

Glucose sensors based on electrospun nanofibers: a review

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Abstract The worldwide increase in the number of people suffering from diabetes has been the driving force for the development of glucose sensors. The recent past has devised various approaches to formulate glucose sensors using various nanostructure materials. This review presents a combined survey of these various approaches, with emphasis on the current progress in the use of electrospun nanofibers and their composites. Outstanding characteristics of electrospun nanofibers, including high surface area, porosity, flexibility, cost effectiveness, and portable nature, make them a good choice for sensor applications. Particularly, their nature of possessing a high surface area makes them the right fit for large immobilization sites, resulting in increased interaction with analytes. Thus, these electrospun nanofiber-based glucose sensors present a number of advantages, including increased life time, which is greatly needed for practical applications. Taking all these facts into consideration, we have highlighted the latest significant developments in the field of glucose sensors across diverse approaches.

Keywords Biosensors · Nanofibers · Electrospinning · Glucose · Nanomaterials

Introduction

Owing to their vast range of application in the fields of medical diagnosis, diabetes management, bioprocess monitoring, food industries, and environmental monitoring, more attention has been given to the development of highly sensitive and selective glucose sensors [1–4]. Diabetes is considered to be a globally prevalent metabolic illness, which causes the blood glucose level to increase to 126 mg/dL or higher (<100 mg/dL for the normal level according to American Diabetes Association) [5]. On a global basis, diabetes is said to affect 382 million people, and is expected to reach half a billion by the year 2035 [6]. The initiative for biosensors dates back to the 1960s with the revolutionary study of Clark and Lyons, followed by the work of the first enzyme-based glucose sensor by Updike and Hicks in 1967 [7, 8]. These studies provided compelling evidence about the amount of oxygen consumed in the glucose oxidase (GOx)-catalyzed reaction of glucose oxidation. Consequently, extensive research has been undertaken, studying the various types of glucose sensors, including optical and electrochemical sensors [9–16]. Generally, glucose sensors can be broadly divided as GOx-based sensing (i.e., enzymatic glucose sensing) and nonenzymatic glucose sensing.

Enzymatic glucose detection involves the oxidation of glucose in the presence of GOx enzyme, which has been extensively utilized for constructing several sensors for glucose detection, mainly because of their high sensitivity and selectivity to glucose. For the fabrication of these sensors, immobilization of enzymes on a suitable matrix along with their stability is critical [17–19]. Nevertheless, these sensors

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involve highly complex procedures of immobilization and also display lack of long-term stability. In addition, the sensing abilities of these enzymes are very much prone to differences in pH and temperature during measurements, because of their nature. Thus, greater attention has been devoted for the development of nonenzymatic glucose sensors, suppressing the disadvantages of enzymatic biosensors. Whether enzymatic or nonenzymatic, the analytical performances can be largely increased by using unique nanostructure materials [20–38].

As a well-known fact, the morphology of nanomaterials in sensors has a vital part in determining their activity, selectivity, and stability in a catalytic process. Various studies from the literature have provided evidence that the exotic variety of these nanomaterials of different morphologies, including nanowires, nanospheres, nanosheets, nanofibers, and flower-like nanostructures, have achieved enhanced performance in monitoring and detection of glucose [21–32]. Also, the stability of these nanoparticles has to be given equal importance and consideration, apart from controlling their size. In order to avoid the agglomeration of the nanomaterials, a robust support system has to be in place for the particles to maintain their individualistic characteristics. Interestingly, the fabrication of enzymes requires the immobilization of enzymes on solid interfaces, which can be obtained by various strategies, such as physical adsorption, covalent attachment, and physical entrapment or encapsulation, etc. Although progress is being made in the current scenario, some novel host materials, such as graphene, carbon nanotubes, ordered mesoporous silica-based materials, etc., are being utilized in glucose biosensors because of their large surface area and good biocompatibility [33–40]. Besides, the expenses involved in the reproducible production of nanomaterials and nanostructures are of high importance. Also, the unstable nature and loss of enzyme activity during immobilization process affects the thermal and chemical stability, sensitivity, and reproducibility of glucose sensors. Recent years have seen developing interest on colorimetry-based detection, which has several advantages, including high sensitivity, simplicity, and low cost [41–50]. A variety of fluorescent nanoparticles have been used as colorimetric probes [51–53]. Among various techniques, electrospinning is considered to be a facile and inexpensive technique for large-scale synthesis of nanofibers, characterized by exceptional length and uniform diameter ranging from tens of nanometers to several micrometers. Successful usage has been recorded for electrospun nanofibers and their composites in the fields of sensors, water purification, etc., because of their large surface area, flexibility, and porous structure [54–66]. These features of large surface area-to-volume ratio, high porosity, and interconnectivity of nanofibers prove them to be compelling for enzyme immobilization [67]. This is because the enzyme loading can be authentically increased, along with a significant decline in diffusion resistance of substrates.

To the best of our knowledge, not many reviews have reported on electrospun nanofibers-based glucose detection. Our review is one of the first to highlight the electrospinning approach and list its applications in various kinds of glucose sensors. The primary goal of our study is to provide the reader with a comprehensive understanding of the new advances in the field of electrospun nanofibers and their composites that can be used for increasing sensor performance. We are confident that such advances are vital for developing flexible and adaptable sensors, which will pave the path for new avenues and future research.

Overview of glucose sensor development

Including electrochemical, optical, and electromagnetic spectroscopy biosensors, numerous glucose biosensors have been studied and reported [68–78]. Considering the various approaches involved in glucose sensor, the mechanisms fall into two main categories: (1) enzymatic and (2) nonenzymatic, both of which have been intensively researched and utilized. The basic principle of enzymatic glucose detection is the oxidation of glucose in the presence of air by GOx enzyme, producing gluconic acid. Rightly described as the ‘ideal enzyme’ for glucose oxidation in the review by Wilson and Turner in 1992, these possess a relatively high selectivity, sensitivity, and stability compared with other enzymatic materials [76]. Starting back in the 1962 with the excellent work of Clark and Lyons [7], the first enzyme-based glucose sensor was initiated by Updike and Hicks in 1967 [8]. The conversion of electroinactive substrates to electroactive products with the utilization of enzymes is elaborated in the works of Clark’s original patent of amperometric enzyme electrode [79].

Another enzyme used for glucose sensing is Glucose dehydrogenase (GDH), which is used for fabricating commercial test strips for blood glucose, owing to their ability to operate at lower detection potentials [80–84]. Also, hexokinase-based sensing is used as a reference system mainly for the detection of glucose in blood because of its ultrahigh specificity. However, hexokinase enzyme has not been in wide use in the research of glucose sensing as GOx, due to its high cost, lower stability, and the necessity for ATP in its enzymatic reaction [80, 85, 86]. Various strategies, including physical adsorption, covalent attachment, and physical entrapment or encapsulation have been used for the immobilization of enzymes on solid interfaces [87]. These enzymatic sensors, based on their glucose oxidation mechanisms, can be broadly classified into three generations. The summary of the entire glucose oxidation mechanism is displayed in Fig. 1.

In 1975, Yellow Spring Instrumentation Company devised the first commercial glucose sensor based on the first generation glucose biosensor, which is dependent on the presence of

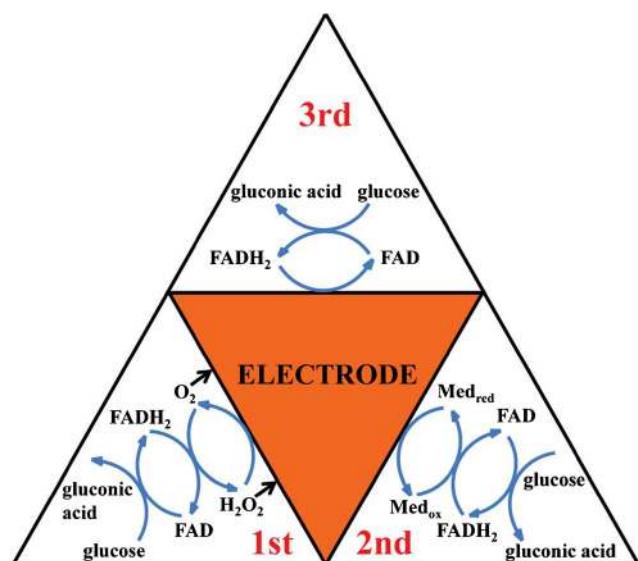


Fig. 1 Summary of enzymatic glucose oxidation mechanisms, presented as first, second, and third. [Reprinted with permission from [80] © 2013 Royal Society of Chemistry]

oxygen as a co-substrate [88]. However, these sensors experienced failure owing to issues regarding the presence of electroactive interference species in the blood and the dependence on free oxygen as a catalytic mediator. In order to overcome these defects, the second generation of sensors was initiated by the usage of synthetic electron accepting-mediators as alternative co-substrates. This included ferrocene derivatives, ferricyanide quinones, and transition-metal complexes [89–92]. Yet again, the second generation sensors also posed challenges because of their size and diffuse molecules. Also, it was difficult to maintain the mediator near the electrode and enzyme and the formation of interference species called hydrogen peroxide. This was followed by the use of third generation of sensors without employing any natural and synthetic electron mediators, facilitating the direct electron transfer between the enzyme and the electrode [88].

Nevertheless, there still remain some disadvantages of enzyme-based glucose determination. Although enzymatic sensors are highly selective, sensitive, fast, and reversible, their chemical and thermal instabilities originating from the intrinsic nature of enzymes as well as their tedious fabrication procedures and high cost prove them to be disadvantageous [88]. This was followed by the presence of complicated enzyme immobilization and critical operating conditions [93]. Also, the activity of enzymes is prone to be affected by external parameters, such as temperature, pH, humidity, and toxic chemicals [94, 95]. This has prompted various enzyme-free sensors to further investigate the electrocatalytic activity and selectivity towards glucose oxidation to address the issues associated with enzymatic sensors. It is to be noted here that the underlying principle of electrocatalysis is the adsorption of analytes to electrode surface.

