# Overview of the Current Nano-Materials, Synthesis, Properties and Characterization


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**Abstract** Point of care testing (PoCT) systems, which enable diagnosis and treatment at or close to the care site, play a crucial role in the control of epidemics and other types of infectious diseases that are spread throughout the world due to their advantages such as short turnaround times, portability, reusability, efficiency, ease of use, and low cost. In particular, nanomaterial-based PoCT systems are widely used due to their excellent chemical and physical properties that allow high analytical performance and simplify the detection process. Therefore, recently, many different types of nanomaterials have been used to develop nanomaterial-based PoCT devices in various platforms. Various kinds of nanomaterials such as metal-based nanoparticles, quantum dots, nanoshells, nanotubes, metal–organic frameworks (MOFs) nanogels, nanofibers, and flexible hybrid composites are used to provide detection, signal generation, transduction, and amplification in PoCT devices. In this context,

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the synthesis methods and controlled physical/chemical properties of these nanomaterials are crucial points to improve the performance of the PoCT devices. In this chapter, we will highlight the synthesis and development strategies of nanomaterials currently used in different PoCT devices, along with existing challenges and future prospects.

**Keywords** Metal NPs · Quantum dots · Nanofibers · Nanogels · Nanoshells · Nanotubes · Metal–organic frameworks (MOFs) · Flexible hybrid composites

## 1 Introduction

Point-of-care (PoC) devices provide fast, on-site, and cost-effective alternatives to traditional laboratory applications that require long analysis times and expensive equipment [113]. Over the last decade, PoC products have been developed as real-time diagnostic products for use outside the laboratory and in laboratories with limited resources. Therefore, PoC technologies are gaining increasing importance in preventing and controlling the spread of diseases [113]. In this context, the design and the detection type of the sensor platforms are very important. Various types of sensor platforms, which have different readout modalities are being developed, including piezoelectric, magnetic, thermal, electrochemical, optical, and colorimetric detection [80]. A sensor platform can be defined as an analytical device and be selectively produced against a particular disease. Practically, a sensor platform operates on the principle that a target analyte can be specifically detected by chemical reactions or biological recognition, resulting in a specific signal that can be measured by different methods. Recently, the use of various nanomaterials has come to the fore to obtain sensitive, reproducible, and precise signals from sensors [84]. This is because nanomaterials have excellent physical and chemical properties compared to their bulk form, such as biocompatibility, large surface area, and specific catalytic activity. These unique properties of nanomaterials make them excellent candidates for the development of detection probes [24, 84]. For this purpose, various nanomaterials such as gold, silver, and polymer nanoparticles, quantum dots, hybrid nanocomposites, and carbon-based nanomaterials with different sizes, shapes, and compositions have been used to develop a PoC testing platform.

In this chapter, the synthesis of different types of nanomaterials in PoC systems and their application in diagnostics will be reviewed.

## 2 Metal-Based Nanoparticles

Metal-based nanomaterials are an important milestone in the advancement of nanoscience, which is currently an advanced research area [99, 109]. The development of metal nanoparticles, which first started with the controlled synthesis of

gold nanoparticles, continued with the synthesis and efforts to elucidate the properties of other metal-based nanomaterials [44]. The unique physical, optical, and chemical properties and functionalities of metal nanostructures, which are largely dependent on sizes, shapes/facets, compositions, and architectures, have attracted the massive attention of researchers in science [32, 35, 90, 99]. Although research with metal-based nanowires and nanoclusters has recently been included in the literature, nanoparticles are still the most commonly used metal-based nanomaterials in point-of-care (PoC) systems [3, 84]. An impressive work involving AgNPs was reported by Yuan et al. [129]. They designed a Tyndall effect-inspired assay (TEA) to detect creatine in human urine by taking advantage of colloidal Cit-AgNPs. The citrate-capped AgNPs with a weak Tyndall effect (TE) signal aggregated after being added to creatine and formed a hydrogen bonding network with creatine tautomers under alkaline conditions, resulting in a significant increase in TE signal that was generated and quantified using a smartphone and a portable laser pointer, respectively. The increase in TE signal that can be seen with the unaided eye is directly proportional to the creatinine concentration in the sample. Additionally, this portable quantitative detection platform may be employed by incorporating it into a smartphone. This metal nanomaterials-based point-of-care test system, which is performed without the use of any sophisticated equipment, has a detection limit of ~50 nM for creatinine that is at least 90 times lower than even the most sensitive conventional colorimetric methods.

Fu et al. designed a PoC test system that will perform simultaneous and visual detection of three different analytes with gold nanoparticles (AuNPs) integrated with three different aptamers, should be cited as an example of the application of these [35]. Aptamers prevent the aggregation of AuNPs in a high-salt environment. This is because aptamers interact with gold nanoparticles, and interfere with the interaction of high salt and AuNPs, thereby preventing their aggregation. Aptamers are stripped from the AuNPs when analytes are present because of the greater interaction between aptamers and the analytes. The color of the solution changed dramatically after AuNP aggregation in the high salt condition, allowing for analyte detection with the naked eye. Three analytes were determined simultaneously and visually at the detection limit of 53 nM, 130 nM, and 11 nM, respectively, with a single sensor using a multi-aptamer. This study resulted in the development of a simultaneous and visible multi-component detection platform, which was also successful with blood and urine samples. In another example proposed by Al-Kassawneh et al., the glucose level in human saliva was colorimetrically determined using a gold nanoparticles tablet (AuNPs-pTab) prepared by encapsulating AuNPs with pulluan, a natural, biodegradable ligand used as both a reducing agent and a capture agent, as a simple point-of-care (POC) test kit [6]. To detect glucose, a detection limit of (LoD) 28.7 μM was performed in buffer solution; however, in artificial and real human saliva samples, LoD values 38.2 and 163.04 μM, respectively, were reached. These tablet sensors, developed by this study, which pioneered the use of the reactive encapsulation technique for glucose detection, will significantly contribute to the design of PoC devices that are ready to use and have the potential for OnSpot colorimetric testing for various diseases. In another study that should be mentioned in this

context, homometallic and heterometallic nanohybrids were synthesized by in situ fabrication of AuNPs, AgNPs, and their plasmonic hybrids using sericin protein as a reducing and capturing agent [15]. A surface plasmon-coupled emission (SPCE) application for mobile phones was used to accomplish attomolar level detection of mefenamic acid using the versatile, polarized, and enhanced fluorescent emission of these nanohybrids.

One of the most crucial points of this study is that it will shed light on the design of point-of-care diagnostic tools that can be developed with green nanotechnology without the need for the use of hazardous chemicals and solvents for different applications in the future.

## 3 Quantum Dots

In recent years, quantum dots (QDs) have received a lot of attention due to their unique optoelectronic properties such as strong absorption, size-dependent photoluminescent emission, high quantum yield (QY), and high optical stability [57, 91]. Different types of QDs have functional properties in a variety of fields, including sensing, optoelectronic devices, biomedicine, and point-of-care (PoC) systems [4, 17]. Although it is stated in many sources in the literature that it should have a size distribution below 10 nm, in fact, the sizes of QDs can reach up to about 30 nm [29, 104]. For a nanometer-sized crystal to be considered a QD, the quantum confinement effect rather than size must be observed. For this, the physical dimensions of nanometer-scale colloidal semiconductor crystals must be smaller than the Bohr radius exciton [104]. Dimensions of QDs generally vary depending on the material from which they are synthesized [4, 111]. The materials used for its preparation are also used to identify the types of QDs [115]. Conventional quantum dots were first prepared as core nanocrystals by combining the III–V, II–VI, and IV–VI groups of the periodic table [4, 111, 115]. Then, with the synthesis of QDs carried out in the form of core–shell nanocrystals, which prevents the leaching of metal ions in the core, the quantum efficiency was increased up to almost 75% [57]. In addition to the high quantum efficiency obtained in this way, it has become the best fluorophore candidate for many applications with its advantages such as extremely broad and intense absorption spectra allowing single wavelength excitation, narrow, symmetric, and size dependent fluorescence spectra, superior photostability and enabling flexibility in excitation [29, 104]. The features that overshadow all these excellent optoelectronic properties are harsh synthesis reaction conditions, complex surface passivation procedure, and especially cytotoxicity created by toxic precursors [17, 111]. Although traditional QDs can be prepared with many different combinations of III–V, II–VI, and IV–VI groups, cadmium-based QDs are the most preferred [115]. However, because of their capacity to attach to thiol groups on essential components in mitochondria and inflict sufficient stress and damage to result in appreciable cell death, cadmium ions were discovered to be the main cause of cytotoxicity of QDs [29]. Their sustained practical application is hampered by this toxicity [115]. For this

reason, researchers have searched for environmentally friendly, biocompatible QDs and have launched them as cadmium-free QDs [58]. Carbon QDs (CQDs), which are obtained from the element carbon, which has been frequently used since the 19th century, were obtained in 2004 by preparative electrophoresis during the purification of single-walled carbon nanotubes [4]. Graphene quantum dots (GQDs) were discovered shortly after the discovery of CQDs, especially due to the combined use of carbon and graphene in electrochemistry applications. The low toxicities of both CQDs and GQDs, as well as the carboxylic acid moieties of GQDs, have allowed these structures to increase in water solubility and allow for biological modification, allowing them to show superiority among other QDs [58]. Another is the next generation $Ag_2Se$ and $Ag_2S$ QDs, which are designated as near infrared QDs class and have been used in biological imaging applications [57]. In addition, although it has only recently been discovered in zero-dimensional black phosphorus QDs synthesized by chemical methods, it has been used in bioimaging, fluorescence sensing, optoelectronic, and flexible devices [4, 111]. The most important features of these structures are small size, high brightness, quick radiation transition rate, good light stability, low biological toxicity and customizable emission spectrum, high quantum yield easily functionalized, and strong biocompatibility, respectively [111]. Finally, in this context, MXene dots should also be mentioned. These quantum dots, which are promising candidates in many fields such as bioimaging, biomedical, and biosensor, are striking with the advantage of a large number of functional groups on their surfaces [4]. The synthesis of QDs is shaped according to their classification [57]. Synthesis of traditional Cd-based QDs was first performed by pyrolysis of organometallic and chalcogen precursors, but since the hydrophobicity of QDs synthesized by this method significantly reduces both their water solubility and biocompatibility, further modification is needed after synthesis. Therefore, researchers focused on the synthesis of hydrophilic QDs. For this, applied to the use of stabilizers such as 3-mercaptopropionic acid (MPA), 2-mercapto ethylamine acid (MA), thioglycolic acid (TGA), and L-cysteine in the aqueous synthetic procedure [57]. Also, microwave-assisted green synthesis, which relies on environmentally sensitive microwave irritation, is one of the popular methods of choice for the preparation of such QDs [48].

Two synthesis approaches have generally been proposed for Carbon QDs and GQDs, which are called natural-based QDs (NQDs). In these methods, which are launched as top-down and bottom-up, top-down is based on the decomposition or exfoliation of large carbon structures or large graphene sheets, while bottom-up is based on the creation of GQDs and carbon QDs from small precursors with solution chemistry methods. Top-down techniques include hydrothermal cutting, solvothermal cutting, electrochemical cutting, nanolithography, microwave-assisted cutting, nanotomy-assisted exfoliation, and ultrasonic shearing; bottom-up techniques like stepwise organic synthesis and cage opening of fullerenes fall under this category as well [48, 91]. There are only a few synthesis techniques recommended for other semiconducting quantum dots. This sort of QDs are often synthesized using several different techniques, including solution-phase-based methods,

microemulsion synthesis, thermally induced disproportionation of solid hydrogen silsesquioxane in a reducing atmosphere, and others [57].

