Flexible Nanobiosensors in Biomolecular Detection and Point of Care Testing

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Abstract

Nano-scaled analytical frameworks or nanobiosensors use nano-conjugated biological materials as a transducing mechanism to detect extremely small amounts of biological, chemical, or physical analytes. Wearable technology, particularly smart gadgets, is becoming increasingly popular, and they have much promise for use in wearable healthcare equipment like ECG monitoring watches and POCT systems. This feature might open the way for personalized diagnosis and analysis,

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allowing biosensors to achieve their main goal of identifying target molecules early, accurately, and individually. Many key qualities, such as remarkable flexibility and the capacity to transmit conductivity onto the flexible material, must be addressed to produce more flexible nanobiosensors. As a result, much research has gone into creating flexible conductive substrates with cutting-edge nanomaterials and manufacturing processes. Low conductivity, brittleness, and the challenge of achieving high flexibility and conductivity in materials should be addressed by inventing and researching novel substrates that combine conductivity and flexibility. This chapter covers a variety of flexible biosensor construction methodologies and flexible material structures. The reported flexible nanobiosensors are also divided and discussed in this chapter depending on the types of target molecules and the biosensors' operating environment. Flexible nanobiosensors for body-attached biosensors for direct and in vitro molecule monitoring are the two study domains, with the hope that these approaches will help overcome and address current constraints and barriers on POCT systems.

Keywords

Nanobiosensors · Flexible sensors · Point of Care Testing · Medical Diagnosis · Polymers

1 Introduction

Point of Care Testing (POCT) and diagnosis are utilized to increase the quality of life and minimize illness, hospitalization, and death linked to a sedentary lifestyle (Price 2001). Although POCT will never totally replace standard laboratory testing, it provides several benefits in patients' health monitoring. Benefits include reduced testing time, continuous monitoring of biomolecular indicators, early detection of emergencies, no requirement for specialists (Noah and Ndangili 2019), user-friendly application, and noninvasiveness measurement. Wearable sensor signals can evaluate personal health issues (Zarei 2017; Pandya et al. 2015). In ordinary life, wearable sensors might be utilized more than simply health monitoring (Daneshpour et al. 2016; Sheeparamatti et al. 2007). They are also used for fitness and sport (Zhang et al. 2009; Lyberopoulou et al. 2016), communications (e.g., human-machine interface) (Altintas 2017; Dahlin 2012), security, business, and lifestyle needs.

Portable and flexible nanobiosensors are becoming increasingly important and popular on POCT (Noah and Ndangili 2019; Zarei 2017). Nano-scaled analytical frameworks or nanobiosensors detect extremely minute quantities of biological, chemical, or physical analytes using nano-conjugated biological materials as a transducing mechanism. The structures apply electrochemical, optical, piezoelectric, thermometric, micromechanical, or magnetic techniques to communicate the needed evidence in signals (Fig. 9.1). The generated signals are based on the idea of the linked antibody or bioligands selectively biorecognizing intracellular or surface biomarkers associated with cancer cells.

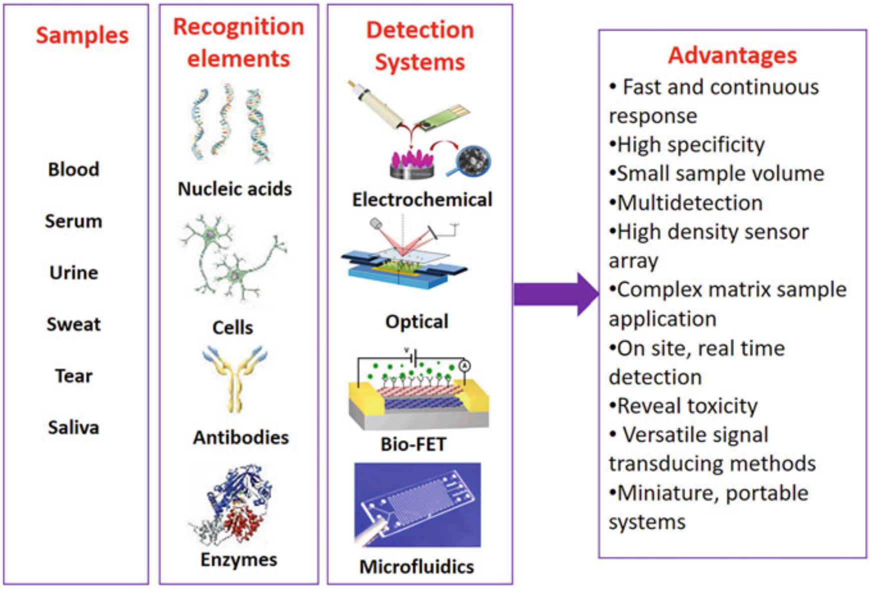

Fig. 9.1 Nanobiosensor components include target samples, biorecognition elements, and such examples of transduction systems with their advantages in analyzing tools

Nanobiosensors that are portable and flexible offer several major advantages: (1) They are more user-friendly; (2) test results may be acquired immediately without having to wait a long time; (3) manufacturing costs are low, which advantages resource-constrained areas; and (4) more appropriate for the application, they may be applied to the skin to achieve more real-time sampling (Pandya et al. 2015; Daneshpour et al. 2016; Price 2001).

2 Nanobiosensors for Point of Care Testing

Nanotechnology is a branch of science that discovers the operation of substances at the molecular and atomic levels. It entails developing and using biological, chemical, and physical systems on a 1–100 nm scale. These materials, also known as nanomaterials or nanoparticles, are revolutionizing science due to their superior chemical, physical, and biological properties, compared to their bulk complements (Sheeparamatti et al. 2007; Zhang et al. 2009), and have a wider variety of applications, particularly in optical, biomedical, catalysis, medical imaging, and electronics (Lyberopoulou et al. 2016; Zhang et al. 2009). Because of their increased catalytic characteristics, electron transport, and ability to be employed in biomolecule labeling and adsorption, they are ideally suited for biosensing (Altintas 2017). Nanoparticles' unique physicochemical features have managed to invent biosensors, such as nanosensors for illness diagnostics at the point of care.