In 1909, Walther Loeb reported the direct electro-oxidation of glucose to gluconic acid in a sulfuric acid solution at a lead anode [96]. Recent past has also observed the development of nonenzymatic glucose sensors by using several electrocatalysts in glucose oxidation. In general, these enzyme-free sensors are considered to be fourth generation sensors. However, the challenges posed in this approach include (1) the restriction in the sensitivity of glucose sensing because of the relatively low kinetics of glucose electro-oxidation on conventional electrodes; (2) the impairment of noble metal electrodes by the irreversibly adsorbed oxidation intermediates of glucose and the adsorbed chloride ions, and (3) the poor selectivity of nonenzymatic glucose sensors, giving the possibility of oxidation of some other sugars and interfering species in the potential range of glucose oxidation [80, 97, 98]. This also includes the expensive nature of these sensors, fouling of electrodes and their instability, making them unfit for practical applications.

Recent years have seen continuous reports of nanomaterials based nonenzymatic glucose sensors, in spite of various challenges posed by enzymatic glucose sensors [99]. This also included the introduction of several types of nanostructured materials, such as metal nanoparticles (platinum [100], gold [101], palladium [102], nickel [103], copper [104]); metal oxides (copper oxide [105], cobalt oxide [106], nickel oxide [107], manganese oxide [108], zinc oxide [109], iron oxide [110]); metal complexes (nickel hexacyanoferrate [111]); alloys (platinum-Lead [112], platinum-ruthenium [113], platinum-iridium [114], platinum-nickel [115], platinum-gold [116], gold-silver [117], gold-ruthenium [118], gold-copper [119]), nickel oxide/carbon [120], platinum/nickel oxide [121], copper/nickel oxide [122], copper/zinc oxide [123], copper/copper oxide [124], palladium/copper oxide [125], titanium dioxide/copper oxide [126], cadmium oxide/nickel oxide [127]); quantum dots (cadmium telluride [128], zinc sulfide [129], cadmium sulfide [130]); polymers (polyaniline [131], *N*-isopropylacrylamide [132]); and carbon based materials (fullerene [133], carbon nanotubes and graphene [134], carbon nanofibers [135]). This review has concentrated solely on presenting the exclusive nature of electrospun nanofibers and their composites for the efficient development of glucose sensors.

Electrospinning approach

Electrospinning has been considered to be an effective method for the fabrication of nanofibers from a wide range of materials. Among the prominent ranges of materials, electrospinning produces nanofibers of polymers, composites, ceramics, and supramolecular structures [136–140]. The comprehensive understanding on the various parameters and processes involved for nanofiber formation permits us to fabricate the desired fiber assemblies. Technically, the process of

electrospinning is defined as the uniaxial elongation of a jet, released from the charged polymer solution in the presence of a strong electric field. The factors affecting the diameter and morphology of the electrospun nanofibers are generally divided into two major categories; materials-related parameters (polymer type, molecular weight, solvent type, viscosity, solution conductivity, surface tension, etc.) and electrospinning process parameters (applied voltage, distance between electrodes, flow rate, nozzle diameter, collector type, etc.) [141–151]. The uniform and defect-free (bead-free) electrospun nanofibers display various features, including high surface area, coupled with excellent porosity, high structural and mechanical properties, flexibility, low basis weight, and cost effectiveness nature. The most compelling benefit in the entire electrospinning process is their efficiency to completely lace together a variety of functional molecules/particles into a nanofibers matrix. Moreover, these functional molecules/particles either disperse into the polymer solution, followed by electrospinning them to produce composites in the form of continuous nanofibers (named in-situ approach) or attaching on the nanofibrous assemblies (named ex-situ approach). Both of the resulting products possess enhanced manufacturing capabilities and use a facile technique and carry remarkable flexibility [151–153]. The eminent feature of high flexibility aids in their easy handling and maintains their reproducibility. In order to obtain high sensitivity towards the analyte, the selection of substrate supporting effective loading of enzymes is essential. High-surface area, optimum porosity, and chemical inertness are some of the ideal features essential to obtain elevated performance for the sensors. Till now, several nanostructured materials have been used successfully as support matrix, including porous silica structures and nanoparticles; and also various approaches can be adopted for the immobilization of enzyme including physical adsorption, cross-linking, and self-assembly [154–156]. The nanoparticles usually limit the mass transfer rate and are also difficult to recycle. Out of different host materials, electrospun fibrous membrane proves to be efficient for achieving improved sensing performance because of its appealing feature of a large surface area and porous structure facilitating enhanced functionalization and high loading capacity, stability, and long life time of enzymes.

There has been great interest in the fabrication of electrospun metal oxide nanofibers and noble metal nanofibers for glucose detection, as these tend to form highly porous three-dimensional networks, possessing high conductivity, minimized diffusion resistance for analytes, and enhanced electron transfer. One of the simplest methods of incorporating glucose oxidase in the nanofibers is by mixing glucose oxidase into the solution, followed by the process of electrospinning, and subsequent change in the current has been noted following immersion of electrospun coated electrode into the glucose solution. A serious problem

encountered in enzyme-based sensor is the loss of enzyme activity attributable to the change in the environmental parameters since the enzymes are used to denature under varying the pH values and temperature. Therefore, protecting the enzymes is of great importance in designing biosensors to enhance the performance. As we looked for further details in the literature, electrospun-based nanofibers and their composites proved to overcome the disadvantages confronted in previous investigations, thus enhancing the overall sensing performance of glucose [29, 36, 157]. This technique has elaborated the stability of the enzymes and their extended application. The following sections brief the importance of electrospun nanofiber based glucose sensing performance under several aspects. We extend our apologies to authors whose works have been unintentionally left out.

Composite fibers

Increasing attention has been devoted for the development of composite materials owing to their ability to combine the features of two components. Current applications have used unique properties of nanoparticles to be delivered as fillers of composites or as coating materials. It is the property of this polymer-nanoparticle composite that has enhanced the flexibility, stability, and the conformational ability for the formation of complicated structures, while retaining the nanoparticle traits [158–160]. While the polymer network serves as a template medium, it also acts as the stabilizing agent for the nanoparticles on a long-term basis and proves to be a landmark in protecting their usability and function. One of the key parameters that are responsible for enhancing the performance of the composites includes the uniform distribution of nanoparticles in the polymer matrix. Selectivity promoted by surface modification plays a major role for sensor application. However, due to the large specific surface energy, the nanoparticles have shown a tendency to aggregate [161, 162], resulting in unavoidable circumstances, as the nanoparticles start to distribute inhomogeneously in the polymer matrix, finally losing their function. Despite introducing several methods to prepare composites, challenges have been faced, including random distribution and aggregation of nanoparticles in polymer matrix.

Proving to be an attractive metal for the oxidation of glucose, the catalytic activity of gold (Au) toward glucose oxidation is said to be increased by depositing Au nanoparticles on a supporting matrix [163, 164]. This is evident in the works of Li, C. et al., in 2012, where an enzymeless glucose biosensor based on polypyrrole nanofibers-supporting Au nanoparticles (Au/PPyNFs) is demonstrated [165]. Polypyrrole nanofibers (PPyNFs) have been considered as one of the leading conducting polymers and are widely used as a supporting matrix in electrochemical sensors. Their wide usage is attributed to good physical and electrical properties, excellent

environment stability and biocompatibility, and ease of preparation. Considerable effort has been gained for the application of conducting polymer to bioelectronic surfaces to resolve the challenges posed by enzyme-based biosensors [166, 167]. This has been made possible by increasing the signal-to-noise ratio and thereby serving as a suitable matrix for the immobilization and entrapment of enzymes.

The recent investigation has also supported the functional retaining of GOx post-entrapment in conducting polymers, and is found to be more resistant to denaturation towards changes in pH or temperature [168]. A new and novel approach was demonstrated by Yang G. et al., for the fabrication of enzyme entrapped conducting polymer nanofibers, thus offering higher sensitivity and increased life time compared with conducting polymer film counterparts [169]. Sufficient research has been done on the application of poly(3,4-ethylenedioxythiophene) (PEDOT) in amperometric biosensors because of its higher chemical stability and electrical conductivity [170]. Figure 2a–e display the fabrication process of GOx-incorporated PEDOT on the microelectrode array. The process involves the electrodeposition of the GOx incorporated-PEDOT films (PEDOT F-GOx) onto the surface of platinum (Pt) microelectrode arrays by electropolymerization. Then, the poly(L-lactide) (PLLA) nanofibers were produced directly on Pt microelectrode arrays to obtain GOx incorporated-PEDOT nanofibers (PEDOT NFs-GOx). To obtain GOx-incorporated PEDOT nanofibers (PEDOT NFs-GOx), poly(L-lactide) (PLLA) nanofibers were first directly electrospun on Pt microelectrode arrays. Subsequently, electrochemical deposition of PEDOT on the Pt microelectrodes and around PLLA nanofibers was performed in a similar manner to the PEDOT F-GOx. Figure 2h–m display the optical and SEM images of Pt microelectrode arrays, PEDOT F-GOx, and PEDOT NFs-GOx on the Pt sites. The authors have highlighted four advantages of the designed sensor, which are the presence of nanoscale matrix for the entrapment of GOx, reduced impedance, increased entrapment of GOx within PEDOT, and detection of glucose at lower potential.