In the characterization of QDs, parameters such as optical properties, size, and morphology are examined with advanced devices. While UV-VIS and photoluminescence spectroscopy are preferred for optical characterization, devices such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), dynamic light scattering (DLS), and X-ray diffraction (XRD) are used for size distribution. It has been reported that the tools used for morphological and structural characterization are X-ray photoemission spectroscopy (XPS), nuclear magnetic resonance spectroscopy (NMR), Rutherford backscattering spectrometry (RBS), atomic force microscopy (AFM), field emission scanning electron microscopy (FESEM), and Fourier transform infrared spectroscopy (FT-IR) [4, 29].

In recent years, the use of fluorescent probes in PoC testing systems has offered great advantages in terms of the accuracy of the detection system and the simplicity of the readout system. In addition, the use of fluorescent materials such as quantum dots in PoC systems is cheaper and easier to convert into disposable chips than other methods, so it is more suitable for real-time use in the field [21]. Therefore, as exemplified below, the use of QDs in PoC systems has become quite common in recent years. A study emphasizing the use of quantum dots in point-of-care applications has been reported by Zhang and Shi(Jingfei) [134]. The antibiotic tetracycline (TC), which is now a severe hazard to both public health and the environment, was used in this study to create a coordination complex with the ion $Eu^{3+}$, from which a faint luminescence was produced. Then, by transferring energy from $MoS_2$ QDs with a strong fluorescence property to the Eu-TC coordination molecule, the initial fluorescence intensity was significantly increased. In the study, TC between 10 nM and 60 μM was determined with a detection limit of 2 nM with MoS2 QDs used as both the indicator and enhancer of the ratiometric probe. Additionally, color recognition software was used to adapt this sensor to the smartphone-based portable platform, and visual quantitative detection was carried out sensitively, quickly, and in real time with a detection limit of 0.05 μM.

Another study, which has been reported to design even more efficient PoC testing systems with quantum dots, has been brought to the literature by Sun et al. [98]. Four metal ions were monitored within the scope of this study, on-site, user-friendly, real time, selective manner utilizing a paper-based analytical instrument constructed using S quantum dots. The research is based on the idea that S quantum dots provide a different visual signal with each ion, particularly green for $Fe^{3+}$, brown for $Co^{2+}$, bright yellow for $Cd^{2+}$, and precipitate for $Pb^{2+}$. This consists of three layers such as isolation, reaction, and base, and it has several spots where the assay will take place. The images obtained after interacting with metal ions were used for on-site and visual determination with the help of a smartphone-based platform and color recognition software. In this ion-responsive platform, a smart strategy was created by integrating multiresponsive blocks into S dots, allowing multiple logic operations (i.e., yes, not, and, inhibit, and nor) for determination. Finally, with this quadruple analyte responsive platform, $Fe^{3+}$, $Co^{2+}$, $Cd^{2+}$, and $Pb^{2+}$ ions were not only determined at

the detection limit of 0.59, 0.47, 0.82, and 0.53 μM, respectively, but also a point-of-care testing (PoCT) system that could be created for various analytes was successfully introduced to the literature.

## 4 Metal–Organic Frameworks (MOFs)

MOFs are hybrid materials consisting of a large surface area, low density, and highly porous inorganic and organic units. In the last decade, different types of hybrid MOFs with a wide range of uses have been reported based on polymer, metal oxide, carbon, metal nanoparticle, and biomolecule [86]. In addition, MOF-PoC test platforms used in different sensor-based diagnostic and detection applications have been reported recently. The organic units that makeup MOFs are anions such as carboxylate, cyano compounds, imidazole derivative polyamines, phosphonate, sulfonate, and heterocyclic compounds. Metal ions or clusters called secondary structural units (SBUs) form the inorganic units of MOFs [86]. The solvo(hydro)thermal method is generally used for the synthesis of MOFs (Fig. 1). The synthesis is carried out using an autoclave at high temperatures and pressure above the boiling point of the solvent. Under solvothermal conditions, starting reagents can undergo unexpected chemical transformations that can lead to the formation of new ligands. Therefore, optimum reaction conditions must be provided [16]. In addition to these methods, other alternative synthetic methods such as diffusion, mechanochemical, electrochemical, microwave, and ultrasonication methods have been developed in recent years [10, 86].

In the diffusion method, solvent/solvent mixtures with a low boiling point are mostly preferred and the reacting species are transported slowly in the presence of the solvent. Thus, crystal growth and nucleation occur over time at the interface point [89]. Electrochemical synthesis of MOFs can occur in a maximum of 2 h at ambient temperature and pressure. The metal ion is added to the reaction mixture containing organic ligands and electrolytes by anodic dissolution. The method has advantages such as high efficiency, low energy consumption, and the absence of counter ions. In this way, it allows the controlled synthesis of MOFs. Many MOFs prepared by electrochemical methods such as ZIF-8, MOF-5, HKUST-1, MIL-100(Al), MIL-53(Al),

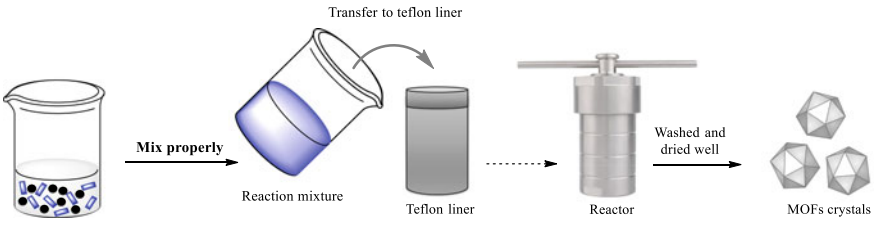


**Fig. 1** Schematic presentation of the hydrothermal synthesis route of MOFs

and $NH_2$-MIL-53(Al) have been developed in the literature [7, 37]. Mechanochemical synthesis of MOFs occurs by solid-state organic reaction with less or no solvents. Furthermore, this method allows for large-scale production of MOFs in shorter reaction times and lower temperature conditions compared to diffusion and solvothermal methods [34]. MOF synthesis by ultrasonication is based on the chemical transformation of molecules under high-energy ultrasonic radiation (20 kHz–10 MHz). Compared with other techniques, it provides simple operating conditions, high efficiency, easy controllability, and short reaction time [10]. MOFs are characterized by several methods such as X-ray diffraction, single crystal X-ray diffraction, scanning electron microscopy (SEM), inductively coupled plasma optical emission spectroscopy (ICP-OES), thermal gravimetric analysis (TGA), nuclear magnetic resonance (NMR) spectroscopy, and Brunauer–Emmett–Teller (BET) analysis [43]. Recent studies show that MOFs have been the focus of researchers for POC tests in many different usage areas with their superior properties [12]. Zhang et al. reported a fluorescent lanthanide-based MOF (L-MOF-enzyme) composition to detect glucose in serum and urine [135]. The composite was prepared by an immobilization between $Eu^{3+}$@UMOF and glucose oxidase (GOx). Herein, glucose is oxidized by GOx and the $H_2O_2$ produced can quench the fluorescence of $Eu^{3+}$@UMOF. The fluorescent intensity of $Eu^{3+}$@UMOF corresponds to the glucose concentration (CGlu). In the system integrated with the detector, CGlu has three different concentration ranges (0.1–10 μM, 10–10 mM, and >10 mM). Three different outputs; (L(low), M(medium), and H(high)) corresponding to these three concentrations can be determined with the naked eye. The prepared detector provides the detection of glucose levels in the urine with high selectivity and sensitivity. It allows on-site diagnosis without going to the hospital for complex examinations, especially for diabetics. Chen et al. reported a high-sensitivity PoC test fluorescent nanosensor for tetracycline [22]. Tetracycline is an antibiotic frequently used in medicine against bacterial infections. However, its misuse leads to tetracycline residues in animal foods and affects human health. The probe (FL:LZIF-8-Cit-Eu) was prepared by encapsulating fluorescein (FL) in 1-histidine modified ZIF-8 (LZIF-8) and chelating it with the citrate complex. When FL:LZIF-8-Cit-Eu is exposed to tetracycline, a characteristic $Eu^{3+}$ sensitive fluorescence is formed as a result of the coordination between $Eu^{3+}$ and tetracycline. The results demonstrate fast (<20 s), high selectivity, and high sensitivity (LOD = 5.99 nM) PoC detection of tetracycline. Yan et al., on the other hand, prepared a lanthanide-based MOF platform Eu(TATB) for the detection of Sulphamethazine (SMZ), which are another frequently used antibiotic in medicine [123]. Nanoscale Eu(TATB) is prepared by the microemulsion method and has a stable red luminescence in an aqueous solution. In addition, it was embedded in the prepared lanthanide-based MOF filter paper and integrated into the smartphone imaging system. Thus, a paper-based MOF-PoC test system was designed to monitor SMZ.

## 5 Carbon Nanotubes

Since they have excellent electrochemical properties, physical–chemical stability, mechanical strength, and a large surface area, carbon-based nanomaterials like carbon nanotubes (CNT) are highly in request when creating point-of-care diagnostic tools that can diagnose and treat illnesses quickly, sensitivity, and affordably. CNT are obtained by $sp^2$ hybridization of graphite in the form of hollow cylindrical tubes with a high surface-to-volume ratio. Based on the number of walls, CNT are classified into three groups such as single-walled nanotubes (SWNT), double-walled nanotubes (DWNT), and multiwalled nanotubes (MWNT). CNT are generally used for bioimaging endowing superior optical properties and assisting easy incorporation of contrast agents such as fluorescent probes, radionuclides, and organic/inorganic nanomaterials with a high ratio for MRI (magnetic resonance imaging), CT (computed tomography), PET (positron emission tomography), and SPECT (single-photon emission computed tomography), etc. CNT serve as an important option for health care platforms, but their hydrophobic nature is one of the major obstacles to the use of CNT in sensing applications, drug delivery, photothermal therapy, and other applications.

The structure and individual properties of CNT have been demonstrated to be precisely dependent on the synthesis methods [87]. Many different methods have been introduced with the studies on high purity production demand, synthesis at low temperatures, and increasing production capacity, and classification has been made as synthesis from solid carbon and gaseous carbon, inspired by the states of materials applied in production. In this part, most typical synthesis strategies are discussed in detail; all of which have been extensively studied. One of the first techniques for creating carbon nanotubes was the arc discharge method. The procedure involves creating a space between two graphite rods, one of which serves as the anode and the other as the cathode, causing an arc to form, and using a direct current to make nanotubes. In the arc discharge process, the nanotubes produced by bombarding a target made of pure graphite are multiwalled, but the nanotubes produced by bombarding a target made of catalysts like Co, Ni, Fe, or Y are single-walled. The anode particle's core contains the catalysts. MWCNT are produced by this method with high crystallinity. Transition metal catalysts must be used in this method for the formation and growth of SWCNT. In theory, the arc discharge approach and the laser evaporation method are comparable. This method uses a laser source rather than an electric discharge to generate a high temperature on a carbon target. Although the laser evaporation method is suitable for producing higher quality SWCNT with higher mechanical strength than the arc discharge method, it is not preferred because of its high cost and low production capacity. For the last two decades, carbon fibers and their filaments have been produced using the chemical vapor deposition method of hydrocarbons in combination with a metal catalyst. The chemical vapor deposition method has several advantages compared to previous synthesis methods. It is a simpler and more economical technique as production takes place at lower temperatures and pressures. The most common techniques for analyzing the general

morphology of CNT samples include electron microscopy, atomic force microscopy (AFM), nuclear magnetic resonance (NMR), electromagnetic spectroscopy, XRD diffraction, and light scattering techniques. In fact, IR, NMR, and Raman spectroscopy are used to confirm the presence of functional groups on CNTs. CNT offer attractive PoC biosensing applications due to having remarkable electro-chemical properties. The recognition process of CNTs principally relies on various enzymatic processes that produce electroactive species for the detection of metabolites, protein biomarkers, and ions [49, 138]. Additionally, recognition elements may be aptamers, antibodies, oligonucleotides (DNA or RNA), ligands, and whole cells. Many research articles have assessed the development of CNT-based biosensors for RNA detection identifying overexpressed microRNA (miRNA)-specific patterns in cancer diagnosis. For example, an electrochemical microRNA (miRNA) nanosensor, which uses CNT and electroactive polymer films, has a low detection limit of ca. 8 fM and has been used for the detection of human prostate metastatic cancer cells [101]. Similarly, Topkaya et al. reported early, label-free electrochemical detection of prostate cancer [77]. As seen in Fig. 2, another work SWCNT-based antibody conjugated optical nanobiosensor has been used for prostate cancer biomarker urokinase plasminogen activator (uPA) detection via surface-enhanced Raman spectroscopy (SERS) in whole serum, plasma, and blood [116].

