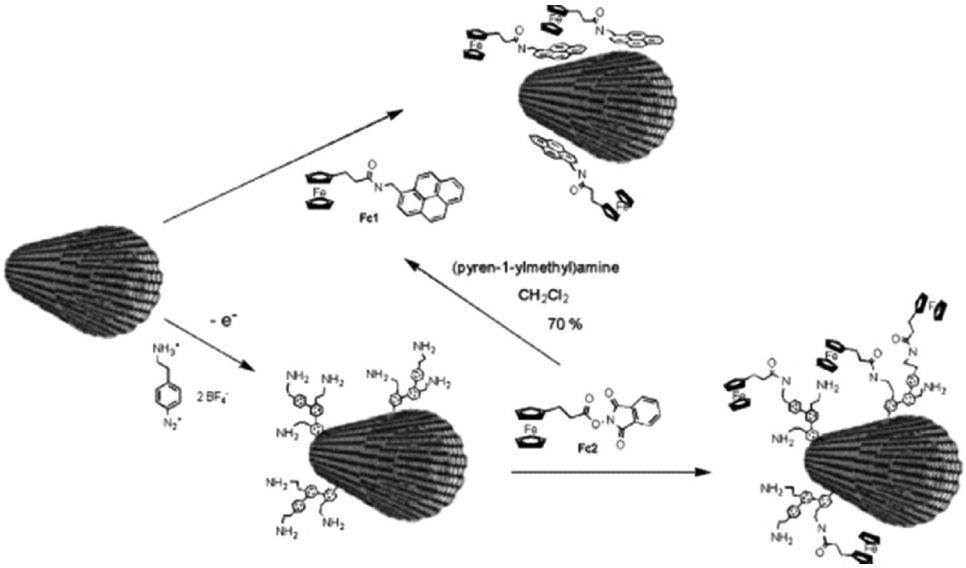


Fig. 7. Functionalization of MWCNTs with ferrocene. Up – by π-stacking and down via covalent grafting, reprinted with the permission of Ref. [104].

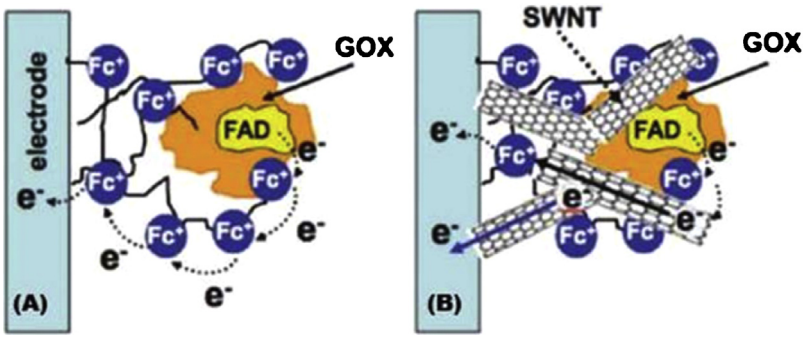


Fig. 8. (A) redox polymer (Fc-C6-LPEI) and GOx, (B) self-exchange mechanism of electron transfer through the SWNTs, reprinted with permission of Ref. [112].

media, surface functionalization of CNTs with ionic/hydrophilic groups [113] or with water-soluble polymers [114] is used.

The dispersed SWNTs in water soluble polymer BPEI used the imine groups as a base to chain Fc redox centers to the SWNT–BPEI matrix before the enzyme GOx adsorption. The enzyme-functionalized CNTs (hybrid systems linkage of the CNTs/PEI with the GC surface) linked through the electrode offer operative charge transport matrices, large surface areas, and facile electrical communicating features (Fig. 9) [108].

There are other transition metal redox polymers, like Os and Ru that have been used in biosensors. For constructing ideal electrochemical biosensors, it should have good linear range, stability and sensitivity and free from common problems like leaching, immobilization and interferences. As discussed earlier the FBPDs have been used to remove above mentioned problems by designing large surface molecules with effective enzyme loading, decreased working potential and increased lifetime of electrodes [19,28,29,36,37,112]. Antiochia et al. [96] reported on an osmium polymer immobilized into CNT paste electrode for detection of fructose and sucrose, and achieved wide linear range and low detection limit compared to results reported by using ferrocene [84]. Recently Antiochia et al. [115] reported osmium complex with PANI for glucose biosensors and reported excellent linear range in comparison to ferrocene polyaniline-modified electrodes [116]. Particularly in the development of peroxide biosensors, FBPDs play a crucial role in improving stability, sensitivity of sensor and the work done by Armada et al. [70] was found to be the best in improving sensitivities and detection limits but selectivity of peroxide was not discussed by using FBPDS [98,117–120].