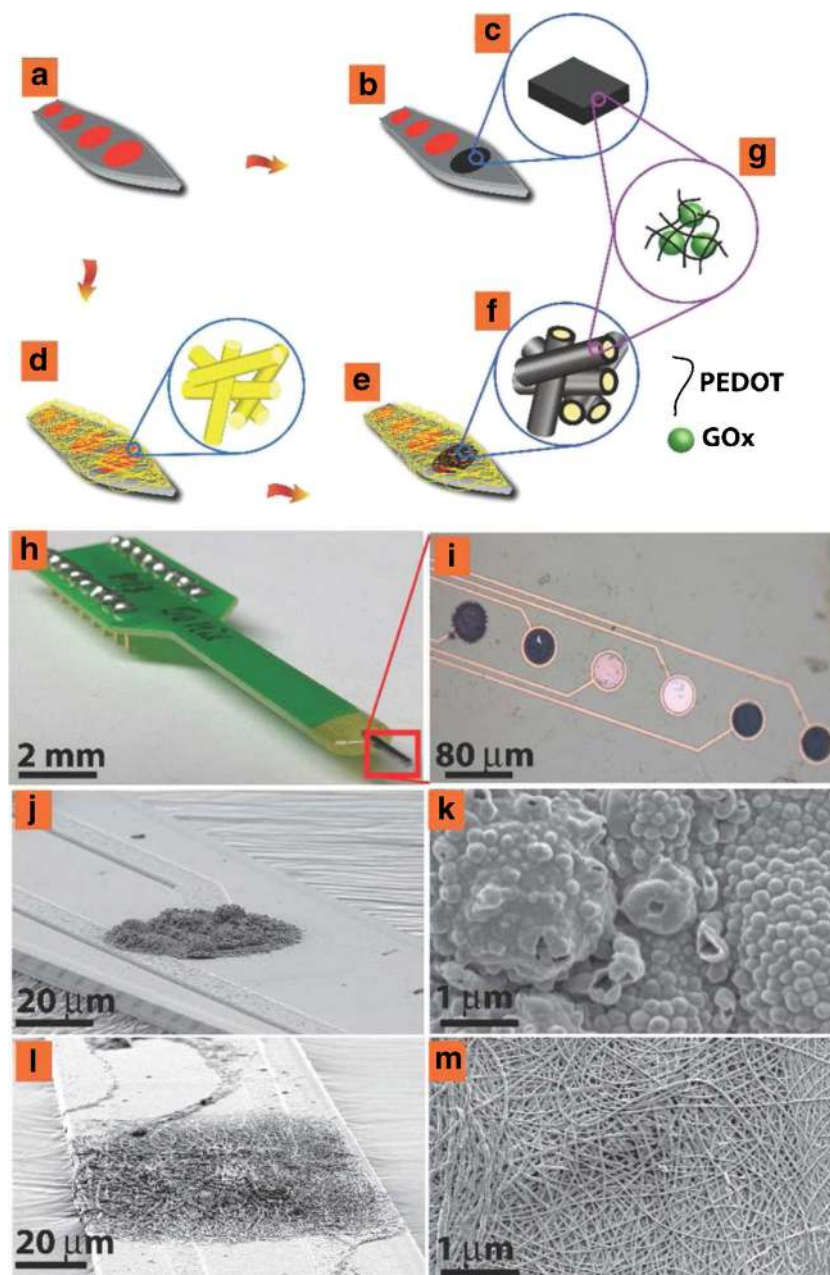
In the recent past, carbon-based nanoscale materials such as graphene [171], carbon nanofibers (CNFs) [172], carbon nanotubes (CNTs) [173], and carbon foam [174] to be used as immobilization matrix because of their strong electrocatalytic activity and minimization of surface fouling onto electrochemical devices has been explored. The immobilization of biomolecules onto the surface of electrospun carbon structures has seen the emergence of a new class of glucose sensors with improved performance characteristics. Liu Y. et al. demonstrated the nickel (Ni) nanoparticle-loaded carbon nanofiber paste (NiCFP) based nonenzymatic glucose sensor [175]. In this approach, the polyacrylonitrile (PAN)/Ni acetylacetonate (NiAA) composite fibers were prepared by using electrospinning method. Then, electrospun PAN/NiAA

composite fibers were subjected to carbonization at highest temperature to obtain Ni loaded carbon nanofiber (diameter 200–400 nm) nanocomposite. The SEM image of NiCF nanocomposite clearly confirmed the good distribution of Ni nanoparticles on the surface of the carbon nanofibers as demonstrated in Fig. 3A. It can be demonstrated from the TEM image that the nanoparticles, having a diameter of about 50 nm, are embedded in the CF matrix, emphasizing the fact that they are not easily detachable from the NiCF nanocomposite (Fig. 3B). Thus, the NiCFP electrodes were prepared by mixing them with mineral oil. The prepared renewable NiCFP electrodes exhibited strong and quick amperometric response with detection limit of 1 μM , without being poisoned by chloride ions. The resulting response of the proposed glucose sensor was found to be highly sensitive and stable, which can be attributed to the electrocatalytic performance of the strongly embedded Ni nanoparticles on carbon fibers and their characteristics of chemical inertness.

Among the diverse advantages of electrospun nanofibers, their capacity to adapt to the variety of nanoparticles on their surface is noteworthy [176, 177]. Recent studies by Li M. et al. demonstrated the nonenzymatic glucose detection based on series of bimetallic MCo (M = Cu, Fe, Ni, and Mn) nanoparticles anchored/embedded electrospun carbon nanofibers (CFs) [178]. The schematic representation of the preparation procedure for CuCo-CFs and the comparison of their catalytic effect to other MCo-CFs are shown in Fig. 4. The various composites such as Co-CFs, FeCo-CFs, NiCo-CFs, and MnCo-CFs were also prepared by following the same protocol. The observed results show the structural advantages of the 3-D network films and the synergistic effect of the Co(III)/Co(IV) and Cu(II)/Cu(III) redox couples, with the CuCo-CFs displaying the best detection efficiency (sensitivity of 507 $\mu\text{A cm}^{-2} \text{ mM}^{-1}$, with a response time within 2 s, a linear range from 0.02 to 11 mM), good reproducibility, and long-term stability. The outcome has shown that the catalytic abilities follow the order of CuCo-CFs > FeCo-CFs > NiCo-CFs > Co-CFs > MnCo-CFs. It is notable that the high surface-to-volume ratio, complex pore structure, and extremely long length of electrospun CuCo-CFs render the direct electrocatalytic oxidation and amperometric detection of glucose.

Uzun, S. D. et al. have successfully displayed an efficient surface design based on functional composite fibers for effective encapsulation of biomolecules [179]. The graphite rod electrode surfaces was first modified by coating with nylon 6,6 nanofibers and 4% (w/w) multiwalled carbon nanotubes (MWCNTs), incorporating nylon 6,6 nanofibers (nylon 6,6/4MWCNT). Then, conductive polymer PBIBA (poly-4-(4,7-di(thiophen-2-yl)-1H-benzo[d]imidazol-2-yl)benzaldehyde) was uniformly coated on nylon 6,6 and nylon 6,6/4MWCNT fibers to obtain a high electroactive surface as illustrated in Fig. 5a, b. The observed results confirmed the uniform coating of PBIBA all over the nanofiber surface, which might be the

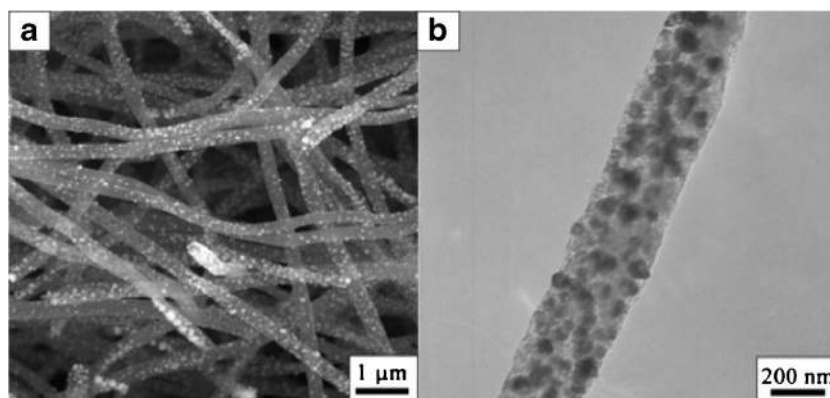
Fig. 2 Schematic of fabrication process of GOx-incorporated PEDOT on the microelectrode array: (a) Pt microelectrode array. (b), (c) Electrodeposition of GOx-incorporated PEDOT film (PEDOT F-GOx). (c) Electrospinning of PLLA nanofibers on the microelectrode array. (d), (f) Electrodeposition of PEDOT around the PLLA nanofibers to form GOx-incorporated PEDOT nanofibers (PEDOT NF-GOx). (g) Schematic of entrapment of GOx within PEDOT structure. (h) Optical micrograph of entire microelectrode array. (i) Optical micrograph of microfabricated electrodes showing two uncoated Pt sites and four GOx-incorporated PEDOT sites. (j) Scanning electron micrograph of PEDOT F-GOx. (k) Higher magnification SEM of PEDOT F-GOx. (l) Scanning electron micrograph of PEDOT NFs-GOx. (m) Higher magnification SEM of PEDOT NFs-GOx. [Reprinted with permission from [169] © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim]



result of the porous morphology. The proposed surface design is expected to increase the surface area of the coated conducting polymer. The presence of aldehyde groups in polymeric structures facilitates the effective immobilization of glucose oxidase (GOx), considered to be a model enzyme by covalent binding. Owing to the rough structure of the surface, these enzyme molecules can easily penetrate into the polymeric layer. Thus, the most efficient, stable platform has been prepared by combining the PBIBA and nanofibers. This was due to the strong covalent bonds between GOx and nanofibrous composite coated surfaces. The produced glucose biosensors reveal good stability, promising I_{\max} values (10.03 and 16.67 μA for nylon 6,6/PBIBA and nylon 6,6/4MWCNT/PBIBA modified biosensors, respectively).

Particular detailing has been provided to the direct electron transfer (DET)-based detection towards the advancement of mediator less biosensors (i.e., devices that do not want any extra reagents in a sample to detect the enzyme's substrate). This method, called the DET, occurs between the active redox enzymes and conductive nanomaterials, playing a critical role in developing electrochemical devices [180, 181]. As can be seen, if an enzyme that is immobilized on an electrode surface is found to be capable of DET and retain its bioactivity, it is utilized in sensors without adding mediators or promoters

Fig. 3 SEM image (A), TEM image (B), and EDX spectra (C) of the NiCF nanocomposite. [Reprinted with permission from [175] © 2009 Elsevier B.V.]



onto the electrode surface or into the solution. However, it is quite difficult for an enzyme to achieve a direct electrochemical reaction because of several factors. One would include denaturation of enzymes when they are adsorbed on the electrode surface, resulting in loss of their electrochemical activities and bioactivities. Secondly, the large 3-D structure of enzymes and the resulting inaccessibility of the redox centers prove them to be complex to get the desired DET between enzymes and electrode surfaces. Interestingly, much effort has been applied to devise solutions for the issues discussed above, resulting in varied degrees of success.