For the sensitive detection of carcinoma antigen-125, zinc oxide-fabricated MWCNT nanowire immunosensors have been prepared by simple and low-cost electrospinning techniques [81]. Increased sensing performance has been found for BSA functionalized MWCNT-ZnO nanowire immunosensor with an excellent limit of detection (0.00113 U/mL) (Fig. 3).

In another study, a sensor was designed to detect hybridization processes of small DNA and RNA oligonucleotides in vivo with a label-free approach that converts carbon nanotube photoluminescence into spectral changes. The mechanism of action was determined by dielectric, electrostatic factors, and molecular dynamics simulations. They showed that the sensor facilitates multiple sensing using various nanotube chirality and monitoring concurrently of toehold-mediated DNA-strand displacement, which results in signal response reversal. It has also been demonstrated by in vivo optical experiments by implanting that the designed sensor is extremely resistant to non-specific interactions with biological molecules and allows direct detection from serum and urine [41].

SWCNT field-effect transistor biosensors are known for offering the highest level of sensitivity [8]. However, it also provides high selectivity and distinguishes the real signal from other signals in an uncontrolled environment. In a study, they demonstrated the successful integration of a new peptide aptamer with SWCNT field-effect transistors for the specific and sensitive recognition of Cathepsin E, one of the cancer biomarkers. SWCNT were prepared via the CVD method. It is then integrated into a SWCNT field-effect transistor device. The constructed sensors were found to exhibit high selectivity at low concentrations in not only phosphate-buffered saline (2.3 pM), but also human serum (0.23 nM). In conclusion, it has been shown that SWCNT FET sensors modified with peptide aptamer can be used as a remarkable platform for PoCT applications [102].

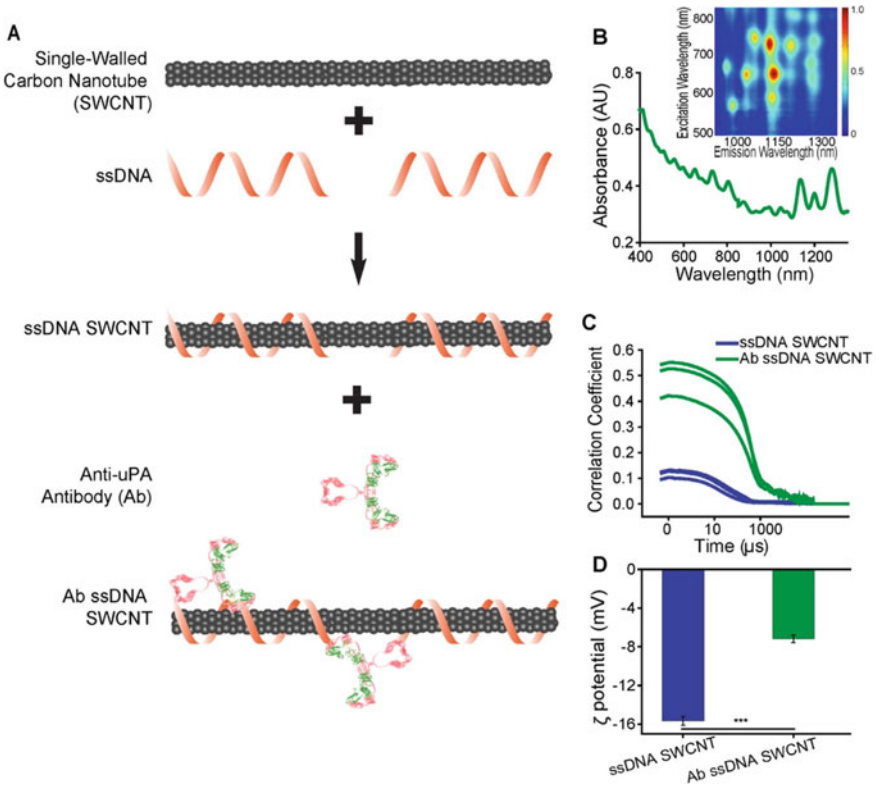


**Fig. 2** Schematic representation of the synthesis and characterization of Anti-uPA-DNA-SWCNT nanobiosensor. Adopted from Williams et al. [116]

## 6 Nanoshells

Nanoshells are defined as a class of nanoparticles with a dielectric core of 10–300 nm in size, covered with an ultrathin metal shell [47]. Nanoshells have great tunable optical properties and these optical properties can be tunable depending on their size and making them good candidates for PoCT. There are different methodologies to obtain nanoshells, which use dielectric cores as templates to grow metal shells on their surfaces. Also, several synthetic approaches can be used to fabricate hollow nanoshells.

Zhou et al. first synthesized metal nanoshells with an inner dielectric $Au_2S$ core surrounded by a gold shell in 1994 [11]. A gold nanoshell refers to a filled or hollow core surrounded by a spherical layer of gold. According to the gold shell thickness and nanoparticle size, the optical characteristics of gold nanoshells can be tuned for biomedical applications. Different core types can be used to fabricate gold nanoshells. Silica is often used as a core material, because of its superior properties for the fabrication of gold nanoshells by several approaches including

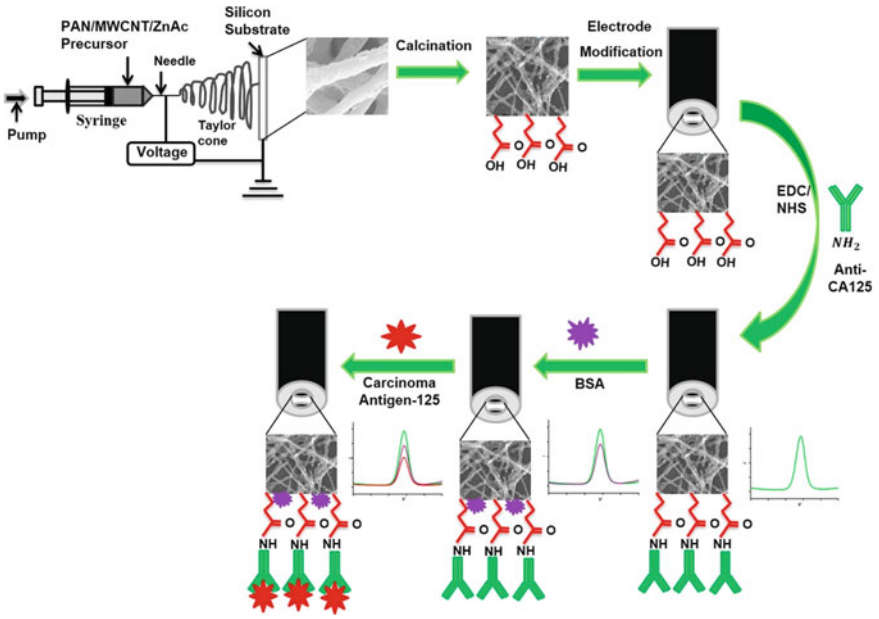


**Fig. 3** Schematic representation of the one-step biofunctionalization electrospun MWCNT nanowire immunosensor for the detection of carcinoma antigen-125. Adopted from Paul et al. [81]

surfactant-assisted method, deposition–precipitation method, sonochemical gold seeding method, sandwiched gold seeded shell synthesis, and one-pot synthesis method. Surfactant-assisted seeding method involves using surfactants such as 3-aminopropyltriethoxysilane (APTES), which is a linker to provide $NH_2$ groups on silica nanoparticles. The amine-functionalized silica nanoparticles could link to gold when a gold colloidal mixture was added [114].

Deposition–precipitation (DP) is a method generally used to form directly gold seeds on a silica core (Fig. 4) [50]. Subsequently, the surface of the silica nanoparticles is decorated with APTES. These amine-functionalized silica nanoparticles are seeded with gold hydroxide nanoparticles. To synthesize gold nanoshells by the DP method, $HAuCl_4$ is hydrolyzed by adding NaOH to give a yellowish gold hydroxide solution. Silica nanoparticles were then added, and the orange-brown colored solution included $Au(OH)_3$ nanoparticles loaded onto silica nanoparticles. A basic gold hydroxide solution (K-gold) and sodium borohydride were added to $Au(OH)_3$ seeded silica nanoparticles to grow nanoshells by reduction of gold. The color of the solution can be red, purple, or green depending on the shell thickness [82].

Another most used core material of nanoshell systems is polymeric nanoparticles. There are several approaches to fabricating gold nanoshells on a polymer core including solvent-assisted method, combined swelling heteroaggregation method, gold colloid seeding method, and gold ion seeding method. In the solvent-assisted

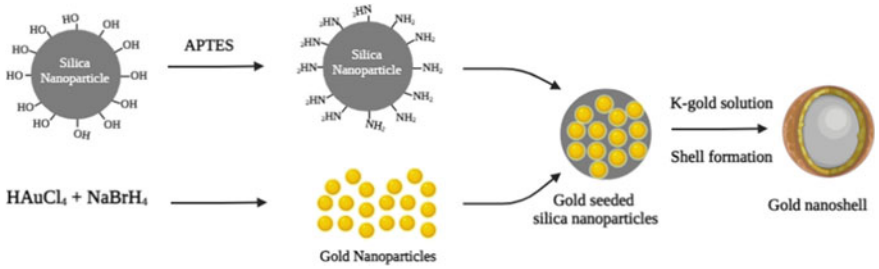


**Fig. 4** Synthesis of gold nanoshells on silica core by DP method. Created with BioRender

method, the polymer as a core material is immersed in a solvent that contains gold salt. When the polymer swells, gold ions can permeate into the polymer core to form a gold shell on the polymer core [133].

The gold colloid seeding method involves the formation of gold nanoshells that cover the polymer core by electrostatic interactions or covalent bonds when adding gold colloid solution which forms gold seeds on the surface [63]. By using low metal concentration and controlling reaction conditions, the reduction of gold ions led to the formation of nanoshells on an unfunctionalized polymer surface in the gold ion seeding method. Different reaction conditions such as pH, reducing agent concentration, and temperature affect the morphological characteristics of nanoparticles [13].

Hollow gold nanoshells can be fabricated by using a silica core to synthesize gold nanoshells as described and then using hydrogen fluoride (HF) to remove the silica core. Other methods including sacrificial template method, template galvanic replacement method, electrochemical synthesis method can be also used to prepare hollow gold nanoshells. The sacrificial template method requires two steps for the fabrication of hollow gold nanoshells. First, cobalt nanoparticles which act as a template for the gold nanosphere formed in the presence of sodium borohydride. Then sodium borohydride is removed before adding $HAuCl_4$ solution. After gold nanoshells are formed, air exposure causes oxidation of the residual cobalt, leading to the formation of a hollow gold nanoshell [2]. Also, silver nanoparticles act as a template for the fabrication of hollow gold nanoshells by using the template galvanic replacement method. Redox reaction between $Au^{3+}$ and $Ag^{(0)}$ induced gold shell formation and after the pitting process, hollow nanoshells are formed [62].