4. Performance of glucose biosensors containing ferrocene-based polymers and derivatives

Mediators establish an electron transfer by contacting redox center of enzyme and acts as charge transporters [121,122]. The electro-active compound (mediator) can minimize the effect of interferences, decrease operating potential of the electrodes, and improve the linear response range and sensitivity of the sensor [123]. The chemical modification of redox-relay groups with enzymes [124–126] or the immobilization of enzymes in redox-active polymers [127–130] has been utilized to create electrical communication between electrodes and biocatalysts.

Ferrocene-based materials received sharp interest of researchers from the last few decades due to the reversibility and easy external control of the redox process [19,131–144]. The unique features of ferrocene based derivatives, wide linear range (LR), low detection limit (DL), high sensitivity and minimal interferences are considered aspects analogous to the recent development in glucose biosensors. The various factors, which influence rate of electron transfer between Fc and enzyme, are discussed below.

4.1. Metal co-ordination

Metal co-ordination to the conjugated polymer backbone facilitates electronic interaction between the electroactive metal centers and the polymer backbone [145]. A greater amount of amines on the polyethyleneimine support can give improved complexation with the anionic GOx and a smaller electron-transfer space between the FAD site of GOX and the Fc redox centers. This minimized electron-transfer space would result in a greater efficiency and degree of electron transfer and, henceforth, improved current densities [146]. Cameron and Pickup have reported electron transfer between the ruthenium sites in the conjugated polymer backbone, rather than by hopping through the polymer backbone without metal centers [147]. The primary motivation behind studying the progress of metal co-ordinated polymers is to acquire synergistic electronic communication among the metal centers and the polymer backbone. Such types of interactions are often weak. The strongest combination is seen in ferrocene based structures where the metal form parts of the backbone [145].

4.2. Spacer of the ferrocene to polymer

Enhanced flexibility of the spacer inside its aqueous environment can raise the likelihood of a fast and facile electron transfer between the electrode surface and enzyme's active site. Flexibility in the covalent immobilization of mediator molecules can be used as an overall principle for electron transfer among sterically mismatched sites [41,148]. Tran et al. reported on the effects of integrating SWNTs into redox polymer enzyme hydrogels. The hydrogels were created by joining the enzyme glucose oxidase with a redox polymer (Fc-C6-LPEI) in which Fc was attached to LPEI by a six-carbon spacer. Incorporation of SWNTs into these films altered their morphology and caused a significant rise in the enzymatic response and sensitivity of subsequent sensor [112].

4.3. Interferences

An interfering molecule is a class or species that is electroactive at the operating potential of the amperometric sensor. Electrochemical interference in blood results in incorrect glucose interpretation by contributing non-glucose-derived electrons. Ascorbic acid (AA), one of the most common interfering substances disturbs the precision of glucose [149,150]. For GBs-based on electrochemical analysis, AA is oxidized at the electrode surface, resulting in the creation of more electrons and generation of superior current. Nieh et al. reported highly selective and stable hydrogen peroxide osmium complexes in which reported mediators work well for peroxidase but not against the oxidase thus making them and ideal interference free peroxide selective biosensor [151]. Other than selectivity another strategy to remove

