



Development strategies of conducting polymer-based electrochemical biosensors for virus biomarkers: Potential for rapid COVID-19 detection

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ABSTRACT

Rapid, accurate, portable, and large-scale diagnostic technologies for the detection of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) are crucial for controlling the coronavirus disease (COVID-19). The current standard technologies, i.e., reverse-transcription polymerase chain reaction, serological assays, and computed tomography (CT) exhibit practical limitations and challenges in case of massive and rapid testing. Biosensors, particularly electrochemical conducting polymer (CP)-based biosensors, are considered as potential alternatives owing to their large advantages such as high selectivity and sensitivity, rapid detection, low cost, simplicity, flexibility, long self-life, and ease of use. Therefore, CP-based biosensors can serve as multisensors, mobile biosensors, and wearable biosensors, facilitating the development of point-of-care (POC) systems and home-use biosensors for COVID-19 detection. However, the application of these biosensors for COVID-19 entails several challenges related to their degradation, low crystallinity, charge transport properties, and weak interaction with biomarkers. To overcome these problems, this study provides scientific evidence for the potential applications of CP-based electrochemical biosensors in COVID-19 detection based on their applications for the detection of various biomarkers such as DNA/RNA, proteins, whole viruses, and antigens. We then propose promising strategies for the development of CP-based electrochemical biosensors for COVID-19 detection.

1. Introduction

To date, human beings have been enduring the COVID-19 pandemic, which was declared by the World Health Organization (WHO) in March 2020. COVID-19 is defined as an infectious disease that is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Caldararo et al., 2021; Liu et al., 2020). Within one year of the first confirmed cases in Wuhan (China), the COVID-19 pandemic has spread throughout the world. It has significantly affected all countries and territories causing a socioeconomic crunch, and till December 2020, approximately 80 million individuals have been infected and more than 1.7 million deaths have occurred. Currently, there are several types of vaccines that have been developed and approved in some countries. However, the long-term protection of these vaccines has not been

confirmed to date (WHO, 2020). Therefore, development of advanced technologies for early and accurate diagnosis of COVID-19 is still very important and should be accorded a priority equivalent to vaccinations. The current gold-standard technology for detecting SARS-CoV-2 is a real-time reverse-transcription polymerase chain reaction (RT-PCR) (Chan et al., 2020; Corman et al., 2020), combined with other techniques such as CT scans, enzyme-linked immunosorbent assays (ELISAs), and serological assays. However, critical limitations and challenges are encountered in their practical applications, as summarized in Table 1. To overcome these problems, biosensors, which are analytical devices comprising a transducer (Drummond et al., 2003), are considered as the next-generation diagnostic technologies for tackling COVID-19 due to their capability to detect various biological analytes, i.e., DNA/RNA, pathogens, viruses, toxins and biomarkers of diseases. Three common

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types of biosensors are optical biosensors (Borisov and Wolfbeis, 2008), electrochemical biosensors (Cho et al., 2020), and photo-thermal biosensors (Ramanathan and Danielsson, 2001). Electrochemical biosensors have attracted a significant amount of attention due to their high sensitivity, selectivity, cost-effectiveness, and fast response. Furthermore, it has been demonstrated that the detection of viruses and pathogens using electrochemical biosensors has exhibited several advantages over traditional diagnostic techniques, including the potential for developing portable and wearable sensor devices and commercial products (Souf, 2016). Therefore, the biosensor is considered an effective, innovative, and promising tool for early diagnosis to prevent the spread of COVID-19 (Bhalla et al., 2020; Morales-Narváez and Dincer, 2020).

In the past decades, many novel materials, such as gold nanoparticles, carbon, graphene, graphene oxides, metal oxides, electrically CPs, and carbon nanotubes (CNTs), were discovered and employed to fabricate electrodes of electrochemical biosensors (Ahmadi and Abour, 2020; Aydemir et al., 2016; Gao et al., 2015; Hwang et al., 2020). When compared with other materials, CPs possess certain interesting properties due to their unique π orbital structure and chain conformation alterations, which lead to excellent sensitivity and selectivity for specific biological molecules and fast electrical signals when they are integrated in biosensors (Aydemir et al., 2016; Heeger, 2001; Naseri et al., 2018). Additionally, CP-based electrochemical biosensors are expected to be facilitated by the ease of tailoring CP properties. It is easy to tailor CP properties by functionalizing or coupling CP monomers with different functional groups (Aydemir et al., 2016), which can lead to a significant improvement in electronic properties as well as electrical stability of CPs. Moreover, it has been indicated that the performance of CP-incorporated biosensors is highly dependent on several crucial

characters including size, shape, structure, electrochemical conductivity, and morphology (Park et al., 2016). Therefore, to expand the applications of CPs in biosensors, many different strategies have been adopted to improve sensitivity, selectivity, flexibility, electrochemical stability, a variety of recognized bio-analytes, and reproducibility. In addition to the grafting of functional groups, the strategies have mainly concentrated on the design of CP nanostructures, such as CP nanowires, nanotubes, and nanospheres or on the association with other functional materials to form hybrid nanoparticles, composites, and hydrogels.

The CP-based electrochemical biosensor is one of the most promising technologies for the early diagnosis of COVID-19 due to its demonstrated potential and advantages. Hence, the development of innovative technology of CP-based electrochemical biosensors is expected to attract significant attention among potential studies related to COVID-19 detection in the near future. However, it is essential to consolidate the existing scientific evidence for using CP-based electrochemical biosensor technology in similar applications. In addition, the construction of electrochemical biosensors based on pristine CPs entails significant challenges and problems related to their amorphous nature and low stability, charge transport properties, and contact with biomolecular biomarkers (Yang et al., 2017a; Yao et al., 2018). Therefore, in this review, we provide a comprehensive overview of recent applications of CP-based electrochemical biosensors for detecting various biomarkers including DNA/RNA, protein, whole virus, and antigens. Furthermore, we evaluate the possible strategies for developing CPs in COVID-19 biosensors. CPs are applicable for constructing flexible and wearable biosensors, which can be used at local hospitals, doctor offices, and even households. The main contents of the study are summarized in Fig. 1.

Table 1

Competitive advantages, applicability, and challenges of different techniques for COVID-19 detection.

Diagnosis techniques	Point of use	Advantages	Disadvantages	Refs
Optical biosensors	Laboratories, hospitals, households Detection of COVID-19 in exhaled breath	Safe, straightforward use, and cost-effective technology Short processing time No need for nucleic acid amplification Potential POC diagnostic tools	Cannot completely replace other techniques such as RT-PCR or ELISA	(Maddali et al., 2020; Shan et al., 2020)
Photo thermal biosensors (Surface Plasmon Resonance biosensor)	Laboratories, hospitals, households Detection of COVID-19 in exhaled breath	Possibility of real-time, rapid, and large-scale diagnosis of COVID-19 Availability for POC devices and commercial purposes	Cannot completely replace other techniques such as RT-PCR or ELISA Damages biomolecule probes and analysts	(Qiu et al., 2020; Shan et al., 2020; Soler et al., 2020)
Electrochemical biosensors: CP-based biosensors	Laboratories, hospitals, households Detection of COVID-19 in exhaled breath	Easy and cost-effective approach and a biocompatible method Possibility for POC diagnostic tools and smart biosensor devices Ease of service, rapid response, miniaturization, and ease of use in molecular diagnostics Large-scale diagnosis technique	Cannot completely replace other techniques such as RT-PCR or ELISA Most pure CPs are unstable and highly amorphous and exhibit low charge transport properties and insufficient interaction with analysts	(Alafeef et al., 2020; Aydemir et al., 2016; Shan et al., 2020; Yang et al., 2017a; Yao et al., 2018)
RT-PCR	Special laboratories and hospitals	The gold-standard diagnostics technique for SARS-CoV-2 infection Exhibits high sensitivity and specificity Several PCR kits are commercialized	In the early stages of the COVID-19 outbreak, a significant rate of false -positive or -negative cases were detected Time-consuming process (2 h) and requires high manpower	(Udugama et al., 2020; Zeng et al., 2020)
CT scan	Special laboratories and hospitals For patients with moderate to severe respiratory symptoms and after negative RT-PCR results	CT scans show high sensitivity (86–98%) Reduction in false-negative rates compared to RT-PCR Useful for the determination of both alternative diagnoses and complications of COVID-19 simultaneously	Low specificity to COVID-19 (25%) because of the overlapping imaging features with numerous other diseases High cost and requires high technical expertise Accurate results depend on several dynamic variables	(Jin et al., 2020; Kwee and Kwee, 2020)
ELISA and other serological assays	Special laboratories and hospitals Use for symptomatic patients after a negative RT-PCR result	Qualitative or semi-quantitative results can be obtained with adequate sensitivity	To obtain the optimal accuracy, highly skilled personnel are required Time- and labor-consuming approaches	(Boonham et al., 2014; GeurtsvanKessel et al., 2020; Sidiq et al., 2020)

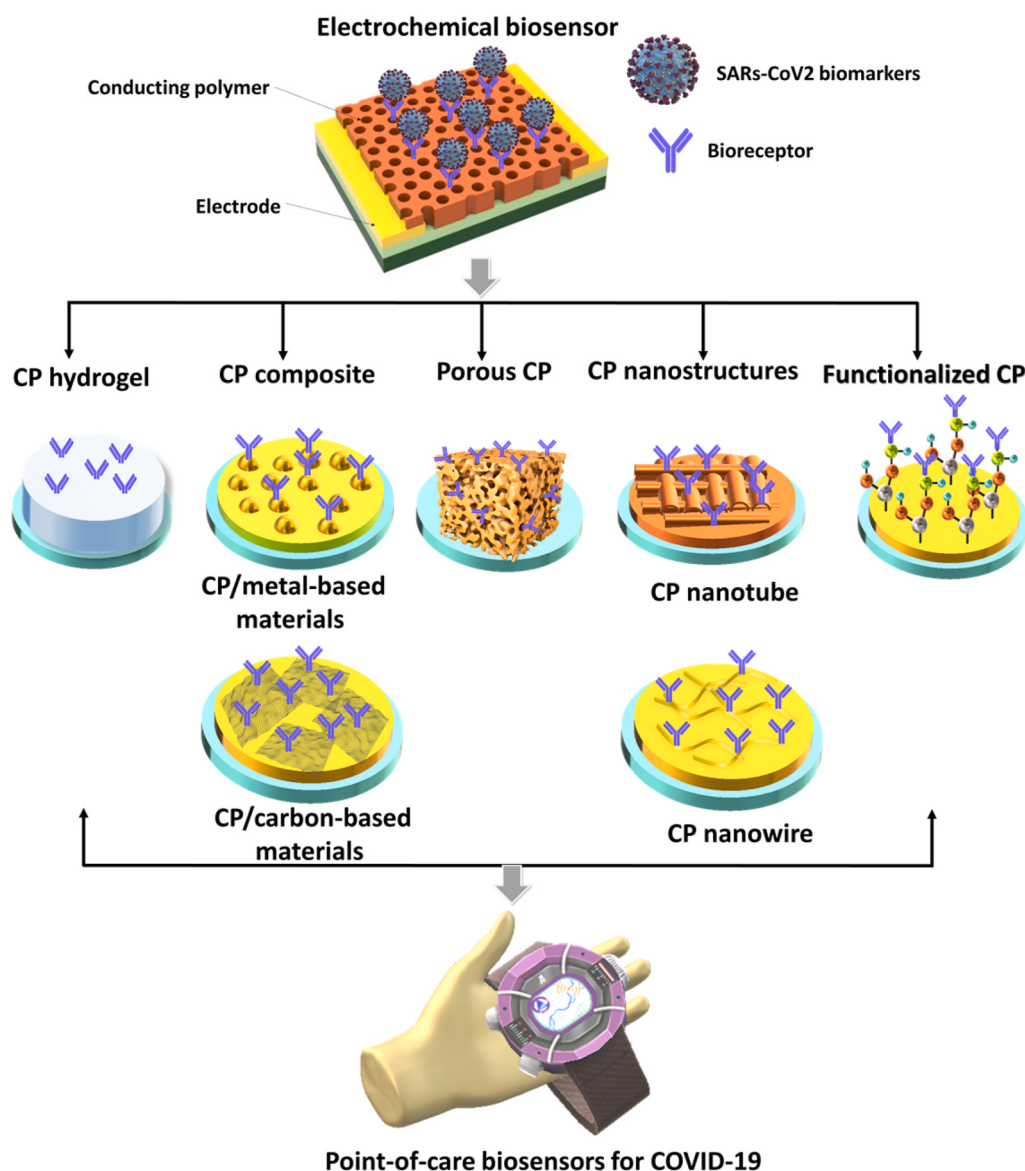


Fig. 1. Schematic summary of the main content of the study.

2. Structural properties and biomarkers of SARS-CoV-2 for electrochemical biosensors

For the development of biosensors, it is necessary to understand the structural properties of SARS-CoV-2 and determine important biomarkers that are available. Based on these properties, the appropriate biomolecule recognitions (probes) can be accurately selected to ensure the highest efficiency for biosensor devices.