Nanoshells can be characterized by advanced devices in terms of parameters such as optical properties, size, morphology, and composition. UV-visible spectroscopy is commonly used to characterize superior optical properties of nanoshells [5]. The ratio of shell thickness and overall diameter of nanoparticles affects the optical characteristics of nanoshells. It is possible to determine the size of the nanoparticles with different characterization tools such as transmission electron microscopy (TEM), scanning electron microscopy (SEM) [69], dynamic light spectroscopy (DLS) [79], and X-ray diffraction (XRD) [9]. Moreover, SEM and TEM provide information about the morphology of nanoparticles such as crystallinity and lattice structure.

Also, the stability and aggregation of nanoparticles can be determined by DLS. XRD is used to determine not only the size and morphological characteristics but also the composition of the nanoparticle. X-ray photoemission spectroscopy (XPS) and energy-dispersive X-ray spectroscopy (EDX) are other methods to evaluate the composition of nanoshells [117]. Nanoshells with unique properties are import for PoCT in terms of having the capability to conjugate antibodies and other biological molecules in immunoassays. PoCT has several advantages such as simplicity, user-friendliness, time-saving, or low cost, and recent studies reveal that nanoshells have been the focus of researchers for PoCT in many areas with their unique properties. Several practical portable analytical platforms have been used for the detection and/or diagnosis via PoCT such as lateral flow assay (LFA). When samples flow through the strip, the analytes interact with recognition molecules and then signals are captured by another recognition molecule (Fig. 5). Commercial LFA platforms can be used for the PoCT of antigens, disease biomarkers, hormones, or microorganisms. For example, Huang et al. developed colloidal gold test strips with Pt nanoshells as a quantitative PoCT method. In their work, myoglobin which is an early biomarker of acute myocardial infarction was used as a model analyte and a pressure-based method was developed to measure potentially the number of various analytes. Colloidal gold combines with the Ag precursor and hydroquinone to generate an Ag shell on the surface. After that, a Pt precursor and ascorbic acid can coat the Ag shell with Pt. After Pt coated nanoshells produce catalytic gas from the decomposing $H_2O_2$. The amount of Pt nanoshells on the test line correlates with increased pressure due to gas output [45].

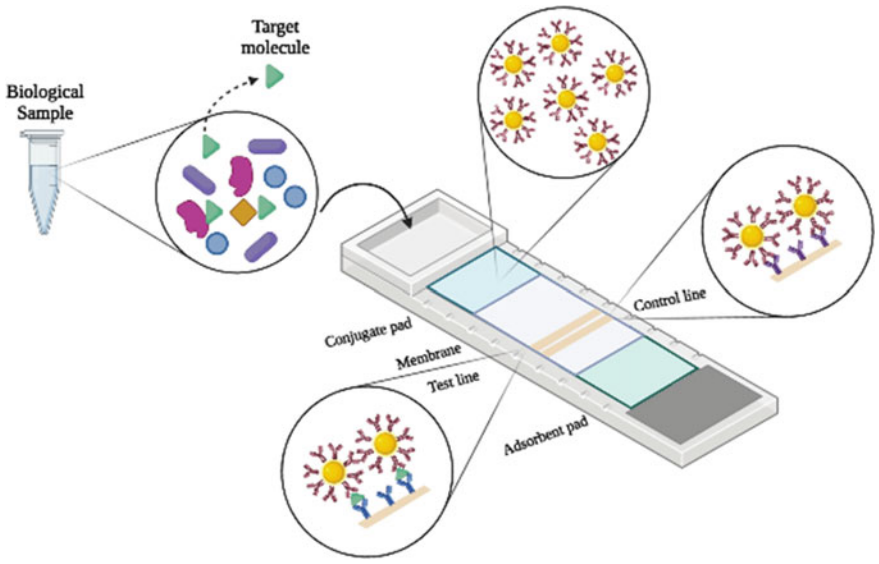


**Fig. 5** The schematic representation of LFA strip decorated with antibody-conjugated gold nanoshells. Created with BioRender

In another work, Srinivasan et al. showed how to use gold nanoshells as a tag for LFA with a remarkable increase in the signal without the need for any additional signal amplification steps for the detection of prostate-specific antigen (PSA). They fabricated the gold nanoshells conjugated with anti-PSA antibodies to target PSA obtained from blood serum samples. This work declares that the portable quantitative PSA screening test has the potential to guide patient care, minimize therapeutic turnaround times, and improve clinical care in areas without diagnostic labs or automated immunoassay systems [96]. Similarly, nanoshell-based PoCT has a great potential to recognize microorganisms with high sensitivity. A different example of gold nanoshells-based LFA was developed for the detection of Chagas disease. Chagas multiantigen conjugated to gold nanoshells recognize circulating human anti-Chagas antibodies with high sensitivity and specificity and it is comparable to commercial methods [70]. For the diagnosis of the tuberculosis, dot blot immunoassay was developed to identify tuberculosis-specific CFP-16 antigen from the clinical urine samples by using the formation of copper nanoshells on the gold nanoparticles' surfaces, which can be quickly observed with naked eye [85]. In a recent study, polyhedral nanoshells were developed as paper strips to detect bovine viral diarrhea virus observably with the naked eye by increasing the signal transmission. By using a new bovine viral diarrhea virus (BVDV) recognizing peptides and designing a copper polyhedral nanoshell on the surface of gold nanoparticles, a dot-blot technique for the rapid diagnosis of BVDV was developed. The copper polyhedral nanoshell served as the quantitative diagnostic of the virus and contributed to the distinctive performance of the peptide-based optical biosensor in detecting the target by enhancing the appearance of the pink dot [52]. The colorimetric assay platforms can be used as a reliable detection kit for point-of-care testing. Although the colorimetric test platforms for dissolved hydrogen sulfide were commonly used, they still have mostly low sensitivity. The creation of effective signal amplification techniques is one potential solution to this problem. Last, of all, nanoshells can benefits such as detection, signal generation, and amplification of signals to produce novel PoCT systems, which make possible diagnosis and treatment at the care-site.

## 7 Nanogels

Hydrogels have been investigated in many applications due to their flexibility, biocompatibility, softness, and high tensile strength [46]. Nanogels (NGs) are nanosized and three-dimensional hydrogels with a particle size between 20 and 200 nm. Physical or chemical cross-interaction between polymer networks leads to permanent nanogels. 3D-dimensional nanogels have features such as adjustable size, swelling ability, flexibility, and large surface area [67]. These properties of the nanogels are adjustable, thus allowing biomedical applications [36, 78]. Traditional laboratory methods used to diagnose pathologies have good selectivity and sensitivity, but they require more time, cost, and staff. The point-of-care testing provides faster and earlier detection of pathologies. Solution-based colorimetric nanosystems and

surface plasmon resonance biosensing are the most commonly used for PoCT [71]. Nano or microgels are of great use in therapeutic and diagnostic applications due to their ability to swell in aqueous solution, ensuring non-specific cell or protein absorption [27, 83]. Nanogels can be defined as chemically or physically cross-linked nanosized polymer networks. Cross-linking of polymer chains ensures a three-dimensional network and high water absorption capacity without dissolution [95]. Generally, nanogels can be prepared in three different ways.

(i) *Physical method*

In this method, physical interactions are reached between polymer chains. These interactions occur between supramolecular contructs without covalent bonding. Compared to other methods, Van der Waals, ionic, hydrophobic–hydrophilic, hydrogen bonds are the driving force for the synthesis of cross-linked networks without additional cross-linking agents. Physical cross-linked nanogels are less stable than chemically cross-linked nanogels [68].

(ii) *Polymerization of monomers*

Polymerization of monomers is an appropriate way for the synthesis of nanogels. The polymerization method works through polymerization of monomer in the presence of initiator, catalyst, and cross-linking agent. Emulsion polymerization, controlled living radical polymerization, and click chemistry are widely used for polymerization of monomers [103]. The emulsion polymerization leads to polymerization of reactive monomer polymers in an aqueous suspension or water-nano emulsion phase [54]. Controlled living radical polymerization method affords the synthesize of well-defined nanogels with high polymer molecular weight, different compositions, and dimensions [68]. Nitroxide-mediated polymerization (NMP), atom transfer radical polymerization (ATRP), and reversible addition-fragmentation chain-transfer (RAFT) polymerization methods are known as SI-CRP methods [76]. Click chemistry is a simple and efficient method and includes copper-catalyzed reactions, copper-free click reactions, and pseudo-click reactions.

(iii) *Cross-linking of polymers*

Covalent cross-linking is widely used for coupling polymer chains to form a gel network [42, 53]. Click chemistry, disulphide-based cross-linking, and amino group-containing cross-linking are methods of cross-linking of polymers. It is possible to produce very different types of functional nanogels using this technique [75].

## *7.1 Classification of Nanogels*

Nanogels can be classified on their behavior as non-responsive and stimuli-responsive nanogels. Stimuli-responsive nanogels change their structural properties in response to internal or exogenous stimuli, including light, pH, temperature, ultrasound, and

magnetic field [33, 72]. These sensitive nanogels are often called "smart" materials. Stimuli-responsive nanogels mostly synthesize from cross-linking of desired monomers. For example, temperature-triggered nanogels tend to swell and deswell at a particular temperature [40, 106]. In this system, external heat ensures remote control and the thermoresponsive nanogels promise controlled and targeted drug delivery. The thermoresponsive polymers such as Poly(N-isopropylacrylamide), poly(amino carbonate), urethane, and polvinylcaprolactam utilized for preparation of stimuli responsive nanogels. pH-responsive nanogels are sensitive to acidic or basic conditions. Hyaluronic acid, alginate, chitosan are natural polymers used for the synthesis of pH-responsive nanogels [20]. Dinh et al. designed pH-responsive coiled-coil peptide-cross-linked hyaluronic acid nanogels (HA-cNGs) for cytochrome C (CC) protein delivery. The HA-cNGs loaded with CC showed a rapid release under mild acidic conditions [28]. In light-responsive systems, photoresponsive molecules are encapsulated in a nanogel. Azobenzenes and spiropbenzopyrans are commonly used in these nanogels' fabrication [1, 14].

The morphology of nanogels is the main point that gives information about the particle size, structure, and shape. Electron microscopes and optical microscopes are mainly used for morphological analysis. Electron microscopes ensure better resolution for imagining smaller nano and microgels. Scanning electron microscope (SEM) and transmission electron microscope (TEM) are widely used to observe the nanogel structure. Dynamic light scattering (DLS) is also the preferred method for measuring size distributions and average sizes in liquids. Charge on nanogels and the effect of cross-linker quantity can be determined by DLS analysis [94, 108]. Wu et al. reported the synthesis of carboxymethyl chitosan-nisin nanogels. TEM analysis was carried out for morphological properties determination. TEM images show that nanogels are spherical in shape and the average size is $45 \pm 5.62$ nm. Compared to the sizes observed by DLS, the TEM results are smaller because the nanogels are swollen in solution. The presence of functional group carboxymethyl chitosan was confirmed with FT-IR spectroscopy [118]. Determination of swelling properties is crucial for the characterization of nanogels. The swelling degree depends on the structure of the nanogel and the environmental parameters (pH, temperature, etc.) [75]. DLS measurement can be used to calculate the swelling ratio. For this aim, particles that swelled at different times, salinities, and temperatures are measured. The average diameter obtained from DLS substituted in different equations and swelling capacity can be calculated [108]. In addition, the swelling ratio can be determined based on the change in mass between dry particles and swollen particles by substituting the corresponding equation [56]. The monitoring of glucose concentration is very important for diabetes patients. The point-of-care tests promising painless, low-cost, and fast detection of glucose concentration [64, 105]. Li et al. reported glucose-sensitive poly (N-isopropylacrylamide)/poly (acrylic acid) (PNIPAM/PAA) (IPN-BAC) interpenetrating nanogels on colloidal photonic crystals (CPs). IPN-BAC nanogels cross-linked with N,N′-Bis(acryloyl)cystamine (BAC) and encapsulated by glucose-sensitive NIPAM/4-Vinylphenylboronic Acid (VPBA) copolymer shell [59]. The PNIPAM nanogels were synthesized by emulsion polymerization.