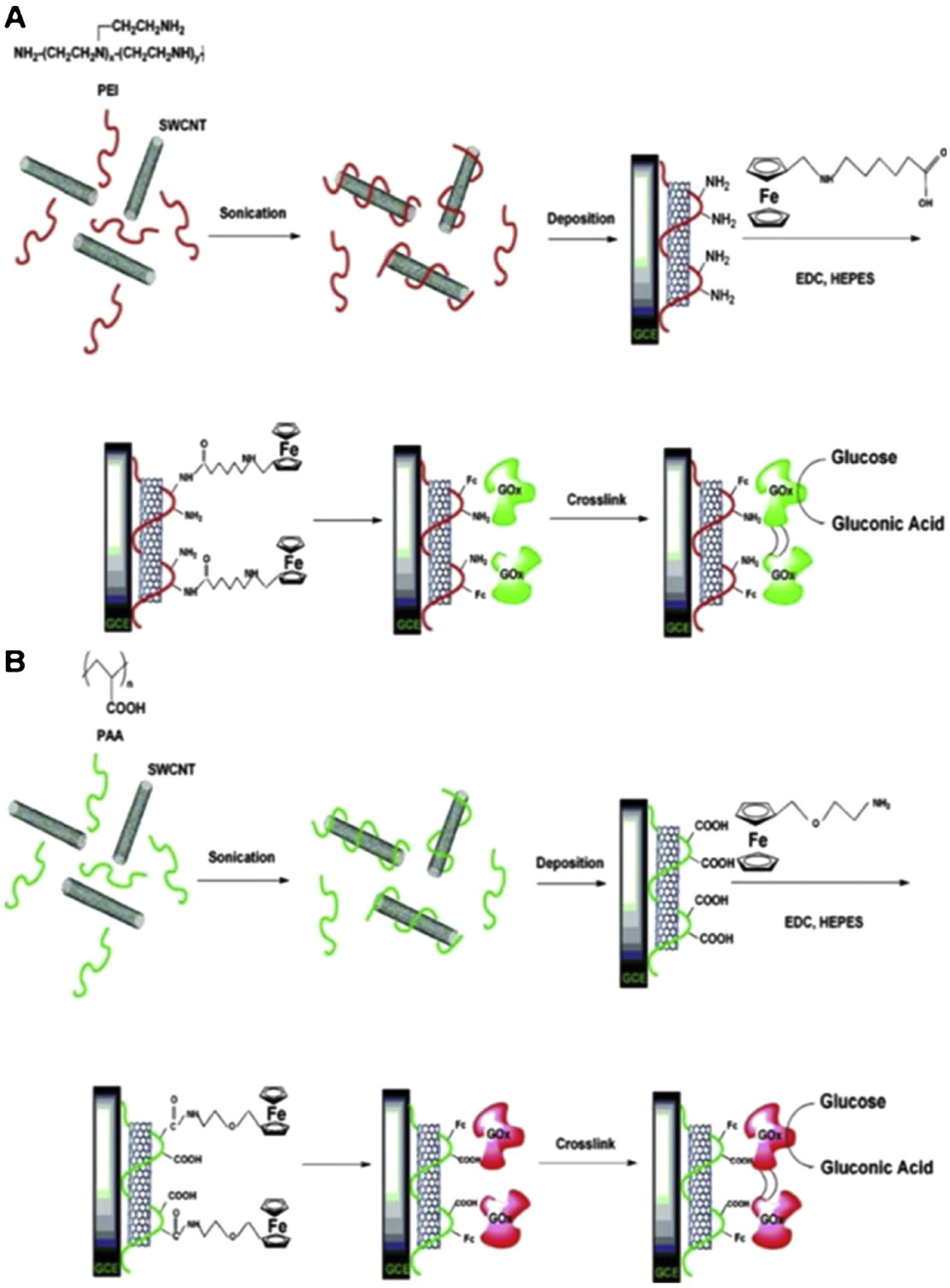


Fig. 9. (A) Assemblage of the combined, electrically contacted, GC-CNTs/PEI-Fc-GOx electrode; and (B) GC-CNTs/PAA-Fc-GOx electrode, reprinted with the permission of Ref. [108].

common interfering species is to operate biosensors at very low applied potential [152]. Nam et al. reported on ruthenium complex as mediator and eliminate interferences from ascorbic acid (AA), dopamine (DA), uric acid (UA) as well as acetaminophen (AMP) [153]. Deng et al. recently demonstrated interference-free glucose biosensors by crosslinking of ruthenium based low potential redox polymer with good linear correlation between the oxidation current and the amount of glucose up to 10 mM [154]. Table 1 summarizes the FBPDs data related to their analytical performance as glucose sensors.

4.4. Crosslinking

Crosslinking in polymer plays a significant role in using them as biosensors applications, as the absence of cross-linkable clusters in polymer chain can limit their usage in biosensors [77,155].

Table 1
Comparison of analytical performances of the different GOx electrodes based on ferrocene-based polymers and derivatives