Biosensors established on nanotechnology have several advantages. The ever-intensifying discoveries in the field of nano-biotechnology-based sensors have produced tremendous technological momentum (Dahlin 2012; Patel et al. 2016), owing to the following benefits:

1. Biomarker identification and data creation that is quick, sensitive, and accurate.
2. Consolidation of traditional detection methods into a single platform.
3. Analysis that is user-friendly, simple, and cost-effective.
4. Test sample reduction for analysis.
5. Multiplexed data can be generated from a single test.
6. The constructions have high stability, repeatability, and portability.

Despite the advantages of nanobiosensors, there are several obstacles to their clinical use (Dahlin 2012; Quesada-González and Merkoçi 2018; Dincer et al. 2017). Here are a few examples:

1. Difficulty integrating result support services that can be observed and controlled by separate devices in POC systems.
2. Additional expenditures associated with the development of biosensors for diagnostics.
3. Developing a generally applicable diagnostic test is difficult because various cancer subtypes have diverse biomarkers.
4. Multiplexing complicates design and manufacture, test formulation, and clarification.
5. Stringent characterization parameters are required to offer meaningful information on nanomaterial storage, functionalization, modification, and usage.
6. Worldwide nanomaterial safety recommendations do not address the toxicological effects of nanomaterials.
7. Valid correlation with existing technology must be demonstrated.

Nano-scaled analytical structures or nanobiosensors detect extremely minute quantities of biological, chemical, or physical analytes using nano-conjugated biological materials as a transducing mechanism. To transfer the necessary data in the formula of signals, the structures utilize electrochemical, optical, thermometric, piezoelectric, magnetic, or micromechanical methods. Nanobiosensors may be classified based on their signal transduction method and biorecognition components. Targets interact with recognition components through these nano-contexts, recognizing a quantifiable or observable signal (Fig. 9.1). The kind of detected signals is used to characterize these biosensors further.

2.1 Nanobiosensors Based on Electrochemistry

The sensor molecules in electrochemical nanosensors are physically attached to the probe surface. A detectable electrochemical signal is generated when the probe interacts strongly and specifically with the target analyte. These sensors are the most well-known sensing systems because of their great stability, sensitivity, quick reaction, and small intrusions (Pandya et al. 2015; Hu et al. 2018; Chandra et al. 2012).

2.2 Nanobiosensors with an Optical Component

Luminescence, fluorescence, FRET (fluorescence resonance energy transfer), phosphorescence, absorption, refraction, and dispersion based detection systems are all used in optical nanobiosensors to provide single or multiplexed analyte detection. Spectroscopic methods identify differentiating features such as energy, amplitude, polarization, phase, or decay time (Han et al. 2017). According to recent articles, optical nanobiosensors may successfully detect cancer biomarkers such as cysteine and miRNAs (Wang et al. 2016; Yang et al. 2017).

2.3 Nanobiosensors with High Mass Sensitivity

These biosensors use micro- or nano-dimensional cantilevers to differentiate living species automatically. The shift in the resonance frequency of the unbound and biomolecule attached cantilevers due to mechanical stimulation shows the observed mass change. Acoustic piezoelectric crystal-based sensors are widely used in mass-sensitive nanobiosensors (Wang et al. 2020; Manjakkal et al. 2019).

2.4 Nanobiosensor with a Calorimetric Sensor

Calorimetric nanobiosensors are based on the energy generated in heat during diverse biological processes. The temperature change between before and after the solution enters and departs is measured with thermistors. Heat may be used as a marker for various biological processes, allowing for nondestructive metabolic evaluations of live cells (Nantaphol et al. 2017; Khan et al. 2014).

3 The Structure of Flexible Nanobiosensors

“Flexible” biosensors, like their “stiff” counterparts, are made up of three elements: (A) a substrate that acts as the system’s basic mechanical support; (B) bioreceptor (s) that has a specific interest in the analyte(s); and (C) active materials that, depending on the detection method, transduce the signal from the bioreceptor(s). The human operator, generally using software, then translates the signals corresponding to the parameter of interest into a readable interface. Figure 9.2 depicts the main substrate components of nanobiosensors, particularly in a flexible design. Figure 9.2 also depicts some of the regions where it is planned to be used. They indicate places that have previously been targeted to detect certain biochemical

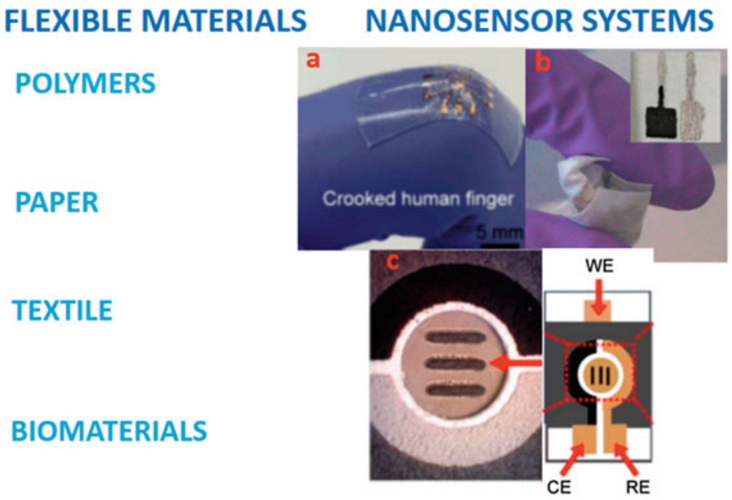

Fig. 9.2 The main substrate components of nanobiosensors, particularly in a flexible design, and some of the regions where they were previously used: (**a**) The stretchable biosensor can change the shape with the movement of the human body. (Adapted with permission from (Wang et al. 2020)); (**b**) the real picture of flexible and wrinkled pH sensor on cloth. (Reformed with permission from (Manjakkal et al. 2019)); (**c**) picture of the paper-based electrochemical device. (Adapted with permission from (Nantaphol et al. 2017). Copyright 2017 American Chemical Society)

targets or are being targeted. Mechanical flexibility, bendability, stretchability, thermal/chemical stability, transparency, biocompatibility, and biodegradability are just a few of the qualities that the substrate (A) must exhibit (Han et al. 2017; Yang et al. 2017; Wang et al. 2016).

