Functionalized Smart Nanomaterials for Point-of-Care Testing

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Abstract Microorganisms especially viruses are one of the major causes of generating serious threats to human health which claims millions of lives annually. Infectious viruses are emerging periodically with their numerous harmful variants such as influenza A virus, Ebola, MERS-CoV-2, most recently SARS-CoV-2(COVID-19), etc. Traditional biochemical and immunological diagnostic methods are limited by sample transportation, processing, high-cost, time-consuming, and expert technicians to operate. Meanwhile, Point-of-Care (POC) devices can be a potential solution to overcome all these drawbacks. These devices provide many benefits in terms of portability, rapidity, low-cost, automation, etc. Nanomaterials of various shapes, size, composition, and physical and chemical properties such as gold nanoparticles, quantum dots, carbon nanomaterials, and hybrid nanocomposites, have been widely used in POC devices to enhance analytical activity and simplify the detection process. In this chapter, we are focusing on various nanomaterials-based POC diagnostic devices for the analysis of viral disease biomarkers. Many more novel, innovative platforms need to come to address the unmet clinical demands. The development of bench-to-bedside and point-of-care devices in recent years has made the term "biosensor" more well known in the scientific community.

Keywords Viral-infections · Biomarkers · Nanomaterials · Biosensors · Nanosensors · Point of care (POC) diagnosis

1 Introduction

Infectious diseases are caused by severe deadly pathogenic microorganisms like bacteria, virus, parasites, and fungi with unknown origin. Infectious diseases can spread rapidly across the global population and pose a life-threatening risk to public

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health in comparison to other diseases [24]. Since 2009, numerous severe life-threatening infectious viruses are emerging periodically with their harmful variants such as Influenza A virus, West African Ebola virus (EBOLA), Middle East respiratory syndrome coronavirus (MERS-CoV), and the recent severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2, named as coronavirus disease (COVID-19)] [26]. Particularly, the outbreak of COVID-19 [61] has caused 350 million of infections and about 5 million of deaths over the past 2 years worldwide. SARS-CoV2 has a higher rate of transmission than SARS-CoV and MERS-CoV [26, 108]. All these infectious diseases are continuously destroying global health, socio-economic conditions, and civilization process of human society. Early-stage detection of infectious viral outbreak is an urgent need to prevent transmission, and contribute effective therapies to save public health. Conventional methods like culturing and microscopy [52] are there for disease detection but they have many limitations like time consuming, microscopy for small size pathogen detection. Biomarkers, the pathogen-specific protein, can be used for diagnosis. Polymerase Chain Reaction (PCR), Western Blotting, Enzyme Linked Immunosorbent Assay (ELISA) [78], Fluorescent Antibody Tests (FAT), and antibody detection, antigen or antibody detection and hemagglutination assay and gene sequencing [70], isothermal amplification techniques [17] and immunochromatography [83] these classical detecting techniques (Fig. 1) have used for accurate diagnosis but these are laboratory-bound, laborious time-consuming process (involving multi-step protocols) and require sophisticated equipment, personnel technicians to handle [62].

Fluorescent [103], chemiluminescent [8], colorimetric [26, 71] and electrochemical [105] based detection techniques are utilized to measure the quantity of viral load. To prevent the transmission of infectious diseases fastest, simple, low-cost detection methods are still in demand. Nowadays, biosensors are more and more useful diagnostic tools for identifying highly contagious infectious diseases [15, 87]. Biosensors are such kinds of devices that can convert biological data to detectable, quantifiable signals like electrochemical, optical, and magnetic signals. Biosensor has two parts—biological signal element and physiochemical transduction part [87]. Signal element includes antibody [60], aptamer [1], and antigen that can bind with target molecule and in transduction part converts the sample into measurable, processable, detectable signal. Depending on transducers, it can be electrochemical, optical, potentiometric, piezoelectric, or thermal [74], as shown in Fig. 2. Biosensors are used in tracking waste, agricultural experiments, forensic testing, and diagnosis of severe diseases. Various biosensor-based detection devices are adopted because of their portability, rapidity, automation, etc. [36, 42, 73]. They have attracted attention because of high sensitivity, rapidity, and low detection limit in real time [42] analysis.

The application of nanomaterials has seen significant increases during the past few decades. Particularly, nanomaterials can enhance the sensitivity, selectivity, analytical performance of biosensor and thus increase the applications of biosensors [19, 20]. The utilization of nanotechnology-based biosensor devices is growing as a promising candidate for detection of infectious diseases [20].