2.1. Structural properties of SARS-CoV-2

An overview of SARS-CoV-2 structure is presented in Fig. 2. The SARS-CoV-2 is an enveloped virus with a positive-sense single-stranded RNA (+ssRNA) serving as the genomic material, and four structural proteins (spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein) that play a role in virus-host cell receptor binding, virion assembly, and release of the virion from the host cell (Mittal et al., 2020). The overall genome sequence of SARS-CoV-2 is identical to that of SARS-CoV-1. However, the structural differences in surface proteins of SARS-CoV-1 and SARS-CoV-2 lead to significantly high affinity and greater efficiency of SARS-CoV-2 in invading host cells

(Zheng, 2020). The S proteins are clover-shaped, type-I transmembrane proteins, and are comprised of three segments: a large ectodomain, a single-pass transmembrane domain, and an intracellular tail (Mittal et al., 2020). The spike proteins of the coronaviruses bind to the angiotensin-converting enzyme 2 (ACE2) receptor of host cells (Cevik et al., 2020; Wrapp et al., 2020). The trimer structure of the ectodomain of S-proteins is covalently stabilized. It consists of the S1 subunit, which contains a receptor-binding domain (RBD), and the stalk-fusion subunit (S2) (Huang et al., 2020b). The E protein is the small viral membrane protein (Nieto-Torres et al., 2011), and it is known to facilitate viral assembly along with M and N proteins (Siu et al., 2008). The triple-spanning membrane glycoprotein M is the most common structural protein in a virion (Mittal et al., 2020) and plays an essential role in virion assembly along with E and N proteins (Siu et al., 2008). The N protein is involved in packaging and stabilizing the viral genome RNA into long, flexible, and helical ribonucleocapsids (RNPs) (McBride et al., 2014). Six accessory proteins derived from sub-genomic RNA are scattered among the structural genes (Mittal et al., 2020). However, not all of the accessory proteins have been experimentally verified (Bojkova et al., 2020; Davidson et al., 2020).

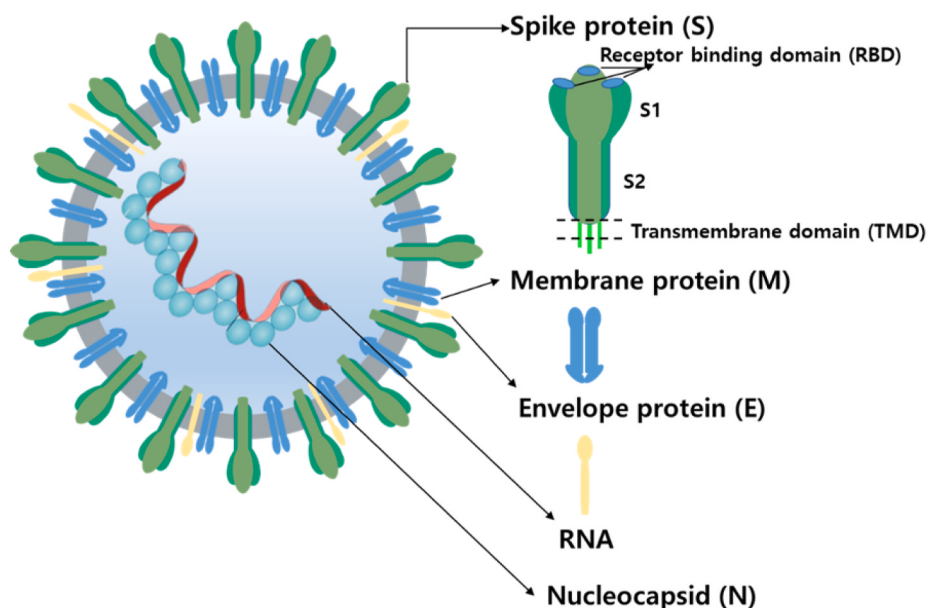


Fig. 2. Schematic structure of SARS-CoV-2 and its biomarkers for diagnosis.

2.2. Biomarkers and detecting mechanisms of COVID-19 electrochemical biosensors

The detection of SARS-CoV-2 is believed to be possible through three main courses of action: (i) direct detection of the entire virus and antigen, (ii) viral RNA detection, and (iii) antibody detection. The main properties and detecting mechanism of COVID-19 electrochemical biosensors are presented in Table 2.

3. Conducting polymers and immobilization techniques

3.1. Conducting polymers in electrochemical biosensors for detecting virus biomarkers

CPs are poly-conjugated polymers that possess interesting properties related to a combination of electrical conductivity and characteristics of organic polymers. Thus, the CPs are one of the most important materials for fabricating electrochemical biosensors (Aydemir et al., 2016). Among CPs, poly(acetylene), poly(3,4-ethylenedioxythiophene) (PEDOT), poly(thiophene), poly(p-phenylenevinylene) (PPV), poly(pyrrole) (PPy), and poly(aniline) (PANI) are commonly used for biosensor applications. Their chemical structure and several properties

are summarized in Table 3. Generally, CPs can be mainly prepared via two approaches, i.e., chemical and electrochemical methods (Aydemir et al., 2016; McCullough, 1998). In terms of biosensor applications, electrochemical polymerization has been widely utilized due to its advantages as follows: (a) it can be conducted at room temperatures with a large surface area of microelectrodes; (b) the film thickness can be controlled in the range of nanometers to micrometers and its shape is easily tunable; (c) the CP film properties can be modulated by various conditions of the process; and (d) the electrochemical polymerization process only takes a few seconds (Wallace et al., 1999). During electrochemical polymerization, monomers are initially oxidized to produce radical cations. Then oligomers are formed by coupling reactions, which leads to the deposition of CPs on the electrode surface.

3.2. Immobilization techniques for recognizing elements on the CPs

To develop CP-based electrochemical biosensors for detecting SARS-CoV-2, immobilization of biomolecule probes, including aptamers, antibodies, ssDNA, and antigens, onto the electrode surface plays a crucial role in the performance of biosensors. Generally, these recognition elements must be directly attached to the biosensor's surface to optimize its sensitivity and operational life. Furthermore, the choice of a suitable

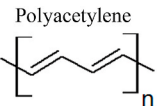
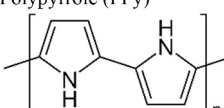
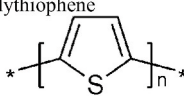
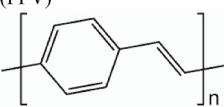
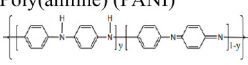
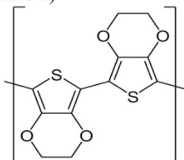
Table 2

Summary of properties and detecting mechanisms of available biomarkers for detecting COVID-19 via electrochemical biosensors.

Biomarkers	Properties	Recognition elements (probes)	Detecting mechanism	Refs
RNA	N gene gRNA E gene RdRp/Helicase (Hel)	CRISPR-Cas12 Aptamer Complementary DNA/ RNA	Complementary interaction of genes	(Broughton et al., 2020; Chan et al., 2020; Chu et al., 2020; Corman et al., 2020; Woo et al., 2020)
Whole virus and Proteins	Receptor binding domain (RBD) Spike protein 1 (S1) Spike protein 2 (S2) N proteins	Antibody Aptamer	Conformational recognition Protein-protein interaction Protein-aptamer interaction	(Seo et al., 2020a, b) Yen et al. (2015)
Antibody	IgM antibody IgG antibody Neutralizing antibodies: SNAb, REGN-COV2, S309	S proteins N proteins The receptor-binding domain (RBD)	Protein-antibody interaction Antigen-specific antibody response Inhibiting the interaction of RBD and human angiotensin-converting enzyme 2 (ACE-2)	(Li et al., 2020; Yen et al., 2015) (Pinto et al., 2020; Weinreich et al., 2020; Yang et al., 2020a)

Table 3

Summary of preparation methods and properties of common conducting polymers in electrochemical biosensors.

Polymers	Preparation	Properties	Refs
Polyacetylene 	Emulsion polymerizations Dispersion polymerizations Precipitation polymerizations Suspension polymerizations Self-assembly	Water insolubility and low solubility in organic solvents Conductivity (undoped): trans-polyacetylene ($4.4 \times 10^{-5} \Omega^{-1}\text{cm}^{-1}$) and cis-polyacetylene ($1.7 \times 10^{-9} \Omega^{-1}\text{cm}^{-1}$)	(Hirayama et al., 1996; Klavetter and Grubbs, 1988; Li et al., 2014)
Polypyrrole (PPy) 	Electrochemical synthesis Chemical oxidation	Solubility in DMSO, chloroform, chlorobenzene, and tetrachloromethane Conductivity: $10\text{--}7.5 \times 10^3 \text{ S/cm}$ Environmental stability, compatibility	(Dicks et al., 1993; Ivanova et al., 2017; Song et al., 2000)
Polythiophene 	Electrochemical synthesis Chemical synthesis	Insolubility in ordinary solvents High conductivity: $10\text{--}10^3 \text{ S/cm}$	Das et al. (2015)
Poly(phenylenevinylene) (PPV) 	Polymerization of quinodimethane intermediates Nucleophilic polycondensation Metathesis polymerization Palladium-catalyzed cross-coupling	Water insolubility Low conductivity: $10\text{--}13 \text{ S/cm}$	Blayney et al. (2014)
Poly(aniline) (PANI) 	Chemical oxidative polymerization Electrochemical oxidative polymerization	Insolubility in the common organic solvents, solubility in NMP, DMSO, DMF, and THF Conductivity: + Insulator form: 30–200 + Conductive form: $\sigma \geq 1 \text{ S/cm}$ Environmental stability and compatibility	Zare et al. (2020)
Poly(3,4-ethylenedioxythiophene) (PEDOT) 	UV-irradiation polymerization Oxidation polymerization Electrochemical polymerization Photo-electrochemical polymerization	Available aqueous dispersion Conductivity: $0.4\text{--}400 \text{ S/cm}$ Low density, excellent thermoelectric performance	(Minudri et al., 2020; Zhang et al., 2019)

immobilization strategy is mainly based on the type of biological elements. Ideally, the immobilization process should satisfy the following requirements: (i) it should be an efficient and simple method, and (ii) no damage should occur to the recognition probe (Ahuja et al., 2007). Therefore, physical adsorption, covalent attachment, and entrapment are common techniques that can be used for the immobilization of SARS-CoV-2 probes (Lakard, 2020; Rashid and Yusof, 2017). These techniques are illustrated in Fig. 3 and summarized in Table 4.

4. Development strategies of conductive polymer-based electrochemical biosensors for virus detection: potential for SARS-CoV-2

4.1. Functionalized conducting polymers

New functional electrically conducting materials play a key role in electrochemical biosensors applications. As previously mentioned, functionalities on CPs were often employed in biosensors to produce a covalent attachment of biological molecules that play the role of recognition probes (Peng et al., 2009). Furthermore, functionalized CPs exhibit excellent processability and enhanced applicability in practical applications of biosensors due to the presence of a number of intrinsic redox states (Kang et al., 1997). The CPs function in two ways: (i) During monomer synthesis, the functional entity is incorporated into the monomer; (ii) Post-polymerization coupling of the targeted functionality to built-in generic coupling sites in the monomer unit (Kang et al., 1997). Over the last quarter-century, several techniques have been

developed to control and modify the surfaces of CPs (Matsuda and Sugawara, 1995).

The surface of the CPs can be modified by physical and chemical methods (Ravichandran et al., 2010). The surface roughness can be increased by producing micro-porous films based on polystyrene sphere templates, growing CPs within layered hydrogels (Yang et al., 2016), and forming 'fuzzy' structures by blending with biomolecules. Chemical modifications use biomolecules as dopants or immobilize bioactive moieties in/on the CPs surface.

The creation of an interface between CPs and SARS-CoV-2 probes is considered one of the most important strategies for fabricating electrochemical biosensors for COVID-19 detection. Thus, the development of novel techniques to modify the CP surface, including covalent and non-covalent methods, considers the upward tendency of recent studies on electrochemical biosensors (Date et al., 2011). For non-covalent methods, an affinity-based surface modification strategy was recently developed based on the phage display methodology. Affinity techniques have attracted significant interest because the bulk conductivity of the modified materials is still maintained and can be used under physiological conditions (Nickels and Schmidt, 2013). Recently, peptides, which are derived from virus particles, were developed for affinity-based surface modification of CPs with retained binding properties (Clauder et al., 2020; Khoo et al., 2009). DNA/RNA, antibodies, enzymes, and aptamers were successfully immobilized onto CP electrodes by using affinity techniques (Aydemir et al., 2016). For example, Nickels and Schmidt (2013) reported the non-covalent surface modification of PPy polymer with a 12 amino acid peptide (T59) using the

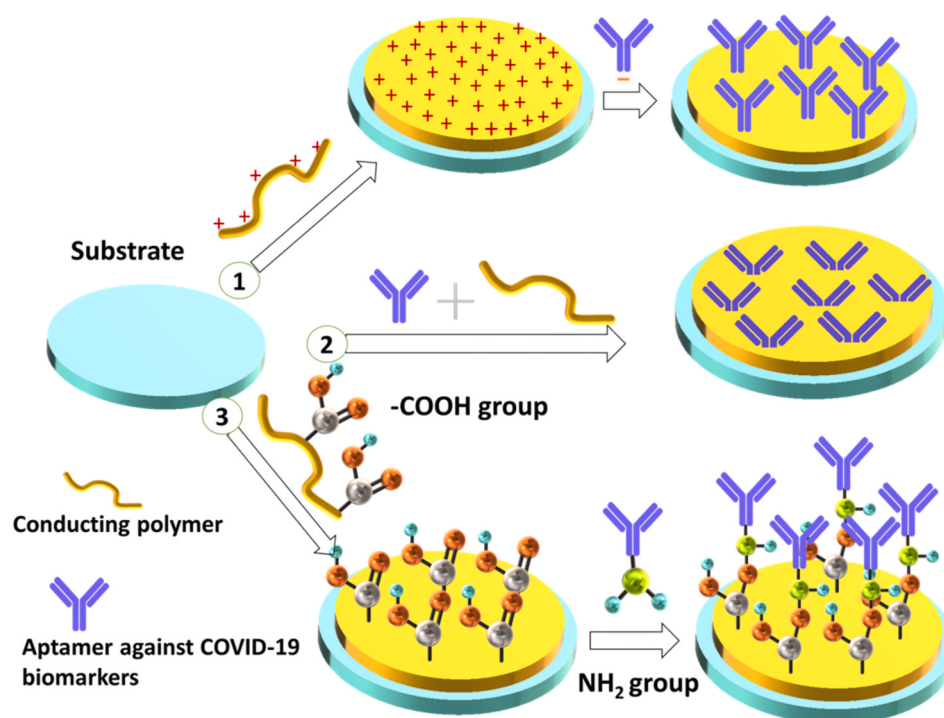


Fig. 3. Schemes of immobilization strategies: (1) physical adsorption, (2) electrochemical entrapment, (3) covalent attachment.