Zhang, X. et al. developed a DET-based glucose biosensor based on nitrogen-doped carbon nanospheres@carbon nanofiber (NCNSs@CNFs) composite [182]. The electrospun polypyrrole nanospheres doped polyacrylonitrile nanofibers (PPyNSs@PAN NFs) is subjected to thermal treatment to obtain NCNSs@CNFs. Thus, the as-prepared material can serve as an ideal substrate for the immobilization of GOx and realize the efficiency of DET of GOx without any pretreatment. Also, the mass diffusion of the matrices can be improved by the highly porous open structure of NCNSs@CNFs facilitating

the DET between the active centers of GOx and the modified electrode. In the recent past, studies have determined that the change in the GOx structure was the underlying reason for the denaturation of GOx upon its absorption on the nanostructured surface and the subsequent loss of enzyme function. Interestingly, the observed results have highlighted the prominence of electrospun NCNSs@CNFs composite film to serve as a convincing platform for the construction of the DET based sensors.

Metal oxide nanofibers

As the properties of the substrate material prove to have a direct influence on the faradaic current of glucose oxidation, the selection of substrate electrode plays a critical role. Hence, nanostructured one-dimensional metal oxides such as zinc oxide, cobalt oxide, copper oxide, nickel oxide, manganese oxide etc. based glucose sensors have gained increased attention, owing to their large specific surface area, high electron mobility, chemical stability, electrochemical activity, and biocompatibility [43–48]. Several efforts have been successfully

Fig. 4 Synthesis of CuCo-CFs hierarchical networks and their glucose detection performance. [Reprinted with permission from [178] © 2014 Elsevier B.V.]

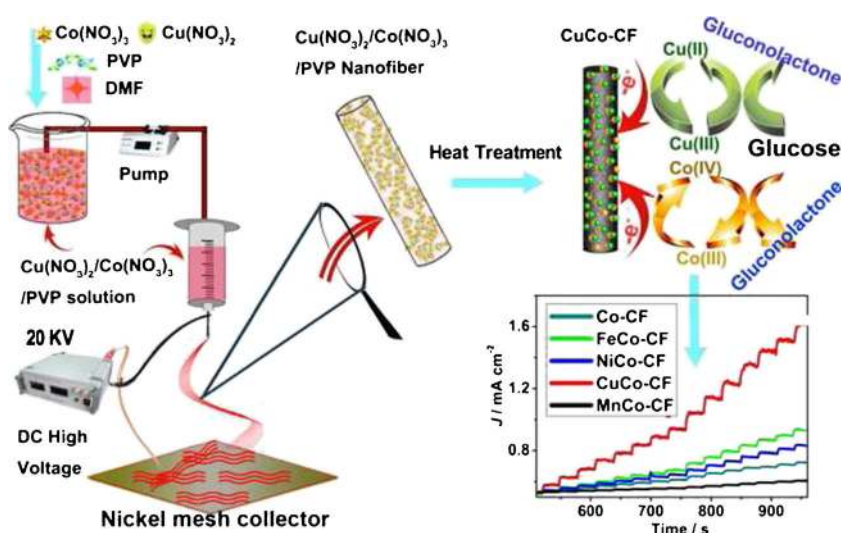
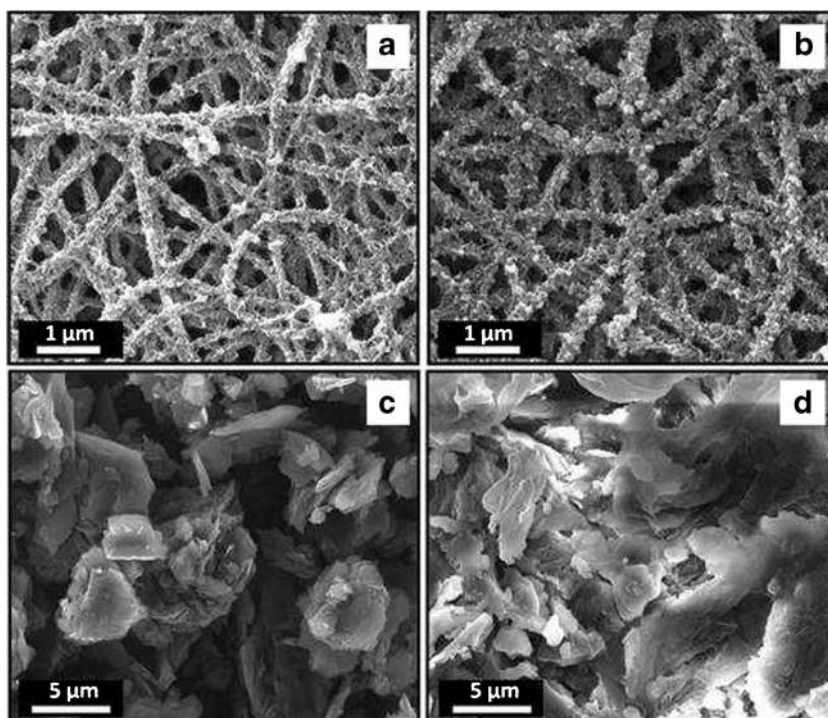


Fig. 5 Representative SEM images of (a) nylon 6,6/PBIBA and (b) nylon 6,6/4MWCNT/PBIBA surfaces before GOx immobilization; (c) nylon 6,6/PBIBA and (d) nylon 6,6/4MWCNT/PBIBA surfaces after GOx immobilization under optimized conditions. [Reprinted with permission from [179] © 2014 American Chemical Society]



forwarded by various research groups for the efficient preparation of metal oxide nanofibers using electrospinning method. The resulting outcome emphasized the emergence of the electrospinning method to be a compelling technique for the construction of composite and inorganic nanofibers that has various applications including glucose sensor [183–197]. Metal oxide nanofibers are prepared in a two-step procedure (i.e., first the organic phase in composite nanofibers is removed via calcinations at high temperature). The key factors playing an important role in determining the morphology and properties of the metal oxide nanofiber include calcination temperature, heating rate, time, and environment. Recent studies and analyses have proven that the metal oxide nanofibers exhibit solid performance for the detection of glucose in the absence of enzymes.

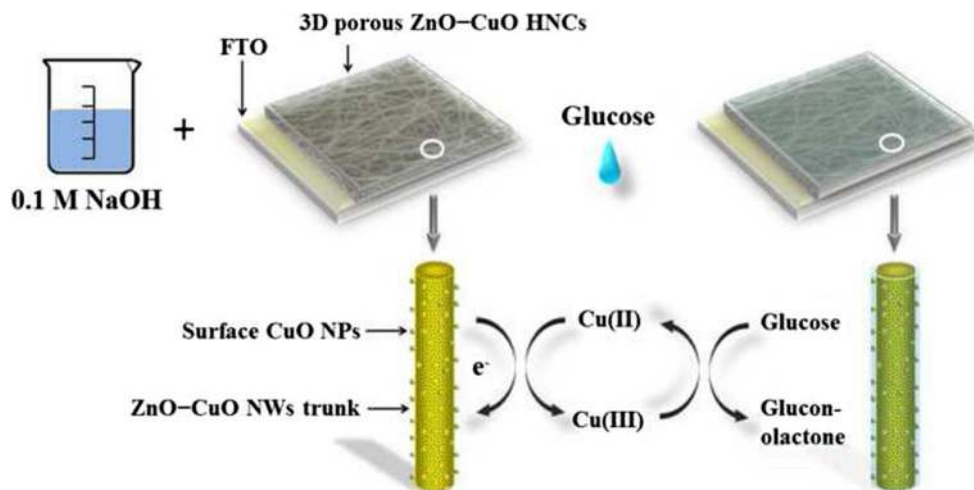
Following this, the electrochemical properties of metal oxide nanofibers have been improved by incorporating several metals and nanoparticles [28, 198–200]. Reported to be one of the most prominent materials, zinc oxide (ZnO) nanofibers possess significant characteristics of biocompatibility, nontoxicity, stability, and electrochemical activities. A three-dimensional network was devised by Zhou, C. et al. [201] consisting of 1D ZnO–CuO hierarchical nanocomposites (HNCs) and studied their enzymeless sensing properties by varying the thickness of three-dimensional network towards glucose. For a comparison study, pure CuO NWs and mixed ZnO/CuO NWs were also prepared by electrospinning. The resulting response of the nonenzymatic process towards glucose is as shown in Fig. 6. High demand has been observed for reducing the sensor to a single probe level due to it lower

financial profit, high sensitivity with lower detection limit and faster response time.

Ahmad, M. et al. have successfully demonstrated a single ZnO nanofiber (ZnO-NF)-based highly sensitive amperometric glucose sensor [190]. In the study, the ZnO-NF was prepared by calcination of electrospun poly(vinyl pyrrolidone) (PVP)/zinc acetate composite fiber. The fabrication of single NF-based glucose sensor and its mechanism is illustrated in Fig. 7. First, using a high resolution microscope, the ZnO-NF is transferred to a conventional gold electrode (with 3 mm diameter). This is followed by wetting the as-prepared ZnO-NF/gold electrode by phosphate buffer (PB) solution and subsequent air drying for 2 h. Since the ZnO-NF is known to have poor adhesion towards the supporting materials, it is strongly expected to decrease sensitivity and selectivity over time. Thus, poly(vinyl alcohol) (PVA) solution is dropped onto the ZnO-NF/gold electrode, followed by drying to form a film on the individual NF, after which GOx/L-Cys is added on the surface of the ZnO-NF/gold electrode. Here, the washing step is adopted to remove the excess amount of adsorbed GOx on the surface of electrode. Thus, the altered electrode for glucose sensor is finally fabricated and obtained.