It is worth noting that a single system can have one or more of these features, and all of them in many cases. The substrate (A) is the device's most important component, as it provides strong support, interacts with the surface, keeps the biosensor parts together, and guarantees that the device functions properly. The recognition (B) and transduction (C) elements must be combined on the substrate and stable and adaptive to the same mechanical conformations without delaminating or removing due to deformation. The following part covers the materials and fabrication/design principles used in flexible nanosensors.

3.1 Materials and Configurations

One of the most important processes in device manufacture is selecting the substrate, which serves as the basis for the biosensor. The qualities and functions result from the substrate's ability to sustain them (Khan et al. 2014; Windmiller and Wang 2013). By explanation, mechanical elasticity is a significant characteristic because it allows analytes and sensing/transducing components to interact more efficiently by adapting to the physical dynamics of essentially nonrigid and frequently nonlinear settings. For example, a substrate that adheres better to the surface's contours is more probable to offer a broad interaction area for collecting samples such as physiological liquids. While such devices are principally intended to extend the range of biomolecular recognition, they can be utilized for other applications (e.g., medication administration) (Wang et al. 2016).

Material selection may be influenced by the intended use location (e.g., external or internal location on the biological system). Some of the instances of location-based demands put on flexible devices are shown in Fig. 9.2. Surface conformability is affected by mechanical deformations. Bendability, conformability, stretchability, and wear resistance. Fracture resistance is frequently imparted using two methods: (1) use rigid conductive or semiconductive materials with specific geometrical or structural designs to impart flexibility, or (2) use stiff conductive or semiconductive materials with specific structural or geometrical designs to impart flexibility (e.g., twisting or wave patterns). While some materials and procedures discussed below were created for larger flexible devices, they represent basic design perceptions that may be adapted to flexible biosensors or have already been done. First, we will go over some of the features of mostly used flexible substrate materials.

3.2 Substrate Materials on Flexible Nanobiosensors

3.2.1 Synthetic Polymers

Because of their versatility and processability, synthetic polymers have become one of the greatest widely used substrates, enabling the creation of flexible designs and low prices with high efficiency. Some of the well-studied polymers used to produce flexible substrates utilized in bioanalysis systems include polyimide (PI,) polyethylene terephthalate (PET), polyethylene naphthalate (PEN), and polydimethylsiloxane (PDMS) (Lau et al. 2013; Liao et al. 2015; Segev-Bar et al. 2013). PET is an artificial polyester fiber extensively used in plastic bottles, clothes, and as an electrical insulator (Reddish 1950). Because of its thermal stability, mechanical properties, inertness, and low price, it is a feasible alternative to silicon-based materials. The polymer is routinely pressed into ultratiny films to provide high-interaction surfaces, optically transparent, that offer flexibility and adaptability to various shapes and configurations (MacDonald 2004). PEN (also known as Teonex®) is an artificial polyester with increased intrinsic properties (hydrolytic and chemical resistance, thermooxidative and thermal resistance, and UV resistance), which makes it appropriate for use as a plastic substrate (Murakami et al. 1995). PEN has superior optical transparency and an oxygen barrier in optical devices, providing it an advantage. Although PEN is stiffer than PET, its inherent bendability allows it to be flexible (Barlow et al. 2002; Lechat et al. 2006).

Screen printing technology has prepared it simpler to create ultrathin microelectrodes and additional micro contact devices, increasing their application (Mościcki et al. 2017). Polyimides (PI) are flexible polymer fibers that can easily bend, mold, and fold and are widely utilized in industrial applications (Kapton® is one commercially accessible version). They exhibit excellent dielectric, structural, thermal stability, and dynamic tensile strength. These materials are versatile and easy, and they may be used for various purposes. Metal deposited PIs can increase conductivity, and photo-sensitive PIs have been created (Liaw et al. 2012). In bioelectronics, thin-film and double-layer films have been employed as substrates for fuel cells, brain implants, and other devices (Xiao et al. 2008; Lee et al. 2004).

PDMS (polydimethylsiloxane) is a silicone-based elastomer widely used in soft lithography and microfluidics (Qin et al. 2010). PDMS is used in various biomedical devices, including catheters, cartilage implants, and membrane oxygenators. PDMS devices' low cost, thermal stability, chemical inertness, and oxygen permeability have aided their rapid acceptance (Mata et al. 2005). PDMS is preferred as a flexible substrate above most other polymer-based flexible substrates because of its high elasticity, low modulus, and optical transparency. Because it is oxygen permeable, nontoxic, and biocompatible, it is suitable for in vitro and in vivo applications (Patrito et al. 2007). Other nanomaterials and nanoparticles can be combined with PDMS to make multifaceted structures such as implantable electrodes (SadAbadi et al. 2013) and lab-on-a-chip (Klemic et al. 2002).

3.2.2 Paper

Paper is an esthetically appealing and cost-effective semisynthetic/seminatural substrate for generating rapid POC diagnostics, principally in weak-facilities environments. Paper is adaptable, widespread, and simple to use (Chinnasamy et al. 2014; Martinez et al. 2010). It is commonly employed as a device substrate, either alone or with paper-based structures. Paper substrates may accept various sensing modalities when detecting biotargets, including optical, electrochemical, and electrical (Parolo and Merkoçi 2013; Qiu et al. 2017). Reduce the thickness of cellulose fibers from cm to nm, for example, to obtain optical transparency in the paper (Yao et al. 2017). Paper may be easily molded into composites because of its low weight and porous composition. Paper-based electrodes with multilayer topologies may now be manufactured more easily using screen-printing, nanopatterning, inkjet printing, and other processing methods (Siegel et al. 2010). Because paper absorbs by capillary action, it may be utilized to make lateral flow assays like pregnancy test strips for detecting human chorionic gonadotrophin (Choi et al. 2016). For example, there has been interest in creating quick nucleic acid testing paper tests (Ngom et al. 2010).

While individual cellulose strands may be easily manipulated to change the mechanical characteristics of paper, they can also be delicate and prone to ripping, with limited stability in moist settings. The bioactive paper has been proposed as a composite of paper and other biomaterials. Strengthening polymers such as polyamide-epichlorohydrin and/or glyoxalated polyacrylamides (GPAM) can be used to make cellulose fibers and nanofibers (CNFs) have a stronger and longer-lasting wet-strength impact (PAE) (Pelton 2009). Because cellulose does not break down naturally, efforts to create more biodegradable cellulose fibers have been developed (Jung et al. 2015). Because it is a synthetic material with poor conductivity, biomolecule labeling and doping with metal oxides or conducting polymers are typically required to provide electrochemical capabilities (Pelton 2009).