PNIPAM/PAA IPN nanogels were then synthesized in situ polymerization of acrylamide within the PNIPAM network. The particle sizes and chemical compositions of the nanogels were determined using DLS and X-ray photoelectron spectroscopy analysis, respectively. The glucose-sensitive core-shell nanogel showed a color change from blue to green depending on glucose concentration [59]. Sharmila and Shankaran fabricated a hydrogel-based nanoplasmonic colorimetric food sensor probe for the detection of melamine (MA) with a detection limit of $\times 10^{-7}$ M. They showed colorimetric sensing of MA in plasmonic nanomaterials (AuNPs) in solution and hydrogel phases. The AuNPs incorporated plasmonic hydrogels were prepared by the chemical and physical cross-linking of cellulose acetate on citrate and β-cyclodextrin (βCD) stabilized on gold nanomaterials. Both AuNPs in solution and hydrogel phases show similar selectivity and sensitivity [93]. Another research group developed localized surface plasmon resonance (LSPR) based poly(N-isopropylacrylamide-co-methacrylic acid) (PNM) on silica gold nanoshells (AuNS@PNM) biosensor [25]. The nanoshells have concentration-dependent red shifts in the LSPR wavelength of AuNS@PNM. PNM nanogels were synthesized on core-gold nanoshells (AuNSs) using the precipitation polymerization method. Nanogel-modified AuNSs were dialyzed at room temperature and centrifuged to remove unbond PNM nanogels. The TEM images of AuNS@PNM showed that a flower-like architecture had been achieved. In this design, PNM hydrogels can change their refractive index as a result of protein binding. The AuNS@PNM composite exhibits the detection of changes in the concentration of lysozyme and lactoferrin. Figure 6 shows that the shift is small at low protein concentrations. The concentration-dependent shift of the LSPR wavelength can be easily measured with a portable spectrometer [25].

## 8 Nanofibers

Nanofibers are ultra-fine webs of solid fibers with a small pore size, a small diameter, and a high surface area [61]. Lowering fiber diameters to the nanoscale can cause a significant increment of specific surface area to 1000 $m^2/g$. Nanofiber that has a comparatively small volume can comprise plenty of dense nanofibers. The high surface area provides a remarkable ability to attach or release functional groups, adsorbed molecules, ions, and various types of nanometer-scale particles [61].

Electrospinning has attracted a lot of attention from scientists working in the area of creating ultrathin fibers among other technologies such as phase separation [38], template synthesis [74], chemical vapor deposition [97], and sol–gel method [66]. Electrospinning is a reproducible technique that provides flexible operation and, as a result of its simplicity mainly used. Nano-sized fibrous materials can easily made using electrospinning technology with high efficiency and flexibility in a short time [18]. It offers various chances for shape, chemical composition, structural, and function-based fiber customization. These controllability characteristics endow the nanofiber material with several outstanding attributes that can meet the demands of different industries [110]. A high-voltage power supply, a syringe-driven spinneret

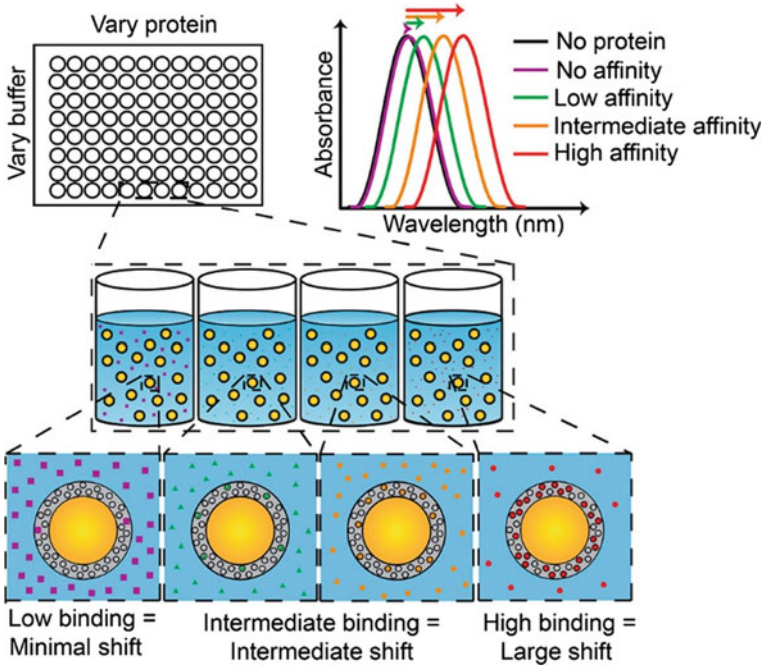


**Fig. 6** Schematic diagram of LSPR-based biosensor. Adapted from [25]

connected to a pump and a grounded collector are the main components of electrospinning systems (Fig. 7). The electrospinning process, which is based on the theory of electrostatics, is the use of electrostatic repulsion forces in a strong electric field to produce nanofibers. While the solution to be electrospun is in the syringe, a strong electric field is created between the syringe nozzle and the collector. Due to the potential difference between the nozzle and the collector, the solution droplet at the nozzle acquires a cone-shaped distortion as the solution is ejected. The polymer mixture is pulled into fibers under high pressure during the electrospinning process and then deposited on the collector to create a web of randomly or aligned fibers [19].

The potential use of nanofibers to develop biosensors has been investigated. Miniaturization of designed platforms can also be facilitated by nanofibers. Different physical surface modification methods (layer by layer, atomic deposition), chemical methods (oxidation, cross-linking, hydrolysis, grafting), and thermal methods (heat press, calcination) are utilized to improve nanofiber-based biosensors characteristics [92]. As a result of their interconnectivity properties and large surface area-to-volume ratio, electrospun nanofibers are excellent materials for immobilization. Strong electrophilic functional groups on the nanofiber are employed by indirect immobilization techniques which are generally straightforward. Between the nanofiber and the biomolecule, cross-linkers act as an intermediary. While some

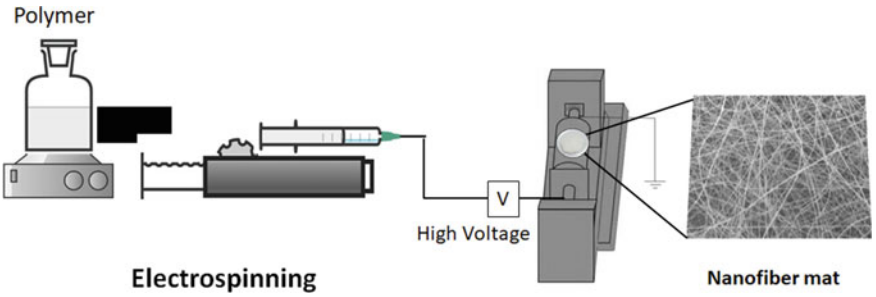


**Fig. 7** Electrospinning process for the production of nanofibers

cross-linkers can be found in the final product, others expedite the reactions. For this purpose, the electrospun nanofibers with excellent properties and diverse functions can be modified by physical/chemical methods. Thus, they are potential materials to be employed by point-of-care (POC) biosensors and microfluidic-based analytical systems. Nanofibers have been investigated as ultrasensitive biosensors for POC cancer diagnosis, circulating tumor cell detection in cancer patients, malaria diagnosis, urea, glucose, cholesterol, bacteria detection, etc. Because high surface area property gives nanofibers the ability of ultrasensitive detection by providing them with binding sites in large quantities. More bioreceptors could be located on the surface or the inside of nanofibrous, thus increasing sensitivity [61]. In colorimetric POC detection applications, enzymes should be immobilized on the nanofibrous mat frequently with an adsorption technique [112]. Then, the nanofiber mats were dried usually at 25 °C and used in colorimetric detection with the color gradient scale. In another example, an anti-CAP monoclonal antibody immobilized onto the surface of poly(vinyl-co-ethylene) nanofibers to establish chloramphenicol (CAP) and use for the colorimetric biosensor for CAP [136].

Dhawane et al. [26] fabricated a POC, visual detection kit using chitosan nanofibers via electrospinning for the detection of cholesterol. In this study, uniform chitosan nanofibers (60–90 nm diameter) free of beads, were obtained. Interaction between the enzymes and the chitosan nanofibrous mat was important for the enzyme loading. For this reason, the electrospinning was performed to produce three nanofibrous mats with different thicknesses (6, 12, and 18 h electrospinning time) to find maximum enzyme loading. After 6 h immobilization time, a higher enzyme-loaded (3.8 U/mL) nanofiber was obtained. The nanofibrous mat was, therefore, used for the detection of cholesterol. It was based on a colorimetric method. Results showed that a color scale was developed when nanofiber mats loaded with reacting enzyme contact different concentrations of cholesterol (50–300 mg/dL). As a result, a simple method can be incorporated into a POC strip for cholesterol detection. Li et al., [60] produced electrospun polyethylenimine/poly(vinyl alcohol) (PEI/PVA) nanofibrous films decorated with Au nanorods (NRs) are signal output elements for the multicolor visual POCT of PSA proteins. The proposed aptasensing strategy provided PSA quantifying and semiquantifying in Au-NRs colloidal solution. Au-NRs/PEI/

PVA electrospun nanofibrous films displayed good accuracy, low detection limit, broad linearity, POCT characteristic, and satisfactory reproducibility. Considerably, this method can demonstrate a clear semiquantitative visual effect near the 4.0 and 10.0 ng/mL PSA concentration cutoffs. This has been used as a measure of the incidence of prostate cancer. In one study, electrospun nanofibrous membranes with magnetic nanoparticles have been developed and optimized for rapid and sensitive electrochemical detection of the pathogen bacterium: *E. coli* O157:H7. The biosensor showed linear detection of five different cell concentrations from $10^1$ to $10^4$ CFU/mL in 8 min. Results of the study show that the application of the low-cost and rapid biosensor can be extended to other organisms in field tests [65]. Overall, the trend and prospects are indications of possibilities to promote the implementation of nanofiber and nanofiber-miniaturized system hybrid for the next generation of diagnostic platforms point-of-care testing.

## 9 Flexible Hybrid Composites

Flexible nanomaterials have received increased research interest with the development of science and technology [131]. Recently, scientists have demonstrated to flexibility and stretchability of various nanomaterials at both macro and micro scales and focused on novel techniques for the design and synthesis of flexible nanomaterials. Flexible nanomaterials are smart materials that can be deformable, bendable structures, and have the ability to return to their original shape. Especially, combination of flexible nanomaterials with polymers provides great flexibility [23]. The unique properties of flexible nanomaterials allow fabrication of new generations of flexible and wearable electronics. Flexible and wearable electronics can be attached to human skin and biological tissue to enable the monitoring of biological signals. Tracking biological signals generated by the human body provides health assessment and points of diagnosis diseases [120]. In order to collect accurate information from the human body, sensors as the main component of flexible and wearable electronics are required to be flexible and have ideal stretchability [132]. Currently, electronic sensors are generally constructed with rigid materials such as metal or semiconductor. The mechanical properties of these materials are not suitable for the human body as well their lack of flexibility and sensitivity are not appropriate for healthcare monitoring [130]. Recently, considerable efforts have been dedicated to the development of flexible and wearable electronics with good mechanical deformability, stretchability, sensitivity, and comfortable wear for healthcare monitoring [39]. In the field of flexible wearable electronics, sensors are composed of a substrate, a conductive filler, sensing elements, and encapsulation materials [31]. The selection of material and design strategy are important factors in the fabrication of flexible and stretchable sensors [88]. In a flexible and stretchable sensor, component materials need to be designed with good mechanical strength and electronic properties. The flexibility, stretchability, and conductivity properties of materials used in the flexible wearable sensor are the main important criteria to obtain high-performance sensing systems.