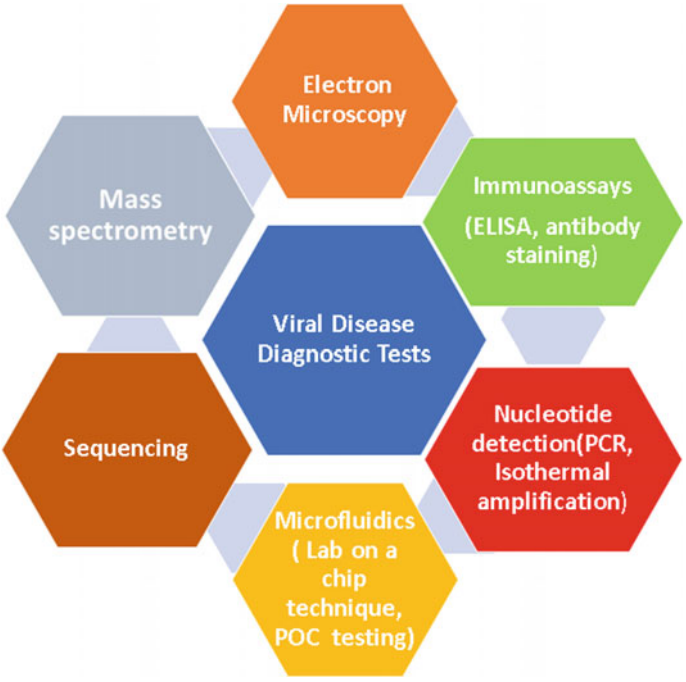

Fig. 1 Available diagnostic tests of viral diseases

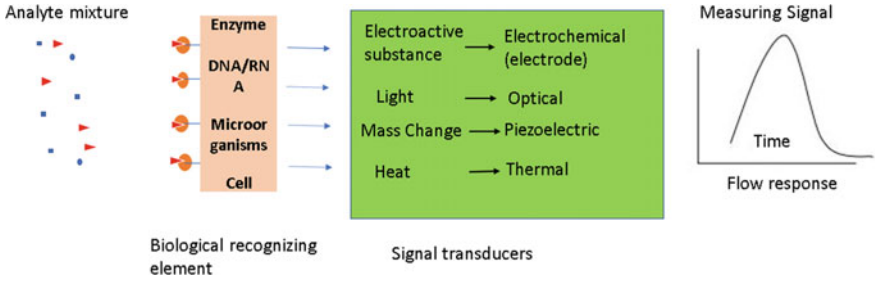

Fig. 2 Schematic diagram of a typical biosensor with all its main components

The tremendous rapid improvement in nanotechnology has imposed a great impact on biosensing. Nanomaterials can be used in specific biosensing system by modulating their physical and chemical properties like morphology, size, surface charge, etc. [45]. Nanomaterials are the synthetic element that ranges within 1–100 nm [29]. It is feasible to improve the sensitivity [7], selectivity, and analytical performance of nanosensors due to the large surface to volume ratio and presence of surface groups of nanomaterials [29, 53]. For example, quantum dots can be used for high

quantum yield in fluorometric detection [2]; gold nanoparticles have considerably higher extinction coefficient than normal dyes in colorimetric detection.

In this book chapter, a variety of nano biosensors are described for detection of viral diseases. Biosensor is compared to traditional diagnostic devices, resource-limited POC devices can be a potential solution for earlier disease detection. Biosensor plays a vital role in constructing POC devices in order to detect the presence or concentration of biomarkers in bodily fluids. POC-based platforms are highly effective, low-cost, user-friendly, rapid, and act in small sample volume. The term "Point of Care" refers to medical diagnostic kit tests carried out close to the location and moment of patient care. Here we will discuss current nanomaterial-based POC testing biosensing devices and how they can improve their effectiveness.

2 Nanomaterials in Disease Diagnosis

Diagnostic tests are a crucial element of any successful approach intended to control new and re-emerging viral diseases and are crucial at every step, from early diagnosis to successful treatment. The development, validation, and implementation of diagnostic tests are challenging, time-consuming processes. The accuracy of nucleic acid amplification test is heavily reliant on taking sample, types, storage, and transportation. False negative results can be obtained if the sample is not taken appropriately or the subject is tested early or lately after viral exposure. To enable rapid screening, new diagnostic platforms that are precise, focused, quick, and simple to use are required. Nowadays research has been shifted to another dynamic diagnosis based on nanomaterials. The efficacy of detection may be improved by NPs' wide surface area, which enables for effective interaction with target analytes. Several nanomaterials have been employed to increase the analytical sensitivity and minimize the detection limits of diagnostic tests. Nanomaterials' unique properties make them appropriate for use in cutting-edge viral detection systems.