3.2.3 Textiles and Fibers

To provide strong support for the active sensing region, textiles can be manufactured as filaments (1D), woven, knitted, or shaped into various 2D structures (Stoppa and Chiolerio 2014; Windmiller and Wang 2013). Because of their natural flexibility, durability, and stability, wool, cotton, and synthetics (polyester, nylon, etc.) are excellent possibilities. Various manufacturing procedures can be used to mix textile substrates with conductive materials. To make conductive filaments, fabrics have been immersed in or drop-coated onto conductive polymers (Ding et al. 2010). Textiles can also produce conductive strands (Akşit et al. 2009). Lightweight, convenient, integrated functions, low cost, simple operation, and real-time display are just some of the benefits of migrated electrochemical/electrical structures on textile substrates, bridging the gap among influential electroanalytical devices and meeting the demands of daily, even dense usage.

Stability throughout long wash cycles is also a concern when using wearable clothing. The creation of textile-based carbon electrodes (TCEs) on the flexible waistband of clothes was prepared by screen-printing carbon-based ink deposited by thermal curing (Yang et al. 2010). These electrodes can withstand much mechanical stress without breaking or peeling. The TCEs' electrochemical performance was outstanding despite repeated stretching or bending, and they could sense 0–25 mM H2O2 and 0–100 M NADH for glucose detecting on sweat samples. Conductive fabrics have been used to manufacture transistors and traditional electrochemical biosensors. PEDOT: PSS was screen-printed on a textile substrate to create flexible TCEs (Gualandi et al. 2016).

3.2.4 Metals

Flexible substrates have also been made using thin metallic foils. While they can benefit biosensors, their application in conventional electronics has been more prevalent (Huang et al. 2011). Metal foils (made of titanium, stainless steel, copper, and molybdenum) can provide great thermal strength for roll-to-roll processing with a depth of 0.05 mm or less (Liao et al. 2012). The foils may readily bend at this point while still delivering the improved conductivity associated with metal substrates (Qu et al. 2001). Furthermore, flexible foil substrates are beneficial because they may be manufactured to any size while allowing for functionality tuning by stacking or depositing additional metals (Mathew et al. 2003). Metallic foils have shown potential as thin-film and solar cell transistor substrates, notwithstanding their scarcity in producing flexible biosensors (Howell et al. 2000; Park et al. 2003). External bending and compression are more robust to metallic foil substrates than stretched substrates (Gleskova et al. 2002). Metallic foils as flexible biosensor substrates have obvious limitations. Metallic foils are more expensive to manufacture than plastic foil materials such as PI or PEN.

The deposition of practical electronic designs on metallic foil materials is a high-temperature procedure. These approaches are generally incompatible with sensitive bioreceptor molecules and are energy and time-intensive (Howell et al. 2000). External bending and compression are more robust to metallic foil substrates than stretched substrates (Gleskova et al. 2002). Metallic foils as flexible biosensor substrates have obvious limitations. To begin with, metallic foils are more expensive to manufacture than plastic foil substrates such as PI or PEN.

3.2.5 Biomaterials

Biomaterials (sometimes called biobased materials) are made from reusable sources. Biomaterials are created through bioprocessing, biosynthesis, and biological refinement from basic materials such as legumes (Voisin et al. 2014), grains (Diouf-Lewis et al. 2017), bamboo powder (Hsieh et al. 2006), straw (Paranthaman et al. 2009), and other rare materials (Nair and Laurencin 2007; Kumar et al. 2018; Stagner 2016; Rivas et al. 2016). Polymer materials are used in almost every aspect of people's life.

However, excluding natural plastics/rubber and a few other materials, most polymer resources rely extensively on fossil fuels (coal and mostly oil), resulting in major pollution, human health issues, and environmental damage (Brunner and Rechberger 2016). Polymers that are both environmentally friendly and sustainable have become more important in preserving fossil energy and decreasing greenhouse gas emissions. Many attempts to make biodegradable materials with biobased components have been made (Sheldon 2014; Ummartyotin and Pechyen 2016).

Chemically manufactured biomaterials include the following: Agricultural feedstock such as potatoes, maize, and other carbohydrate feedstock was used to make the first generation of biobased polymers. Another form of biomaterial is natural biopolymers, such as nucleic acids, proteins, and polysaccharides (chitin, cellulose). Chemical synthesis may also be used to make biodegradable polymers like polyhydroxyalkanoates (PHAs), polyurethanes (PUs), polylactic acid (PLA), and polydopamine (PDA).

4 Fabrication Techniques for Flexible Biosensing Platforms

Nanobiosensors technologies have piqued attention in recent decades to track one's health in real time. However, many of these gadgets still lack significant flexibility, size, and comfortability because of a lack of logical design and production procedures. It is necessary to build next-generation integrated nanobiosensing systems with needed flexibility and downsizing for improved devices. The main fabrication techniques for the flexible nanoobiosensors are detailed below.

4.1 Sputtering

While nanobiosensors must meet various requirements, imparting conductivity is the greatest critical improvement on behalf of the deployment of electrochemical flexible biosensors. Sputtering conductive metals over nonconductive flexible substrates is one of the many techniques to impart conductivity. It can be a quick, straightforward, and operative approach to producing an electrochemical biosensor system. The development of conductive layers is dependent on physical processes in the sputtering process. In particular, conductive metal layers over nonconductive substrates can be uniformly generated by removing metal elements from metal targets' surfaces and blasting them onto the substrate surface using plasma or gas energetic particles (Libansky et al. 2017; Baptista et al. 2018). This technology has been used to create a tinny metallic conductive layer in numerous disciplines, including electrode creation and biosensor development (Hallot et al. 2018; Rahmanian et al. 2018). Sputtering has also been utilized to build high-conductivity electrochemical biosensors by deposition of new metals on the electrode and these applications (Roditi et al. 2019).