The sensing mechanism involves the oxidation of glucose by GOx(OX) to gluconolactone, while reduction of GOx(OX) takes place to form GOx(R). By reacting with the oxygen present in the solution, the consumed GOx(OX) could be regenerated from GOx(R). Consequently, hydrogen peroxide (H₂O₂) production occurs in this process, which can be quantitatively detected on the modified electrode (please refer to equation in Fig. 7a).

Fig. 6 Reaction mechanism of 3D porous ZnO–CuO HNCs electrodes. [Reprinted with permission from [201] © 2014 Nature Publishing Group]

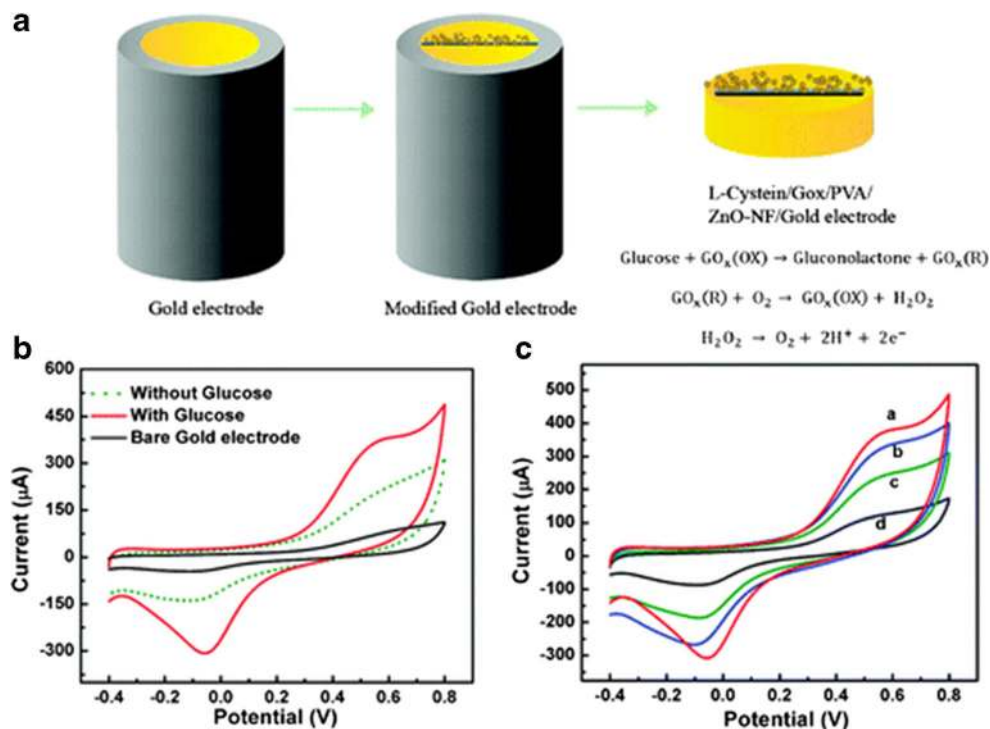


The cyclic voltammetric (CV) sweep curves of the bare (black line) and ZnO-NF-modified gold electrode without glucose (dotted line) and with 100 μM glucose (red line) at the scan rate of 100 mVs^{-1} in the range -0.4 to 0.8 V is clearly displayed in Fig. 7b. In contrast to the bare and modified electrode without glucose, there is significant increase in the oxidation current, relating to the oxidation of glucose by GOx catalysis. Additional attention is required for the stability of the nanofibers morphology because of the damaging property of the metal oxide nanofiber when being transferred on the electrode. Also, critical factors such as calcination, temperature, heating rate, and environment play vital roles in proving

the properties of the nanofibers. Interestingly, two major events were observed during the calcination of composite nanofibers; the escapist attitude of polymers after decomposition and the crystallization of the metal oxide nanoparticles [202].

In general, the process of electrode preparation involves the dispersion of metal oxide nanofibers in suitable solvents by using the process of ultrasonication, followed by casting the suspension to the electrode surface to immobilize metal oxide nanofibers. In addition to the challenge of being time-consuming, this process also was found to affect the morphology [203]. An efficient method was demonstrated by Liu, G.

Fig. 7 (a) Schematic presentation of the modified gold electrode and the mechanism of the glucose sensing on the modified electrode. (b) Cyclic voltammograms of the bare and modified gold electrode without and with 100 μM glucose in pH 7.0 PB solution. (c) Cyclic voltammograms of the biosensor in PB solution (pH 7.0) containing 100 μM glucose at a scan rate of (a) 100 mVs^{-1} , (b) 80, (c) 50, and (d) 20 mVs^{-1} . [Reprinted with permission from [190]. © 2010 American Chemical Society]



et al. for enhancing the stability and sensing performances of CuO NFs–ITO nonenzymatic glucose sensors, based on in situ electrospinning fiber [204].

First, the precursor solution with $\text{Cu}(\text{NO}_3)_2$ dissolved in poly(vinyl pyrrolidone) (PVP) was subjected to direct electrospinning on an indium tin oxide (ITO) surface. Then, calcination was performed in air to remove the matrix polymer of PVP and subsequently convert the precursor fibers into CuO nanofibers. Electrode preparation by this technique was found to be simple, convenient, and, most importantly, ensured fast electron transfer between the CuO nanofibers and the ITO electrode, which improved the overall sensitivity of the sensor towards glucose. Since the CuO nanofibers on the ITO surface possess high stability and faster response towards glucose, it is convenient to directly use them as a working electrode for detection of glucose.

Furthermore, research has been directed towards the enhancement of sensing performance by using synergistic effects of two components. It has been observed that the immobilization of metal nanoparticles onto the metal oxide nanofibers increases the sensitivity of the sensor. The fabrication of silver nanoparticles modified cupric oxide nanofibers (Ag/CuO NFs) for nonenzymatic glucose sensors has been performed by Zheng, B. et al. [189]. Figure 8 schematically describes the preparation process for Ag/CuO NFs on ITO electrodes. Interestingly, it has been found that the response time is faster than the enzyme-based glucose sensor because of its direct deposition of electrospun NFs on the ITO electrode surface. Although there exists a narrow linear working range as seen in Fig. 9D, the sensitivity of the Ag/CuO NFs–ITO towards glucose at 0.50 V is about 2.4-fold higher than the CuO NFs–ITO. The resulting outcomes stress the

enhancement of sensor sensitivity by the incorporation of AgNPs into CuO NFs. The underlying reason behind the mechanism is that AgNPs not only improve the electron transfer between the Ag/CuO hybrid NFs and the ITO electrode but also between the Ag/CuO NFs and the glucose molecules present in the solution.

Recent reports have shown that the well-defined porous nanostructures are proven to be ideal electrode materials towards glucose oxidation as they possess larger surface area, high porosity, and open geometry, reinforcing the mass and electron transport of electrolytes at the electrode–electrolyte interface. Three different kinds of electrospin-based nanofibers (NiO–Ag nanofibers, NiO nanofibers, and porous Ag) have been prepared by Ding, Y. et al. [198]. The preparation method is a two-step procedure that involves the electrospinning of $\text{Ni}(\text{NO}_3)_2$ – AgNO_3 –PVP, $\text{Ni}(\text{NO}_3)_2$ –PVP, and AgNO_3 –PVP precursor nanofibers and a subsequent calcination process as described earlier.

In order to investigate the potential application of the prepared nanofibers in nonenzymatic glucose sensing, a comparative study has been performed. Subsequent results highlight the improved electrocatalytic property towards glucose electro-oxidation for NiO–Ag hybrid nanofibers, compared with pure NiO nanofibers or porous Ag. For successful application in sensors, selectivity is as challenging as important to nonenzymatic glucose sensors because of the coexistence of the oxidative species such as ascorbic acid (AA) and uric acid (UA) with glucose in human blood, and the lack of such selectivity is a major drawback in nonenzymatic glucose sensors. The response of the porous Ag/GCE to 0.125 mM AA and 0.33 mM UA is shown in Fig 10A, which clearly indicates the porous Ag/GCE exhibited 17-fold and 55-fold higher

Fig. 8 The preparation process of Ag/CuO NFs–ITO electrode. [Reprinted with permission from [189] © 2014 Elsevier B.V.]