2.1 Graphene

The International Union for Pure and Applied Chemistry (IUPAC) defines graphene as a "single carbon layer of graphite structure characterizing its nature by analogy to a polycyclic aromatic hydrocarbon of quasi-infinite dimension" [37]. Graphene is composed of sp2-hybridized carbon atoms and is organized as a thick, single atom, two-dimensional planar nanosheet that mimics a hexagonal or honeycomb structure. It demonstrates a number of exceptional qualities, including a catalytic nature, high surface area, mechanical strength, and conductivity. Due to this, graphene is a very desirable nanomaterial for platforms with sensitive biosensors and fast transistors [76].

In the area of biosensors, graphene and its oxygenated derivatives, such as graphene oxide (GO) and reduced graphene oxide (rGO), are emerging as a significant class of nanomaterials. GO nanosheets are highly hydrophilic due to the oxygenated functional groups they contain, which facilitates chemical functionalization. Inorganic nanoparticles such as metals, metal oxides, semiconducting nanoparticles, quantum dots, organic polymers, and biomolecules can be easily combined with graphene, GO, and rGO nanosheets to produce a variety of graphene-based nanocomposites with improved sensitivity for biosensor applications [55].

Chekin et al. [21] designed porous reduced graphene oxide (prGO)—molybdenum sulphide (MoS2) modified glassy carbon (GC) electrodes for the sensitive and precise detection of the L1-major capsid protein of the human papillomavirus (HPV) [21]. Teymourian et al. [91] described a straightforward electrochemical DNA hybridization biosensor based on Fe_3O_4/r-GO nanocomposite with great sensitivity and specificity to detect HIV [95]. Based on an undecorated graphene oxide (GO) platform, Hu et al. [44] reported a straightforward, label-free approach for DNA hybridization associated with the gene fragment of the HIV-1 pol gene [44].

Using graphene as a sensing platform, Gong et al. [41] developed a straightforward, precise impedimetric DNA biosensor for the sensing of the HIV-1 gene. Torrente-Rodrguez et al. [96] showed the SARS-CoV-2 RapidPlex, which is a portable, wireless, graphene-based electrochemical platform for detecting COVID-19 very quickly [96]. For label-free detection of the H1N1 influenza virus, Singh et al. [87] reported the development of a unique microfluidic chip combined with an RGO-based electrochemical immunosensor. Afsahi et al. [3] created a reasonably priced and transportable graphene-enabled biosensor to identify the Zika virus using an immobilized monoclonal antibody with a high level of specificity [3]. Real-time, quantitative detection of native Zika virus (ZIKV) antigens can be accomplished using Field Effect Biosensing (FEB) and monoclonal antibodies covalently bonded to graphene. For the detection of dengue E protein in blood serum, a label-free immunosensor has been constructed [84]. In another study, Yakoh et al. created an immunosensor based on graphene oxide (GO) that is sensitive and specific for the detection of immunoglobulins produced against SARS-CoV-2 [104]. Beduk and group recently unveiled a miniature electrochemical biosensor based on laser scribed graphene (LSG) with three-dimensional gold nanostructures for the diagnosis of COVID-19 [14].

2.2 Carbon Nanotubes (CNTs)

Biosensor manufacturing heavily relies on carbon-based materials, of which CNT, like graphene, is one allotrope of carbon. Dr. Iijima's discovery of CNTs in 1991 has been going on for 32 years [46], and the pertinent research has been continually broadened and developed over time. A crimping graphene layer forms the cylindrical CNTs. CNTs can be split into single-walled CNTs (SWCNTs) and multi-walled CNTs depending on the number of layers (MWCNTs).