Sputtering has been utilized in various studies to build flexible nanobiosensors because it is easier to employ than other methods for producing conductive layers. Sputtering indium oxide (In_2O_3) on a PET substrate was allegedly used to create a very sensitive and flexible electrochemical biosensor for monitoring glucose levels in body liquids (Fig. 9.3a). The additional study employed the sputtering procedure

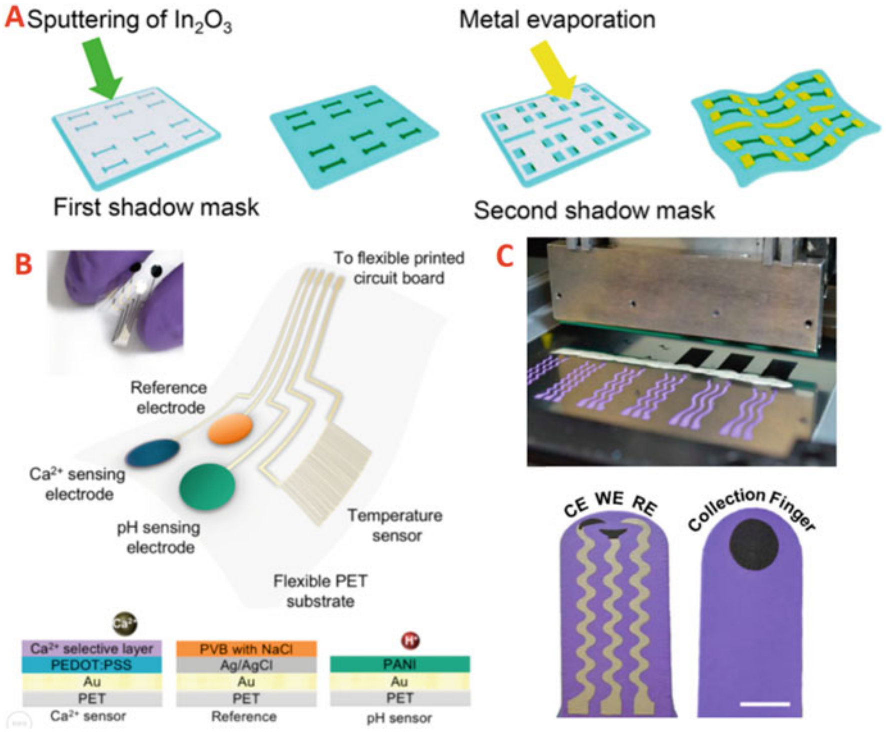

Fig. 9.3 Flexible nanoobiosensor fabrication techniques: (**a**) a schematic depiction of In2O3 sputtering on PET. (Adapted with permission from (Liu et al. 2018). Copyright 2018 American Chemical Society); (**b**) a diagram representation of a flexible biosensor produced by photolithography for observing various targets covering pH, ions, and temperature. (Adapted with permission from (Nyein et al. 2016). Copyright 2018 American Chemical Society); and (**c**) using printing technique to make a flexible glove biosensor with a three-electrode setup. (Adapted with permission from (Mishra et al. 2017). Copyright 2017 American Chemical Society, further permissions related to the material excerpted should be directed to the ACS)

to cover a flexible PET substrate with nickel oxide (NiO) to develop a flexible lactate biosensor evaluated using a potentiometric device (Chou et al. 2018). Choi et al. employed metal sputtering on nonconductive polymer material while introducing original nanostructures (i.e., MoS_2 nanoparticles). To enhance the electron transfer process and generate a highly sensitive biosensor system to detect HIV-1 surface protein and glucose, the researchers constructed a sandwich assembly consisting of sputtered gold coatings and a spin-coated MoS_2 layer positioned among the sputtered gold films (Yoon et al. 2019). However, the sputtering technique has drawbacks when introducing three- or two-electrode structures made up of reference or counter electrodes on conductive and flexible electrodes.

More innovative approaches for the direct usage of electrode structures on flexible materials are needed to develop flexible electrochemical biosensors that can be used in wearable devices, even if they are not as practical and simple as the sputtering approach.

4.2 Lithography

Finer techniques capable of exquisitely granting conductivity on flexible substrates beyond the nonspecific deposition that results from sputtering are required to establish an electrochemical system directly on flexible substrates or to develop multiple-target monitoring systems on a miniaturized chip. One example of such implementations is advanced conductive nano-electrodes (Smith 1986). The lithography technique, widely utilized for silicon-based electronic devices, fits the characteristics listed above (Barcelo and Li 2016). Photolithography is a contemporary lithography technique that employs a photo-sensitive photoresistor that may be imprinted on a substrate using a predesigned photomask and laser exposure. This approach might be used, for example, to make tiny conductive electrodes on flexible substrates.

Furthermore, employing an electrochemical structure constructed on a flexible material using the photolithography approach, a flexible multiple-target detecting system was described to observe pH changes and temperature simultaneously (Fig. 9.3b) (Nyein et al. 2016). Other lithography methods, like soft lithography, electrochemical lithography, or electron-beam lithography are frequently used in addition to photolithography to construct flexible nanobiosensors (Chen 2015). Flexible silver nanowire films created by soft lithography, for example, have been proposed for hydrogen peroxide (H_2O_2) detection (Lee et al. 2016; Zhang et al. 2017). Lithography technologies have been employed to construct intricate electrochemical flexible biosensors with completely joined electrochemical systems or biosensors accomplished by concurrently distinguishing several targets, similar to the experiments detailed above.

Although sensitive lithography methods are among the most efficient tools for building electrochemical flexible biosensors that can sense many targets or produce a completely integrated circuit system, they have downsides such as expensive equipment, difficult processes, and high expenses. As a result, processes for producing adaptable electrochemical biosensors that are reasonably inexpensive, simpler, and more accessible are required. As a result, several studies are being conducted, containing the use of current lithography procedures such as etching inkjet maskless lithography (E-IML) and salt impregnated inkjet maskless lithography (SIIML), to reimburse for lithographic techniques' boundaries and increase their performance, allowing the development of extremely well-organized flexible nanobiosensors (Hondred et al. 2019, 2020).