Moreover, flexible sensing systems are required to maintain their performance and mechanical stability under mechanical stress. The flexible wearable sensors generally fabricated by using flexible substrate and nanomaterials. Among the flexible substrates polymeric materials including polydimethylsiloxane (PDMS), ecoflex, polyimide (PI), polyethylene terephthalate (PET), polyurethane (PU), and rubber are generally used for the fabrication of flexible sensors due to their intrinsic flexible properties [51]. Flexible and wearable electronics can also be integrated papers, membranes, patches, and so on for point-of-care testing [100]. Flexible carbon-based nanomaterials (graphene, carbon nanotubes (CNTs), nanosheets, nanowires, and nanoparticles) are widely used in flexible sensor fabrication as conducting nanofillers [55].

There are two strategies to obtain flexible and stretchable sensors. The first one is to exploit intrinsically flexible/stretchable materials, and the other is to use a structural design strategy. To fabricate flexible and wearable sensors, a variety of nanomaterials have been utilized such as carbon-based nanomaterials and metallic nanomaterials. Intrinsic stretchability/flexibility in the sensor platform is achieved by integrating these conductive fillers into the flexible materials [126]. This stretchable and flexible sensor system can be developed by using different synthesis methods such as mixing elastomeric substrate with conductive fillers, surface coating, deposition, and printing processes [119]. These methods are conducted to the distribution of conductive fillers homogenously in the elastomeric materials. The ultimate goal is to obtain flexible and stretchable composite sensors in whole processes. Moreover, materials designed with appropriate geometries such as serpentine, percolating network, kirigami, and wave/wrinkle enable the transforming nonstretchable materials into the fabrication of stretchable structure materials [30, 137]. For example, the stretchable wavy structure can be obtained by depositing or transferring metallic materials [119, 127].

Evaluating the performance of the fabricated flexible sensor system is also important to obtaining reliable healthcare monitoring systems. In order to fabricate a flexible and wearable sensor system with high performance, some parameters such as sensitivity, linearity, hysteresis, response time, and stability should be taken into consideration. Electromechanical characterization is generally carried out to determine the suitability of these parameters for flexible and wearable sensors [51]. Different characterization methods such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), X-ray diffraction (XRD) analysis, Fourier transform infrared (FTIR) spectrometer, and atomic force microscopy (AFM) are also exploited to display photographs of materials' nanostructure, structure sensing activity, and sensing mechanism [128]. In addition to the characterization and synthesis methods of the flexible and wearable sensors mentioned above, the fabrication of them depending on the application area is an important consideration.

Point-of-care testing which provides patient-centered diagnosis and real-time health monitoring has become a boasting desire recently [73]. At this point, flexible and wearable sensors stand out as a cornerstone for point-of-care testing. These flexible and wearable sensors that can be integrated into the human body enable real-time monitoring and recording of human physiological and biological vital signals for disease diagnosis and health status. These signals produced by the human body

such as mechanical, electrical, and biological signals can be related to health indicators [107, 120]. Flexible and wearable sensors can be designed to measure at a variety of health indicators such as body motions, body temperature, pulse rate, electrocardiograms (ECGs), blood pressure, breathing rate, and so on [121].

Yang et al. [125] prepared a novel flexible Ag/CNTs-PDMS composite film for the early diagnosis of Parkinson's disease. This flexible sensor was prepared in three stages. Firstly, CNT film was transferred to the PDMS substrate and transformed the CNT into a wrinkled structure. Secondly, Ag film was deposited upon the wrinkled CNT film by ion sputtering method. Lastly, they assembled the flexible and wearable sensor. Yamamoto et al. [122] developed integrated simple flexible sensor systems sensitive to both electrocardiogram (ECG) signal and skin temperature to monitor health condition change based on ECG signal and dehydration and heat stroke applications. This flexible sensor was developed by using printing technology on a flexible PET film and CNT was used as a conductive filler. Breath sensors that can be attached to human skin are useful flexible materials for the diagnosis of diseases including breathlessness, bronchial asthma, and sleep apnea. Yan et al. [124] developed a flexible $AgVO_3$-nanowires breath sensor by merging the $AgVO_3$ NWs with Au-interdigitated electrode on a PI substrate. This sensor system highly sensitive to humidity air shows the resistance change when the human subject exhales and inhales. This flexible sensor system possesses consistency and repeatability to monitor human breath with different respiratory rates, flexible sensor system could offer opportunities early for diagnosing and treating breath related diseases. These potential development of flexible and wearable sensor systems in the fields of point care testing system may provide achieving personalized early diagnosis diseases in the near future.

## 10 Conclusion and Future Aspects

In this chapter, we have discussed the synthesis and characterization of current nanomaterials and their application in nanomaterial-based biosensors for point-of-care diagnostics. Nanomaterial-based POC test platforms have excellent and promising potential in current clinical diagnostics. However, there are still some obstacles that need to be overcomed, such as high cost, limitations in large-scale applications, relatively low reproducibility, and so forth. The direction of current studies is to develop nanomaterial-based POC testing platforms that overcome these obstacles and provide more effective, reproducible, accurate, and efficient results. We believe that in the very near future, various nanomaterial-based POCT devices will be developed and used in clinical trials.

## References


1. Abdolahinia ED, Barati G, Ranjbar-Navazi Z, Kadkhoda J, Islami M, Hashemzadeh N et al (2022) Application of nanogels as drug delivery systems in multicellular spheroid tumor model. J Drug Deliv Sci Technol 68:103109
2. Adams S, Thai D, Mascona X, Schwartzberg AM, Zhang JZ (2014) Key factors affecting the reproducibility of synthesis and growth mechanism of near-infrared absorbing hollow gold nanospheres. Chem Mater 26(23):6805–6810
3. Adil LR, Parui R, Khatun MN, Chanu MA, Li L, Wang S, Iyer PK (2022) Nanomaterials for sensors: synthesis and applications. In: Advanced nanomaterials for point of care diagnosis and therapy, Elsevier, pp 121–168
4. Aftab S, Shah A, Erkmen C, Kurbanoglu S, Uslu B (2021) Quantum dots: synthesis and characterizations. In: Electroanalytical applications of quantum dot-based biosensors. Elsevier, pp 1–35
5. AkbaráAshkarran A, MostafaáAkbari S, RezaáHormozi-Nezhad M (2015) Determination of nanoparticles using UV-Vis spectra. Nanoscale 7(12):5134–5139
6. Al-Kassawneh M, Sadiq Z, Jahanshahi-Anbuhi S (2022) Pullulan-stabilized gold nanoparticles tablet as a nanozyme sensor for point-of-care applications. Sens. Bio-Sens. Res. 38:100526
7. Al-Kutubi H, Dikhtiarenko A, Zafarani HR, Sudhölter EJ, Gascon J, Rassaei L (2015) Facile formation of ZIF-8 thin films on ZnO nanorods. CrystEngComm 17(29):5360–5364
8. Alabsi SS, Ahmed AY, Dennis JO, Khir MM, Algamili A (2020) A review of carbon nanotubes field effect-based biosensors. IEEE Access 8:69509–69521
9. Amirthalingam T, Kalirajan J, Chockalingam A (2011) Use of silica-gold core shell structured nanoparticles for targeted drug delivery system. J Nanomed Nanotechnol 2(6)
10. Annamalai J, Murugan P, Ganapathy D, Nallaswamy D, Atchudan R, Arya S et al (2022) Synthesis of various dimensional metal organic frameworks (MOFs) and their hybrid composites for emerging applications—A review. Chemosphere, 134184
11. Averitt R, Sarkar D, Halas N (1997) Plasmon resonance shifts of Au-coated $Au_2S$ nanoshells: insight into multicomponent nanoparticle growth. Phys Rev Lett 78(22):4217
12. Azhar MR, Abid HR, Tade MO, Periasamy V, Sun H, Wang S (2018) Cascade applications of robust MIL-96 metal organic frameworks in environmental remediation: proof of concept. Chem Eng J 341:262–271
13. Bao H, Bihr T, Smith A-S, Taylor RNK (2014) Facile colloidal coating of polystyrene nanospheres with tunable gold dendritic patches. Nanoscale 6(8):3954–3966
14. Bhaladhare S, Bhattacharjee S (2022) Chemical, physical, and biological stimuli-responsive nanogels for biomedical applications (mechanisms, concepts, and advancements): a review. Int J Biol Macromol
15. Bhaskar S, Rai A, Ganesh KM, Reddy R, Reddy N, Ramamurthy SS (2022) Sericin-based bio-inspired nano-engineering of heterometallic AgAu nanocubes for attomolar mefenamic acid sensing in the mobile phone-based surface plasmon-coupled interface. Langmuir 38(39):12035–12049
16. Biemmi E, Christian S, Stock N, Bein T (2009) High-throughput screening of synthesis parameters in the formation of the metal-organic frameworks MOF-5 and HKUST-1. Microporous Mesoporous Mater 117(1–2):111–117
17. Biju V (2014) Chemical modifications and bioconjugate reactions of nanomaterials for sensing, imaging, drug delivery and therapy. Chem Soc Rev 43(3):744–764
18. Cao X, Chen W, Zhao P, Yang Y, Yu D-G (2022) Electrospun porous nanofibers: pore-forming mechanisms and applications for photocatalytic degradation of organic pollutants in wastewater. Polymers 14(19):3990
19. Che H, Yuan J (2022) Recent advances in electrospinning supramolecular systems. J Mater Chem B 10(1):8–19