CNTs work efficiently in mechanics. CNTs have an elastic modulus that is equal to that of diamond. Moreover, CNTs have excellent conductivity because they share a sheet structure with graphene. CNTs are also very promising in terms of optical modulation and heat conduction. CNTs also have a variety of benefits, such as their light weight, high specific surface area, chemical stability, superior electrochemical performance, etc., which have the potential to further research in the field of biomolecular detection in medicine [98, 25]. The enormous specific surface area of CNTs offers a variety of reactive sites, facilitating interactions with a variety of biomolecules. For this reason, CNT-based detection systems have gained a lot of attention in recent years [13, 51] with researchers using them all over the world to identify pathogens [43] and viral pathogens [47, 5] Cabral et al. [18] developed a hybrid hyaluronic acid-CNT film-based label-free immunosensor to detect anti-HBc antibodies. The immunosensor responded linearly to anti-HBc up to 6 ng ml^{-1} with a LOD of 0.03 ng ml^{-1} [18]. Pinals and coworkers [80] developed a single-walled carbon nanotube (SWCNT)-based optical sensing method that can find SARS-CoV-2 by S protein recognition [80]. A SWCNT-based semiconductor FET was used by Shao et al. [85] to identify SARS-CoV-2 antigens [85].

2.3 Metal Nanoparticles

Metal NP-based diagnostics are utilized to facilitate in the early diagnosis of infections in humans, especially at the level of a single cell. The rapid detection time, specificity, and sensitivity of metal NPs are important for point-of-care mobile nanodevice development. In order to increase biomolecule detection, several metal NPs, including gold, silver, copper, and cadmium sulfide, have recently been utilized in a wide range of sensors [49].

2.3.1 Gold Nanoparticles (AuNPs)

Because of their excellent sensitivity and selectivity, Au NPs are increasingly being used in biosensors that rely on optical and electrochemical processes. Au NPs-based devices may be used in POC devices in this context to improve trace concentration detection techniques and diagnostics [49]. In order to quickly diagnose SARS-CoV-2, a rapid IgM-IgG mixed antibody kit was developed using a mixture of gold nanoparticles [4]. In a different study, Ma et al. [63] presented an immunological assay based on a label-free electrochemical technique for identifying the hepatitis C virus' core antigen [63]. In this study, an electrochemical immunosensor was constructed combining the synergistic effects of gold nanoparticles, zirconia nanoparticles, and chitosan.

Mashhadizadeh and Talemi [66] successfully created a very accurate and precise hepatitis B DNA biosensor utilizing AuNPs [66]. In this study, mercaptobenzaldehyde was employed for the improved detection of an HBV viral short DNA sequence.

2.3.2 Silver Nanoparticles (AgNPs)

Silver is a special nanoparticle with significant plasmonic characteristics. Due to their distinctive optical properties and band gaps, Ag NPs have been investigated as a potential nanoparticles for the early detection and diagnosis methods in optical biosensors .

In order to facilitate the early diagnosis of HIV, a fluorescent Ag NPs test was designed to detect HIV-1 p24 antigen. It has been demonstrated that the linear detection range is between 10 and 1000 pg mL^{-1} [56]. Cao et al. [20] developed a biosensor that uses the fluorescence activity of silver nanoclusters to detect the target DNA sequence of the (HIV), (HBV), and (HTLV-I) genes.

2.3.3 Copper Nanoparticles (CuNPs)

CuNPs have received a lot of attention because of their enormous potential to replace more costly nanoparticles. Due to small size and high surface-to-volume ratio, CuNPs can interact intimately with viruses and are able to quickly identify them [69].

Using copper nanoparticles, Chen et al. (2010) developed an ultrasensitive electrochemical biosensor for identifying the influenza A virus [22]. With a detection limit as low as fM levels, this biosensor is capable of detecting the single-stranded DNA (ss-DNA) of the influenza A virus. Copper nanoclusters were used by to create a colorimetric biosensing technique. With this particular biosensor, it is likely to recognize the Hepatitis B virus DNA with the naked eye [64].

2.3.4 Cadmium Sulfide (CdS) Nanoparticles

CdS NPs are a strong candidate for photocatalysis because of their favorable bioactivity and good light-driven behavior [49]. For the purpose of diagnosing Hepatitis B surface antigen (HBsAg) via monitoring fluorescence intensity, a strong luminous Polyamidoamine (PAMAM) dendrimers modified CdTe@CdS-based ultrasensitive fluorescence immunosensor was developed [10]. Based on highly stable and photoelectrically active CdS nanorods modified with beta-cyclodextrin (-CD@CdS NRs), a new photoelectrochemical biosensor was developed to identify HIV DNA [35].

3 Nanomaterial-Based Sensors for Diagnosis of Infectious Diseases

Biosensors that merged with nanomaterials have been studied extensively to meet the demand in clinical diagnostic fields [11]. Nanomaterials are well suited for attaching targeted molecules to increase sensitivity because of their high surface-to-volume ratio [93]. The rapid and real time detection of small volume of sample from patients makes it most potential for robust detection of diseases and biomarkers of cancer. These POC-based devices offer sensitivity, selectivity, portability, rapid, and accurate results by using simple blood, serum, sputum, and urine samples from patients. These are advantageous for medical diagnosis, particularly in home, health-care center without using any complex instrument. According to different types of signals, colorimetric, fluorescent, SERS-based, and electrochemical biosensors are described here.