4.3 Printing

Due to its capacity to effectively construct gentle structures on any substrate by covering any chemical in the solution, printing has also benefited from widespread adoption because of its accessibility (Parameswaran and Gupta 2019). Many printing methods have commenced being applied in medicine and biology, notably in biosensors, as spraying sophistication and printing velocity improve. Printing technology has been utilized to construct various biosensors due to its ability to appropriately print biomolecules and new nanomaterials on substrates to build functional and biocompatible coatings to improve compact biosensors. Printed microfluidic-based bioanalysis devices, for example, have been created by printing (e.g., inkjet printing) polymer layers on surfaces (Loo et al. 2019; Ali et al. 2018).

The benefits of printing technologies, in particular, allow for fine control of the conductive substrate structure, which is essential for the construction of electrochemical flexible biosensors. Many biomaterials and unique conductive nanomaterials may be printed on flexible surfaces to provide conductivity or construct electrochemical systems (e.g., paper-based substrates). In one work, SNP ink was used to print silver inter-digital electrodes on a PET material via an inkjet printer for pathogen detection (Ali et al. 2018). A flexible enzymatic biosensor was developed in another investigation for simultaneous glucose observing (Pu et al. 2018).

Furthermore, printing is a low-cost way of generating reusable paper-based biosensors for POCT, lately involving much interest in the biosensor business (Arduini et al. 2019; Cao et al. 2020). In addition to paper-based biosensors, wearable lab-on-a-glove structures have been built using three-electrode systems: the counter, working, and reference electrodes on flexible gloves (Fig. 9.3c) (Barfidokht et al. 2019). Furthermore, 3D printing has recently attracted much interest as a breakthrough new-generation production technique. In biology, 3D printing has much potential for various applications, containing tissue engineering (Patra and Young 2016), because of its exceptional capability to build precise biological assemblies such as three-dimensional synthetic organs or tissues. These benefits of 3D printing might be leveraged to create flexible electrochemical biosensors (Sharafeldin et al. 2018).

4.4 Other Techniques

There are other efficient and inventive ways to build flexible electrochemical biosensors in addition to the three fundamental manufacturing procedures listed above; however, they are not as extensively utilized as the approaches listed above. Using metal ion solutions and basic electrochemical procedures, electrodeposition is a common approach for producing highly conductive films on superficial semiconductive or conductive surfaces. To make an ultrasensitive glucose biosensor, electrodeposition of platinum nanoparticles was used on a flexible graphene-modified PI substrate.

Electrospinning has also been utilized on several substrates to create patterned polymer membranes. Flexible polysulfone fiber mats were made by combining this technology with spray-based layer-by-layer deposition processes. A CNT-based conductive film was generated on these flexible rugs to develop a biosensor system (Saetia et al. 2014). An additional recent study (Cho et al. 2015) described producing biosensor devices employing a high-rate nanoscale offset printing procedure with guided nanomaterial assembly and transfer. By adjusting assembly settings, SWCNTs were formed at the required places with good homogeneity and controlled high density, resulting in a more stable and reusable biosensor device. They overcame some challenges connected with nanosensors, including unstable, non-reproducible detecting ability because of the unpredictable and chaotic SWCNTs assembly arrangement and the high price and difficult CVD construction technique. To make this platform, electrospinning was employed for polyacrylonitrile (PAN) nanofibers, subsequently carbonized. Chemical vapor deposition (CVD) and electrochemical/mechanical exfoliation are two additional novel ways to build flexible biosensors that have been effective (Luo et al. 2020; Zhang et al. 2019).

5 Current Applications of Flexible Nanobiosensors

Many electrochemical flexible biosensors have been built and published using the unique materials and manufacturing processes represented in this chapter. This chapter divides and discusses the reported flexible nanobiosensors based on the sorts of target molecules and the biosensors' working environment. The two research fields are flexible nanobiosensors for body-attached biosensors for direct and in vitro molecule monitoring.

5.1 Nanobiosensors with a Wide Range of Flexibility for In Vitro Monitoring

Flexible nanobiosensor research's ultimate objective is to be used in the creation of wearable biosensors. When using wearable biosensors to directly observe target molecules on the body, it is important to select target molecules and compensate for the biosensor's high sensitivity by removing noise signals from the environment and other undesirable molecules. As a result, current flexible nanobiosensor research focuses on improving selectivity and sensitivity while maintaining flexibility and stability under various physical situations. Small biological molecules that may affect health (e.g., lactate and glucose) and are linked to certain illnesses are the major target molecules of flexible nanobiosensors. Although many in vivo measurable glucose biosensors have progressed to the point that they are no longer required, flexible glucose biosensors for real-time observing glucose levels in the body to avoid diabetes mellitus are still required. As a result, a series of flexible glucose biosensors (Anusha et al. 2018; Pu et al. 2018) have recently been revealed. Choi et al. employed MoS_2 nanoparticles to procedure a sandwich assembly of MoS_2/gold/gold nanofilms on a PI material to greatly increase the sensitivity of flexible biosensors (Yoon et al. 2019). Sputtering was employed to construct the sandwich structural film quickly and effectively, resulting in gold films and a spin-coating MoS_2 coating (Fig. 9.4a). The developed flexible biosensor has outstanding glucose detection capabilities (detection limit: 10 nM), great selectivity, and the capacity to maintain its structure and function even after being bent repeatedly.

Furthermore, electrochemical flexible glucose biosensors based on graphene and carbon nanomaterials such as CNT have recently been produced (Bandodkar et al. 2016; Yoon et al. 2020) by utilizing the extremely conductive features of these carbon nanomaterials. Flexible nanobiosensors based on hybrid nanomaterials, including 3D porous graphene and platinum nanoparticles were also created to simultaneously monitor many targets (such as pH, electrocardiographic signals, and glucose), which might be used to create wearable smart devices (Xuan et al. 2018). To create this integrated system, the graphene nanowall-modified copper foil was created on the PET material using the CVD process, and the three-electrode system was printed straight on the flexible material. The recently constructed lactate biosensor displayed exceptional resiliency even after twisting and bending.