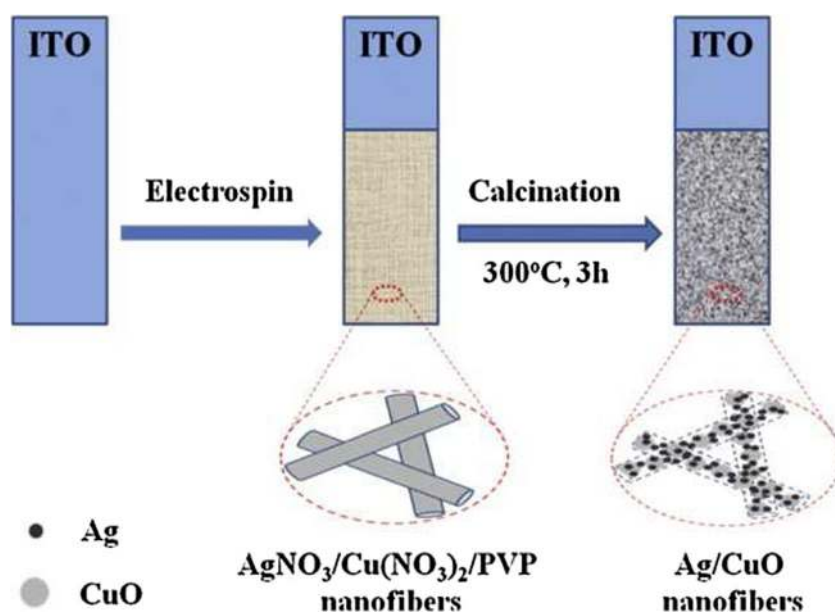
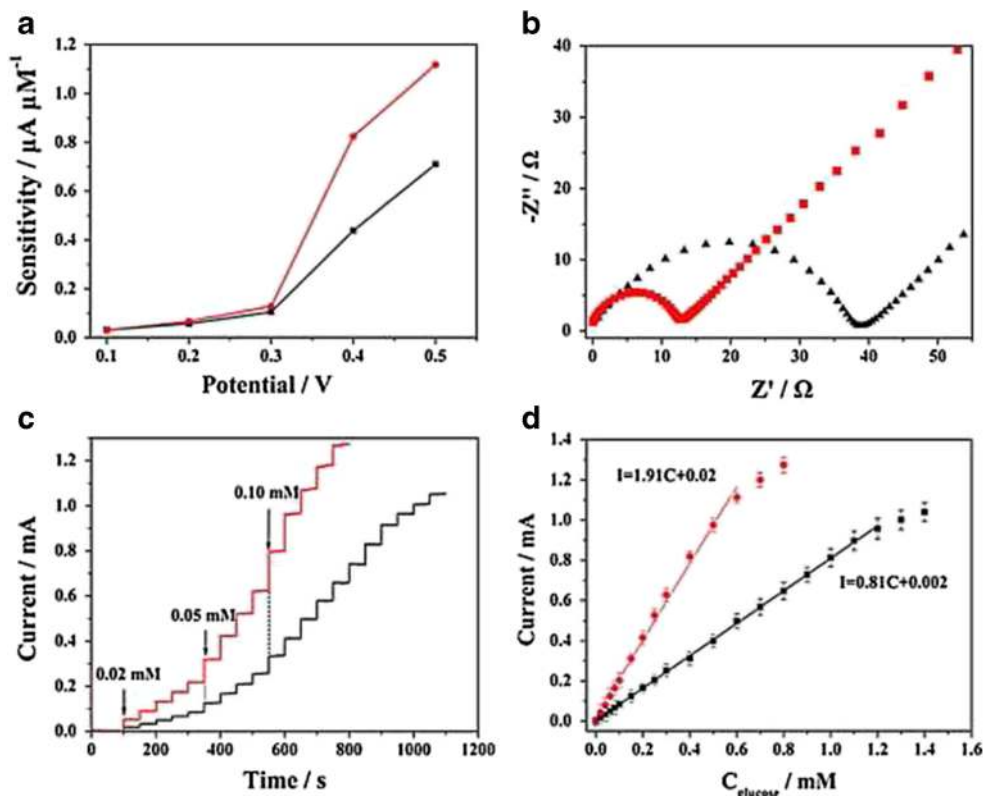


Fig. 9 (A) Effect of applied potential on the sensitivity of Ag/CuO NFs-ITO and CuO NFs-ITO electrodes to glucose. (B) Nyquist plots of Ag/CuO NFs-ITO and CuO NFs-ITO electrodes in 0.10 M KCl solution containing 5.0 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ redox couple. (C) Amperometric response of Ag/CuO NFs-ITO and CuO NFs-ITO to successive additions of glucose at an applied potential of 0.50 V. (D) Calibration curves obtained from (C). Red and black lines are Ag/CuO NFs-ITO and CuO NFs-ITO electrode, respectively. (The preparation process of Ag/CuO NFs-ITO electrode. [Reprinted with permission from [189] © 2014 Elsevier B.V.]



response than that of 4 mM glucose at 0.1 V. Better explanation can be offered by the catalytic activity of porous Ag towards AA and UA oxidation.

Colorimetric detection

Over the past few decades, remarkable advancement has been achieved in the development of glucose sensors by taking the benefits of huge number of several nanostructured materials. Most of the efficient analytical tests are time-consuming, require complicated data-collection and processing procedures, and involve sophisticated scientific instruments and professional operators. These procedures turn out to be expensive and thereby limit their extensive application. Among these methods, the colorimetric approach proves to be promising in addressing all these issues with ease, attributed to its low cost, simplicity, and practicality. This method proves to be advantageous such that the color change occurring in the presence of analytes can be read out by the naked eye without the need for any sophisticated instrument. The resulting features of the colorimetric sensor provide more comfort for field analysis and point-of-care diagnosis [205–209]. Recent past has observed the study of several fluorescent probes and their colorimetric sensing performance in various analytes such as toxic metal pollutant and explosives [210–212].

Furthermore, other varieties of solid matrices have also been successfully adopted to integrate the fluorescent probes,

thereby improving the overall sensor performance for field applications [213–216]. The resulting solid support proves to be an ideal platform to retain their stability against varied atmosphere conditions and also provide easy accessibility to probe analytes. Nevertheless, many of the selected supports do not meet the demands, and persistently affect the reactivity and sensitivity of the sensor performance. Although sufficient selectivity and high sensitivity are obtained with these enzymatic sensors, the disadvantages, including chemical and thermal instabilities originating from the intrinsic nature of enzymes and complicated fabrication procedures, limit their analytical applications. Interestingly, electrospun nanofibers prove to dismiss all these detriments owing to their large surface area and excellent flexibility. This section focuses on the various developments in the field of colorimetric sensing using electrospun nanofibers.

Ji, X. et al. have demonstrated a novel “ready-to-use” glucose test strip based on a polyurethane hollow nanofiber membrane by utilizing two commonly used chromogenic agents, 2, 2'-azinobis-(3-ethylbenzthiazoline-6-sulphonate) and *o*-dianisidine as probes [217]. A coaxial electrospinning procedure has been set up to prepare the hollow nanofiber membrane-based testing strips for glucose measurement. A schematic illustration of the set-up for coaxial electrospinning and the reaction mechanism of the bi-enzyme system for glucose detection are shown in Fig. 11. For colorimetric detection, glucose oxidase (GOD), horseradish peroxidase (HRP),

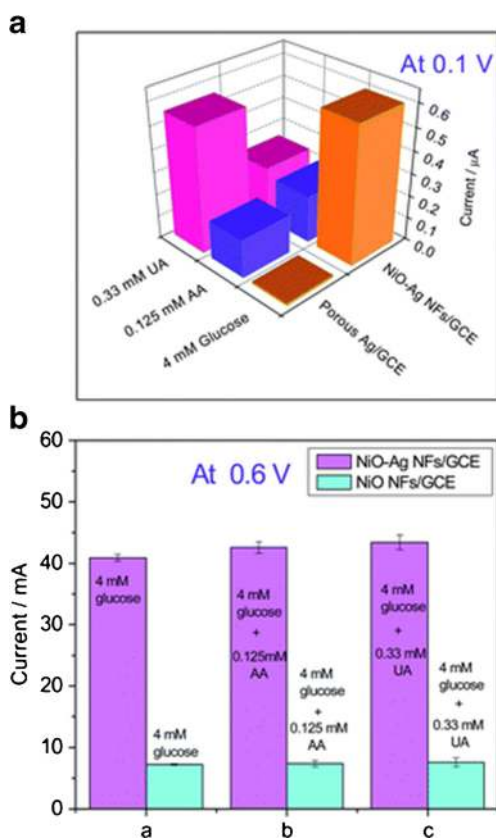


Fig. 10 (A) The response of the porous Ag/GCE and the NiO-Ag NFs/GCE to the addition of 4 mM glucose, 0.125 mM AA, and 0.33 mM UA in 0.1 M NaOH at an applied potential of 0.1 V; (B) the response of the NiO NFs/GCE and the NiO-Ag NFs/GCE to the addition of 4 mM glucose, 4 mM glucose with 0.125 mM AA, and 4 mM glucose with 0.33 mM UA in 0.1 M NaOH at an applied potential of 0.6 V. [Reprinted with permission from [198] © 2010 Royal Society of Chemistry]

and chromogenic agent (ABTS or *o*-dianisidine) co-immobilized as a spun hollow nanofiber membrane was immersed in different concentrations of glucose solution (1 mL) prepared using PBS buffer (pH 7.0, 50 mM). Similarly, a control test was performed with blank hollow nanofibers that have no enzymes and chromogenic agent. At first, small round-shaped sensor strips in the diameter of 10 mm were prepared by cutting hollow nanofiber membranes immobilized with GOD, HRP, and *o*-dianisidine, and then 10 μ L of glucose solutions at varied concentrations were added onto the sensor strips. The prepared test strips can be operated in “dip-and-read” mode as an optical biosensor because of their unique “all-in-one” feature.

The visual colorimetric detection of test strips upon the addition of 10 μ L glucose samples of different concentrations is shown in Fig. 12. A quick formation of rufous color spot was noticed on the surface of the *o*-dianisidine-test strip following addition and the maximum intensity of the color reached at about 30 s, and further it was stable for 10 min. Notably, the increases in color intensity correspond to the

increase in glucose concentration. As can be seen from Fig. 12B, an excellent correlation between the DR and glucose concentration was obtained in the range of 0.1–50 mM with a regression correlation coefficient of 0.999. The developed test strips also demonstrated excellent long-term storage stability. The prepared test strips are suitable for practical clinic applications because of their broad detection range and excellent stability. Furthermore, the simplicity in hollow nanofiber membrane preparation and also the advantages in simultaneous in situ co-immobilization of multiple substances pave a way for the development of a great variety of biosensors possessing multienzymes and coenzymes or chromogenic agents for measurement.

Due to large Stokes shift, strong photostability, high quantum efficiency, and high oxygen quenching efficiency, luminescent transition-metal complexes have been widely used for fabricating optical oxygen biosensors and glucose biosensors. Zhou, C. et al. developed a fast and sensitive glucose sensor using iridium complex-doped polystyrene electrospun optical fibrous membrane (EOF) [218]. Iridium(III) bis(2-phenylbenzothiazolatoN,C2') acetylacetonate [(bt)2Ir(acac)] was used as luminescence probe. The fibrous membrane was fabricated using a one-step electrospinning technique and further functionalized with glucose oxidases (GOD/EOF). The SEM image in Fig. 14A shows that the obtained EOF exhibits a porous fibrous membrane and its fibers are evenly and randomly distributed. The average diameter of the fiber was \sim 1.4 μ m, which was calculated from 65 diameter values of randomly selected fibers. Due to the presence of doped iridium complex, the fibrous membrane emitted yellow luminescence (562 nm) when excited at 405 nm (Fig. 14B).