3.1 Colorimetric Biosensors

There is diversified signal readout like electrochemical, colorimetric, and fluorescent. Among them, colorimetric biosensors offer low cost, rapid diagnostic tool that can be monitored by simple color change that is visible in naked eyes. There are many shortcomings of traditional colorimetric sensors but nanomaterials have prominent optical properties that help to process the nanosensors potential for diagnosis of viral diseases. Colorimetric detection strategies play an important role in establishing paper-based POC devices. Nanomaterials can convert the signal from pathogen through unique mechanisms to amplified measurable visual signal. The usage of AuNPs in colorimetric nanosensors has become widespread. Because of the surface plasmon resonance (SPR), visible light is significantly absorbed by AuNPs [29]. For instance, in solution, AuNPs have a red absorption peak at 520 nm [48]. The SPR property of AuNPs depends on a variety of variables, including size [77], shape [28], and interparticle distance. Several AuNP-based colorimetric biosensors have been reported till date. A combined paper-based biosensor and loop-mediated isothermal amplification (LAMP) for nucleic acid detection are proposed [27, 29]. A plasmonic ELISA has been developed to detect disease specific biomarker [77]. Alcohol dehydrogenase enzyme is currently used to measure the colorimetric readout. In this reaction, ethanol and NAD+ are used and then HAucl4 and Au seeds are added (Fig. 3). Acetaldehyde and NADH are produced from ethanol and NAD+ by alcohol dehydrogenase. NADH can reduce the HAucl4 to Au and makes large purple AuNPs from yellow AuNPS seeds. The specific antigen (HBs Ag) and α-fetoprotein (AFP) can be detected by this plasmonic ELISA [29]. $1 \times 10–12$ g/ml is the visible lower concentration of detection limit. Catalase is used in this method [28]. Human immunodeficiency virus type I (HIV-1) capsid antigen p24 can be thus detected with an ultralow limit of detection (LOD) of $1 \times 10-18$ g/mL [29]. Recently, a colorimetric test based

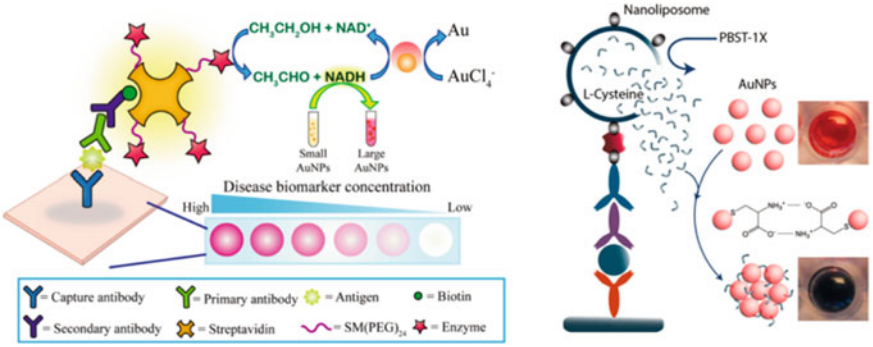

Fig. 3 Colorimetric diagnostic kit, Alcohol dehydrogenase mediated ELISA for the diagnosis of Hepatitis B surface antigen [29, 77]. If the target is present, alcohol dehydrogenase enzyme enlarges the AuNPs and from the color yellow to purple

on AuNPs has been used to detect SARS-CoV-2 nucleic acids with the naked eye [68, 91]. In this study, AuNP had been conjugated with thiol-modified antisense oligonucleotide of SAR-CoV-2. In the presence of RNA target, the AuNP agglomerate turns blue and RNA is cleaved by RNaseH from hybrid and forms precipitate due to AuNP agglomerate [29]. This assay time takes less than 10 min. Silver nanoparticle is also used for colorimetric detection. Multicolor AgNPs are also used for detection of dengue, yellow fever, and Ebola viruses (EBOV) [29, 106]. Nanozymes are nanomaterials with enzymatic activity that have equivalent catalytic activity but most resilient under various circumstances [39]. A unique type of Lateral Flow Assay has been developed by using magnetic nanoparticles for detection of EBOV [29, 33].