20. Chen X, Li R, Wong SHD, Wei K, Cui M, Chen H et al (2019) Conformational manipulation of scale-up prepared single-chain polymeric nanogels for multiscale regulation of cells. Nat Commun 10(1):2705
21. Chen X, Liu X, Zhang C, Meng H, Liu B, Wei X (2022) A rapid fluorescent aptasensor for point-of-care detection of C-reactive protein. Talanta 249:123661
22. Chen X, Xu J, Li Y, Zhang L, Bi N, Gou J et al (2023) A novel intelligently integrated MOF-based ratio fluorescence sensor for ultra-sensitive monitoring of TC in water and food samples. Food Chem 405:134899
23. Cheng Y, Li Z, Gao J, Yu H-D, Zhang G (2022) Introduction to flexible nanomaterials: microscopic mechanisms and macroscopic applications. Nanoscale Adv 4(7):1716–1717
24. Colombo M, Carregal-Romero S, Casula MF, Gutiérrez L, Morales MP, Böhm IB et al (2012) Biological applications of magnetic nanoparticles. Chem Soc Rev 41(11):4306–4334
25. Culver HR, Wechsler ME, Peppas NA (2018) Label-free detection of tear biomarkers using hydrogel-coated gold nanoshells in a localized surface plasmon resonance-based biosensor. ACS Nano 12(9):9342–9354
26. Dhawane M, Deshpande A, Jain R, Dandekar P (2019) Colorimetric point-of-care detection of cholesterol using chitosan nanofibers. Sens Actuators B Chem 281:72–79
27. Din F, Choi JY, Kim DW, Mustapha O, Kim DS, Thapa RK et al (2017) Irinotecan-encapsulated double-reverse thermosensitive nanocarrier system for rectal administration. Drug Delivery 24(1):502–510
28. Ding L, Jiang Y, Zhang J, Klok H-A, Zhong Z (2018) pH-sensitive coiled-coil peptide-cross-linked hyaluronic acid nanogels: synthesis and targeted intracellular protein delivery to CD44 positive cancer cells. Biomacromolecules 19(2):555–562
29. Drbohlavova J, Adam V, Kizek R, Hubalek J (2009) Quantum dots—Characterization, preparation and usage in biological systems. Int J Mol Sci 10(2):656–673
30. Duan L, D'hooge DR, Cardon L (2020) Recent progress on flexible and stretchable piezoresistive strain sensors: from design to application. Prog Mater Sci 114:100617
31. Erdem Ö, Derin E, Zeibi Shirejini S, Sagdic K, Yilmaz EG, Yildiz S et al (2022) Carbon-based nanomaterials and sensing tools for wearable health monitoring devices. Adv Mater Technol 7(3):2100572
32. Fan Z, Huang X, Tan C, Zhang H (2015) Thin metal nanostructures: synthesis, properties and applications. Chem Sci 6(1):95–111
33. Fathi M, Abdolahinia ED, Barar J, Omidi Y (2020) Smart stimuli-responsive biopolymeric nanomedicines for targeted therapy of solid tumors. Nanomedicine 15(22):2171–2200
34. Friščić T (2012) Supramolecular concepts and new techniques in mechanochemistry: cocrystals, cages, rotaxanes, open metal–organic frameworks. Chem Soc Rev 41(9):3493–3510
35. Fu X, Gou M, Zhang Y, Su H, Zhao H, Liu C, Han J (2022) Simultaneous and visual detection of multiple dopes by an aptamer/AuNPs sensor. New J Chem 46(38):18128–18132
36. Gu Z, Biswas A, Joo K-I, Hu B, Wang P, Tang Y (2010) Probing protease activity by single-fluorescent-protein nanocapsules. Chem Commun 46(35):6467–6469
37. Guerrero VV, Yoo Y, McCarthy MC, Jeong H-K (2010) HKUST-1 membranes on porous supports using secondary growth. J Mater Chem 20(19):3938–3943
38. Guillen GR, Pan Y, Li M, Hoek EM (2011) Preparation and characterization of membranes formed by nonsolvent induced phase separation: a review. Ind Eng Chem Res 50(7):3798–3817
39. Ha M, Lim S, Ko H (2018) Wearable and flexible sensors for user-interactive health-monitoring devices. J Mater Chem B 6(24):4043–4064
40. Hajebi S, Abdollahi A, Roghani-Mamaqani H, Salami-Kalajahi M (2019) Hybrid and hollow poly (N, N-dimethylaminoethyl methacrylate) nanogels as stimuli-responsive carriers for controlled release of doxorubicin. Polymer 180:121716
41. Harvey JD, Jena PV, Baker HA, Zerze GH, Williams RM, Galassi TV et al (2017) A carbon nanotube reporter of microRNA hybridization events in vivo. Nat Biomed Eng 1(4):0041
42. Hennink WE, van Nostrum CF (2012) Novel crosslinking methods to design hydrogels. Adv Drug Deliv Rev 64:223–236

43. Howarth AJ, Peters AW, Vermeulen NA, Wang TC, Hupp JT, Farha OK (2017) Best practices for the synthesis, activation, and characterization of metal–organic frameworks. Chem Mater 29(1):26–39
44. Hu X, Dong S (2008) Metal nanomaterials and carbon nanotubes—Synthesis, functionalization and potential applications towards electrochemistry. J Mater Chem 18(12):1279–1295
45. Huang D, Lin B, Song Y, Guan Z, Cheng J, Zhu Z, Yang C (2018) Staining traditional colloidal gold test strips with Pt nanoshell enables quantitative point-of-care testing with simple and portable pressure meter readout. ACS Appl Mater Interfaces 11(2):1800–1806
46. Jhawat V, Gulia M, Maddiboyina B, Dutt R, Gupta S (2020) Fate and applications of superporous hydrogel systems: a review. Curr Nanomed (Former: Recent Patents Nanomed) 10(4):326–341
47. Jin Y (2014) Multifunctional compact hybrid Au nanoshells: a new generation of nanoplasmonic probes for biosensing, imaging, and controlled release. Acc Chem Res 47(1):138–148
48. Jouyandeh M, Khadem SSM, Habibzadeh S, Esmaeili A, Abida O, Vatanpour V et al (2021) Quantum dots for photocatalysis: synthesis and environmental applications. Green Chem 23(14):4931–4954
49. Justino C, Silva L, Duarte K, Freitas A, Rocha-Santos T, Duarte A (2012) Determination of volatile organic compounds in human breath by optical fiber sensing. Int J Environ Ecol Eng 6(8):541–544
50. Kah JC, Phonthammachai N, Wan RC, Song J, White T, Mhaisalkar S et al (2008) Synthesis of gold nanoshells based on the depositionprecipitation process. Gold Bull 41:23–36
51. Khalid MAU, Chang SH (2022) Flexible strain sensors for wearable applications fabricated using novel functional nanocomposites: a review. Compos Struct 284:115214
52. Kim MW, Park H-J, Park CY, Kim JH, Cho CH, Park JP et al (2020) Fabrication of a paper strip for facile and rapid detection of bovine viral diarrhea virus via signal enhancement by copper polyhedral nanoshells. RSC Adv 10(50):29759–29764
53. Kishimura A, Koide A, Osada K, Yamasaki Y, Kataoka K (2007) Encapsulation of myoglobin in PEGylated polyion complex vesicles made from a pair of oppositely charged block ionomers: a physiologically available oxygen carrier. Angew Chem Int Ed 46(32):6085–6088
54. Kousalová J, Etrych T (2018) Polymeric nanogels as drug delivery systems. Physiol Res 67
55. Lee G, Zarei M, Wei Q, Zhu Y, Lee SG (2022) Surface wrinkling for flexible and stretchable sensors. Small 18(42):2203491
56. Lei W, Xie C, Wu T, Wu X, Wang M (2019) Transport mechanism of deformable microgel particle through micropores with mechanical properties characterized by AFM. Sci Rep 9(1):1453
57. Li J, Zhu J-J (2013) Quantum dots for fluorescent biosensing and bio-imaging applications. Analyst 138(9):2506–2515
58. Li Q, Liu L, Liu J-W, Jiang J-H, Yu R-Q, Chu X (2014) Nanomaterial-based fluorescent probes for live-cell imaging. TrAC Trends Anal Chem 58:130–144
59. Li X, Li X, Shi X, Peng M, Lu X (2019) PNIPAM-based colloidal photonic crystals above phase transition temperature and its application in naked-eye glucose-detection. Eur Polymer J 120:109230
60. Li ZY, Han L, Meng S, Hu R, Yang YH, Yang T (2022) Target-induced tripedal G-quadruplex DNAzyme for multicolor visual point-of-care testing of biomarkers using Au nanorods-decorated electrospun nanofibrous films. Sens Actuators B Chem 371:132510
61. Lim CT (2017) Nanofiber technology: current status and emerging developments. Prog Polym Sci 70:1–17
62. Lin AY, Young JK, Nixon AV, Drezek RA (2014) Encapsulated Fe3O4/Ag complexed cores in hollow gold nanoshells for enhanced theranostic magnetic resonance imaging and photothermal therapy. Small 10(16):3246–3251
63. Liu S, Su W, Ding X (2016) A review on microfluidic paper-based analytical devices for glucose detection. Sensors 16(12):2086
64. Liu X, Gao C, Gu J, Jiang Y, Yang X, Li S et al (2016) Hyaluronic acid stabilized iodine-containing nanoparticles with Au nanoshell coating for X-ray CT imaging and photothermal therapy of tumors. ACS Appl Mater Interfaces 8(41):27622–27631

65. Luo Y, Nartker S, Wiederoder M, Miller H, Hochhalter D, Drzal LT, Alocilja EC (2011) Novel biosensor based on electrospun nanofiber and magnetic nanoparticles for the detection of E. coli O157: H7. IEEE Trans Nanotechnol 11(4):676–681
66. Ma W, Zhang S, Xie C, Wan X, Li X, Chen K, Zhao G (2022) Preparation of high mechanical strength chitosan nanofiber/nanoSiO2/PVA composite scaffolds for bone tissue engineering using sol-gel method. Polymers 14(10):2083
67. Maddiboyina B, Desu PK, Vasam M, Challa VT, Surendra AV, Rao RS et al (2022) An insight of nanogels as novel drug delivery system with potential hybrid nanogel applications. J Biomater Sci Polym Edn 33(2):262–278
68. Mauri E, Giannitelli SM, Trombetta M, Rainer A (2021) Synthesis of nanogels: current trends and future outlook. Gels 7(2):36
69. Mayle KM, Dern KR, Wong VK, Sung S, Ding K, Rodriguez AR et al (2017) Polypeptide-based gold nanoshells for photothermal therapy. SLAS TECHNOLOGY: Transl Life Sci Innov 22(1):18–25
70. Medina-Rivera M, Cárdenas WB, Erickson D, Mehta S (2022) Gold nanoshells-based lateral flow assay for the detection of chagas disease at the point-of-care. Am J Trop Med Hygiene, tpmd211119–tpmd211119
71. Misra SK, Dighe K, Schwartz-Duval AS, Shang Z, Labriola LT, Pan D (2018) In situ plasmonic generation in functional ionic-gold-nanogel scaffold for rapid quantitative bio-sensing. Biosens Bioelectron 120:77–84
72. Molina M, Asadian-Birjand M, Balach J, Bergueiro J, Miceli E, Calderón M (2015) Stimuli-responsive nanogel composites and their application in nanomedicine. Chem Soc Rev 44(17):6161–6186
73. Mondal S, Zehra N, Choudhury A, Iyer PK (2020) Wearable sensing devices for point of care diagnostics. ACS Appl Bio Mater 4(1):47–70
74. Munir MM, Widiyandari H, Iskandar F, Okuyama K (2008) Patterned indium tin oxide nanofiber films and their electrical and optical performance. Nanotechnology 19(37):375601
75. Noreen S, Pervaiz F, Shoukat H, Ijaz S (2021) An updated review of novel nanogels as versatile
76. Nothling MD, Fu Q, Reyhani A, Allison-Logan S, Jung K, Zhu J et al (2020) Progress and perspectives beyond traditional RAFT polymerization. Adv Sci 7(20):2001656
77. Nur Topkaya S, Ozkan-Ariksoysal D (2016) Prostate cancer biomarker detection with carbon nanotubes modified screen printed electrodes. Electroanalysis 28(5):1077–1084
78. Oishi M, Nagasaki Y (2010) Stimuli-responsive smart nanogels for cancer diagnostics and therapy. Nanomedicine 5(3):451–468
79. Park HH, Srisombat L-O, Jamison AC, Liu T, Marquez MD, Park H et al (2018) Temperature-responsive hydrogel-coated gold nanoshells. Gels 4(2):28
80. Pashchenko O, Shelby T, Banerjee T, Santra S (2018) A comparison of optical, electrochemical, magnetic, and colorimetric point-of-care biosensors for infectious disease diagnosis. ACS Infect Dis 4(8):1162–1178
81. Paul KB, Singh V, Vanjari SRK, Singh SG (2017) One step biofunctionalized electrospun multiwalled carbon nanotubes embedded zinc oxide nanowire interface for highly sensitive detection of carcinoma antigen-125. Biosens Bioelectron 88:144–152
82. Phonthammachai N, Kah JC, Jun G, Sheppard CJ, Olivo MC, Mhaisalkar SG, White TJ (2008) Synthesis of contiguous silica−gold core−shell structures: critical parameters and processes. Langmuir 24(9):5109–5112
83. Pinelli F, Saadati M, Zare EN, Makvandi P, Masi M, Sacchetti A, Rossi F (2022) A perspective on the applications of functionalized nanogels: promises and challenges. Int Mater Rev, 1–25
84. Quesada-González D, Merkoçi A (2018) Nanomaterial-based devices for point-of-care diagnostic applications. Chem Soc Rev 47(13):4697–4709
85. Rafique R, Baek SH, Nguyen TP, Park KY, Kim EB, Kim JG et al (2018) Gold-copper nanoshell dot-blot immunoassay for naked-eye sensitive detection of tuberculosis specific CFP-10 antigen. Biosens Bioelectron 121:111–117
86. Raptopoulou CP (2021) Metal-organic frameworks: synthetic methods and potential applications. Materials 14(2):310