Table 4

Summary of the main properties, advantages, and drawbacks of immobilization techniques.

Techniques	Properties	Advantages	Disadvantages	Refs
Physical adsorption	Exploiting the electrostatic interactions between the positively charged CP surface and negatively charged SARS-CoV-2 probes, as well as other interactions (hydrophobic, van der Waals forces) in the adsorption of antibodies and other proteins	No requirement of the functionalization to monomers and probes No damages to biomolecule probes	Highly pH-dependent binding forces and a small number of attached recognition elements The interaction forces are relatively weak and biomolecules (DNA probes) are only immobilized on the outer layer of CP, and thus, they can be leached from the interface over time	(Ahuja et al., 2007; Norde, 1986; Thompson et al., 2003)
Covalent immobilization	Biomolecule probes are modified and functionalized by adding -NH ₂ , -COOH, and other groups, and these probes are then covalently attached to functionalized monomers or CP polymers	Low diffusional resistance and high stability under stress Resolve the drawbacks of the electrochemical entrapment and adsorption methods as well as improve probe accessibility Offers strong chemical binding and short response time	Decreased activity of biomolecules probes Uncontrollable reactions, causing damages or loss of probes Direct explosion of probes to the solution, resulting in poor stability Delay in interactions due to large diffusional barriers	(Guler Gokce et al., 2018; Kannan et al., 2011; Minett et al., 2002; Peng et al., 2007, 2009; Zhu et al., 2015)
Electrochemical entrapment immobilization	This method relies on the electrochemical oxidation of a suitable monomer on the corresponding CPs via a solution containing SARS-CoV-2 probes	Straightforward and prolonged immobilization for molecular probes with several advantages such as its simplicity and reproducibility	Damage to probes (particularly DNA) due to the use of high potentials during the electrochemical polymerization Poor target accessibility to the incorporated probes Limited application over a wide range of CPs due to requirements of water solubility	(Barisci et al., 1998; Cosnier, 1999; Mandli and Amine, 2018; Minett et al., 2002; Wang and Jiang, 2000; Wang et al., 1999)

phage display technique. The results demonstrated that the T59 peptide can be used for modifying the surface of PPy, and it enhances the interaction and immobilization of probes on PPy. Additionally, it was demonstrated that surface modification of CPs can also provide highly sensitive and anti-fouling properties for biosensors. In another study, Wang et al. (2020a) successfully developed an RNA biosensor with ultra-sensitivity and low-fouling properties by modifying the surface of the PANI polymer using peptide sequences (an antifouling biomolecule) (Fig. 4a). When compared with RNA-biosensors without surface modification and antifouling capability, the electrochemical biosensor designed from the peptide-functionalized PANI exhibited a highly

specific property to complement the RNAs. Notably, it was demonstrated that the presence of antifouling peptides on the PANI surface does not significantly affect the sensitivity of the biosensor. Therefore, the use of peptides or other low-fouling molecules to functionalize CPs can be a potential strategy to develop anti-fouling biosensors for detecting COVID-19. Furthermore, CPs exhibit the potential of extending the development of COVID-19-based electrochemical biosensors without encountering biofouling.

Surface-grafting polymers, which are also considered polymer brushes, are an important tool for surface modification or functionalization of CPs. Polymer brushes exhibit several interesting properties due

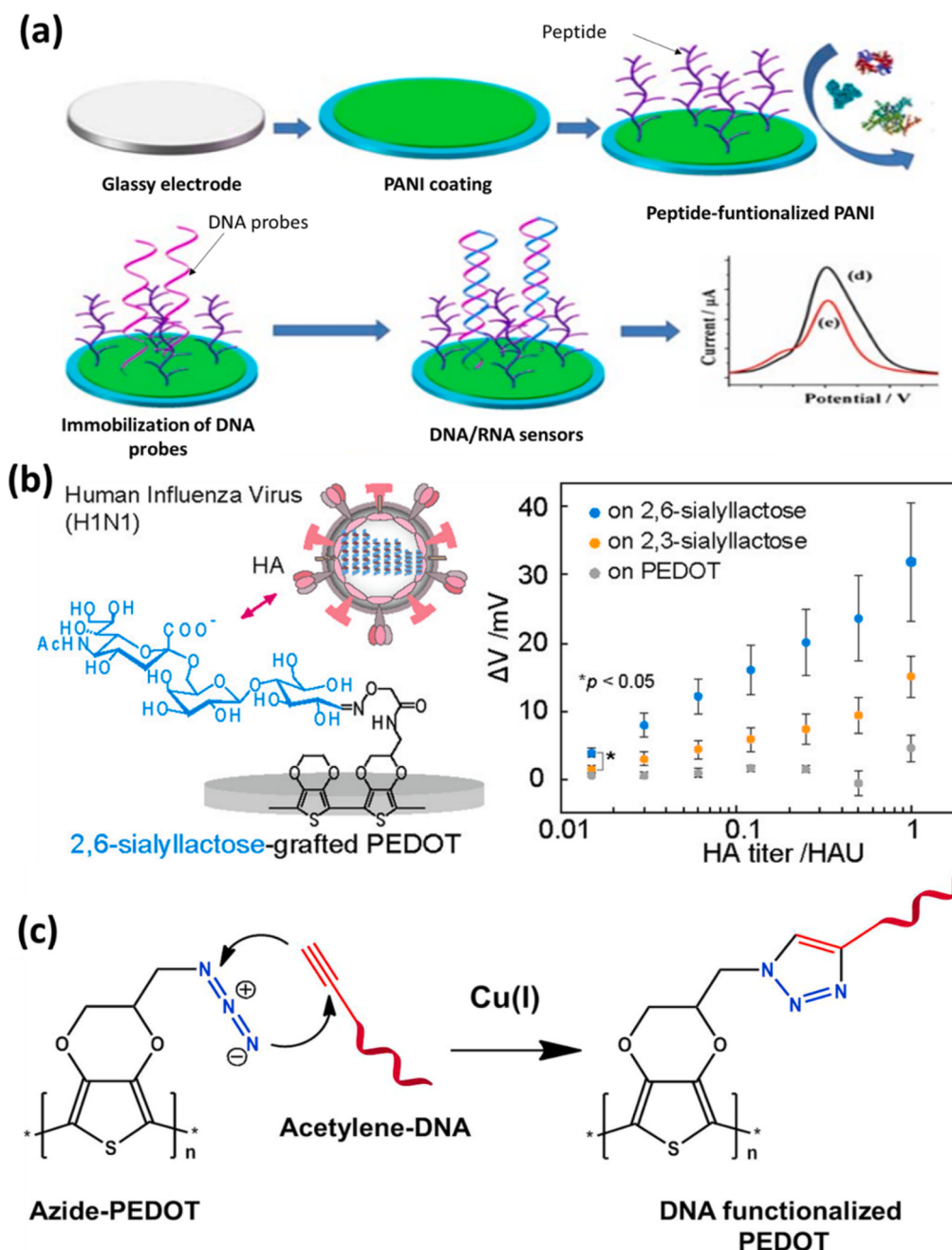


Fig. 4. (a) Schematic illustration of the preparation process of antifouling RNA biosensors using peptides for surface modification of PANI polymer. Reproduced with permission from (Wang et al., 2020a); (b) Biosensor based on PEDOT grafted sialyllactose for human influenza A virus detection. Reproduced with permission from (Hai et al., 2017); (c) Functionalization of PEDOT for DNA biosensor using CuAAC reaction. Reproduced with permission from (Galán et al., 2015).

to a strong covalent bond between the polymers and the face, including easier patterning, precise control of the surface property, and better stability (Wang et al., 2020b). Surface-grafting polymers can significantly improve long-term operation and cyclic testing of biosensors. The CP brushes exhibit flexibility and compatibility with substrates and can be used for the design and fabrication of flexible biosensors. Hai et al. (2017) developed a highly sensitive and specific electrochemical biosensor by grafting CPs with trisaccharide for label-free detection of the human influenza A virus (H1N1), which is also an influenza virus with a disease presentation similar to that of SARS-CoV-2 (Fig. 4b). In the study, the authors functionalized PEDOT via an electrochemical polymerization process. The trisaccharides comprising Sia- α 2,6'-Gal-Glu (2,6-sialyllactose) are covalently grafted to the side chain of the CPs as ligands for the recognition of the H1N1 virus. The 2,

6-sialyllactose-grafted PEDOT polymer exhibits an excellent specificity to H1N1 virus recognition and can be used for developing flexible devices and point-of-care testing systems for human influenza viruses, especially SARS-CoV-2, given its potential ease of mass production due to printing technologies.

The term “click chemistry” introduced by Kolb et al. (2001) corresponds to a series of chemical reactions that can generate stable new substances by combining small units through hetero-atom links (CX-C). For electrochemical biosensor applications, especially immuno-sensors, research has focused on click chemistry due to its mild reaction conditions, fast reaction, high selectivity, and high synthesis efficiency (Daugaard et al., 2008). Among various click reactions, Cu^+ -catalyzed Azidealkyne Cycloaddition (CuAAC) is selected for the synthesis of functional CPs due to ease in purification, versatility, and high product

yields (Meldal and Tornøe, 2008). Hence, CuAAC was recently employed in combination with various detection techniques and used to fabricate highly sensitive biosensors for different targets, especially DNA (Huang et al., 2020a). For example, Galán et al. (2015) introduced a DNA biosensor based on electrodes prepared from functionalized-PEDOT via CuAAC reaction (Fig. 4c). In the study, azido-derivatives conducting PEDOT electrodes were designed to detect viruses using an acetylene-terminated DNA probe. The PEDOT-based biosensor exhibited a low limit of detection and a highly selective property for targeted viruses without necessitating microelectrode fabrication processes or labeling techniques. The results predict that the development of label-free and reagentless DNA biosensors, based on CuAAC reaction to functionalize CPs, is a potential approach for the

early detection and diagnosis of many viruses including SARS-CoV-2.

4.2. Conducting polymer nanostructures

Evidently, electrochemical biosensors constructed from bulk polymers typically exhibit a long response time because the target biomolecules slowly penetrate the CPs (Xia et al., 2010). However, analytes can be pre-treated into CP nanostructures, such as nanotubes, nanofibers, and nanowires, at a significantly faster rate due to the unique structure of the CP nanostructures. Furthermore, CP nanostructures typically display a larger specific surface area and porous structure and can be considered as excellent materials for immuno-sensor and biosensor applications (An et al., 2004; Bangar et al., 2009;