Solvent compatibility is an important criterion for making composite luminescent probe for sensing. DMF (*N,N'*-dimethylformamide) was selected owing to its remarkable disperse capability for (bt)2Ir(acac). Thus, to avoid the self-quenching and leaching effects during the luminescent measurements, the (bt)2Ir(acac) molecules can be uniformly and stably doped within the PS matrix. Glucose oxidase (GOD)/EOF was prepared by covalently immobilizing GOD on the surface of EOF by using UV irradiation and glutaraldehyde cross-linking, which was further used for detection of glucose. Owing to the large surface area of the GOD/EOF, a large amount of immobilized GOD, efficient GOD biocatalyst reaction, and efficient oxygen quenching, high sensitivity and specificity and a quick response time in glucose detection can be attained. The schematic illustration of the GOD/EOF quickly detecting glucose is depicted in Fig. 13. The GOD/EOF's luminescence intensity was greatly increased following addition of glucose and reached a stable value within 1 s as illustrated in Fig. 14C.

The underlying reason for the fibrous membrane with a high surface-to-volume ratio and a porous structure, diffuse efficiency of both the glucose and oxygen molecules into the

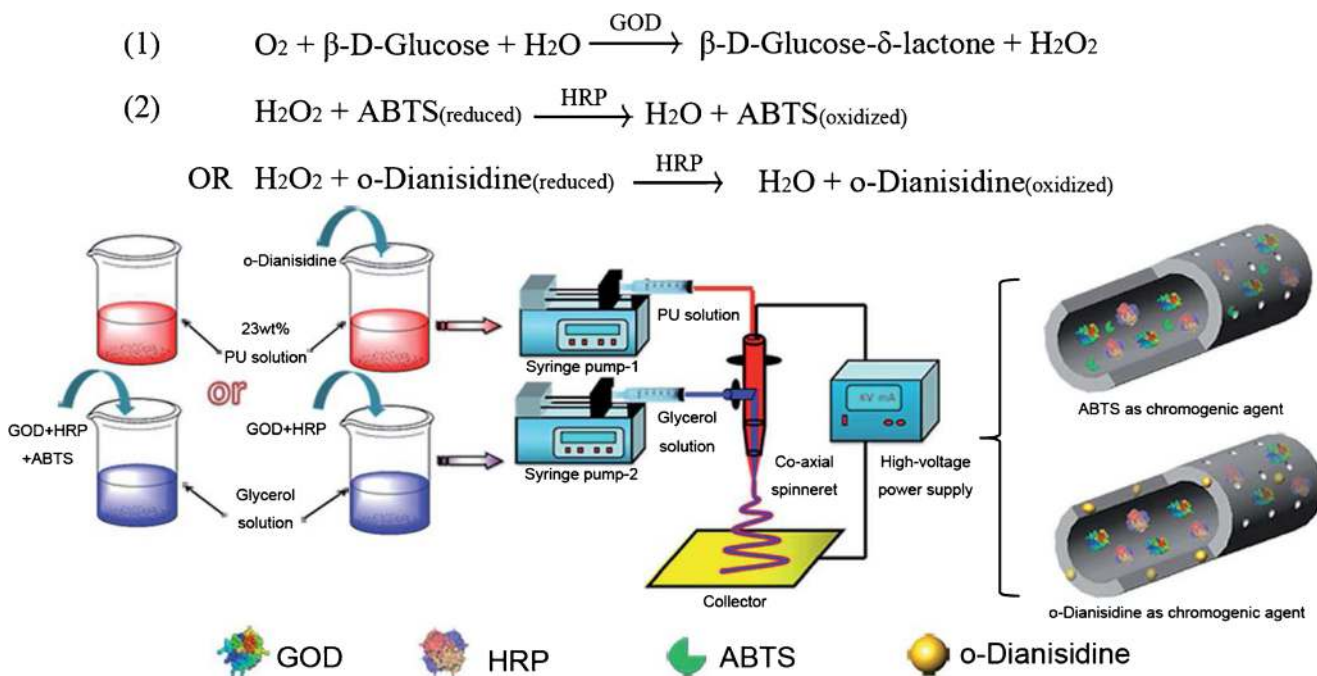


Fig. 11 Schematic illustrations of the bi-enzyme reaction for glucose measurement and the setup for coaxial electrospinning to prepare hollow nanofiber membrane-based glucose testing strips. During coaxial electrospinning, GOD, HRP, and chromogenic agent (ABTS or

odianisidine) were simultaneously immobilized in situ in the hollow nanofiber membrane. [Reprinted with permission from [217] © 2014 Royal Society of Chemistry]

EOF interior could be enhanced, as well as a fast electron or energy transfer between the fibers and dissolved oxygen could be realized. As shown in Fig. 14D, at the same level of glucose concentrations, the GOD/EOF by irradiation has higher luminescence intensity compared with that without irradiation. It was demonstrated that these irradiated PS fibers can be used as an effective biosensor support matrix for fabricating biosensors.

The detection limit was of 1.0×10^{-10} M (S/N = 3), superior to that of reported glucose biosensor with 1.2×10^{-10} M. It has been found that in diabetic patients, in vivo glucose

monitoring permits continuous glucose monitoring and facilitates intensive control of blood glucose concentrations [219–221]. One of the first applications for such a device was demonstrated by Shichiri et al. in 1982 [222]. For the current scenario, challenges posed by these systems include long-term stability, inflammatory, biofouling, calibration, and selectivity. Also, it has been found that the stability of the implantable sensors reduce the frequency of implantation and replacement, thus resulting in long-term in vivo glucose monitoring with less effort by patients and less tissue damage. This designs the ideal sensor, supporting minimum

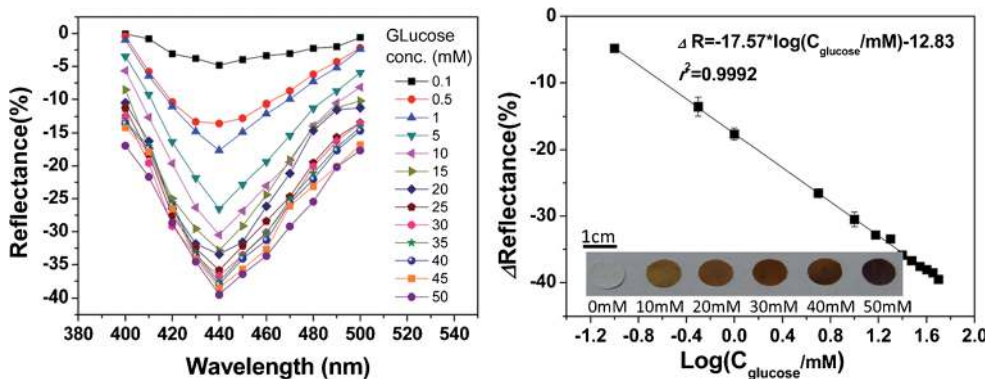
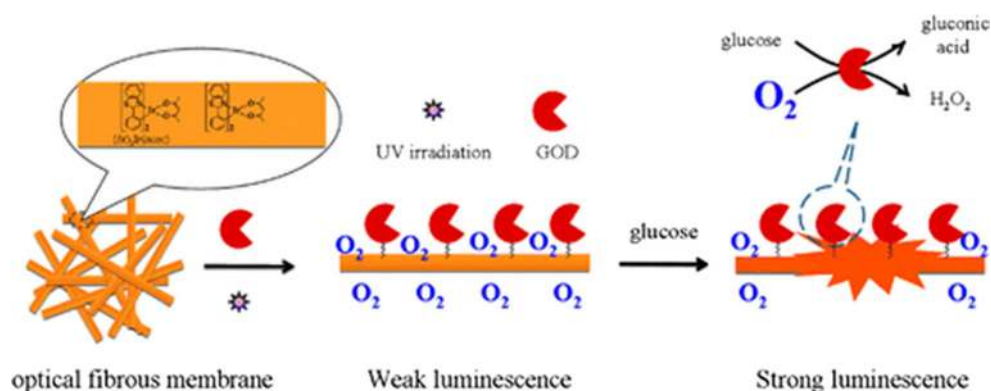


Fig. 12 Optimal detection of glucose by measuring the color intensity changes on the testing strip with *o*-dianisidine as chromogenic agent. (A) Differential reflectance spectra of the membrane test strips upon reaction with glucose solutions of different concentrations for 30 s. (B) Correlation between the ΔR of test strips and the log of glucose concentration. The

inset picture demonstrates the visual color change in response to the change in glucose concentration of the *o*-dianisidine test strip. The diameter of the membrane is 1 cm. [Reprinted with permission from [217] © 2014 Royal Society of Chemistry]

Fig. 13 Schematic illustration of the GOD/EOF quickly detecting glucose [Reprinted with permission from [218] © 2013, American Chemical Society]



replacement, thereby bringing in vivo sensor closer to practical implementation. However, the complete potentiality of long-term in vivo glucose monitoring is yet to be fully explored and realized as current fluorescence-based sensors cannot be maintained at an implantation site and their response to blood glucose concentrations over an extended period.

Although several nanosensors have been devised for in vivo glucose monitoring, their limited residence time at the site of injection proves to be challenging. Still, it has been found that the in vivo experiments show the ability of the fluorescent glucose-responsive sensors to track changes in glucose levels for up to 1 h. These issues have been addressed by immobilizing sensors within gels, microworms, etc. The microworm-based fluorescent sodium sensor was developed by Ozaydin-Ince, G. et al., and has been used for monitoring

the sodium concentration in vivo after subcutaneous injection [223].

Interestingly, it was evaluated that gel immobilization enhanced sensor residence time at the injection site over the course of 1 h [224–226]. However, it does not sustain its long life for sensor migration because of the small size of nanosensors to diffuse out of the gels. Yet, the functionality of a sensor to efficiently sustain for a longer time under physiological conditions is highly desirable. Literature shows evidence about the ability of boronic acids to irreversibly bind to glucose under physiological conditions. The first scientific study on this was reported by Yoon and Czarnik using anthracenyl boronic acid, which produced a measurable change in fluorescent intensity upon binding to glucose in solution [227].