3.2 Electrochemical Sensors

Electrochemical sensors monitor changes in charge uniformity on the surface of transducers using impedimetric, potentiometric, or amperometric principles [9, 31, 57]. This kind of sensor has three different kinds of electrodes: a working electrode, a counter electrode, and a reference electrode. In order to increase the analytical performance of sensors, nanomaterials are used in their manufacturing. Nanomaterials have the capacity to increase surface area, electrocatalytic activity, and electron transfer rate. Due to their high conductivity, carbon nanotubes and graphene are frequently used in electrochemical biosensors. Single-type nanomaterials, such as CNTs, AuNPs, or hybrid nanocomposites made of various nanomaterials, such as a mix of CNTs and AuNPs, are also acceptable [92] (Fig. 4). For example, Omidi's group constructed an electrochemical biosensor for detecting PSA utilizing graphene oxide-gold nanostructures, with detection limits of 0.2 and 0.07 ng/mL for total and free prostate specific antigen (PSA), respectively [79]. Layqah and coworkers developed a nanoimmunosensor to detect the spike protein S1 of MERS-CoV2.

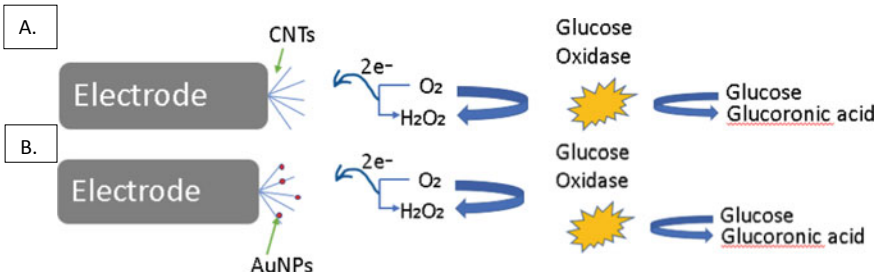

Fig. 4 Schematic diagram of nanomaterial-based Electrochemical Biosensor, **a** single type of nanomaterials (CNTs); **b** Hybrid type of nanocomposite (mixture of CNTs and AuNP) are used

AuNP provides a wider range of biomarker detection in this sensor [58, 32]. This immunosensor exhibits an enhanced sensitivity of 0.4 pg/pg for the detection of the MERS virus at concentrations between 0.001 and 100 ng/mL.

Several types of electrochemical sensors have been developed for detection of dengue NS1 protein [30]. Electrochemical sensors show greater sensitivity in detection of virus than conventional ELISA.

When target nucleic acids bind to DNA or RNA on the surface of electrochemical sensors, the surface of the electrode changes, and a signal is recorded by the speed at which electrons are transferred between the probe and electrode.

Nowadays aptamers are getting more focused on showing more sensitivity with target molecule. Hence, electrochemical sensors are very stable, highly sensitive, and very specific. Using advancements in microelectronics and microelectrode production, electrochemical approaches make it simple to miniaturize immunoassays. In order to sensitive measure of C-reactive protein (CRP) in human serum, Kakabakos et al. developed a disposable screen-printed immunosensor [54]. CRP is a liver-produced acute-phase protein that serves as a helpful biomarker for inflammation and can help predict myocardial infection, peripheral artery disease, stroke, and sudden cardiac death. In this study, a sandwich-type immunoassay employing CRP-capturing antibodies coupled on bismuth citrate-modified screen-printed electrode.

3.3 Optical Sensors

Optical sensors are excellent for detecting multiple target molecules simultaneously. These sensors quantify the optical characteristics of transducers during the interaction between the target molecule and the recognition element [40, 89]. Scientists have developed a unique type of optical sensor to recognize MERS particle. This can be seen in naked eyes, and do not need any experimental equipment. This reaction happens when pyrrolidinyl peptide nucleic acid is present [94]. It shows the aggregation and di-aggregation of silver nanoparticle with target DNA. Another type of optically silicon-coated optical sensor has been created to detect human rhinovirus

by Ostroff and colleagues [75]. Surface Enhanced Raman Scattering (SERS) can also be used for detection of virus based on optical technique of Surface Plasmon Resonance (SPR). This sensor can provide good sensitive results within 30 min.

4 Current POC Devices

One of the essential ways to prevent the outbreak of infectious diseases is through early diagnosis. POC devices, which do not require highly trained employees or expensive machinery, are more effective at fending off infectious diseases in low-resource area [65]. The World Health Organization (WHO) stated certain criteria of POC devices [68, 88] like a. specific, b. sensitive, c. affordable, d. rapid, e. strong, f. big infrastructure-free [29] (Fig. 5) [34].