Additionally, it is claimed that a flexible alcohol nanobiosensor has been deployed in various contexts (Cinti et al. 2017). This biosensor can even differentiate among different beers' alcohol levels with its high sensitivity. Most research has focused on glucose and lactate as target molecules for electrochemical flexible biosensors because these substances are easily accessible and can be observed on the body via a wearable biosensor, which is the long-term objective of electrochemical flexible biosensors. However, there have recently been attempts to progress electrochemical flexible biosensors for in vitro observing of other chemicals, which might widen the target molecules' wearable biosensors in the future.

Electrochemical flexible biosensors may also be used to observe the states of live cells in vitro, and these investigations detect other target chemicals. Living cells are influenced by their surroundings, including the microenvironment and niches, which affect cell-substrate interactions and the chemicals produced by affected cells. Some researchers have used electrochemical flexible systems to analyze cell-secreted chemicals, including the cytokine tumor necrosis factor-a (TNF-a) and dopamine (Kim et al. 2019; Park et al. 2019). A flexible conductive PANI/PVAN bilayer-modified bacterial cellulose film was recently used to detect the release of neurotransmitters by neural stem cells cultured on a flexible material during differentiation

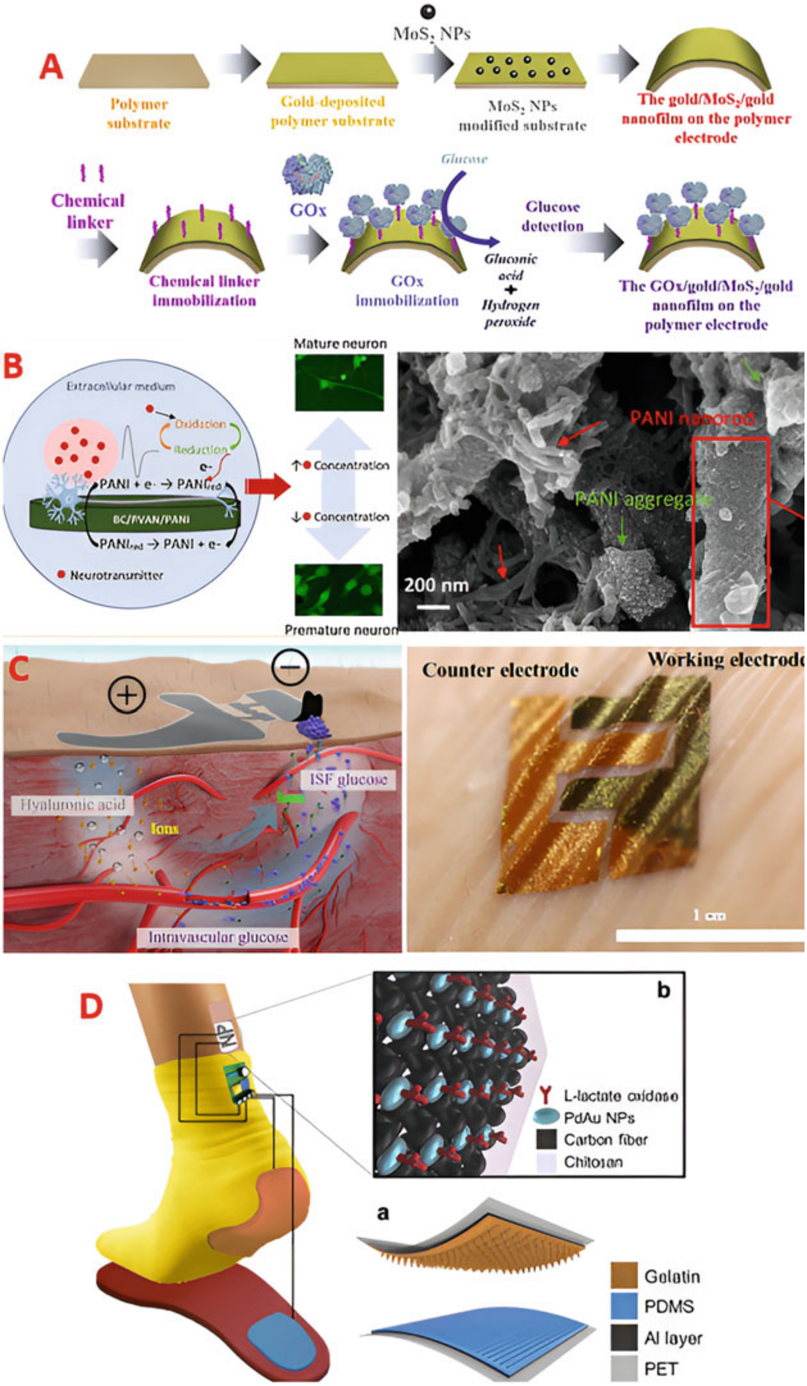

Fig. 9.4 (**a**) The glucose-detecting capabilities of the suggested flexible nanobiosensor from ref., as well as the fabrication technique of a glucose biosensor based on a sandwich assembly of gold/

(Rebelo et al. 2019). The differentiation of brain stem cells was electrochemically measured straight on the flexible biosensor due to its dual monitoring and cell development (Fig. 9.4b). Many studies on flexible nanobiosensors are underway, intending to lay the framework for developing extremely sensitive wearable biosensing devices.

Another recent study developed a sensitive electrochemical nanobiosensor for diagnosing Invasive Aspergillosis (IA) by detecting the pathogenic glip target gene (glip-T) in a miniaturized experimental setup. 1,6-Hexanedithiol and chitosan stabilized gold nanoparticle-mediated self-assembly of glip probes (glip-P) on gold electrodes were used to make the sensor probe. UV-visible spectroscopy, cyclic voltammetry, and electrochemical impedance spectroscopy were used to characterize it (Bhatnagar et al. 2018).

5.2 Flexible Nanobiosensors with Body-Attached Devices

A few cases have only described flexible nanobiosensors that sense objective molecules straight on the body. Flexible biosensors that are biocompatible and noninvasive and may be attached directly to the body are required. Furthermore, monitoring target molecules in physiological fluids, including blood, tears, and sweat, necessitates a high level of sensitivity. As a result, biosensors have been integrated into particular wearable structures such as mouthguards, wristbands, gloves, and adhesive plasters that may be readily connected to the body while maintaining biocompatibility and high sensitivity (Kim et al. 2015).