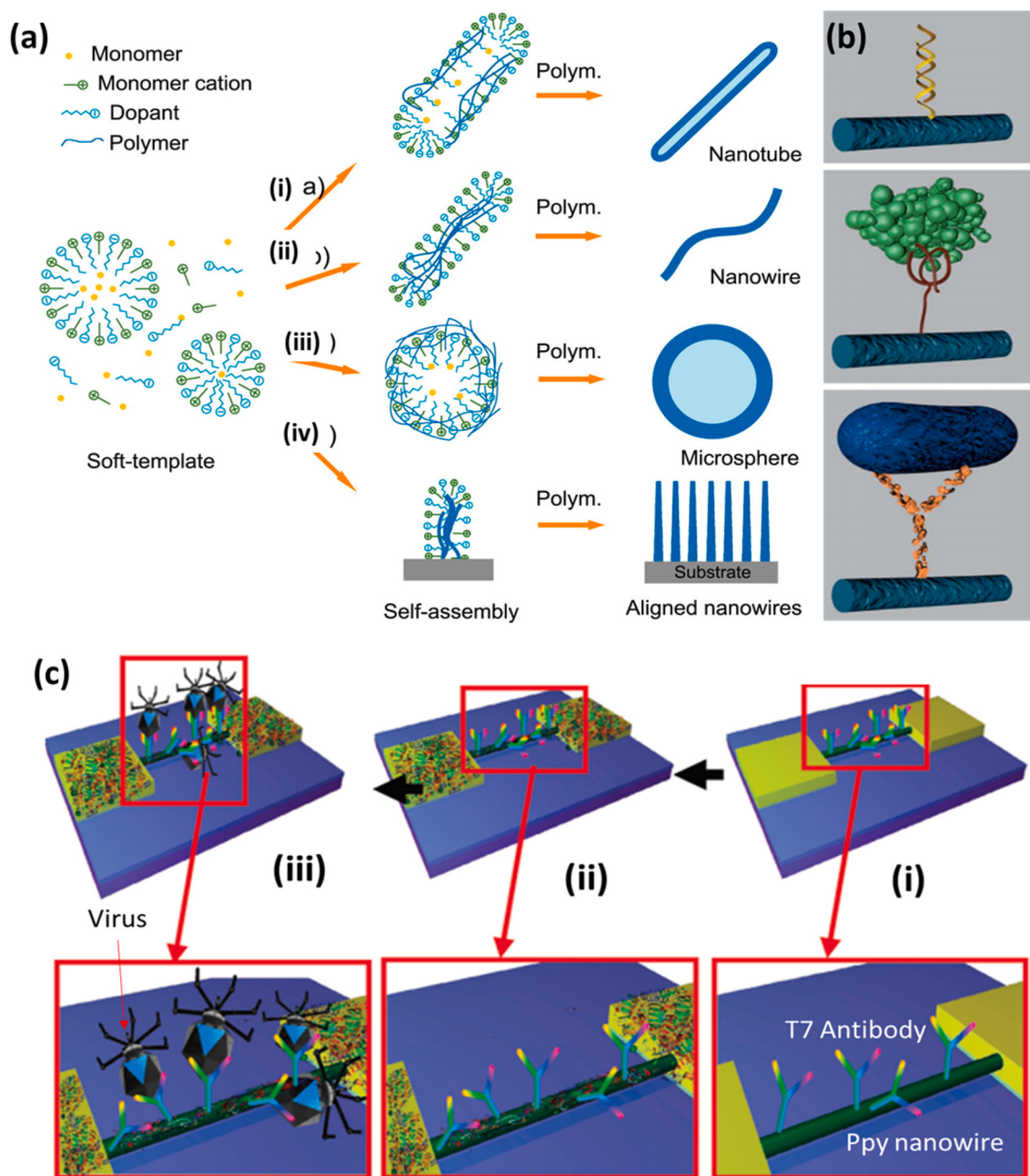


Fig. 5. (a) CP nanostructures for electrochemical biosensors: (i) nanotubes (ii) nanowires and (iii) microspheres Reproduced with permission from (Xia et al., 2010); (b) Proposed approaches for the design of nanowire-based electrochemical biosensors. Reproduced with permission from (Travas-Sejdic et al., 2014); (c) Schematic illustration of PPy nanowires-based electrochemical biosensor for virus detection: (i) T7 antibody-functionalized PPy nanowire, (ii) BSA blocking, and (iii) virus phage interacts with probes on the nanowire surface. Reproduced with permission from (Shirale et al., 2010).

Gangopadhyay et al., 2012). Generally, there are three major steps in the design of an electrochemical biosensor based on CP nanostructures: (i) Fabrication of CP nanostructures using various methods, including template-assisted synthesis, photolithography, e-beam lithography, dip-pen nanolithography, hydrodynamic focusing, and electrochemical polymerization techniques (Gangopadhyay et al., 2012); (ii) immobilization of appropriate biomolecule probes such as DNA, antibody, aptamer, virus or antigens; and (iii) using a suitable readout methodology (Travas-Sejdic et al., 2014). The three types of CP nanostructures that can be used to develop highly sensitive biosensors for COVID-19 detection are CP nanowires, nanotubes, and microspheres (Fig. 5a).

Several methods have been proposed for the preparation of CP nanostructures, which can be divided into two types, template-based (hard-template and soft-template) and non-template methods. These techniques can produce CP nanostructure-based biosensors with high sensitivity, good recovery, and rapid response (Xia et al., 2010). However, these preparation technologies can limit the use of CPs for practical applications in electrical biosensors because of their complicated processes and small production scale. Moreover, controlling morphologies and sizes in the nanometer regime, especially on a large scale, throws up big challenges (Kwon et al., 2012b). The inherent properties of CPs such as low environmental stability and insufficient adhesion to the electrode substrates also impede the development of CP nanostructures used in electrochemical biosensors (Lin et al., 2012; Travas-Sejdic et al., 2014).

4.2.1. Conducting polymer nanowires

Conducting polymer nanowires (CP NWs) are 1D materials that can be employed for the effective transport of electrons, and are often used for designing high-density nanoscale devices. CP NWs-based electrochemical biosensor devices have attracted significant attention in the biosensing field due to the precise control of sensor characteristics (Shirale et al., 2010). Therefore, NWs of different CPs including PPy, PANI, PEDOT, and their derivatives have attracted significant interest in the design and development of electrochemical biosensors (Bangar et al., 2009; Gangopadhyay et al., 2012; Shirale et al., 2010; Wang and Zhang, 2013; Xia et al., 2010). Potential approaches to fabricate CP NWs-based COVID-19 biosensors include detection of nucleic acids, proteins, and whole SARS-CoV-2, which are summarized in Fig. 5b.

Shirale et al. (2010) introduced PPy NWs-based immuno-sensors with high sensitivity and specificity for direct detection of viruses (Fig. 5c). In the study, PPy NWs were prepared using an electrochemical polymerization method based on an alumina template. Antibody probes were then immobilized on single PPy NWs to fabricate a nano-biosensor for sensing corresponding to virus phage. PPy NWs-based biosensors exhibited an ultra-sensitivity, a wide detection range, and optimum selectivity for T7 and MS2 viruses. Bangar et al. (2009) used a similar method and developed a low-cost and portable PPy NWs immuno-sensor to detect relevant antigens clinically. These results indicated the significant potential of PPy NWs in the development and design of biosensors for detecting various viruses, especially SARS-CoV-2.

MicroRNAs (miRNAs) are well known as a special type of non-protein-coding, endogenous, small RNAs, and are considered a crucial class of biomarkers for SARS-CoV-2. Therefore, the use of CPs NWs for sensing miRNAs is an important strategy for COVID-19 detection (Fan et al., 2007; Travas-Sejdic et al., 2014; Wang and Hui, 2019). Wang and Hui (2019) introduced a simple electrochemical patterning strategy to develop ultrasensitive biosensors based on polyethylene glycol (PEG)-PPy NWs substrates. The PEG/PPy NWs biosensor integrated advantages of PEG (biocompatible and antifouling ability) and PPy NWs (high electric activity and versatility). Thus, it improved antifouling properties, exhibited high sensitivity, wide linear range, reproducibility, and excellent selectivity for miRNA assays. Furthermore, the approach is expected to be used for developing any type of RNA or DNA biosensors. In another study, a biosensor was constructed using a co-polymer of PEDOT and COOH-functionalized PEDOT NWs, and this was followed by covalent attachment of an amino-modified probe oligonucleotide

(Kannan et al., 2012). The PEDOT-NW device is a highly sensitive biosensor at a 10 fM concentration of the target oligonucleotide. Additionally, the biosensor can detect oligonucleotide targets without requiring amplification schemes.

4.2.2. Conducting polymer nanotube

The nanotubular structure of CPs was considered an ideal structure to improve electrochemical biosensor performance due to increases in charge-transport rate and surface area (Xiao et al., 2007). It was demonstrated that a DNA-biosensor fabricated using a conducting polymer nanotube (CP-NT) array with well-organized orientation can exhibit a detection sensitivity that is similar to that of the gold nanoparticle or carbon nanotube-based detecting systems. Therefore, CP-NTs are gaining acceptance for developing biosensors for COVID-19 detection. CP-NTs can be chemically or electrochemically synthesized using various templates (Fig. 6a) (Xia et al., 2010). Martin (1994) successfully prepared various CP-NTs, such as PPy, polythiophenes, and PANI, in the pores of a polycarbonate or alumina membrane. Zhang et al. (2002) developed surfactants as a template and dopants to prepare PANI and PPy NTs. Nanofibers of bio-degradable polymers can also be used as a template, which can be selected for the synthesis of CP-NTs (Dong et al., 2004). Based on this template, CPs are electrodeposited on the surface of electrospun nanofibers. Then, these nanofibers are removed to form hollow CP-NTs. It is assumed that the interaction between CPs and templates, such as solvophobic and electrostatic, corresponds to the main mechanism for the growth of CP-NTs.

Developments in CP-NTs created many opportunities to extend the applications of CPs for sensing biomolecule biomarkers, especially DNA or RNA. For example, an ultrasensitive electrochemical biosensor based on PANI-NTs array as the signal enhancement element was successfully fabricated for sensing DNA (Chang et al., 2007). A PANI-NTs array with a good alignment and orientation was prepared on a graphite electrode using a thin nanoporous layer as the template, and oligonucleotide probes were then attached to the NTs. Each PANI-NT was designed to operate as a signal amplification nanodevice. Therefore, the PANI-NTs array modified electrode constitutes a new strategy to develop ultrasensitive DNA biosensors with a high-efficiency route.

4.2.3. Conducting polymer microspheres

Nano/microspheres are known as three-dimensional (3D) polymer networks that possess a cross-linked structure. They have attracted significant attention in immuno-sensors due to their superior advantages over two-dimensional (2D) nanostructures as follows: (i) larger specific surface area and highly enhanced analyte-surface interaction, (ii) high spatial freedom for interaction with targeted biomolecules, and (iii) amenability to multiplexing and screening (Hosseini et al., 2020; Raez et al., 2007). Therefore, conducting polymer microspheres (CP-MPs) were chemically designed and synthesized to promote effective miRNA immobilization in electrochemical biosensors, and this leads to higher sensitivity. Additionally, CP-MPs were also demonstrated to significantly improve other important parameters of miRNA-biosensors including specificity, accuracy, and the limit of detection. Furthermore, CP-MPs can be mass-produced in desirable size ranges and can be used to control properties based on the type of desired biorecognition. Therefore, CP-MPs nanostructures provide a wide range of opportunities to develop effective COVID-19 biosensors based on miRNA biomarkers.

Synthesis of colloidal CP dispersions is an attractive approach for improving CP processability (Digar et al., 1992). Generally, the morphological structure and particle size are the two main properties of CP-MPs (Vincent and Waterson, 1990). Thus, it is assumed that these morphology and size properties should be controlled and tailored according to the purposes of their utilization. Several techniques can be used to synthesize CP-MPs, such as (i) using steric stabilizers (Maeda and Armes, 1994) (ii) electrochemical polymerization without stabilizers (Davey et al., 2000; Sanada et al., 2006) (iii) pulsed sonoelectrochemical method (Atobe et al., 2009) (iv) ultrasonic spray polymerization (Zhang

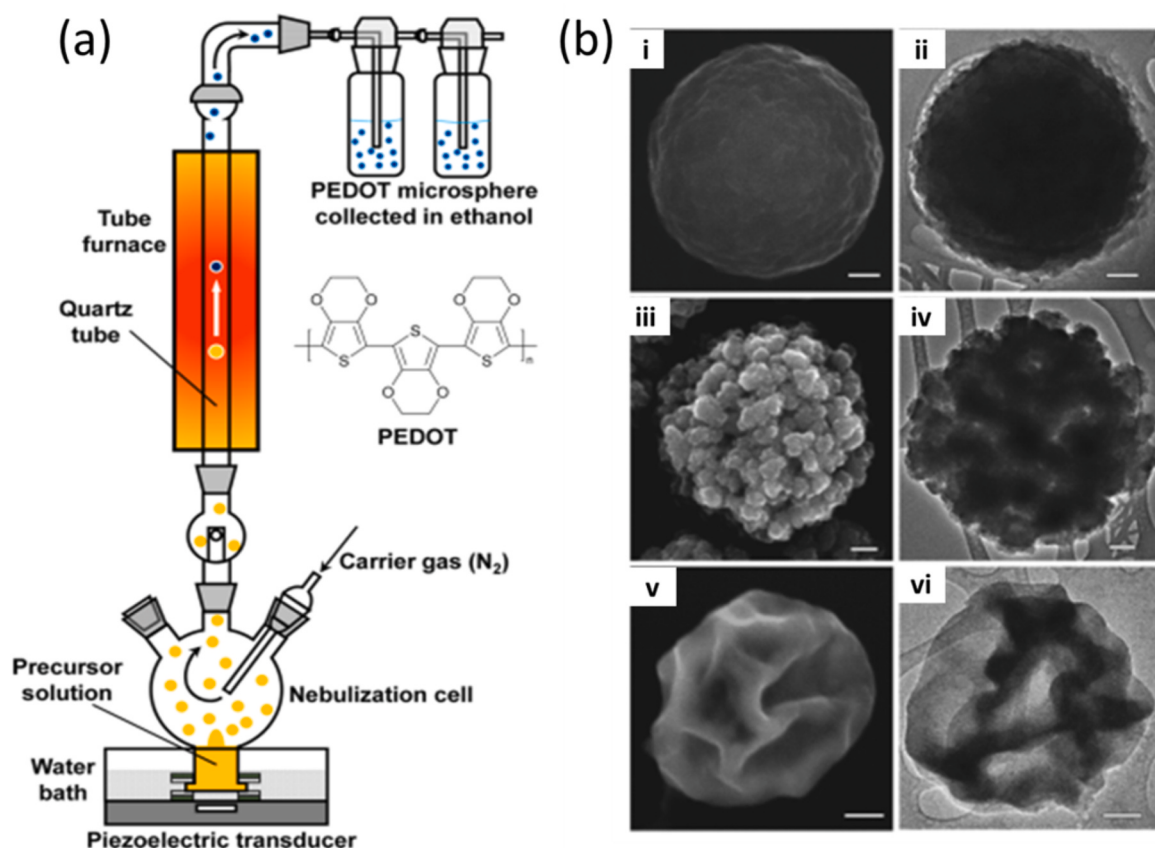


Fig. 6. (a) Preparation process of PEDOT microspheres using ultrasonic spray polymerization, (b) SEM and TEM of three types of PEDOT microspheres: (i, ii) solid microspheres (iii, iv) porous microspheres, and (v, vi) hollow microspheres. Reproduced with permission from (Zhang and Suslick, 2015).

and Suslick, 2015) and microfluidic platform (Lee et al., 2016b). Among these, microfluidics and ultrasonic spray polymerization are two potential techniques for the preparation of CP-MPs for electrochemical biosensors. The microfluidic method can produce highly homogeneous microspheres through a controllable manipulation process (Dendukuri et al., 2007; Lewpiriyawong et al., 2010). Ultrasonic spray polymerization offers a facile, one-step, and scalable process for the production of CP-MPs (Fig. 6a) (Fortunato et al., 2010). Both techniques exhibit excellent potential in controlling the size and morphology of formed microspheres. Specifically, the results indicate that ultrasonic spray polymerization can successfully control CP-MPs morphologies in three types of microspheres, namely porous, solid, and hollow, by selecting oxidants or solvents in the precursor solutions (Fig. 6b) (Zhang and Suslick, 2015).