87. Rathinavel S, Priyadharshini K, Panda D (2021) A review on carbon nanotube: an overview of synthesis, properties, functionalization, characterization, and the application. Mater Sci Eng B 268:115095
88. Ren Z, Qi D, Sonar P, Wei Z (2020) Flexible sensors based on hybrid materials. J Semiconduct 41(4):040402-040402-040402
89. Rodenas T, Luz I, Prieto G, Seoane B, Miro H, Corma A et al (2015) Metal–organic framework nanosheets in polymer composite materials for gas separation. Nat Mater 14(1):48–55
90. Saleh TA (2020) Nanomaterials: classification, properties, and environmental toxicities. Environ Technol Innov 20:101067
91. Sari E (2022) Synthesis and characterization of high quantum yield graphene quantum dots via pyrolysis of glutamic acid and aspartic acid. J Nanopart Res 24(2):37
92. Schneider R, Facure MH, Chagas PA, Andre RS, dos Santos DM, Correa DS (2021) Tailoring the surface properties of micro/nanofibers using 0d, 1d, 2d, and 3d nanostructures: a review on post-modification methods. Adv Mater Interfaces 8(13):2100430
93. Sharmila S, Shankaran DR (2022) Plasmonic nanogels for naked-eye sensing of food adulterants. Anal Methods 14(45):4703–4712
94. Sindhu RK, Gupta R, Wadhera G, Kumar P (2022) Modern herbal nanogels: formulation, delivery methods, and applications. Gels 8(2):97
95. Soni KS, Desale SS, Bronich TK (2016) Nanogels: an overview of properties, biomedical applications and obstacles to clinical translation. J Control Release 240:109–126
96. Srinivasan B, Nanus DM, Erickson D, Mehta S (2021) Highly portable quantitative screening test for prostate-specific antigen at point of care. Curr Res Biotechnol 3:288–299
97. Stassen I, Styles M, Grenci G, Gorp HV, Vanderlinden W, Feyter SD et al (2016) Chemical vapour deposition of zeolitic imidazolate framework thin films. Nat Mater 15(3):304–310
98. Sun Z, Qing M, Fan YZ, Yan H, Li NB, Luo HQ (2022) Quadruple analyte responsive platform: point-of-care testing and multi-coding logic computation based on metal ions recognition and selective response. J Hazard Mater 437:129331
99. Syedmoradi L, Daneshpour M, Alvandipour M, Gomez FA, Hajghassem H, Omidfar K (2017) Point of care testing: the impact of nanotechnology. Biosens Bioelectron 87:373–387
100. Takaloo S, Zand MM (2021) Wearable electrochemical flexible biosensors: With the focus on affinity biosensors. Sens Bio-Sens Res 32:100403
101. Tran H, Piro B, Reisberg S, Tran L, Duc H, Pham M (2013) Label-free and reagentless electrochemical detection of microRNAs using a conducting polymer nanostructured by carbon nanotubes: Application to prostate cancer biomarker miR-141. Biosens Bioelectron 49:164–169
102. Tung NT, Tue PT, Thi Ngoc Lien T, Ohno Y, Maehashi K, Matsumoto K et al (2017) Peptide aptamer-modified single-walled carbon nanotube-based transistors for high-performance biosensors. Sci Rep 7(1):17881
103. Ullah A, Lim SI (2022) Nanogels: update on the methods of synthesis and applications for cardiovascular and neurological complications. J Drug Deliv Sci Technol 103879
104. Valizadeh A, Mikaeili H, Samiei M, Farkhani SM, Zarghami N, Kouhi M et al (2012) Quantum dots: synthesis, bioapplications, and toxicity. Nanoscale Res Lett 7:1–14
105. Van Enter BJ, Von Hauff E (2018) Challenges and perspectives in continuous glucose monitoring. Chem Commun 54(40):5032–5045
106. Wang C, Xu H, Liang C, Liu Y, Li Z, Yang G et al (2013) Iron oxide@ polypyrrole nanoparticles as a multifunctional drug carrier for remotely controlled cancer therapy with synergistic antitumor effect. ACS Nano 7(8):6782–6795
107. Wang H, Li S, Lu H, Zhu M, Liang H, Wu X, Zhang Y (2023) Carbon-based flexible devices for comprehensive health monitoring. Small Methods, 2201340
108. Wang H, Lin M, Chen D, Dong Z, Yang Z, Zhang J (2018) Research on the rheological properties of cross-linked polymer microspheres with different microstructures. Powder Technol 331:310–321
109. Wang H, Sugiarto S, Li T, Ang WH, Lee C, Pastorin G (2016) Advances in nanomaterials and their applications in point of care (POC) devices for the diagnosis of infectious diseases. Biotechnol Adv 34(8):1275–1288

110. Wang J, Zhang S, Cao H, Ma J, Huang L, Yu S et al (2022) Water purification and environmental remediation applications of carbonaceous nanofiber-based materials. J Clean Prod 331:130023
111. Wang L, Xu D, Gao J, Chen X, Duo Y, Zhang H (2020) Semiconducting quantum dots: modification and applications in biomedical science. Sci China Mater 63(9):1631–1650
112. Wang S-G, Jiang X, Chen P-C, Yu A-G, Huang X-J (2012) Preparation of coaxial-electrospun poly [bis (p-methylphenoxy)] phosphazene nanofiber membrane for enzyme immobilization. Int J Mol Sci 13(11):14136–14148
113. Wang X, Li F, Guo Y (2020) Recent trends in nanomaterial-based biosensors for point-of-care testing. Front Chem 8:586702
114. Wang Y, Qian W, Tan Y, Ding S, Zhang H (2007) Direct electrochemistry and electroanalysis of hemoglobin adsorbed in self-assembled films of gold nanoshells. Talanta 72(3):1134–1140
115. Wegner KD, Hildebrandt N (2015) Quantum dots: bright and versatile in vitro and in vivo fluorescence imaging biosensors. Chem Soc Rev 44(14):4792–4834
116. Williams RM, Lee C, Heller DA (2018) A fluorescent carbon nanotube sensor detects the metastatic prostate cancer biomarker uPA. ACS Sens 3(9):1838–1845
117. Wu C, Yu C, Chu M (2011) A gold nanoshell with a silica inner shell synthesized using liposome templates for doxorubicin loading and near-infrared photothermal therapy. Int J Nanomed 807–813
118. Wu C, Zhi Z, Duan M, Sun J, Jiang H, Pang J (2023) Insights into the formation of carboxymethyl chitosan-nisin nanogels for sustainable antibacterial activity. Food Chem 402:134260
119. Wu S, Peng S, Yu Y, Wang CH (2020) Strategies for designing stretchable strain sensors and conductors. Adv Mater Technol 5(2):1900908
120. Xiang L, Zeng X, Xia F, Jin W, Liu Y, Hu Y (2020) Recent advances in flexible and stretchable sensing systems: from the perspective of system integration. ACS Nano 14(6):6449–6469
121. Xu K, Lu Y, Takei K (2021) Flexible hybrid sensor systems with feedback functions. Adv Func Mater 31(39):2007436
122. Yamamoto Y, Yamamoto D, Takada M, Naito H, Arie T, Akita S, Takei K (2017) Efficient skin temperature sensor and stable gel-less sticky ECG sensor for a wearable flexible healthcare patch. Adv Healthcare Mater 6(17):1700495
123. Yan J, Zhang J, Zhang M, Shi G (2022) Lanthanide metal-organic framework as a paper strip sensor for visual detection of sulfonamide with smartphone-based point-of-care platform. Talanta 237:122920
124. Yan Z, Zhang S, Gao M, Zhu Z, Li J, Huang Z et al (2023) Ultrasensitive and wide-range-detectable flexible breath sensor based on silver vanadate nanowires. ACS Appl Electron Mater
125. Yang Y, Luo C, Jia J, Sun Y, Fu Q, Pan C (2019) A wrinkled Ag/CNTs-PDMS composite film for a high-performance flexible sensor and its applications in human-body single monitoring. Nanomaterials 9(6):850
126. Yao S, Ren P, Song R, Liu Y, Huang Q, Dong J et al (2020) Nanomaterial-enabled flexible and stretchable sensing systems: processing, integration, and applications. Adv Mater 32(15):1902343
127. Yao S, Zhu Y (2015) Nanomaterial-enabled stretchable conductors: strategies, materials and devices. Adv Mater 27(9):1480–1511
128. Yoon Y, Truong PL, Lee D, Ko SH (2021) Metal-oxide nanomaterials synthesis and applications in flexible and wearable sensors. ACS Nanosci Au 2(2):64–92
129. Yuan F, Xia Y, Lu Q, Xu Q, Shu Y, Hu X (2022) Recent advances in inorganic functional nanomaterials based flexible electrochemical sensors. Talanta, 123419
130. Yuan K, Sun Y, Liang F, Pan F, Hu M, Hua F et al (2022) Tyndall-effect-based colorimetric assay with colloidal silver nanoparticles for quantitative point-of-care detection of creatinine using a laser pointer pen and a smartphone. RSC Adv 12(36):23379–23386
131. Yuan Z, Han S-T, Gao W, Pan C (2021) Flexible and stretchable strategies for electronic skins: materials, structure, and integration. ACS Appl Electron Mater 4(1):1–26

132. Zazoum B, Batoo KM, Khan MAA (2022) Recent advances in flexible sensors and their applications. Sensors 22(12):4653
133. Zhang J, Liu J, Wang S, Zhan P, Wang Z, Ming N (2004) Facile methods to coat polystyrene and silica colloids with metal. Adv Func Mater 14(11):1089–1096
134. Zhang J, Shi G (2022) Rational design of MoS2 QDs and $Eu^{3+}$ as a ratiometric fluorescent probe for point-of-care visual quantitative detection of tetracycline via smartphone-based portable platform. Anal Chim Acta 1198:339572
135. Zhang Y, Yan B (2019) A point-of-care diagnostics logic detector based on glucose oxidase immobilized lanthanide functionalized metal–organic frameworks. Nanoscale 11(47):22946–22953
136. Zhao C, Si Y, Pan B, Taha AY, Pan T, Sun G (2020) Design and fabrication of a highly sensitive and naked-eye distinguishable colorimetric biosensor for chloramphenicol detection by using ELISA on nanofibrous membranes. Talanta 217:121054
137. Zhao S, Li J, Cao D, Zhang G, Li J, Li K et al (2017) Recent advancements in flexible and stretchable electrodes for electromechanical sensors: strategies, materials, and features. ACS Appl Mater Interfaces9(14):12147–12164
138. Zhu Z (2017) An overview of carbon nanotubes and graphene for biosensing applications. Nano-Micro Lett 9(3):25