A disposable and wearable glove-shaped electrochemical biosensor for detecting synthetic opioids and fentanyl was developed by one research group. Using 3D-printed molds, the researchers developed a three-electrode system on the glove-shaped material. They then created a three-electrode system with a working electrode (carbon ink layer), a counter electrode (carbon ink layer), and a reference electrode (Ag/AgCl ink layer) using screen-printing technology (Mishra et al. 2017).

A composite nanomaterial comprised of ionic solution (IL, 4-(3-butyl-1-imidazolio)-1-butanesulfonate), polyethyleneimine (PEI), and carbon nanotubes (CNT) was produced over the working electrode to improve the biosensor's sensitivity. The developed biosensor successfully detected fentanyl in a timely and

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Fig. 9.4 (continued) MoS_2/gold nanofilms on a PI material utilizing spin-coating and sputtering methods. (Reprinted from (Yoon et al. 2019), Copyright (2019), with permission from Elsevier.); (**b**) conductive PANI/PVAN bilayer-modified flexible bacterial cellulose sheet for observing neurotransmitters generated by neural stem cells throughout stem cell separation, and fluorescent photographs of segregated cells created on flexible materials. (Reprinted (adapted) with permission from (Rebelo et al. 2019). Copyright 2019 American Chemical Society.); (**c**) a diagram of the ETC system for blood glucose observing, as well as a photograph of the created wearable biosensor on the body (Y. Chen et al. 2017b); and (**d**) schematic pictures of a self-powered electrochemical lactate nanobiosensor from ref., which is made up of two separate flexible systems (one for lactate detection and other for energy harvesting). (Reprinted from (C.-H. Chen et al. 2017a). Copyright (2017), with permission from Elsevier) efficient manner (detection limit: 10 mM). A lactate nanobiosensor made up of the two devices stated above displayed good lactate detection capacity using the energy supplied by physiological action. This self-powered nanosensor system is a novel technique to create compact, wearable sensing devices that can run for long periods, are biocompatible, and do not require external power (C.-H. Chen et al. 2017a). To establish this new system, the authors created two flexible electrochemical systems: one made of PDMS, an aluminum, and gelatin film on a PET material to produce biochemical energy from human running or walking when worn straight on foot, and another made of LOx, carbon fibers, Pd/Au bimetallic nanoparticles, and chitosan for lactate sensing coupled to an energy-harvesting system (Fig. 9.4c).

Furthermore, tattoo-style wearable biosensors can be used to observe important bioindicators in real time (Mishra et al. 2018; Jia et al. 2013). Patch-shaped or bandage electrochemical wearable biosensors that can be straight and noninvasively implanted at any place on the body are the most actively explored among the many types of structures used in wearable devices in the current study (Imani et al. 2016; Bariya et al. 2018). Wearable nanobiosensors based on electrochemical twin channels (ETC) were employed to detect blood glucose noninvasively (Y. Chen et al. 2017b). Prussian blue, GOx, gold, poly(methyl methacrylate) (PMMA), and PI were used to make this biosensor. Intravascular blood glucose might be pushed out of the vessel and dejected to the skin's surface, where the biosensor was worn, piercing hyaluronic acid and enduring glucose refiltration and external conveyance, using the proposed ETC system (Fig. 9.4d). This biosensor offered an attractive solution for nonstop glucose observing for noninvasive medical claims based on the properties of this ETC system, which included glucose transit and noninvasive sensitivity detection. Modified microneedle sensors on the bandage-shaped biosensor were constructed to sense tyrosinase, a cancer-based target molecule linked to melanoma (Ciui et al. 2018).

In recent work, the researchers produced a new nanocomposite containing Au-nanorattles-reduced graphene oxide for the label-free detection of serotonin using a glassy carbon probe electrode device. In addition, the probe was utilized to determine serotonin in standard settings, including dose-dependent research and analytical results produced using differential pulse voltammetry (DPV). The probe's practical implications were investigated using the spike and recovery approach in serum, urine, and in vitro cell samples (Mahato et al. 2019).

6 Conclusion and Future Perspectives

Flexible nanobiosensing technologies have shown to be a significant step forward in developing next-generation analytical tools. Given the growing popularity of wearable technology, particularly smart devices, they offer much potential for usage in wearable healthcare devices like electrocardiogram monitoring watches and POCT systems. This capability might pave the way for individualized diagnosis and analysis, allowing biosensors to meet their primary aim of detecting target molecules early, precisely, and individually.

Because they encounter all of the conditions for flexible biosensor improvement, electrochemical methods are among the numerous existing biosensor measurement techniques suited for biosensing applications. The best strategy for the work may be identified and applied using various electrochemical techniques available, including DPV, CV, and EIS. Electrochemical technologies also have a variety of advantages, including quick response, high sensitivity and selectivity, natural shrinkage, ease of operation, and mobility, which make them ideal for building flexible biosensors. As a result, a wide range of flexible nanobiosensors as wearable biosensor technologies have been thoroughly researched recently. To develop further flexible nanobiosensors, many critical properties must be addressed, including exceptional flexibility and the ability to transfer conductivity onto the flexible material. As a result, much study has been accompanied on developing flexible conductive substrates using cutting-edge nanomaterials and manufacturing techniques.

Low conductivity, brittleness, or the difficulty of obtaining high flexibility and conductivity in materials should be addressed by developing and studying new substrates that combine conductivity and flexibility. The production of unique and new materials and the synthesis of materials under research are thought to improve the benefits of individual materials and counteract the disadvantages. Furthermore, rather than manufacturing a substrate using a single manufacturing method, it is envisaged that a novel fabrication procedure may be designed to reimburse for the constraints of each method by concurrently integrating two or more fabrication processes. These techniques will help overwhelm and resolve existing limits and barriers.

Furthermore, even if the best substrate materials and manufacturing methods are established, obstacles remain, such as developing acceptable energy resource solutions and biosensors' capability to function on the frame without extra apparatus. Several obstacles must be explained to build functional wearable biosensors in the future. Converging biosensor research with other critical disciplines like electronics and energy might tackle these issues shortly. Additionally, for commercialization, the mass construction system of flexible conductive materials should be accomplished by lowering the complicated production procedure for new materials and reducing the tough manufacturing procedures for biosensors. If these contests are overcome, flexible nanobiosensors will likely be employed in customized POCT systems.

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