Electrode	RT (s)	LR (mM)	DL (μM)	Sensitivity ($\mu A\,mmol^{-1}\,L\,cm^{-2}$)	Interferences	Reference
C/Fc-siloxane polymer	30	16.0	–	0.74	–	[159]
GC/poly (aniline Me-Fc)	–	1.0	–	0.6×10^{-3}	–	[157]
Graphite-Teflon/Fc	–	0.01–0.8	–	8.75	–	[172]
Pt/interacting Fc siloxane polymer	–	1.0	2.86	2.8	–	[173]
Pt/permethyl ferrocenyl polymers	–	55.0	–	0.11	–	[174]
PMFD-1	5–10	4.0	12.8	5.51	Negligible	[175]
PMFD-2	5–10	4.0	25.0	7.29	Negligible	[175]
PMFD-3	5–10	4.5	22.1	7.43	Negligible	[175]
$Py_{0.2}/PyCO_2H_{0.2}/PyFc_{0.6}$	2	1.0–4.0	6.9	1.796	Negligible	[42]
$Th/ThCO_2H/ThFc$	4	0.5–3.0	2.5	0.04	Negligible	[17]
Py-Fc	~4	1.0–18	–	0.05	–	[176]
MWCNTs/Chi-BSA-Fc/GOD	–	0.010–30	–	7.8	Negligible	[177]
LPEI-Fc/GCE	–	0.005–0.1	–	73	–	[136]
$PyCO_2H$/Ppy-Fc/GOx/GCE	–	1.0–4.0	–	1.796	–	[42]
MWCNT-PAP-Fc/ITO	–	5.0–50	–	0.83	–	[101]
FC-20/Chi/GOx/GCE	30	1.0–6.0	–	0.86	–	[82]
GNPs/CD-Fc/GOD/GCE	–	0.08–11.5	–	18.2	–	[46]
FMC/AMWNTs/GCE	–	0.01–4.2	–	10.56	–	[97]
FMC-BSA/MWNTs/ormosil/GCE	5	0.05–20	–	0.26	Negligible	[10]
CS-Fc/MWCNTs/GCE	–	0.005–1.5	–	13.08	–	[178]
BPEI-Fc/GOx/SPCE	32	0.5–4.5	–	27	–	[57]
BPEI-Fc/PEDOT:PSS/GOx/SPCE	22	0.5–4.5	–	66		[57]
PAMAM-Fc/GOx	~3	1–22	0.48	6.54	Negligible	[73]
SCC-BFc/GOx	<10	1.9–13.0	1.0	5.3	Negligible	[20]
LDHs/MeOHFc/GOD	5	0.006–0.386	3	0.060	Negligible	[169]
GC/Fc-PE-SGS	<10	80	0.3	–	No effect	[170]
PAA-PEG-Fc-50/silica/GOx	–	10	–	1.9	–	[171]
ITO-g-P(GMA-GOD)-b-P(FMMA)	<20	0–5	0.4 ± 0.1	3.6	–	[172]
ITO-g-P(FMMA)-b-P(GMA-GOD)	<20	0–17	0.4 ± 0.1	10.9	–	[172]
Poly(GMA-co-VFC)/GOx	–	0.1–6.0	3	–	Negligible	[91]
GOx-FcCD-PLL-CNT/GC	–	1.0×10^{-5} to 2.90×10^{-3}	2.2	–	Negligible	[83]
FMC-AFSNPs/CS	–	1.0×10^{-5} to 4.0×10^{-3}	3.2	–	Negligible	[173]
Nafion-GOx/SWNT	–	0.25–3	97	9.32	No effect	[102]
Nafion-GOx-PDDA-SWNT/GC	–	0.5–5.5	83	–	–	[174]
CHIT-Fc/GOx	~20	2.0–16	0.565	–	–	[97]
Fc-branched-Chi	–	0.02–7	–	8.1	–	[81]
MWNT-Fc-Chi	–	0.012–3.8	–	25	Negligible	[175]
MWNT-Fc	–	0.01–4.2	–	10	No effect	[97]
Carbon film-BSA-Fc	–	0.05–2.7	–	0.051	Negligible	[176]
Cellulose/FMA	–	1–5	0.18	–	Negligible	[166]

RT = Response time, LR = Linear range and DL = Detection limit.
GOx or GOD = glucose oxidase; PMFD = polymethylferrocenyl dendrimer; Py = pyrrole; PyFc = pyrrole ferrocene; SCC = sono-gel carbon material; BFc = 1, 2-diferrocenylethane; Th = thiophene; Th–COOH = thiophene-3-acetic acid; Th-Fc = dicyclopentadienyl iron-1, 4-dienylm-ethyl-2-(thiophen-3-yl) acetate; GCE or GC = glassy carbon; PE-SGS = polyelectrolyte sol–gel derived silica; PAA = poly acrylic acid; PEG = polyethylene glycol; FMMA = ferrocenylmethyl methacrylate; GMA = glycidal methacrylate; CS/Chit or Chi = Chitosan; VFC = vinyl ferrocene; PDDA = poly (dimethyldiallyl ammonium chloride); SWNT = single-walled carbon nanotubes; FcCD = ferrocene-carbonyl-β-cyclodextrin; PLL = poly-L-lysine; CNT = carbon nanotube; FMC = ferrocene mono carboxylic acid; AFSNPs = acid-modified magnetic core-shell Fe_3O_4@SiO_2 nanoparticles; LPEI = linear polyethyleneimine; PAP = poly-aminoethylphenylene; GPNs = gold nano particles; FMC/AMWNTs: ferrocene monocarboxylic acid-modified 3-(amino propyl) triethoxy-silane enwrapping multiwalled carbon nanotubes; BSA = acid-bovine serum; C60-Fc-CS-IL-GCE: the conjugation of fullerene, ferrocene, chitosan, ionic liquid, and glucose oxidase (GOx) PAMAM = Poly (amido amine); BPEI = branched poly-ethylenimine; SPCE = screen-printed carbon electrode; PEDOT = poly(3,4-ethylenedioxythiophene); PSS = poly(styrene sulfonate); MWNT = Multi walled nanotubes.