4.3. Porous conducting polymers

Porous conducting polymers (PCPs) are typical CPs that combine the advantages of porous structures and the unique electrochemical characteristics of CPs (Song et al., 2020). Generally, methods to induce pores into CPs can be divided into two classes based on the use of a template and include: (i) template-free or direct synthesis methods such as electro-polymerization technique, chemical polymerization, electro-spinning, and spin coating method; and (ii) template methods including hard-template and soft-template techniques. Given the special structure, PCPs exhibit several superior advantages over conventional CPs as follows: (i) significantly larger specific surface area, which enables the provision of more active sites for chemical reactions and possibilities for molecular interactions (Bai and Shi, 2007; Hatchett and Josowicz, 2008); (ii) high electrical conductivity due to decreased charge-transfer resistance; (iii) providing shorter diffusion path of molecules and ions,

(iv) excellent reuse property, outstanding environmental stability, and long shelf-life (An et al., 2004; Luo et al., 2007). Thus, PCPs were considered the most promising candidates for the fabrication and design of various biosensors. They can significantly improve response sensitivity and reduce signal time in immuno-sensors.

By exploiting the advantages of PCPs, a wide range of PCP-based electrochemical biosensors were successfully developed and designed to detect protein, RNA, and DNA. Liu et al. (2018) developed a biosensor with high sensitivity and selectivity for detecting alpha-fetoprotein (AFP) (Fig. 7). The biosensor was fabricated by doping poly (sodium 4-styrene sulfonate) (PSS) into the three-dimensional (3D) porous PANI using a hard-template method. Given a porous structure with high surface area, high conductivity, and functional groups, 3D PANI can provide a perfect substrate for deposition and immobilization of AFP antibody probes in an electrochemical biosensor. The results in the study indicated that the AFP immuno-sensor exhibited high performance in terms of the detection of the target protein. Specifically, the 3D porous PANI-based immuno-sensor can detect a wide range of AFP protein concentration levels (0.01–1000 pg mL⁻¹). When compared with a planar PANI-based biosensor, the porous PANI biosensor exhibited twice the sensitivity, thereby improving efficiency associated with the PCPs structure. In another study, Sun et al. (2017) successfully combined porous PEDOT and PANI NWs to fabricate a reagentless and label-free voltametric immuno-sensor to detect antigens. Results demonstrated that the PEDOT with a porous structure and high conductivity plays an important role in supporting the growth of PANI nanowires (NWs), while PANI NWs are responsible for the immobilization of antibody probes and generation of response signals. Based on the aforementioned properties, the PEDOT/PANI immuno-sensor exhibits excellent temporal stability, selectivity, and sensitivity with a detection limit of as low as 0.7 pg mL⁻¹. Therefore, the integration of PCPs with

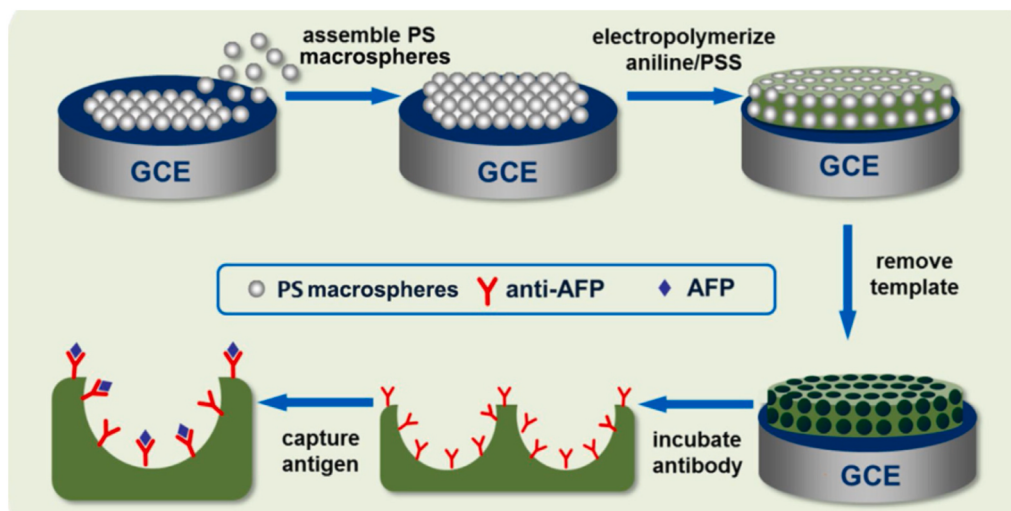


Fig. 7. Fabrication process of the immuno-sensor based on porous PANI. Reproduced with permission from (Liu et al., 2018).

functionalized CP-NWs can offer an ideal platform for the development of various biosensors. The results of extant studies indicated that the development of biosensors based on PCPs is a promising strategy for detecting COVID-19.

4.4. Conducting polymer nanocomposites

Most pure CPs typically exhibit limitations in terms of poor selectivity, low sensitivity, and poor stability (Prakash et al., 2013). To overcome the problems, CP composites (CPCs), which are typical materials that integrate CPs (a primary component) with other conducting or insulating materials, are used to enhance electronic properties and sensing performance (Chowdhury et al., 2019). When compared with each counterpart, CPCs exhibit a more diverse morphology, a larger edge plane/basal plane ratio, better electronic properties, simpler synthesis, high sensitivity, excellent selectivity, reversible doping/dedoping processes, controllable electrochemical/chemical properties,

biocompatibility, and good stability under different environmental conditions (Shrivastava et al., 2016; Zhao et al., 2020). Therefore, it has been demonstrated that CPCs can be employed as excellent transducers in biosensors. Several CPCs and their applications in biosensors for various biomarkers including DNA, RNA, protein, antibodies, and whole virus are summarized in Table 5. Based on the summarized data, four main groups of materials can be conjugated with CPs to form composites for electrochemical biosensors: carbon-based materials, metal nanoparticles, metal oxide nanoparticles, and other polymers. It is assumed that composites can be used as potential candidates for fabricating electrochemical biosensors for detecting COVID-19.

4.4.1. Conducting polymer/carbon materials composites

Given the potential of using building blocks to construct 1D, 2D, and 3D structural materials, carbon-based materials, such as carbon nanotubes (CNTs), graphene, and graphene oxide (GO), have been commonly used to integrate CPs in composites (Cong et al., 2014; Hangarter et al.,

Table 5
Summarized electrochemical biosensor applications of conducting polymer composites.

Composites	Probe/biomarkers	Detecting range	LOD	Refs
Conducting polymers/carbon-based materials composites				
PEDOT/CNT	Biotinylated aptamer/DNA	1.0–1.0 × 10 ⁸ fg/mL	0.5 fg/mL	Thakur et al. (2017)
PPy/CNT	ssDNA probe/DNA	1.0 × 10 ⁻⁵ –3.0 × 10 ⁻⁸ mol/L	1.0 × 10 ⁻⁸ mol/L	Cai et al. (2003)
PPy/MWCNTs	ssDNA probe/DNA	1 fM–100 nM	0.3 fM	Miodek et al. (2015)
PANI/graphene	ssDNA probe/DNA	0.1 pM–1 μM	0.01 pM	Zheng et al. (2015)
PPy/graphene	Anti-VEGF RNA aptamer/RNA	–	100 fM	Kwon et al. (2012a)
PPy/graphene	Adenine and Guanine	Adenine: 0.06–100 μM Guanine: 0.04–100 μM	0.02 μM 0.01 μM	Gao et al. (2014)
PEDOT:PS/RGO	ssDNA probes/DNA	50 fM–2 μM	17 fM	(Dağcı Kıranşan and Topçu, 2020)
PANI/GQDs	Antibody/Whole virus	1 fg/mL–100 pg mL ⁻¹	0.8 fg/mL	Chowdhury et al. (2019)
PANI/GO	Negative ssDNA/DNA	1.0 × 10 ⁻¹⁵ –1.0 × 10 ⁻⁸ mol/L	2.5 × 10 ⁻¹⁶ mol/L	Yang et al. (2013)
Conducting polymers/metals or metal oxide nanoparticles composites				
PEDOT/AuNPs	ssDNA probes/DNA	150 pM–1 μM	–	Spain et al. (2013)
PPy/AuNPs	ssRNA probe/RNA	100 aM–1 nM	78 aM	Tian et al. (2018)
PANI/AuNPs	Biotinylated DNA probe/ <i>E. coli</i>	4–4 × 10 ⁶ CFU	4 CFU	Shoae et al. (2018)
PEDOT/AuNPs	Antibody/disease biomarker	0.001–1000 U/mL	0.32 mU/mL	Han et al. (2020)
PPy-PEDOT/AgNPs	ssDNA/DNA	10 ⁻¹⁴ –10 ⁻¹¹ M	5 × 10 ⁻¹⁵ M	Radhakrishnan et al. (2013)
PPy/AgNF	PNA/miRNA-21	0.20 fM–1.0 nM	0.2 fM	Kangkamano et al. (2018)
PEDOT: PSS/Fe ₂ O ₃	Antibody/CEA protein	4–25 ng/mL	–	Kumar et al. (2019)
PPy/CeO ₂	ssDNA/DNA	1.0 nM–1 μM	0.29 μM	Nguyet et al. (2019)
PANI/Ag–Cu	–/ <i>E. Coli</i>	–	10 ⁸ CFU	Abdullah et al. (2014)
Conducting polymers/conducting or insulating polymer composites				
PANI/PAA	ssDNA probes/DNA	5.0 × 10 ⁻⁸ –2.0 × 10 ⁻⁷ M	2 × 10 ⁻⁸ M	Gu et al. (2005)
PPy nanowire/PEG	DNA probe/RNA	0.10 pM–1.0 nM	0.033 pM	Wang and Hui (2019)
PPy/PEDOT:PS	DNA/-	–	–	Tekoglu et al. (2020)
PEDOT/PEG	Antibody/protein	0.001–10 fg/mL	0.0003 fg/mL	Cui et al. (2016)
PPy/PAA	ssDNA probe/DNA	1–50 μM	0.01 nM	Kannan et al. (2011)

2013; Wang et al., 2018). In electrochemical biosensor applications, graphene, which is a 2D material with a single layer of six-member carbon rings, exhibits a limitation in its interfacial interactions due to low intrinsic reactivity. GO, in contrast, which contains several functional groups such as $-\text{COOH}$, $-\text{OH}$, or $\text{C}-\text{O}-\text{C}$, is known as an active graphene material (Salavagione et al., 2014). Thus, CNTs can be classified into two types: single-walled CNTs (SWCNTs) and multi-walled CNTs (MWCNTs) and both types can be used in biosensors. The structures can improve the performance of electrochemical biosensors due to the synergistic effects of carbon materials and CPs (Wang et al., 2018). Additionally, CPs effectively improve the conductivity and electrochemical characteristics of carbon-based materials without any damage to their structure. Therefore, CPCs based on carbon materials are potential candidates for electrochemical biosensor devices and immuno-sensors (Naveen et al., 2017).

Some methods were employed to synthesize CPCs based on carbon materials, such as vapor polymerization, template-oriented synthesis, chemical functionalization, in situ generations of CP composites, etc. However, based on the advantages and disadvantages of each technique, we propose that biosensors based on CPs-carbon materials composites can be designed and fabricated via a convenient approach for detecting COVID-19. The approach involves electrochemical polymerization techniques, which can easily control the film's morphology, thickness, chemical state, and conductivity (Fig. 8). Based on this approach, the fabricating process of biosensor devices includes two main steps: (1) preparation of a thin-film electrode via electrochemical polymerization and (2) immobilization of aptamer/probes.

In the last decade, the efficiency of CP-carbon material composites was demonstrated in electrochemical biosensors for detecting DNA, RNA, and viruses. Given this scientific evidence, they are considered for applications involving the detection of COVID-19. To increase the sensitivity of biosensors for detecting adenine and guanine (i.e., two important bases of DNA and RNA sequences), Gao et al. (2014) developed a novel biosensor based on porous structure thin films of over-oxidized PPy/graphene composite. The overoxidized composite films

exhibit a low background current and improved electroactive surface area, which is the main reason for enhancements in the selectivity and sensitivity of biosensors. Additionally, results indicated that with the positively charged surface and specific structure, the overoxidized PPy/graphene composite can easily adsorb negative charge biomarkers via electrostatic adsorption. Cai et al. (2003) fabricated a novel electrochemical biosensor for directly detecting DNA by coupling PPy with MWCNTs as an application strategy of CNTs in preparation of CP composites. In the study, the COOH -functionalized MWCNTs were electrochemically polymerized with PPy to form a composite and the ssDNA probe was then immobilized on the surface of the electrode with the covalent interaction with MWCNTs during the electro-polymerization process. The results demonstrated that the biosensor based on PPy/MWCNTs composites exhibited high sensitivity along with other advantages such as simplicity and fast response. In another study, Miodek et al. (2015) also employed a PPy/MWCNTs composite to fabricate a highly sensitive biosensor for detecting DNA via a novel approach. The nanocomposite was synthesized via electrochemical polymerization and PPy was wrapped on MWCNTs. The surface of the MWCNTs-PPy composite was functionalized and modified with NH_2 -functionalized dendrimers and COOH -modified ferrocene and the ssDNA probes were covalently immobilized on the electrode. The PPy/MWCNTs composite-based biosensor exhibited a high performance for sensing DNA with high sensitivity (LOD of 0.3 fM), and the system exhibited the potential for further application in pathogen diagnostics.