Fig. 14 SEM image (A) and luminescence microscopy image (B) of the EOF. The inset shows the diameter distribution of the EOF. The fast response (C) of the EOF when the concentration of the added glucose increases from 1.7×10^{-9} M to 4.4×10^{-9} M. Effects of UV irradiation and GOD amount (D) in a 1.0 mM glucose solution. Each data was obtained from an average value of three replicate measurements. All relative standard derivation was less than 3.0% ($n = 3$). pH 7.0 PBS buffers. [Reprinted with permission from [218] © 2013, American Chemical Society]

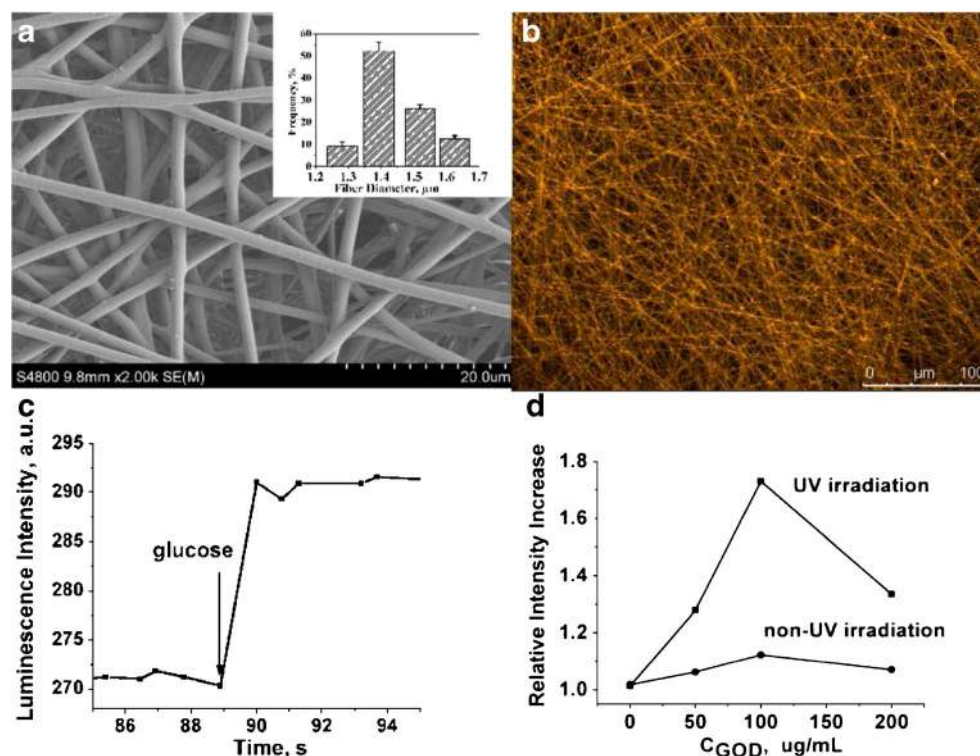
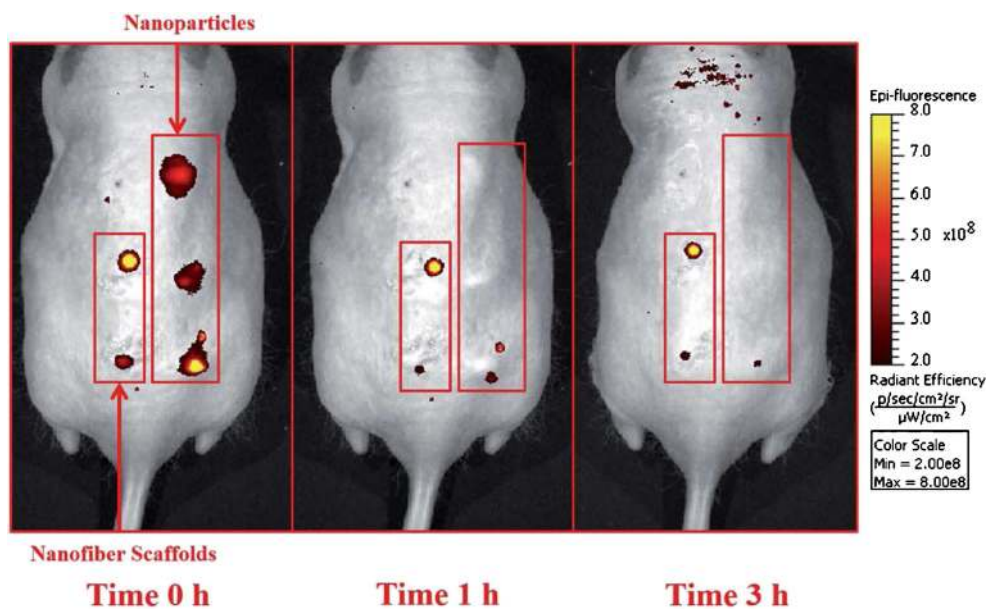


Fig. 15 In vivo comparison of glucose-sensitive nanoparticles and nanofiber scaffolds. Mice were injected with glucose-sensitive nanoparticles and nanofiber scaffolds along their backs and then imaged with a fluorescent small animal imager for 1 h and then at 3 h post-injection. Shown here are the fluorescent images from one mouse over this time frame. [Reprinted with permission from [228] © 2015 Royal Society of Chemistry]



Also, recent studies by Balaconis, M. K. et al. showed the development of a stable glucose-sensitive nanofiber for in vivo monitoring of glucose [228]. A competitive binding interaction between boronic acids and diols on either alizarin or glucose is the reason for the sensors' response to glucose. The boronic acid binds to the diol on alizarin and statically quenches the fluorescence in the absence of glucose. If the concentration of glucose increases, these molecules displace the alizarin and result in fluorescence. The spherical or nanofiber nanosensors are implanted subdermally (Fig. 15) to demonstrate that the nanofiber nanosensors enhance resident time at the

implantation site and their loss in signal is directly compared with in vitro signal loss.

As a result, the loss of radiant efficiency at the injection site is significantly higher than the signal loss observed in vitro for spherical nanosensors. The reason for in vitro signal loss is attributable to leaching of boronic acid from the hydrophobic core, and the difference in signal loss between in vivo and in vitro is ascribed to nanosensor diffusion away from the implantation site. Conversely, a very closely matched signal loss between the in vivo and in vitro experiments was noticed after 1 h, and they were further comparable after 3 h, as illustrated in Fig. 16.

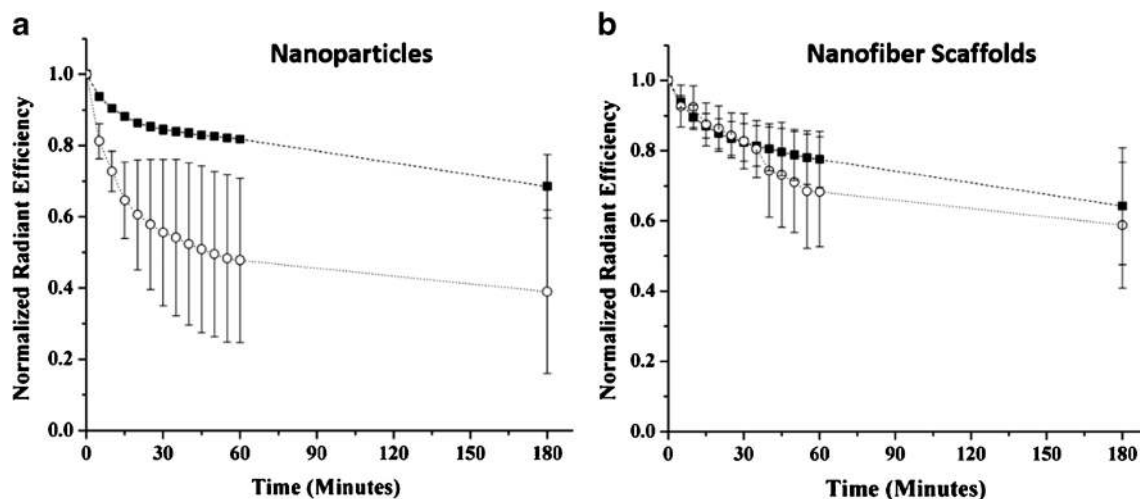


Fig. 16 Fluorescence measurements of glucose-sensitive nanoparticles and nanofiber scaffolds over time in vivo. (A) The average normalized total radiant efficiency of glucose-sensitive nanoparticle scaffolds both in vivo (○) and in vitro control (■) were plotted over time. (B) The average normalized total radiant efficiency of nanofiber scaffolds both in vivo (○) and in vitro control (■) were plotted over time. The

normalized in vivo average for nanoparticles and nanofiber scaffolds was calculated across three different mice with $n_{\text{nanoparticles}} = 8$ and $n_{\text{nanofiber scaffolds}} = 6$ injection spots. Similarly, the normalized in vitro average was calculated from $n_{\text{nanoparticles}} = 8$ and $n_{\text{nanofiber scaffolds}} = 7$. Error bars represent standard deviations. [Reprinted with permission from [228] © 2015 Royal Society of Chemistry]

Concluding remarks

This review addresses all recent notable developments in the field of electrospun nanofiber-based glucose sensors using various mechanisms. An excellent opportunity for effective immobilization of enzymes on their surface, along with enhanced interaction with analytes, improved oxidation process, and prolonged stability has been provided with the introduction of electrospun nanofibers in glucose sensing. Our in-depth analysis has implied greater performance by the electrospun nanofiber-based sensors than the existing nanomaterial-based sensors even though they are very active. Remarkable results have proven that the combination of electrospun nanofibers and incorporated functional nanomaterials provide an efficient platform for developing a potential glucose sensor. The splendid features of electrospun nanofibers, with a special emphasis on their versatility and simplicity, are considered to be advancement in glucose sensing research. Nevertheless, a major challenge in developing a sensor is its leaching effect of functional nanomaterials, biocompatibility, and toxicity. As there is limited evidence to support the toxic nature of electrospun nanofibers and their composites, the safety and risks involved are an area of concern for future use and further research. Therefore, much effort is required to further explore the integration of newer materials with nanofibers for the emergence of an ultrasensitive, biocompatible, stable, and reliable sensor device for real-world applications.

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Conflict of interest The authors declare no conflicts of interest.

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