Numerous studies have shown that the impact of crosslinking on redox polymers is critical for the glucose recognition with ferrocene-based polymers. This is because more narrowed Fc molecules would need more energy to oxidize [56,57,112].

4.5. Polymer backbone flexibility

The decline of flexibility of the polymer chain that occurs upon cross-linking, resulting in a reduced electron-transfer efficacy between Fc moieties, may also be the reason of lower current density compared to the non-crosslinked carbon paste system. Some studies described on flexible environment of BPEI proofs its improved degree of electron transport as mediator between enzyme and electrode [56,57]. The reduced flexibility of BPEI support resulted in difficulty of the electron transfer between the enzyme and the polymer mediator which caused modification of the elementary catalytic properties of the enzyme electrode. Nevertheless, the polymer hydrogel being a large molecular system assist a stream of electrons from the enzyme to the electrode and clearly acts as an electron-relay system and not as a diffusional mediator [156].

Glucose electrochemical biosensors are the most popular and the most developed type among all biosensors. Though it is vastly studied, a thorough discussion of biosensors cannot be completed without considering different electrochemical biosensors which are in fact underdeveloped.

Electrochemical biosensors for recognition of DNA are of special concern due to their low cost, quick response and inspiring miniaturization of current microelectronics [157].

FBPDs have used as electrochemical markers in detection of DNA biosensors, giving a severe redox response of the polymer film and a difference in Fc oxidation intensity leads to probe target hybridization and sequence specific detection of DNA. The extraordinary sensitivity of Fc toward neighboring medium of polymers improved the recognition performance of DNA biosensors [115,158–161]. Furthermore, Jiao et al. reported on dopamine biosensors which detect dopamine with high selectively and sensitivity in presence of AA and UA. In this proposed

model enhanced electrocatalytic property toward DA is due to the enhanced electron transfer brought on by the stable and strong π–π stacking interaction between Fc and SWTs [162].

Shim et al. recently synthesized a Fc-catalyzed AA oxidation-based very sensitive thrombin aptamer sensor by immobilization of a thrombin binding aptamer covalently on 3D-conducting polymer nanorods electrodes (3D-CPNEs). These electrodes were made by the coating of a conducting polymer film on the surface of 3D-Au nanoparticles [160].

5. Conclusion and future prospects

The role of FBPDs in the progress of glucose biosensors can be envisioned from the tremendous increase in reported literature of the past few decades. Interferences of readily oxidizable species, for instance ascorbic acid (AA), uric acid (UA), dopamine (DA) as well as acetaminophen (AMP) in blood samples can be avoided due to lower electrode potential. Ferrocene is an ideal candidate for low redox potential between inserted surface of enzyme and electrode. The problems associated with immobilization of the GOx with electron-mediator (ferrocene) such as mediator leakage from electrode surface, poor electron transport, poor stability and chain rigidity can be avoided by using dendrimers, conducting polymers (polypyrrole, polythiophene), CNTs, chitosan and polyethylenimine with ferrocene. These FBPDs have many advantages like their large surface area, excellent electrical conductivity, and stability with flexible chain length properties. Recently several research groups successfully developed high performance GBs by using ferrocene with metal complexes (ZnO [163]), conducting polymers (polypyrroles [43] and polythiophenes [17]), nanoparticles (gold [164] and platinum [165]), natural polymers (cellulose [166] and chitosan [167]) and CNTs [168]. Although for GBs applications, electrical conductivity, stability, low cost, biocompatibility, sensitivity and selectivity of FBPDs are reported, but additional issues in evaluating the commercialization of GBs and particular mediated glucose biosensors are still worthy of sharp consideration. The main challenges in commercialization are still linked to the topics which are withdrawn from biology. Moreover, the construction of biosensors is an active research area, and time is needed to design robust, low cost GBs with higher efficiency and acquire new type of enzyme based bio-electronic devices by using FBPDs. GOx-based electrochemical GBs containing Fc are presumed to be perfect models for mediated electron transfer enzyme electrodes production. In this perspective, textural and electrochemical properties of FBPDs will undoubtedly open new directions for the development of biosensor.

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