Recently, graphene quantum dots (GQDs) were discovered as a potential carbon-based material for the synthesis of nanocomposites and fabrication of electrochemical biosensors (Dutta Chowdhury et al., 2018; Fan et al., 2015). By using the nanocomposite composed of GQDs and PANI nanowires, an ultrasensitive electrochemical biosensor was successfully developed by combining interfacial polymerization and self-assembly (Chowdhury et al., 2019). In the study, the sensitivity of the biosensor was found to be significantly higher due to the application of different external electrical pulses during the virus accumulation process and the expansion of the surface of the virus particle and

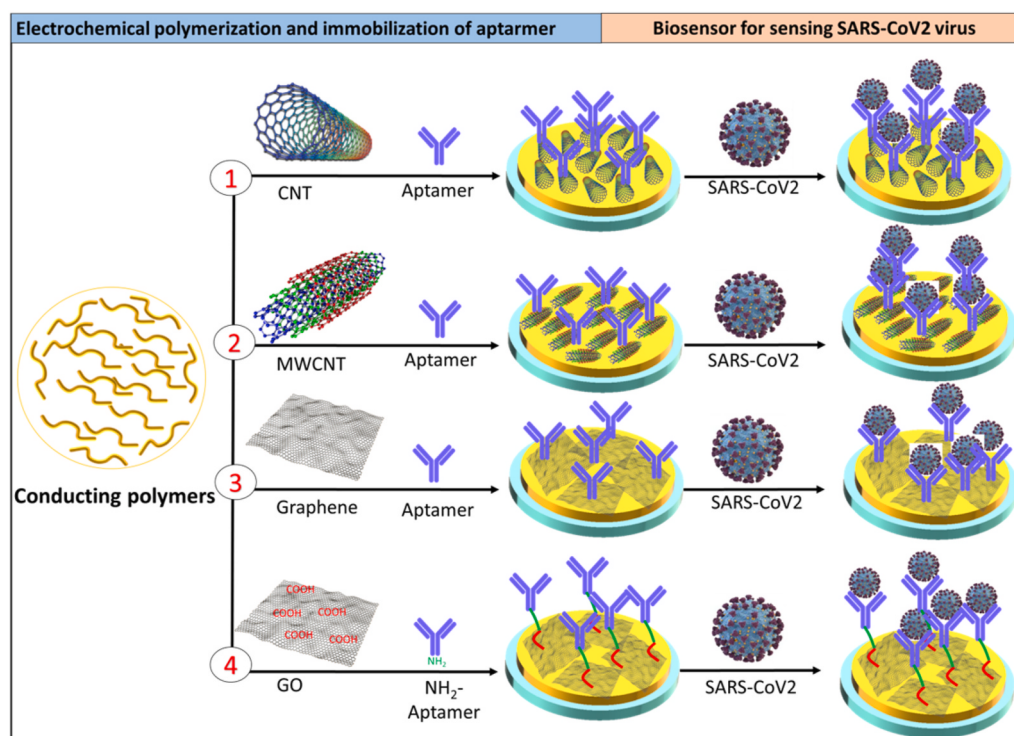


Fig. 8. Composites based on the integration of conducting polymer and carbon-based materials for COVID-19 electrochemical biosensors: (1) CPs and CNT composite; (2) CPs and MWCNT composite; (3) CPs and graphene composite; and (4) CPs and GO composite.

antibody-conjugated PANI chain length. The biosensor exhibited a sensitivity similar to RT-PCR, an accurate method that is commonly used to detect viruses. Recently, owing to several advantages including large surface area, flexibility, lightness, good mechanical, and electrochemical properties, 3D graphene-based materials (e.g., reduced graphene oxide (rGO)) were used in the design of ultrasensitive biosensors (Zhang et al., 2012). Additionally, rGO contains several functional groups and exhibits good dispersion in aqueous solutions. Thus, it can be easily incorporated and distributed in the CP network (Lei et al., 2014). Dağcı Kırışan and Topçu, (2020) introduced a PEDOT:PSS/rGO composite that can be used as an electrode in a DNA biosensor. In the biosensor system, PEDOT:PSS plays the role of a skeleton to cover the rGO layers and provides a significant improvement in mechanical strength and electrochemical properties due to a relative reduction in

pore size of the 3D composite material. The results indicated that the biosensor based on the PEDOT:PSS/rGO composite exhibits excellent conductivity (158 S cm^{-1}), sensitivity (LOD of 17 fM), flexibility, free-standing property, and durability (>700 times its weight). Hence, it is considered suitable for detecting other pathogens and viruses.

4.4.2. Conducting polymer/metal and metal oxide nanoparticle composites

Metal/Metal Oxide nanoparticles are called metal-based nanoparticles (MNPs) and comprise Au, Pt, Ag, Pd, Ni, Cu, TiO_2 , MnO_2 , ZnO , and Fe_3O_4 . They exhibit several unique characteristics and thus can be used to synthesize composites in combination with CPs (Naveen et al., 2017). Generally, composites of CPs and MNPs (CP-MNPCs) inhibit agglomeration and restacking of metal NPs due to steric hindrance and electrostatic interactions. Additionally, results indicated that these

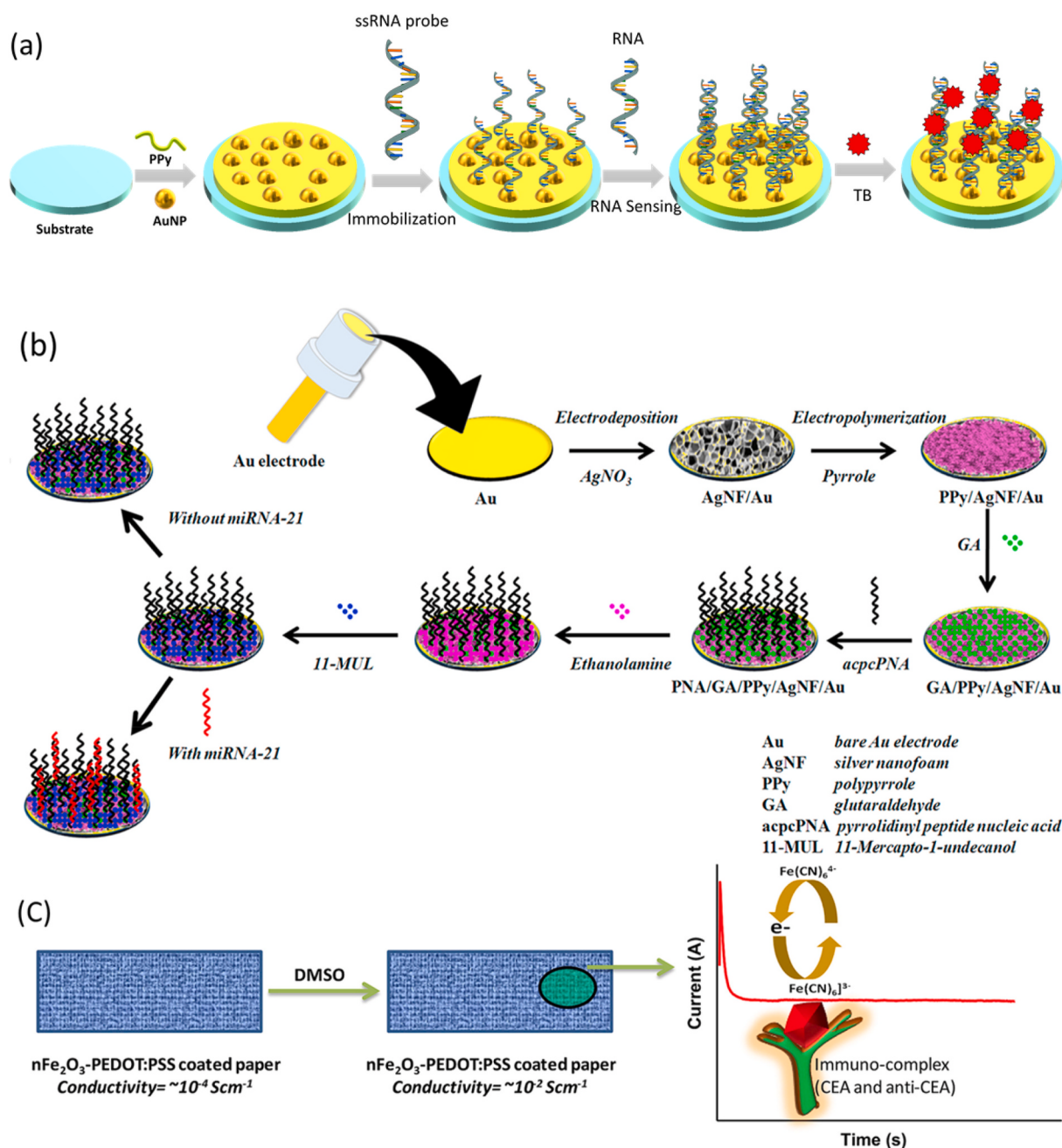


Fig. 9. (a) Schematic illustration of an electrochemical biosensor based on PPy/AuNPs composite for RNA detection (b) Fabrication procedure of a label-free biosensor based on PPy/AgNF composite for RNA detection. Reproduced with permission from (Kangkamano et al., 2018); (c) Immuno-sensor based on Fe_2O_3 -PEDOT composites for detecting pathogens. Reproduced with permission from (Kumar et al., 2019).

composites can improve electron transport rates between electrodes and electrolytes in electrochemical biosensor devices. Therefore, CP-MNPC composites have attracted significant attention in the development of electrochemical biosensor devices, especially for DNA and RNA detection (Table 5) because the MNPs offer a convenient surface for immobilizing strand DNA probes and simultaneously enhance conductivity, which facilitates the hybridization process throughout 3D film formation (Bai et al., 2019).

It was reported that Au and Ag NPs are among common metal NPs that are integrated with CPs to prepare active composite materials for electrochemical biosensors. Spain et al. (2013) successfully prepared a nanocomposite composed of AuNPs and PEDOT and applied it to construct high-sensitivity DNA biosensor devices. The results indicated that the nanocomposite can easily immobilize DNA due to a large surface area. It also exhibits excellent conductivity and good porosity, thereby significantly decreasing signal-to-noise current ratios and increasing the sensitivity. Furthermore, a vapor-phase polymerization method was used in the study to fabricate the composite film. This is considered a suitable and compatible approach with superior advantages such as low cost, mass-scale production, and production of high sensitivity biosensors. The results demonstrated that nanocomposite materials of AuNPs and CPs can be used to design electrochemical biosensors for the DNA of a pathogen. Similarly, Tian et al. (2018) used a composite of AuNP and PPy to fabricate a label-free and simple electrochemical micro-RNA biosensor. Fig. 9a shows its fabricating process. In the study, Toluidine blue (TB) was used as a redox indicator to leverage its ability of signal amplification. AuNPs superlattice is the supporting material for the study. AuNPs were coated with PPy polymer and this composite was self-assembled to form a superlattice and simultaneously immobilize ssRNA probes. A new strategy involving the use of TB for signal amplification was employed and ultra-sensitive detection of microRNA was achieved with a LOD of 78 aM. The biosensor enables reproducibility and especially exhibits an excellent response in the real sample.

Silver nanoparticles (AgNPs) were recently employed as a promising material for the fabrication of RNA biosensors. Kangkaman et al. (2018) proposed the use of a porous silver nanofoam (AgNF) to develop electrochemical biosensors by incorporation with CPs in a composite. In the study, three main components including CPs (PPy), AgNF, and peptide nucleic acid (PNA) were used to prepare a label-free miRNA biosensor (Fig. 9b). During the preparation, AgNF was deposited on an Au electrode, which was followed by the functionalization of PPy for immobilization of PNA probes. The biosensor was used to evaluate the detection performance with an RNA biomarker from pathogens and indicated that the biosensor exhibited good sensitivity with a very low LOD (0.20 fM), high specificity to the biomarker, and good recoveries (81%–119%). Specifically, PNA probe lengths can affect the biosensor performance. The results suggested that AgNF can be used to fabricate a composite with CPs for RNA biosensors, and PNA can be used as an alternative probe for DNA in this type of biosensor.

Recently, conducting paper-based electrochemical biosensors attracted significant interest for a wide range of applications for smart sensing devices due to low cost, high flexibility, and disposability. It was indicated that metal oxides can be used in the development and design of numerous paper biosensors (Wang et al., 2018). A label-free, flexible, lightweight, and disposable conducting paper immuno-sensor was introduced based on a composite of iron oxide (Fe_2O_3) and PEDOT:PS (Fig. 9c) (Kumar et al., 2019). In the study, a facile method was proposed to fabricate electrochemical paper biosensors by the deposition of Fe_2O_3 NPs on PEDOT:PSS polymer layers. The biosensor exhibited high efficiency with high sensitivity and long-term stability for detecting a pathogen biomarker (carcinoembryonic antigen-CEA). It was observed that the conductivity of PEDOT:PS was significantly enhanced from 6.8×10^{-4} to 1.92×10^{-2} S/cm due to treatment with a dimethyl sulfoxide DMSO solvent. The n Fe_2O_3 -incorporated PEDOT:PSS also enhanced the sensing performance and signal stability. Furthermore, the biosensor

exhibited potential applicability in real patient samples. The lightweight, disposable, and sensitive paper biosensor was developed from composites of metal oxides and CPs and can be used in smart point-of-care devices for the detection of pathogens.