Pregnancy test strips, and blood glucose meters are the commonly used POCT test kits. By merging the detection technique with nanotechnology, various new POC devices have been reported for early disease diagnosis.

At the beginning, it is known that lateral flow assay is used for detecting only HCG to confirm the woman is pregnant or not. Nowadays this LFA is reported for confirming many target analytes, and biomarkers of infectious diseases. Samples can be different types like blood, urine, sweat, swab, etc. [81]. LFAs are widely used POC devices because of its affordability, quick-response, and robustness. Yet, the broader field is still hampered by its low sensitivity and lack of measurement capability. Numerous attempts have been made to enhance the analytical performance of LFA [50, 97]. The four basic components of traditional LFA are the sample pad, conjugate

Fig. 5 Assured criteria POC test devices according to World Health Organization (WHO) [34]

pad, nitrocellulose membrane, and absorbent pad. The sample pad ensures contact between the liquid sample and the strip. Nanogold-labeled antibodies are already preloaded on the conjugate pad for signal production [38]. The nitrocellulose membrane has two lines drawn on it: the control line and the test line. The control line is used to ensure that the testing is running smoothly while the test line is utilized to detect the target analyte. The liquid sample flows across the strip due to the capillary force, and if the target is available, both lines can be seen on the control and test lines. Only one control line appears when the target molecule is absent. AuNP was used for first-generation lateral flow assay. The label has a color, so that it is visible in naked eyes. The sensitivity of first-generation lateral flow assay was very low. Analytical performance of LFA is enhanced by labeling with various nanoparticles like quantum dots, upconversion nanoparticles [41, 99]. The optical signal is measured by strip readers equipped with specialized optics. Lateral flow tests, commonly used in medical diagnostics, are straightforward, affordable, and typically yield results in 5–20 min. Several POCT devices have been created in recent years by combining LFA with other technologies like loop-mediated isothermal amplification (LAMP), polymerase chain reaction (PCR), and CRISPR [67]. CRISPR-based Cas12 based LFA can detect SARS CoV-2 from paitent's RNA sample within 40 min [100] (Fig. 6).

Microfluidic technology has the capacity to process small amounts of fluid that meet to advantages in different fields [107, 101]. In recent years, the rapid uptake of cellphones with embedded sensors has opened up new opportunities for the POC detection of infectious illnesses [23]. Detection of antibodies against EBOV, a serological POC test using an LFA has been proposed [16].

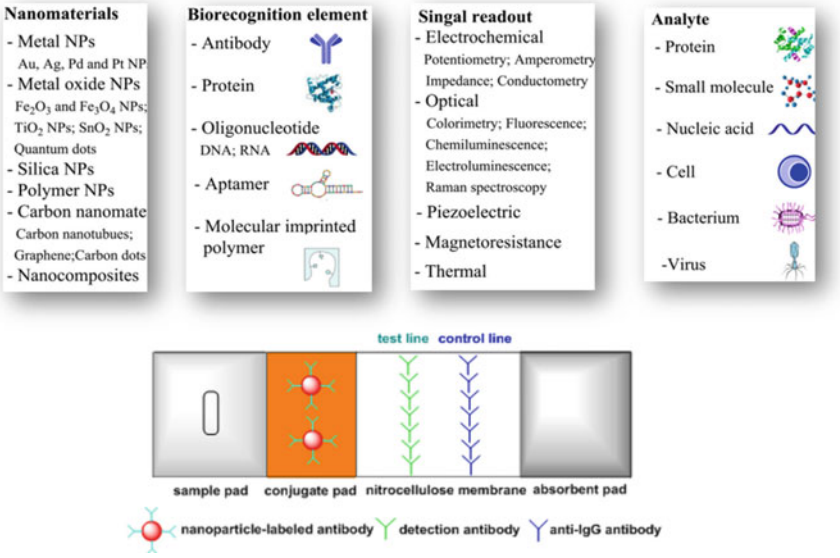

Fig. 6 Schematic diagram of typical lateral flow assay (LFA) [100]

The best method to stop an outbreak is to easily, quickly, and affordably identify infectious pathogen in a sensitive and selective manner. POC is essential to improve clinical outcomes in healthcare administration. POC devices enable untrained staff to diagnose patients quickly and accurately at their homes, critical care units, or medical facilities.