4.4.3. Conducting copolymers

The design and discovery of excellent immobilization matrixes that can enhance the electron transfer and simultaneously maintain the bioactivity of biomolecule probes is a crucial strategy in electrochemical biosensor applications for sensing genes and pathogens. Conducting copolymers (CCPs) are considered potential materials for electrochemical biosensors due to their several interesting properties as follows: (i) simple deposition process on the electrode substrate surface; (ii) easy control of thickness; and (iii) redox conductivity (Soylomez et al., 2013). A copolymerization method is one of the most common and feasible techniques for the preparation of CCPs. Furthermore, CCP-based electrochemical biosensors can be considered potential candidates for the detection of DNA, RNA, protein, and pathogens (Yasen et al., 2020). Existing studies indicated that CPs can be integrated with other CPs or insulating polymers such as polyethylene, polyvinylchloride, polycarbonate to form CCPs (Cui et al., 2016; Gu et al., 2005; Kannan et al., 2011; Tekoglu et al., 2020; Wang and Hui, 2019).

Recent strategies for developing electrochemical biosensor devices employ advanced polymers and especially biocompatible polymers due to their outstanding physiochemical properties, excellent biocompatibility, and easy modification process (Luo et al., 2013). Several studies developed electrochemical biosensors for detecting virus, DNA, RNA, and proteins based on the integration of biocompatible polymers and CPs (Table 5). For example, Cui et al. (2016) used a well-known biocompatible polymer, poly(ethylene glycol) (PEG), to synthesize CCPs for integration with PEDOT (Fig. 10). Based on the approach, the biocompatibility of PEG was synergized with the outstanding features of PEDOT, such as high conductivity and stability, to produce a potential composite material for designing a protein biosensor. PEG was doped into the PEDOT matrix through negatively charged SH groups and the composite was then deposited onto the glass substrate. In the biosensor system, AuNPs were used to improve the immobilization of antibody probes and various other biomolecules. The CCPs of PEDOT/PEG exhibited a flake-like nanostructure with a large surface area and excellent stability. Additionally, the PEDOT/PEG-based biosensor exhibited excellent sensing performance with ultra-sensitivity (LOD of 0.0003 fg/mL) and high selectivity. Because it comprises a hydrophilic PEG polymer, the PEDOT/PEG-based biosensor exhibits good anti-fouling ability and the capability to detect biomarkers in real samples (human serum). Thus, it has high applicability in clinical diagnosis. Electrochemical biosensors based on CCPs, especially in the case of biocompatible polymers, can be considered as a potential approach to construct biosensors for detecting COVID-19.

4.5. Conducting polymer hydrogels

Conducting polymer hydrogels (CPHs) are considered CP-based materials that combine the advantages of CPs and hydrogels (Guo et al., 2019; Van Tran et al., 2018), thereby exhibiting excellent electrical conductivity, mechanical flexibility, high stretchability, biocompatibility, and ease of processing (Li et al., 2015; Lu et al., 2019). Some CPs, including PEDOT, polythiophene, PPy, and PANI, can be utilized to synthesize CPHs by covalently or physically cross-linked reactions (Li et al., 2018; Lu et al., 2019; Shi et al., 2015b; Wei et al., 2020). CPHs are considered potential candidates for the fabrication of high-performance biosensors due to their advantages related to interfaces and enhanced sensing performance for electrochemical bioelectrodes (Guo et al., 2019; Li et al., 2015). These advantages help (i) increase the effective interface area of CPs in the 3D organic matrix (ii) facilitate immobilization of biomolecular probes due to linkages between soft and hard materials (iii) provide high density and promoting electron collection and (iv)

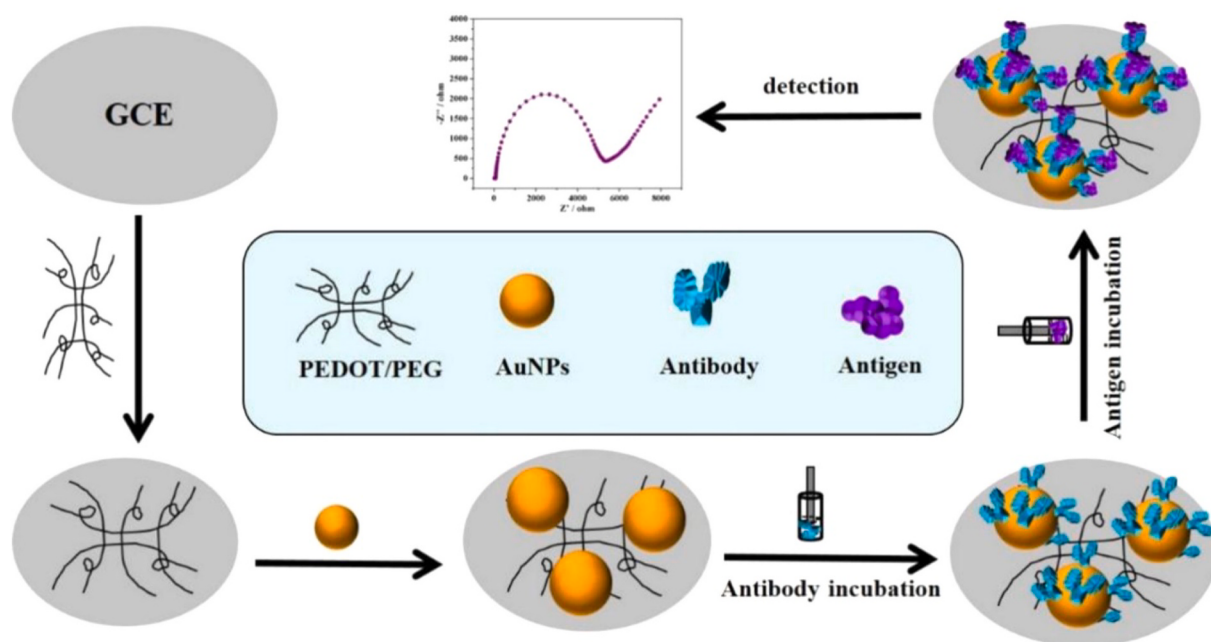


Fig. 10. Schematic illustration of the preparation of a PEDOT/PEG conducting copolymer-based electrochemical biosensor for detecting protein. Reproduced with permission from (Cui et al., 2016).

reduce the impedance (Zhao et al., 2013). Based on these unique features, CPH-based electrochemical biosensors demonstrate higher sensitivity, lower detecting limitation, and faster response time compared to conventional CPs-based electrochemical biosensors. For example, a sensitive, rapid, and antifouling biosensor for detecting miRNA biomarkers was successfully constructed by the assembly of PANI and phytic acid (PA), and DNA probes were immobilized onto PANI/PA interface (Fig. 11a) (Yang et al. 2020b). The PANI/PA hydrogel possesses multiple pore structures, excellent antifouling ability, and good electrochemical properties, and thus the proposed biosensors exhibit high sensing performance to the microRNA biomarker: low limit of detection (0.34 fM) and wide linear range of concentration (1.0 fM–1.0 pM). In summary, CPHs-based electrochemical biosensors can be applied to detect COVID-19 given their high stability, antifouling property, mechanical flexibility, biocompatibility, high stretchability, facile processability, and high sensitivity and selectivity.

Based on the aforementioned properties, CPH can be considered a unique smart material in biosensors because it can satisfy the requirements of advanced biosensor technologies (Shi et al., 2015a). Their high mechanical flexibility, excellent stretchability, and ease of preparation make CPHs suitable for next-generation wearable, implantable, and portable electrochemical biosensor devices. Furthermore, upon the fabrication of portable biosensor devices, patterning of electrodes into various geometries is the most crucial step (Kim et al., 2011; Kleber et al., 2017; Wang et al., 2017). However, poor stability and solubility in aqueous conditions are the problems that limit the patterning ability of conventional CP materials with complex designs (Lee et al., 2016c; Yao et al., 2017). In contrast, CPHs exhibit excellent patterning capacity using simple methods. For example, Lu et al. (2019) fabricated highly conductive, stable, and stretchable hydrogel patterns by using a simple method using volatile additive dimethyl sulfoxide and controlled dry annealing and rehydration. The study demonstrated that pure PEDOT:PSS hydrogels can be effectively patterned into complex geometries in free-standing and robust laminate forms (Fig. 11b). Additionally, this CPH exhibited a significantly long-term mechanical and electrochemical stability in wet physiological conditions over three months. Thus, the CPHs potentially offer a new avenue for CP applications in electrochemical biosensors for next-generation advanced bioelectronic devices. Furthermore, this corresponds to a potential strategy to develop

electrochemical biosensors for detecting COVID-19.

5. Conducting polymers in flexible and wearable electronic biosensors for COVID-19

Existing studies have focused on flexible and stretchable biosensors for POC testing systems based on their potential applications in customized personal health monitoring systems (Gao et al., 2016; Park et al., 2012; Trung and Lee, 2016; Yang et al., 2017b). The aforementioned biosensors usually possess certain superior advantages such as light-weight, ultra-conformability, portability, noninvasive, and implant ability (Lee et al., 2016a; Salvatore et al., 2014). Generally, flexible biosensors are fabricated based on simple infrastructure and expected to satisfy the demands for self or ambulatory testing (Xu et al., 2019). Normally, a flexible biosensor is usually comprised of three main components: (i) a flexible substrate with high mechanical flexibility to support the entire system (Pang et al., 2015); (ii) electrodes for exporting the electronic signals (Ramuz et al., 2012); and (iii) sensing elements (bioreceptors) for capturing and recognizing analytes (Xu et al., 2014). Currently, the development strategies of flexible and stretchable biosensors mainly focus on the discovery and synthesis of novel multifunctional materials that can be used as sensing elements (Rong et al., 2018; Xu et al., 2019; Yang et al., 2017b). It has been proposed that CPs can be potentially evaluated in the context of flexible biosensor applications. A wide range of studies used CPs as bioreceptors in flexible biosensors to detect different biomarkers (Khodagholy et al., 2012; Liao et al., 2015; Liu et al., 2016; Lu et al., 2014; Weng et al., 2014). Therefore, it is predicted that using CPs to construct and design flexible and wearable biosensor devices will be an important strategy in the early detection of COVID-19 in the future.

Organic field-effect transistors (OFETs) and organic electrochemical transistors (OECTs) are expected to constitute key flexible electronic biosensors that can be broadly applied in the detection of pathogens and biomolecules due to their primary advantages including miniaturization, low cost, and mass production (Bhalla et al., 2020). Commercial CMOS technology is used to prepare OFETs-based biosensors (Bausells et al., 1999; Syu et al., 2018; Tsai et al., 2010). It is assumed that CPs that exhibit certain important properties, such as high stability in the oxidized state, good water dispensability, simple processability, visible

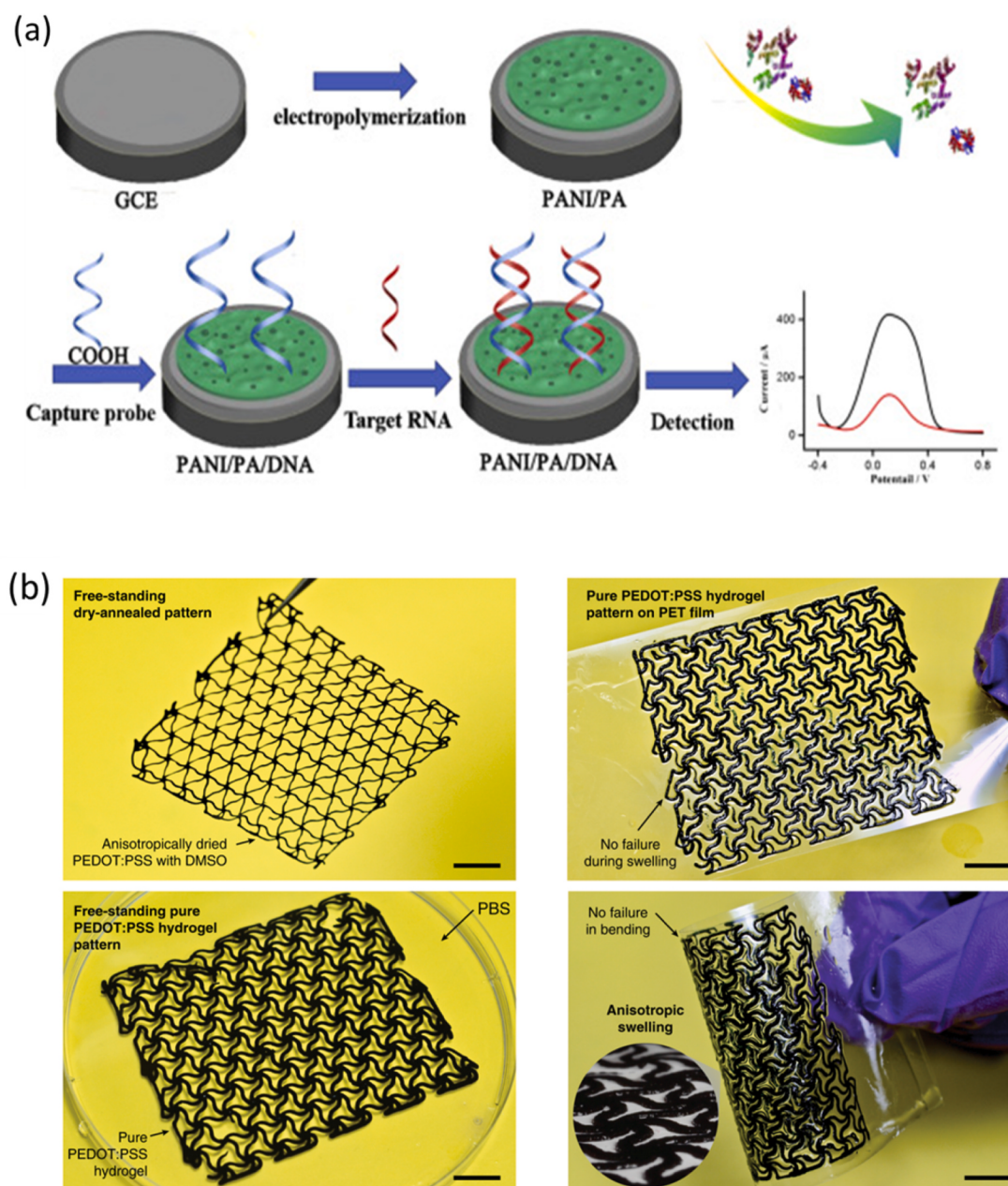


Fig. 11. (a) Preparation of a PANI/PA-based electrochemical biosensor with antifouling ability for miRNA detection. Reproduced with permission from (Yang et al., 2020b); (b) Patterning of pure PEDOT:PSS hydrogels: Free-standing pure PEDOT:PSS pattern and robust laminate of pure PEDOT:PSS hydrogel pattern. Reproduced with permission from (Lu et al., 2019).

light transmission, and high conductivity, can be potentially applied in flexible biosensors to detect pathogens (Xu et al., 2019). Based on the aforementioned properties, PPy, PANI, and PEDOT are CPs that can be employed as active materials in flexible biosensors (Xu et al., 2019; Yang et al., 2017b).

Due to their intrinsic flexibility, tunable conductivity, biocompatibility, and low cost, PEDOT:PSS were utilized as flexible CP electrodes to fabricate OECT-based biosensors for detecting bacteria (He et al., 2012), biomarkers (Kumar et al., 2016), glucose (Liao et al., 2015), and DNA/RNA (Lin et al., 2011). It was demonstrated that PEDOT:PSS-based OECT flexible biosensors exhibit an impressive performance in terms of POC monitoring. To facilitate the fabrication of flexible OECT-based biosensors for sensing DNA/RNA, the OECT transistors were integrated with the flexible microfluidic systems (Bernards et al., 2006; Yang et al., 2009). For example, the Lin group developed a DNA biosensor by

integrating a flexible microfluidic system with an OECT transistor that is prepared by a PEDOT:PSS active layer and an Au gate electrode (Fig. 12a) (Lin et al., 2011). In the proposed system, the OECT transistor is cast and patterned on a polyethylene terephthalate (PET) substrate with high flexibility and then integrated with a poly(dimethylsiloxane) (PDMS)-based microfluidic device on the top. This biosensor system exhibits excellent flexibility when both its sides can be easily bent without damage (Fig. 12b). In terms of sensing performance, the PEDOT:PSS flexible biosensor device can detect DNA targets at low concentrations (1 nM). Therefore, the integration of CPs-based OECTs and microfluidic systems can be considered a potential approach to prepare flexible, highly sensitive, low-cost, and disposable biosensors for the detection of DNA and pathogens (especially COVID-19).

Recently, CPs were hybridized or combined with graphene-based materials that are known as conducting polymer/graphene composites

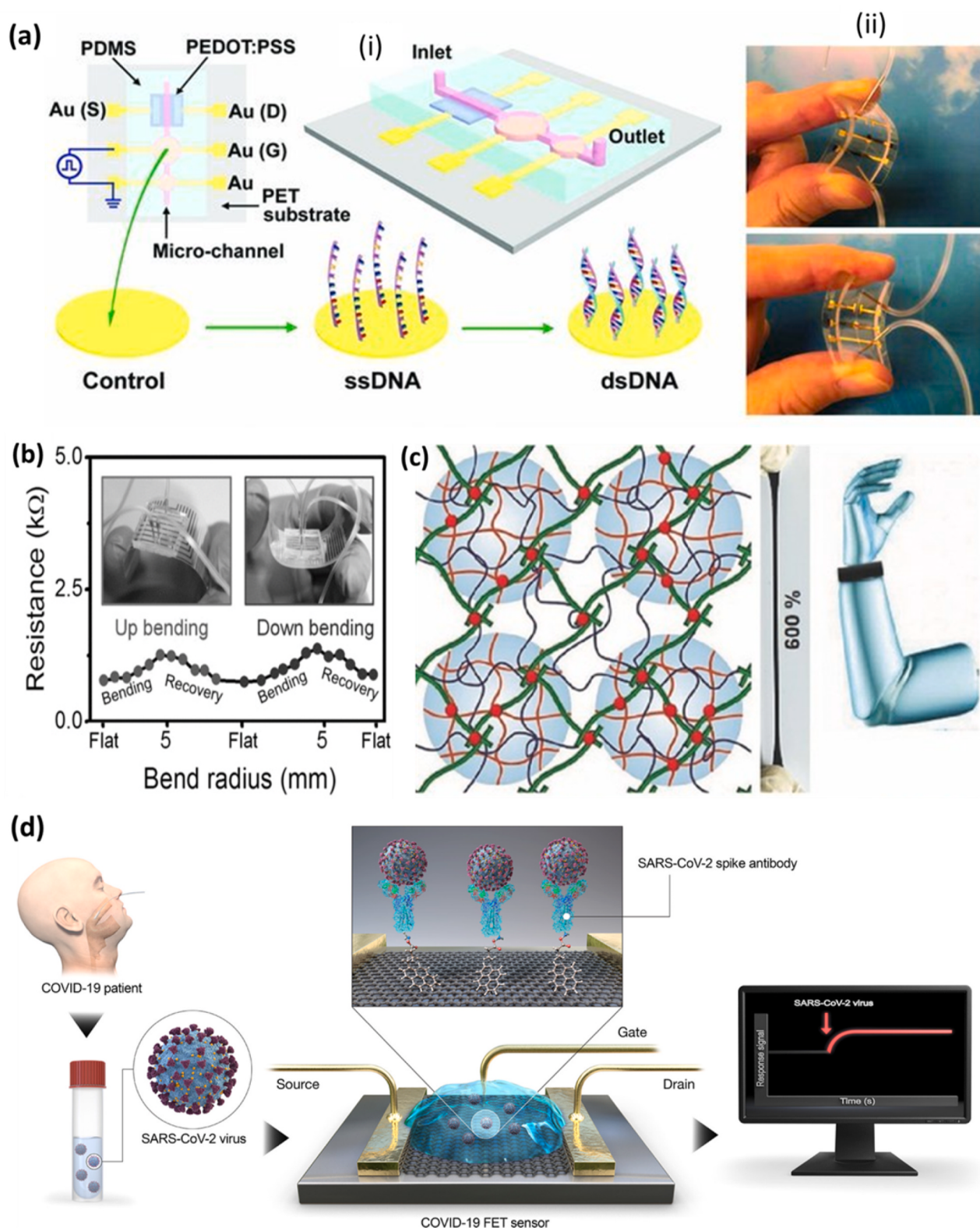


Fig. 12. (a) Flexible DNA biosensor based on the integration of PEDOT:PSS-based OECT and flexible microfluidic systems: (i) fabrication process, (ii) photographs of the bent. Reproduced with permission from (Lin et al., 2011); (b) Flexible biosensors for different bending radius during bending and relaxing. Reproduced with permission from (Kwon et al., 2013); (c) PAAM/PANI-based hydrogel as an electronic skin fixed on forefinger of a human hand (Duan et al., 2016); (d) Graphene-based biosensor device for detecting SARS-CoV-2. Reproduced with permission from (Seo et al., 2020b).

(CP/GE) (Lei et al., 2014). These composites have been increasingly used in flexible biosensors due to a synergic effect concerning increased surface area, lower resistance, high environmental stability, and a high amount of analytical recognition sites. Generally, CPs play an important role in enhancing the sensing performance of flexible biosensors fabricated using CP/GE composites because they act as conducting conduits that interface with analytes and graphene (Hangarter et al., 2013). Existing studies indicate that OFET transistors designed by direct patterning using CP/GE composites exhibited easier integration with microfluidic devices and better electrical properties when compared with pristine graphene (Bunch et al., 2007; Park et al., 2009). Kwon and colleagues successfully designed a novel liquid ion-gated OFET flexible immuno-sensor using large-scale CP/GE nanocomposites with close-packed carboxylated PPY NP arrays (Fig. 12b) (Kwon et al., 2013). The synergistic effect of graphene and CP led to a high sensing performance of CP/GE hybrid immuno-sensors at a low concentration of analytes. Additionally, the CP/GE hybrid immuno-sensor device exhibited a high mechanical bendability and durability, thereby indicating that the CP/GE hybrid system constitutes a potential approach for the development of flexible and wearable biosensor devices. For sensing SARS-CoV-2 in clinical samples, Seo et al. (2020b) fabricated an OFET biosensor by using graphene sheets as active materials (gate of the transistor) and a specified antibody (bioreceptor) to counter the spike of SARS-CoV-2 proteins (Fig. 12d). The results of the study suggested that the graphene-based OFET biosensor exhibited high sensitivity and selectivity to SARS-CoV-2 spike protein at concentrations corresponding to 100 fg/mL and even in clinical samples. Based on the aforementioned studies, we can conclude that the development of flexible and wearable biosensor devices based on CP/GP composites can be a potential strategy for state-of-the-art technologies in biosensors to detect COVID-19.

Based on its unique properties, CPH is also considered an ideal candidate for the fabrication of flexible biosensor devices (Rong et al., 2018). Duan et al. (2016) fabricated a robust and force-sensitive hydrogel with a novel microsphere structure as a potential material for flexible design and wearable biosensors. The hydrogel was prepared by in situ polymerizations of polyacrylamide and PANI into swollen microspheres of chitosan (Fig. 12c). In the hydrogel system, chitosan microspheres exhibit a uniform dispersion into the hydrogel network, and the chitosan microspheres strengthen and enhance the stretchability and mechanical stability (strain 600%) of the hydrogel system. Additionally, PAAm/PANI creates a surface self-wrinkling structure, which enhances the sensitivity of biosensors. Furthermore, the CPH microspheres display rapid response time and long-term electrical stability. Therefore, the results indicated that CPHs constitute materials that can potentially be used for the development of wearable electronic biosensor devices and they are likely to be selected as active materials for designing flexible biosensors to detect COVID-19.

6. Conclusion and perspectives

CT scan, RT-PCR, and ELISA assays as well as various diagnostic kits have been developed to detect COVID-19 in laboratories. Unfortunately, most hospitals in regions experiencing severe outbreaks are overwhelmed, and the number of suspected cases that are unconfirmed has been increasing. Therefore, advanced diagnostic technologies with excellent ultra-sensitivity, specificity, portability, and wearability are crucial for managing the rapidly evolving COVID-19 pandemic. Biosensors have been demonstrated as effective tools for early diagnosis, on-site, rapid, and ultrasensitive detection of SARS-CoV-2. Given their unique properties and advantages in terms of high sensitivity, selectivity, flexibility, processability, and commercial application, CPs can be used for the development of advanced biosensors for COVID-19 detection. Thus, CP-based biosensors can be considered as one of the trending technologies to develop advanced sensors for the early diagnosis of COVID-19. In particular, flexible and wearable CP-based biosensors can serve as an innovative technology in POC systems for COVID-19

detection. In the future, CP-based biosensors are expected to be developed and commonly utilized in local hospitals, laboratories, doctor's offices, airports, or other high-traffic areas, and even at home.

The development of CP-based biosensors for COVID-19 detection entails a few significant limitations caused by their instability, low crystallinity, poor charge transport properties, and insufficient interactions with biomolecule biomarkers of pristine CPs. To extend the applications of CP-based biosensors, these challenges need to be tackled, which can be done via four main approaches: (i) improving the stability of CPs by functionalizing with various functional groups or blending with various other nanomaterials such as graphene, CNTs, metals, metal oxides, and other insulator polymers; (ii) enhancing the electrochemical and charge transport properties of CPs by forming their nanostructures, including nanotubes, nanowires, and microspheres; (iii) increasing the surface area of CPs through microporous structures, which leads to significantly improved interactions between CP surfaces and biomarkers; and (iv) fabricating CP structures with high flexibility, i.e., CP hydrogels, which can be used to design wearable biosensors. In addition, multiplex CP-based biosensors are crucial for the detection of different COVID-19 biomarkers, as they help increase accuracy. Finally, integrating CP-based biosensors with the Internet of Things and considering the ease of use for the members of the community will increase the practical applications of CP-biosensors, particularly homemade biosensors. With the rapid advancement of CP technology, CP-based biosensors can be used for early-stage detection and significantly contribute to the prevention of the spread of COVID-19. Further, these sensors exhibit the potential to improve sensitivity, selectivity, flexibility, electrochemical stability, reproducibility, and sensing ability to various bioanalytes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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