4.1 Fluid Control

One of the most crucial steps to increase the accuracy of this assay is to control the fluid. It is possible to accomplish this by incorporating a number of pumps and valves into the testing equipment. Size and complexity are taken into consideration to handle this instrument. Many kinds of pumps and valves can be incorporated into microfluidic chips under the control of chip readers [86]. McDevitt's team created a portable microfluidic system for measuring protein biomarker utilizing plastic disposable cartridges [27]. There are a number of paper-based microfluidic devices with no pump for fluid control [6]. In these microfluidic devices, a number of nanomaterials including magnetic nanoparticles, quantum dots, UCNPs, CNTs, and graphene oxides, have been used [72]. By using AuNP-based silver attachment, a group of scientists created a smartphone-based point-of-care platform for detecting avian influenza virus [109]. Using quantum dot-barcoded microbeads, Gao et al. created a microfluidic point-of-care system for detection of biomarkers [102]. Microfluidic assays feature exceptional selectivity and sensitivity compared to lateral flow. Microfluidic devices have been used to find many analytes, such as proteins, enzymes, nucleic acids, cancer cells, bacteria, and viruses [82].

5 Challenges and Future Perspectives

There are still certain restrictions even though nanomaterials are often utilized in biosensors successfully to enhance the analytical performance [50]. Identification of the concentration of potential biomarkers of cancers and cardiovascular diseases is far below the detection limit of traditional methods. Therefore, development of sensitive and specific methods is required. Moreover, cerebrospinal fluid (CSF) has comparatively high amounts of numerous brain-derived biomarkers for neurodegenerative disorders, compared to blood, such as neurofilament light and amyloid beta peptide 42. It could be quite invasive to take this sample. Improved sensitivity can detect biomarkers of dangerous diseases directly from blood. Another potential area is the identification of biomarkers in urine or saliva. Saliva and urine may be easily collected and analyzed, helpful for monitoring diseases. Due to the special properties, nanomaterials can be utilized to increase detection sensitivity. Because nanomaterials have a huge surface area, they may be utilized to load several reporter molecules, such as enzymes and fluorophores, to amplify signals. Moreover, the

sensitivity can be increased by combining various ultrasensitive detection methods with nanotechnology, such as digital PCR and single molecule analysis [90].

Nowadays, most assays are only able to detect one analyte at a time. The components of a biological sample are many and include proteins, nucleic acids, and other tiny molecules. All these biological samples work in a simultaneous manner [59]. Multiplex assays can obtain all the data and increase detection technique. When the sample volume is constrained, the assay is extremely helpful in that time. For instance, the collection of CSFS is mainly invasive. Thus, it is highly desirable to simultaneously detect numerous biomarkers in CSF. For multiplex assays, fluorescent nanomaterials of various sizes and shapes and with various emission wavelengths can be used.

Very few nanomaterial-based sensors are available for clinical trials till date. The reproducibility and robustness of nanomaterial-based sensors are the main issues. Low reproducibility depends on the size of nanomaterials which varies from batch to batch. A common problem in most assays is non-specific interaction as well. So, more study is required to grasp the nano manufacturing process and optimize particle aggregation and surface interactions. To ensure that the measurements are accurate and consistent, quality control is necessary for clinical applications.

6 Summary

The chapter emphasized on the effectiveness of nanostructured materials for enhancing the sensitivity of disposable sensors by amplifying the responses to analyte concentration. The size, shape-dependent physical catalytic characteristics of nanomaterials play main role in the development of biosensor. The nanoparticles considerably increase the surface area of electrochemically active sensors. Biosensor components are required to be integrated into a device that allows simultaneously sample and reagent load, and signal detection in an automated form, called lab-on-chip (LOC) [12]. LOC is a device for analysis that can scale down laboratory operations to a chip format up to a few square centimetres. There has been a sharp rise in the development of lab-on-a-chip instruments for clinical diagnostics over the past decades. Modern POC systems provide quick, easily accessible, trustworthy, real time analyzed information from bodily fluids, and wireless data transfer from smart devices to smartphones or other cloud devices. Among several methods, nanosensor-based POC devices provide sensitive, selective, and rapid results for detecting infectious pathogens. These devices require several detection steps, and signal readout equipment. Microfluidic technologies and smartphone devices offer solution to these problems. Microfluidic techniques can simplify the detection steps and smartphones with built-in sensors can function as portable instruments for signal readouts. Many more novel, innovative platforms need to come to address the unmet clinical demands. The development of bench-to-bedside and point-of-care devices in recent years has made the term “biosensor” more well known in the scientific community.

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